

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 10, 20, 25, 71, 101, 170, 171, 312, 314, 511, 514, 570, 571, 601, 812, and 814

[Docket No. 96N-0057]

National Environmental Policy Act; Revision of Policies and Procedures

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing compliance with the National Environmental Policy Act of 1969 (NEPA) as implemented by the regulations of the Council on Environmental Quality (CEQ). The primary purpose of this final rule is to increase the efficiency of FDA's implementation of NEPA and to reduce the number of NEPA evaluations by providing for categorical exclusions for additional classes of actions that do not individually or cumulatively have a significant effect on the human environment and for which, therefore, neither an environmental impact statement (EIS) nor an environmental assessment (EA) is required. FDA is also amending its regulations to make its NEPA procedures more concise and understandable to the public and to reflect current FDA policy with respect to environmental considerations. The amendments to FDA's regulations governing compliance with NEPA reflect FDA's continuing review of its policies and procedures to determine whether revisions are necessary to ensure full compliance with the purpose and provisions of NEPA and implement the President's reinventing Government initiatives announced in "Reinventing Drug and Medical Device Regulations," April 1995, and "Reinventing Food Regulations," January 1996.

DATES: The regulations are effective on August 28, 1997. For applications or petitions pending before the agency on August 28, 1997, for which the agency has not signed a finding of no significant impact (FONSI) on or before August 28, 1997, the applicant or petitioner may submit an amendment to the application or petition under 21 CFR 10.30(g), 71.6(b), 171.6, 314.60, 514.6, 571.6, 601.2 or 814.37 claiming a categorical exclusion in accordance with § 25.15(d) of this final rule. The applicant or petitioner should state in the amendment that the applicant or petitioner waives the claim for

categorical exclusion if a FONSI has been signed on or before August 28, 1997.

FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of April 3, 1996 (61 FR 14922) (republished May 1, 1996 (61 FR 19476)), FDA proposed to amend its regulations in part 25 (21 CFR part 25) governing compliance with NEPA as implemented by the regulations of CEQ. FDA provided 90 days for public comment on the proposed rule. In addition, in the **Federal Register** of October 22, 1996 (61 FR 54746), FDA announced the placement in the administrative record of additional information and underlying data concerning the proposed rule, and granted a 30-day comment period permitting interested parties to submit comments relating to those categorical exclusions for which additional information was provided. The agency has revised portions of the final regulations in response to comments received on the proposal.

This final rule amending FDA's NEPA procedures increases the efficiency of the agency's implementation of NEPA

by substantially reducing the number of EA's required to be submitted by industry and reviewed by FDA and by providing for categorical exclusions for additional classes of actions that do not individually or cumulatively have a significant impact on the human environment. This final rule also makes the regulations more concise and useful to the public and regulated industry.

II. Comments on the Proposed Rule

FDA received 17 letters, including letters from manufacturers, trade associations, environmental groups, academics, environmental consultants, and the U.S. Environmental Protection Agency (EPA), commenting on the proposed rule. In general, the comments supported FDA's proposed revisions to more efficiently implement NEPA. One manufacturer of human and veterinary pharmaceuticals projected that the final rule would reduce by 75 percent the number of its products that will require EA's, and a pharmaceutical industry trade association estimated that the rule will reduce by 90 percent the amount of environmental information submitted to the agency. FDA's analysis of the impacts of this final rule is included in section III of this document, "Analysis of Impacts."

A. Subpart A—General Provisions

1. One comment stressed the need to have more interaction and greater alignment among the agencies involved in implementing NEPA in order to develop more consistent policies.

CEQ regulations direct agencies with similar programs to consult with each other and with CEQ to coordinate their procedures (40 CFR 1507.3). However, differences in Federal agencies' policies and procedures to implement NEPA are inevitable because each agency has its own distinct statutory mandates. Each agency needs to evaluate and prioritize different environmental risks based on the nature of the agency's actions. CEQ reviews the procedures of all agencies to ensure their conformity with NEPA and CEQ regulations. FDA consults and coordinates with other Federal agencies regarding the protection of the environment to the fullest extent possible.

2. Proposed § 25.5(b)(4) states that increased use of a drug or biologic product may occur if the drug may 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. This section further defines new molecular entity as, "a drug for which the active moiety * * * has not been previously approved or marketed 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." FDA has decided not to include the definition of new molecular entity in § 25.5(b)(4). The term is currently defined in guidance documents issued by the Center for Drug Evaluation and Research (CDER). The agency does not find it necessary to include the definition in its regulations. Parties interested in the definition of new molecular entity should consult the information available from CDER.

3. Proposed § 25.10(c) describes when the environmental planning process begins under NEPA: "For actions initiated by applicants or petitioners, NEPA planning begins when FDA receives a submission from an applicant or petitioner seeking action by FDA." Proposed § 25.10(c) differs from current § 25.10(a), which states that:

For actions initiated by applicants or petitioners, the process begins when FDA receives from an applicant or petitioner an environmental assessment (EA) or a claim that a categorical exclusion applies, or when FDA personnel consult with applicants or petitioners on the NEPA-related aspects of their requested actions.

One comment indicated that current § 25.10(a) is consistent with NEPA and CEQ regulations because it provides for consultation between the agency and applicants or petitioners prior to Federal action. However, the comment contended that proposed § 25.10(c), as it amends current § 25.10(a), is inconsistent with NEPA and CEQ regulations. The comment specifically cites an inconsistency between proposed § 25.10(c) and 40 CFR 1501.2(d), which states that in "cases where actions are planned by private applicants or other non-Federal entities before Federal involvement," agencies shall provide policies or designated staff members "to advise potential applicants of studies or other information foreseeably required for later Federal action," and shall begin the NEPA process "at the earliest time possible."

FDA agrees with the comment. As explained in the preamble to the proposal (61 FR 14922 at 14923, 61 FR 19476 at 19477), FDA intended to eliminate unnecessary language by combining § 25.5 (Policies) and § 25.10 (NEPA planning) into proposed § 25.10 (Policies and NEPA planning). FDA did not intend to change the timing of the initiation of the agency's environmental planning process or to preclude early consultation with FDA prior to Federal action when it proposed the language in § 25.10(c). Thus, because the proposed section does not clearly express the

agency's policy, the agency will incorporate the current § 25.10(a) language, and § 25.10(c) will provide, in relevant part:

For actions initiated by applicants or petitioners, NEPA planning begins when FDA receives from an applicant or petitioner an environmental assessment (EA) or a claim that a categorical exclusion applies, or when FDA personnel consult with applicants or petitioners on the NEPA-related aspects of their requested actions.

4. One comment stated that under CEQ regulations (40 CFR 1501.2(d)), FDA is required to ensure that potential applicants or petitioners prepare an EA prior to the harvest of natural resources, such as the Pacific yew tree, regardless of whether the drug sponsor has filed an application or petition with the agency. The comment requested that the proposed regulations be revised to specifically address the issue of "stockpiling" harvested material prior to submitting an application or petition.

The requirements and procedures of NEPA are triggered by a major Federal action. Until FDA reviews an application or petition, initiates an action, or is consulted regarding potential agency action, no action exists to set the NEPA process in motion, and there is no regulatory requirement for applicants or petitioners to inform FDA of their use of natural resources prior to the submission of an application or petition to FDA. Therefore, FDA cannot ensure that applicants or petitioners prepare an EA prior to the harvest of natural resources. In accordance with 40 CFR 1501.2(d), the agency makes staff available to advise potential applicants or petitioners of studies or other information foreseeably required for later Federal action and commences its NEPA process at the earliest possible time (see § 25.10(c) of this final rule). FDA will request information about stockpiling and harvesting once the NEPA process is triggered by a proposed action.

With regard to the comment's specific concerns about the Pacific yew, the agency published a notice in the **Federal Register** of November 18, 1996 (61 FR 58694), clarifying the environmental information that must be submitted to the agency with a new drug application (NDA), abbreviated new drug application (ANDA), or investigational new drug application (IND) involving paclitaxel derived from or otherwise involving the Pacific yew.

5. One comment requested that proposed § 25.10, which states FDA's overall policy in implementing the NEPA requirements, be modified to indicate that applicants should be involved in the development of agency

policies, procedures, and guidance documents that are designed to interpret, clarify, or elaborate on the requirements placed on applicants to satisfy FDA's statutory obligations under NEPA.

In a notice in the **Federal Register** of February 27, 1997 (62 FR 8961), FDA announced its "Good Guidance Practices" (GGP's), which represents the agency's policy regarding the development and use of guidance documents (hereinafter referred to as the GGP's notice). The GGP's address public participation in the guidance document development process generally. FDA does not believe that it is necessary or appropriate to address public participation in the NEPA guidance document development process specifically. Interested individuals are encouraged to review the **Federal Register** notice and related comments (Docket No. 95P-0110).

6. One comment requested that § 25.10 be revised to provide that a single center official be responsible for addressing and resolving questions raised by reviewers and for mediating conflicts arising between reviewers and sponsors regarding interpretations of the regulatory requirements. The comment also requested that a provision be included that establishes an appeal from the center's responsible official to the Center Director, in the event that the center official is unable to resolve questions raised by reviewers.

FDA does not believe it is necessary to revise proposed § 25.10 as suggested by the comment. Individuals in each center with specialized training and expertise oversee the NEPA review process, resolve questions raised by reviewers, and mediate conflicts between reviewers and sponsors. Actions by reviewers or other center officials may be appealed through the appeals mechanisms already in place in each center to the Center Director and, ultimately, to the Commissioner of Food and Drugs (the Commissioner). Individuals who are interested in obtaining copies of the appeals procedures established in each center may contact the relevant center for such information.

B. Subpart B—Agency Actions Requiring Environmental Consideration

7. Proposed § 25.15(a) states that the failure of an applicant or petitioner to submit an "adequate EA" for a requested action that is not categorically excluded is sufficient grounds for FDA to refuse to file or approve the application or petition. One comment noted that while FDA requires an "adequate" EA, the definition of that

term found in current § 25.22(b) is not included in the proposed regulations. The comment requested that the agency retain the definition of adequate EA in its regulations.

The agency agrees that clarification of when an EA is adequate for filing or approval is appropriate. Consequently, proposed § 25.15(a) has been revised to include the clarifying statements currently found in § 25.22(b):

An EA 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 significantly affect the quality of the human environment.

8. Proposed § 25.15(a) and (d) requires that applicants and petitioners who claim that a categorical exclusion applies to a proposed action certify that the action qualifies for a categorical exclusion, citing the particular exclusion that is claimed, and certify that to their knowledge no extraordinary circumstances exist. One comment specifically welcomed and believed important to the success of FDA's proposals the certification of compliance with the categorical exclusion criteria required in § 25.15(a) and (d). Another comment requested clarification of the certification requirement in § 25.15(a) and (d), questioning whether the categorical exclusion document needs to contain a separate certification indicating the truthfulness and accuracy of the information provided in the certification, or whether the categorical exclusion document alone is sufficient.

Applications and petitions that are filed with the agency are signed by a responsible agent or official of the sponsor, who attests to the truth and accuracy of the information within the application or petition. A separate, signed categorical exclusion document is not needed. Under § 25.15(a) and (d), FDA requires that an applicant or petitioner requesting a categorical exclusion identify the categorical exclusion being claimed, state that the action complies with the categorical exclusion criteria, and state that to the applicant's knowledge no extraordinary circumstances exist. For clarification, § 25.15(a) and (d) have been modified to indicate that a statement, not a certification, is needed.

9. One comment contended that proposed § 25.15(a) and (d) is inconsistent with CEQ regulations in that the CEQ regulations require that the agency use specific criteria to judge whether an action fits within a categorical exclusion (40 CFR 1507.3(b)(2)(ii)) and independently

evaluate the information submitted and be responsible for the accuracy of the information (40 CFR 1506.5). The comment also asserted that proposed § 25.15(a) and (d) departs from existing FDA regulations, which require that applicants claiming a categorical exclusion provide supporting information that the action meets the criteria for the applicable exclusion.

Under current § 25.23(c), a person who claims a categorical exclusion provides information when appropriate that establishes to the agency's satisfaction that the action meets the criteria for the applicable exclusion (emphasis added). Proposed § 25.15(a) and (d) does not reflect a departure from current FDA regulations. In revising its NEPA procedures, FDA has formulated its categorical exclusions to include specific criteria, as required by CEQ's regulations (40 CFR 1507.3(b)(2)(ii)) that in most instances can either be facially determined or confirmed by review of other information submitted as part of the request for action. This approach is consistent with CEQ's view that in most cases additional information should not be required. In the limited instances when it may be necessary, FDA will request additional information as needed to establish to the agency's satisfaction that the criteria for a categorical exclusion have been met.

10. One comment objected to the absence of information in the proposal concerning the actions FDA may take in response to a petitioner or applicant filing a false certification with the agency.

It is a violation of the criminal code (18 U.S.C. 1001) for anyone, in any matter within the jurisdiction of any department or agency of the United States, to knowingly and willfully make any false, fictitious, or fraudulent statement or representation to such department or agency. Enforcement decisions are generally a matter of an agency's discretion. FDA will exercise its enforcement discretion consistent with its statutory responsibilities under all applicable statutes, including NEPA.

11. One comment recommended that the basic physical/chemical characterization of a potential product be included in all EA documents including claims for categorical exclusion.

In the event FDA determines that basic physical/chemical characterization information is relevant to its environmental consideration of a specific proposed action, FDA will request that such information be provided in an EA. FDA intends to issue guidance documents that will provide applicants with information about the

nature and scope of information that should be included in an EA. A claim for categorical exclusion shall comply with § 25.15(a) and (d) and, as discussed in the response to comment 9, should not normally include additional information.

12. Proposed § 25.20 lists broad categories of agency actions that require the preparation of an EA, unless the action qualifies for exclusion. One comment noted that although FDA stated in the preamble to the proposal that the types of actions requiring an EA remain essentially the same as in current § 25.22, the proposal did not include the "catch-all action" in current § 25.22(a)(19): "Action other than one listed in this subsection, unless subject to exclusion under §§ 25.23 and 25.24, that may significantly affect the quality of the human environment." The comment recommended that a clause be retained in new § 25.20 providing that an "EA must be prepared for an action other than one listed in (§ 25.20) that may significantly affect the quality of the human environment."

The list of actions requiring preparation of an EA was not intended to be all-inclusive. The list includes broad classes of actions that require preparation of at least an EA, unless categorically excluded in subpart C of part 25. Under NEPA and CEQ's implementing regulations, FDA is required to consider the environmental impact of each of its proposals for major Federal action that is not categorically excluded. Therefore, it is not necessary for FDA to include the described catch-all clause in the final rule.

13. Another comment noted that proposed § 25.20(i) requires an EA for actions on requests for exemptions for investigational use of food additives, unless categorically excluded under proposed § 25.32(b), and questioned whether the agency expects a claim for exclusion to be submitted for actions involving investigational food additives. The comment asked FDA to clarify its intent.

The intent of the provision in proposed § 25.20(i) is to identify actions involving food additives that ordinarily require an EA, unless the actions are in a specific class that qualifies for a categorical exclusion. Similar to the agency's experience with actions on investigational human and animal drugs, FDA expects that if action were taken on an investigational food additive, such action would qualify for the exclusion under § 25.32(b) of the final rule.

14. Proposed § 25.21 addresses "extraordinary circumstances" under which categories of actions that would

ordinarily be categorically excluded would require preparation of an EA. One comment contended that this exception to categorical exclusions will result in the potential for "regulatory creep," that is, the potential for FDA to implement the exception in a manner that results in an expansion of the degree of FDA review, a lengthening of time for review, and an increased cost of review. The comment expressed particular concern about the opportunity for regulatory creep in relation to applying the exception to categorical exclusions for actions on new animal drug applications (NADA's). The comment suggested that a primary safeguard against misuse of the extraordinary circumstances exception is to ensure that decisions on exceptions are reserved and delegated in part 5 (21 CFR part 5) to a truly responsible official; in the case of actions on animal drugs, to the Director of the Center for Veterinary Medicine.

As the comment recognizes, under CEQ regulations at 40 CFR 1508.4, FDA is required to provide for extraordinary circumstances in which a normally excluded action may have a significant effect on the environment. Under proposed § 25.21 (current § 25.23(b)), FDA requires 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. CEQ regulations, in 40 CFR 1508.27, define "significantly" to require consideration of both the context and intensity of an agency action. Proposed § 25.21 cites § 1508.27 to emphasize that, in implementing its regulations, FDA will rely on the principles established by CEQ for determining whether an extraordinary circumstance exists such that an action, ordinarily excluded, may significantly affect the environment. By definition, a categorical exclusion means a category of actions that has been found not to have a significant effect on the human environment, therefore application of the extraordinary circumstances provision should be limited. Since 1985, in implementing its NEPA procedures, FDA has invoked the extraordinary circumstance exception to categorical exclusions in limited instances and in a manner consistent with CEQ regulations. Section 25.21 lists two examples of extraordinary circumstances where FDA may apply the exception.

FDA declines to modify part 5 to reflect that the authority to determine the existence of extraordinary circumstances related to animal drugs is

reserved to the Director of the Center of Veterinary Medicine. The agency's decision is described in the response to comment 60 below, which discusses the revision of part 5 with respect to all FDA Center Directors.

15. One comment asserted that the extraordinary circumstances provision will not result in the preparation of EA's for applications involving paclitaxel that otherwise meet the criteria for categorical exclusion. The comment stated that the Pacific yew is not classified as an endangered or threatened species under the Endangered Species Act (ESA), nor is the species currently listed in any of the appendices to the Convention on International Trade in Endangered Species of Fauna and Flora (CITES) and expressed concern that agency actions regarding products containing paclitaxel would escape environmental consideration because they do not fall within FDA's examples of extraordinary circumstances. The comment also questioned the standard that the agency has proposed to use in determining whether an action involving wild flora and fauna falls within FDA's second example of extraordinary circumstances, citing FDA's statement in the preamble that the agency:

(I)ntends to closely examine proposed actions that involve FDA-regulated articles obtained from wild flora and fauna and will use the extraordinary circumstances provision to require at least an EA in any instance in which it appears from an examination of the proposed action that the action may cause a species to become endangered or threatened.

Finally, the comment asserted that unlike the ESA, CITES does not speak in terms of endangered or threatened species.

The examples provided by the agency in proposed § 25.21 are illustrative of the types of action that would require an EA despite the fact that the action otherwise qualifies for a categorical exclusion. The two examples are not intended to be an exhaustive list of those actions.

FDA's extraordinary circumstances provision requires that an EA be prepared if a normally excluded action may significantly affect the quality of the human environment. FDA has specifically determined that actions relating to applications involving paclitaxel derived from or otherwise involving the Pacific yew tree fall within the CEQ definition of "significantly" (40 CFR 1508.27) and has documented, in the agreement filed in the U.S. District Court for the District of Columbia in *Oregon Natural Resources Council Action v. Shalala*,

No. 96-1449 PLF (D.C.D.C. Oct. 4, 1996), its intent to require EA's for all actions on applications, except some actions on IND's, involving paclitaxel derived from or otherwise involving the Pacific yew tree. FDA also published a notice in the **Federal Register** clarifying the environmental information that must be submitted to the agency in marketing applications for drug products containing paclitaxel (61 FR 58694).

FDA is clarifying that it will require an EA for an action, including one involving wild flora and fauna, that is ordinarily excluded if the action may have a significant effect on the environment. Where a species of wild flora or fauna may become endangered or threatened, the action may have a significant effect.

The comment is inaccurate in stating that CITES does not speak in terms of endangered or threatened species. The regulations implementing CITES (50 CFR 23.2) note that the appendices include endangered and threatened species and a "Facts" sheet published by the Fish and Wildlife Service explains that Appendix I includes species presently threatened with extinction.

16. One comment expressed concern about the environmental effects of synthetic estrogens in the aquatic environment, specifically those synthetic estrogens in oral contraceptives and estrogenic replacement therapy prescribed for postmenopausal women. The comment requested that until research is available to determine a more accurate critical concentration, FDA consider the use of synthetic estrogens in human drugs to be an extraordinary circumstance so that actions involving estrogen use would require an EA. The authors of the comment state that they have observed significant alterations of gender ratios when developing larval medaka (a fish) were exposed to 0.1 part per billion (ppb) of 17 β -estradiol (naturally occurring) for 4 weeks. Additionally, they cite from a published article that male rainbow trout exposed to 0.002 ppb ethinyl estradiol (used in oral contraceptives) for 3 weeks showed significantly elevated vitellogenin levels and decreased testes weight and compromised spermatogenesis. Concern was also expressed about the potential for higher concentrations of these compounds in certain local areas.

FDA will require an EA for any specific action that ordinarily would be excluded if available evidence establishes that, at the expected level of exposure, a potential exists for a significant effect on the environment.

The agency has considered the request that the use of synthetic estrogens in human drugs be considered an extraordinary circumstance, but has concluded that the available evidence does not support that, at the expected level of exposure, a potential exists for significant effect on the environment. FDA has considered many factors in arriving at this conclusion including normal prescribing patterns for the drugs, medical uses, pharmacological properties, waste water treatment practices and expected introduction and environmental concentrations of the substances. FDA provided its analysis to the EPA for review and EPA agreed with FDA's position on this issue. Therefore, FDA will not generally apply the extraordinary circumstances exception to actions involving synthetic estrogens used in oral contraceptives and hormone replacement therapy that otherwise meet the criteria for categorical exclusion. A report explaining the basis of the agency's decision has been placed in Docket No. 96N-0057. FDA will continue to investigate this issue in general and assess each action on an individual basis to determine whether an extraordinary circumstance exists.

17. Proposed § 25.22 provides for the preparation of an EIS when the responsible agency official finds, as a result of evaluating relevant data and information, that a proposed action may significantly affect the quality of the human environment. One comment recommended that FDA establish specific criteria to determine the need to prepare an EIS. The comment suggested that the agency base the criteria on the number of potentially affected parties or on the formula used by the European Union (EU) to trigger the EU equivalent of an EIS. The EU criteria are based on annual tonnage.

An EIS is prepared when evaluation of data or information in an EA or otherwise available to the agency leads to a finding that a proposed action may significantly affect the quality of the human environment. FDA does not believe it is necessary to further identify criteria for preparing an EIS. CEQ regulations (40 CFR 1508.27) define "significantly" and provide guidance to FDA in its determination of whether an action significantly affects the environment. Furthermore, it is difficult to develop criteria that are more specific and that may be applied with great frequency. Criteria relating to the amount of material produced are not appropriate criteria for determining when an EIS must be prepared. For example, an EIS may not be necessary for FDA-regulated articles produced in

large quantities if environmental depletion mechanisms are identified and/or the material is relatively nontoxic to environmental organisms at expected environmental concentrations.

18. In the preamble to the proposal, FDA stated that it is proposing to remove current § 25.25 (Retroactive environmental consideration) because any request by FDA to an applicant to submit additional information to an existing FDA approval will be made under authority granted to FDA by the Federal Food, Drug, and Cosmetic Act (the act) or the Public Health Service Act (the PHS Act). One comment contended that this proposed action is inconsistent with both CEQ regulations and case law governing implementation of NEPA. The comment stated that FDA was suggesting it could not comply with 40 CFR 1502.9(c)(1)(ii) because its authority to require additional environmental information from applicants only stems from the act or the PHS Act. The comment stated that the Federal court, in *Environmental Defense Fund v. Mathews*, 410 F.Supp. 336, 338 (D.C.D.C. 1976), rejected similar claims when FDA issued its NEPA regulations in the 1970's.

Because the comment misunderstands the agency's stated reasons for proposing to remove current § 25.25, FDA is clarifying them here. Current § 25.25 applies to agency consideration of the need to prepare an EIS after the agency has already taken an action, e.g., promulgation of a regulation or action relating to an approval. NEPA and CEQ regulations both require an agency to consider the environmental impact of its actions before decisions are made and before actions are taken. Thus, the agency must prepare an EIS for an action it has found may significantly affect the environment before it takes the action. NEPA does not apply retroactively; instead, however, if an ongoing project undergoes changes which themselves amount to "major Federal actions," the agency must then prepare an EIS (*Upper Snake River Chapter of Trout Unlimited v. Hodel*, 921 F.2d 232, 234 (9th Cir. 1990)). FDA is removing § 25.25, which concerned retroactive environmental consideration.

The comment cites *Environmental Defense Fund v. Mathews*, 410 F.Supp. 336, 338 (D.C.D.C. 1976), which relates to FDA's 1973 regulations implementing its obligations under NEPA. The case held that, in addition to its other statutory mandates, FDA has a nondiscretionary responsibility under NEPA to take environmental considerations into account in its process of decisionmaking. For the

reasons stated above, elimination of current § 25.25 does not affect this responsibility and is not inconsistent with CEQ regulations or case law.

The agency specifically acknowledges its responsibility to prepare supplements in accord with § 1502.9 in the new regulations (see § 25.42(c)). FDA's discussion in the preamble to the proposed rule was intended to point out that CEQ regulations only discuss when a supplement to a draft or final EIS is needed. CEQ regulations do not specifically address or grant any authority to an agency to request additional information under other circumstances. FDA also wanted to make it clear that once FDA has taken an action, the agency has authority under the act and the PHS Act to request that an applicant submit additional information to an existing approval.

C. Subpart C—Categorical Exclusions

19. One comment found no major issues or problems with the policy and procedure revisions, but expressed concern whether FDA had made adequate analyses to substantiate the proposed categorical exclusions. Another comment stated that the commenter was unable to evaluate the proposed categorical exclusions, specifically the exclusion provided in § 25.31(b), because FDA had not made the information upon which it based its conclusions available to the public.

To provide additional substantiation for its proposed categorical exclusions, FDA supplemented the administrative record for the proposed regulations with additional information. On October 22, 1996, the agency published a notice in the **Federal Register** (61 FR 54746) announcing the availability of specific information, including underlying data, that along with the information in the preamble to the proposed rule supports the categorical exclusions. FDA also reopened the comment period for 30 days for the sole purpose of inviting public comment on those categorical exclusions for which information had been added to the administrative record. The agency received four comments during this extended comment period, three of which addressed categorical exclusions for drug and biologic products. FDA, therefore, believes that it has provided adequate explanation of the categorical exclusions and has provided adequate opportunity for comment on the categorical exclusions by interested parties.

20. Proposed § 25.30(j) revised the categorical exclusion for issuance of certain types of regulations, including current good manufacturing practice

(CGMP) regulations, to categorically exclude regulations based on the hazard analysis critical control points (HACCP) principles. One comment agreed with this change but recommended that HACCP programs incorporate mandatory self audits and independent audits into their requirements.

This recommendation is outside the scope of this rulemaking.

1. Human Drugs and Biologics

21. Proposed § 25.31(a) would categorically exclude FDA action on an NDA, abbreviated application, or a supplement to such applications, or action on an over-the-counter (OTC) monograph, if the action does not increase the use of the active moiety of the drug. FDA intended to include in this categorical exclusion applications for marketing approval of a biologic product. As discussed in the preamble to the proposed rule with regard to NDA's, abbreviated applications, supplements, and OTC monographs, if an action, including action on a marketing application for a biologic product, does not increase the use of the product, there is no change in the level of substance in the environment and, consequently, no increase in any environmental effects associated with the use and disposal from use of the product. Therefore, proposed § 25.31(a) has been modified as follows:

Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety.

22. Proposed § 25.31(b) would categorically exclude FDA action on a marketing application for a human drug, or supplement to such application, or action on an OTC monograph, if the action increases the use of the active moiety but the concentration of the substance in the environment will be below 1 ppb. Several comments generally supported the 1 ppb criterion, but sought minor revisions to or clarifications of the criterion.

One comment suggested that the 1 ppb criterion be changed to 0.1 ppb using the predicted environmental concentration (PEC). PEC is defined as the introduction concentration, corrected based on metabolism/excretion data, on wastewater treatment facility fate information, and on the use of an appropriate stream dilution factor of 10. Two comments suggested that proposed § 25.31(b) be clarified to indicate that the relevant concentration is at the point of entry into the aquatic environment. One of these comments agreed that substances entering the

environment at less than or equal to 1 ppb will have an insignificant environmental impact, but suggested that the standard be an expected introduction concentration because this would give more consideration to potential exposure to primary human receptors which may come in contact with the substance before it degrades or enters a wastewater treatment facility. Another comment suggested that because 1 ppb computes to a production rate of 40,700 kilograms (kg) per year using the calculation method provided in FDA guidance, FDA should add an exclusion for actions relating to human drugs for which the production rate of the active moiety is less than 40,700 kg per year.

FDA agrees to clarify that the 1 ppb requirement is relevant at the point of entry into the aquatic environment, that is, the environmental introduction concentration (EIC). Under current part 25, FDA requires EA's to initially provide an estimate of the quantity and concentration of the substance that is expected to enter the environment. The calculation method suggested by CDER is explained in its "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements" (FDA, November 1995). If environmental fate and effects information for a substance is required in an EA, spatial and temporal concentration and depletion mechanisms will, as appropriate, be used to adjust the EIC to estimate the expected environmental concentration (EEC)/exposure concentration of the product. PEC, as defined by the comment, is the same as the EEC/exposure concentration. The comment's suggested use of a criterion of 0.1 ppb, calculated using a dilution factor of 10, is equivalent to the agency's proposed criterion of 1 ppb calculated without using a dilution factor, in that the same amount of the substance entering the environment would qualify for categorical exclusion under each proposal. It may be appropriate for FDA to consider a dilution factor when estimating a substance's EEC/exposure concentration, based on information provided in an EA, to evaluate the fate and effects of the substance. For the purposes of a categorical exclusion criterion, however, a conservative estimate of the concentration, EIC, will be used.

As explained in the preamble to the proposed rule (61 FR 14922 at 14925, 61 FR 19476 at 19479), based on their method of entry into the environment from use and their physical and chemical characteristics (e.g., water

solubility), human drugs would be expected predominantly to enter the aquatic environment. The data submitted in EA's reviewed by CDER have routinely supported this hypothesis. The data also have routinely shown that in those cases in which an applicant has provided toxicity results for terrestrial organisms in addition to acute toxicity results for aquatic organisms, the drugs are toxic to aquatic organisms at lower levels than they are to terrestrial organisms, suggesting that the use of aquatic organisms is a conservative approach. Proposed § 25.31(b) has been revised to clarify that the relevant concentration is at the point of entry into the aquatic environment.

CEQ regulations require that localized (i.e., site-specific) effects of a substance on the environment be considered, where appropriate (40 CFR 1508.27(a)). Typically, the use of a drug product is spread throughout the United States. However, in the rare instance in which the use of a drug will be localized in one geographic area, a categorical exclusion based on the concentration of a substance at the point of entry into the aquatic environment, such as 1 ppb, provides for an evaluation of the local environmental effect of that drug. The suggestion to add a categorical exclusion based on a set quantity of the drug product, such as 40,700 kg, ignores the possibility of localized use that the agency is required to consider. Therefore, FDA is not adding a categorical exclusion based on production rates.

Concerning potential exposure to primary human receptors, as discussed in *Calorie Control Council, Inc. v. U.S. Department of Health, Education, and Welfare*, No. 77-0776 (D.C.D.C. 1977), the primary concern of NEPA is the impact of agency actions on physical environmental resources, not the public health consequences of a proposed action. Furthermore, NEPA authority is intended to supplement other statutory responsibilities of a Federal agency. FDA already addresses primary receptor issues as public health issues under the act rather than through NEPA evaluation.

As a result of this discussion, proposed § 25.31(b) has been revised to state:

Action on a NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action 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.

CDER's document, "Guidance for Industry for the Submission of an

Environmental Assessment in Human Drug Applications and Supplements," provides a method for calculating the estimated concentration of the substance at the point of entry into the aquatic environment. Other calculation methods may be appropriate. However, such alternative calculations will be reviewed by the agency on a case-by-case basis to determine whether they are appropriate for determining whether the categorical exclusion applies.

23. One comment reiterated a comment made during the initial comment period that the agency needs to broaden "extraordinary circumstances," especially as the provision relates to paclitaxel, and further noted "troubling defects" in the Toxicity Report the agency provided in the administrative record to support the 1 ppb categorical exclusion criterion in § 25.31(b). The defects cited in the comment include: (1) The report is grounded in an evaluation of ecotoxicity in a few select laboratory species, not in wild organisms that may already be stressed by other pollutants; (2) the report appears to be based on EA's submitted by applicants to the agency, and no information is given about how the toxicity figures were obtained and whether certain assumptions were made in the studies; (3) the report does not consider cumulative impacts associated with disposal of the products in the environment, including the potential for bioaccumulation of pollutants over time; and (4) the report provides no scientific explanation, other than citing one article, for dividing the median effective concentration (EC50) or median lethal concentration (LC50) values by 1,000 to arrive at a predicted no observed effect concentration (NOEC). The comment also stated that the Toxicity Report is based on toxicity tests that may be considered antiquated in light of recent efforts by the Organization for Economic Cooperation and Development (OECD) and EPA to revise such evaluations. The comment did not suggest any changes to the proposed regulations.

FDA's extraordinary circumstances provision requires that at least an EA be prepared if a normally excluded action may significantly affect the quality of the human environment. The agency has specifically determined that most actions relating to paclitaxel derived from or otherwise involving the Pacific yew require the preparation of EA's, irrespective of the expected concentration of paclitaxel at its point of entry into the aquatic environment. (See the response to comment 15, above.)

With respect to the alleged defects of the Toxicity Report, environmental risk

assessment initially involves determining the toxic effect of a compound on a few select laboratory species. The test organisms used by the applicants to generate the data in the Toxicity Report are typically the same as those suggested by EPA (see 40 CFR 797) and OECD for this initial screening. CDER evaluates the potential for significant environmental effects by relating the concentrations determined to have toxic effects on these test organisms to the level of the substance expected in the environment. Field studies (i.e., evaluation in actual environmental settings) are generally conducted only when initial evaluation and subsequent intermediate evaluations indicate that the potential for significant environmental harm may exist.

FDA based the proposed 1 ppb categorical exclusion on toxicity data submitted to the agency in EA's. The agency's analysis of the toxicity data is explained in the Toxicity Report. Under 40 CFR 1506.5, the agency asks applicants to prepare an EA and FDA independently evaluates the information in the EA to determine its acceptability. The Toxicity Report provides summary information from the EA's, identifying the location of the detailed EA reports and FONSI's in the public docket. FDA reviewed the test reports provided in EA's and determined that the methodologies, assumptions, and conclusions of the reports were acceptable. Any interested party may obtain additional information regarding the test methods used for each EA from those reports in the public docket.

Impacts on the environment which result from the incremental impact of an action when added to other past, present, and reasonably foreseeable future actions are known as cumulative impacts. Consideration of cumulative impacts is included in the proposed categorical exclusions for human drugs and biologics. Under § 25.31(a), action on a marketing application for a human drug or biologic or action on an OTC monograph may be categorically excluded if the action does not increase the use of the active moiety. However, if an action increases the use of the active moiety, the impacts of that increased use will require environmental analysis unless the action meets other specific categorical exclusion criteria established in § 25.31(b) and (c). The potential for cumulative effects is also considered in the calculation of the EIC of an active moiety of a drug because the applicant bases these estimates on the expected quantities that will be used 5 years in

the future, including the use quantities associated with related FDA applications (see, e.g., Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements, Section III.D.6.e, November 1995).

As stated in the preamble to the proposed rule (61 FR 14922 at 14925, 61 FR 19476 at 19479), one of the criteria for determining that a drug is safe for human use is consideration of its potential to bioaccumulate in body tissue. The vast majority of drugs do not bioaccumulate because that characteristic would raise safety concerns for use of the drugs in humans. If a drug has characteristics that would allow it to bioaccumulate in tissue, the body must have a mechanism to metabolize the compound into a substance that has lower bioaccumulation potential so that it may be cleared from the body. In the EA's that the agency reviewed, bioaccumulation was not an issue.

The practice of using assessment factors in environmental risk assessments is well established. FDA's use of an assessment factor of 1,000 is consistent with EPA's approach (e.g., Zeeman, M., and J. Gilford, "Ecological Hazard Evaluation and Risk Assessment Under EPA's Toxic Substances Control Act (TSCA): An Introduction," in *Environmental Toxicology and Risk Assessment*, ASTM STP 1179, edited by W. Landis, J. Hughes, and M. Lewis, pp. 7-21, American Society for Testing and Materials, Philadelphia, 1993.).

The toxicity tests performed by FDA applicants and described in the Toxicity Report are consistent with contemporary practice and are based on current scientific thinking. Potential future revision of test methods does not render invalid current testing, data obtained as a result of that testing, or conclusions based on that data.

24. One comment stated that under § 25.31(b), FDA will now apparently permit companies seeking approval of metered dose inhalers to forgo preparation of EA's in connection with their marketing applications. The comment asked that the agency make clear in its final regulations that FDA will require EA's with all applications involving metered dose inhalers that release chlorofluorocarbons (CFC's) and that such EA's must thoroughly evaluate the cumulative impacts of CFC's on the Antarctic environment and alternatives that avoid such impacts.

In 1978, FDA finalized a programmatic EIS regarding the use of fluorocarbons in products subject to regulation by the agency under the act (Final Environmental Impact Statement;

Fluorocarbons: Environmental and Health Implications, February, 1978, Docket No. 76N-0640) and announced the availability of the final EIS in the **Federal Register** (43 FR 11316, March 17, 1978). This EIS was used as the basis for prohibiting use of CFC's as propellants in self-pressurized containers if the use of the CFC was not deemed to be essential. As stated in the EIS:

The Commissioner of Food and Drugs has concluded that the continued use of chlorofluorocarbon propellants in self-pressurized containers in products subject to the Federal Food, Drug, and Cosmetic Act (FFD&C) poses an unreasonable risk of long-term biological and climatic impacts.

Accordingly, the Food and Drug Administration is finalizing a prohibition of the nonessential use of chlorofluorocarbons as propellants in self-pressurized (aerosolized) containers in products subject to the FFD&C Act. The products to which the regulation applies are human food, food additives, human drugs, including biological products, animal food, animal drugs, cosmetics, and medical devices. (p. iii)

The EIS further stated:

The selection of fluorocarbon use(s) to be regulated requires a determination of whether or not a particular fluorocarbon use is essential. The Commissioner of Food and Drugs has defined essentiality to mean that there are no technically feasible aerosol or non-aerosol alternatives to using a fluorocarbon in a product and that a product provides a substantial public benefit such as a therapeutic medical benefit. The product need not be indispensable to life, but the benefit must be important and consist of more than added convenience. (p. 89)

A copy of the programmatic EIS has been placed in the administrative record for this rule (Docket No. 96N-0057).

FDA regulations pertaining to the use of CFC propellants in self-pressurized containers are described in § 2.125. CFC's may be used as propellants in a self-pressurized container only if the drug is approved, a petition has been filed as described in § 2.125(f), and § 2.125(e) has been amended to specify the use as essential. The petition requesting an essential use designation must be supported by an adequate showing that: (1) No technically feasible alternatives exist to the use of a CFC in the product; (2) the product provides a substantial health benefit, environmental benefit, or other public benefit that would not be obtainable without the use of the CFC; and (3) the use does not involve a significant release of CFC's into the atmosphere or, in the alternative, the release is warranted in view of the consequences of the use not being permitted. The petition is a public document about which any interested party may

comment before a final determination is made by the agency.

FDA is in the process of establishing a policy for determining when uses of CFC's currently designated essential will no longer be deemed essential under the Clean Air Act due to the availability of safe and effective medical product technology that does not use CFC's. (See Docket No. 97N-0023.)

The agency has, in the programmatic EIS, evaluated the individual and cumulative effects, including the effects on human health, stratospheric ozone, biological systems (nonhuman), and climate, of approvals of marketing applications that result in the release of CFC's. FDA has fulfilled its responsibilities and has adequately considered the environmental issues regarding CFC's. Therefore, a requirement that individual marketing applications for metered dose inhalers that release CFC's must include EA's is not necessary because the environmental information would already be under consideration by the agency in its decision whether to designate an essential use under § 2.125(e). Resubmission of this information to the agency would not be consistent with CEQ goals of reducing excessive paperwork. NEPA supplements, but does not supersede, other statutory responsibilities. NEPA establishes requirements to ensure that an agency considers environmental information in its decisionmaking process. Thus, after a review of the relevant environmental information, FDA may, but is not required to, decline to take an action that may have a significant effect on the environment.

25. Proposed § 25.31 lists the general classes of agency actions relating to human drugs and biologics that are categorically excluded and, therefore, ordinarily do not require the preparation of EA's or EIS's. One comment requested that a categorical exclusion be added to the regulations for "[a]ction on an NDA, abbreviated application, or a supplement to such application, or action on an OTC monograph, if the active moiety has been previously approved by FDA and the concentration in the environment will be above 1 part per billion."

The agency believes that providing a categorical exclusion in § 25.31 for an active moiety that has been previously approved by the agency is inappropriate. FDA does not have any evidence that actions relating to the approval of a drug or biologic for which the active moiety has been previously approved do not individually or cumulatively have a significant effect on the environment. In some cases, the

approval of a new indication or dosage form of a previously approved active moiety could substantially increase the use of the product. In such cases, an EA must be prepared unless the action meets one of the other criteria for a categorical exclusion.

26. One comment requested that proposed § 25.31 be revised to add a categorical exclusion for actions relating to drugs that involve substances that have an environmental concentration greater than 1 ppb (i.e., do not meet the criteria for categorical exclusion under § 25.31(b)) but have a PEC to a predicted no effects concentration (PNEC) ratio equaling less than one.

The agency declines to amend § 25.31 as requested. A PEC/PNEC ratio is one of several commonly used approaches for evaluating environmental effects. To calculate the PEC/PNEC ratio, ecotoxicity studies are performed, results are compared to expected environmental concentrations, and a conclusion is drawn. The calculation also requires use of an assessment factor that will vary depending on the type of ecotoxicity data generated. The PEC/PNEC ratio constitutes an environmental analysis and, therefore, is not an appropriate criterion for a categorical exclusion. If FDA were to use a PEC/PNEC ratio as a criterion for categorical exclusion, FDA would need to review the underlying data that supports the PEC/PNEC ratio, including the assessment factor, and would, in essence, be requiring an EA. Thus, FDA will not add a categorical exclusion for actions relating to drugs based on the calculation of a PEC/PNEC ratio. An applicant is not precluded, however, from using a PEC/PNEC ratio to assess environmental effects in an EA or to aid in determining whether extraordinary circumstances exist such that a proposed action, which is normally excluded, may have an environmental effect.

27. One comment recommended that the categorical exclusion described in proposed § 25.31(c) for naturally occurring substances not include new steroid or hormone modulating drugs.

As explained in the preamble to the proposal (61 FR 14922 at 14926, 61 FR 19476 at 19480), FDA based the categorical exclusion in § 25.31(c) on its finding, after reviewing abbreviated EA's for substances that are naturally occurring, that actions on submissions for these substances will not affect the environment if the action will not significantly alter the concentration or distribution of the natural substance in the environment. No information was provided in the comment to support the need for this change. The available

evidence does not support a finding that new steroid or hormone modulating drugs, at the expected level of exposure, have the potential to significantly affect the environment. Therefore FDA will not modify § 25.31(c). The agency specifically addressed concerns regarding synthetic estrogens used in human drugs in comment 16 of this document. The agency will evaluate each proposed action on an individual basis to determine if extraordinary circumstances exist such that further environmental documentation is needed.

28. One comment requested clarification regarding the definition of "substances that occur naturally in the environment" as that phrase is used in proposed § 25.31(c). The comment suggested that the categorical exclusion be revised to read "substances that either occur naturally in the environment, or are derived from biological systems" or, alternatively, that FDA provide a definition in the regulation.

The agency declines to adopt the language suggested in the comment because the term "or derived from biological systems" is too broad. Not all substances produced by a biological system may be substances that occur naturally in the environment. The biological system, or the substance itself, may be modified such that the substance does not occur naturally in the environment. The comment provided no rationale as to why biologically-derived substances not occurring naturally in the environment should be subject to the categorical exclusion.

FDA intends to clarify which type of actions would fall under this categorical exclusion in guidance documents prepared by each center. FDA-regulated articles may be considered for categorical exclusion under this provision whether they are obtained from natural sources, biological systems, or are chemically synthesized. The agency will consider the form in which the FDA-regulated article will exist in the environment when determining if an action will be eligible for this categorical exclusion. For example, a modified active moiety (e.g., salt) which does not occur naturally may 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 comprised of naturally occurring amino acids or nucleosides, but with a sequence different from that

of a naturally occurring substance, will normally qualify for this categorical exclusion after consideration of metabolism. The same principle will apply to synthetic peptides and oligonucleotides. Living and dead cells and organisms regulated by the agency may also be considered for categorical exclusion under this provision if the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. The agency will rely on the significant amount of information submitted by an applicant in support of a requested action (for example information about metabolism, excretion, and stability; viability (if applicable); and physical/chemical characteristics of the product) in determining whether categorical exclusion under § 25.31(c) is appropriate.

29. One comment requested that the phrase "action on an OTC monograph," which is included in the categorical exclusions in § 25.31 (a), (b), and (c), be changed to "OTC activity" and that the regulation define "OTC activity" as "an action on an OTC monograph or a switch of a drug from prescription to OTC use that is submitted in an NDA or supplement, if the product is already marketed for the proposed use." The comment expressed a belief that the preamble to the proposed rule "is clear on the intent for a prescription to an OTC switch to be considered as a categorical exclusion."

FDA does not believe it is necessary or appropriate to substitute "OTC activity" for "action on an OTC monograph" in § 25.31 (a), (b), and (c). Agency action on any request to switch a drug from prescription to OTC use is already covered in § 25.31 (a), (b), and (c) by the language "action on an NDA, abbreviated application, or a supplement to such application, or action on an OTC monograph." Depending on the circumstances and the applicant's preference, a prescription to OTC switch may be requested using any of these administrative filing mechanisms. As discussed in the preamble (61 FR 14922 at 14925, 61 FR 19476 at 19479), the agency will not elevate form over substance and will treat like actions alike, regardless of the avenue through which the actions are requested. Thus, the same categorical exclusion criteria will apply to NDA's, abbreviated applications, supplements, and "actions on OTC monographs."

Prescription to OTC switches have generally been, and will continue to be, considered by CDER to be actions that

increase use because the potential patient population expands from only those persons who seek treatment under a physician's care to any person who enters a retail establishment that sells OTC products. Therefore, agency action on an OTC switch will be categorically excluded if the criteria of § 25.31 (b) or (c) apply to the action, specifically if the concentration of the substance at the point of entry into the aquatic environment will be below 1 ppb (§ 25.31(b)), or if it is a substance that occurs naturally in the environment and the action will not significantly alter the concentration of the substance in the environment (§ 25.31(c)).

30. Proposed § 25.31(e) would categorically exclude action on an IND from the requirement to prepare an EA. One comment suggested that this exclusion be limited by specifying in the exclusion a ceiling on the quantity (number of doses) to be released into the environment.

As stated in the preamble to the proposed rule (61 FR 14922 at 14926, 61 FR 19476 at 19480), FDA action on an IND in many cases does not significantly increase the use of the drug or the amount of the drug introduced into the environment because the drug is being administered to few patients or is already being marketed for another use. Consequently, no changes in the effect on the environment will occur due to agency action on the IND. In the event FDA action on an IND would increase the use of a drug, the agency's experience has demonstrated that significant environmental effects would not occur because the investigational use is limited and controlled. The dosing regimen for investigational drugs that would result in an environmental introduction concentration of 1 ppb (the concentration below which FDA has found no significant effect on the environment) is not expected for clinical trials held under an IND. Very large clinical trials are rare, but, cumulatively, they enroll approximately 8,000 patients. Those subjects would need to use 14 grams of the active moiety every day for an entire year to result in an environmental introduction concentration of approximately 1 ppb, the concentration below which CDER has routinely observed no significant effects on relevant standard test organisms in the aquatic environment. The level and duration of this dosing regimen, as described, are greater than is expected under clinical trials, thus the addition of a criterion limiting the number of doses is unnecessary.

The preamble to the proposed rule (61 FR 14922 at 14923, 61 FR 19476 at 19477) noted that categorical exclusion

criteria relating to toxicity, which includes current § 25.24(c)(4), "if * * * waste will be controlled or the amount of waste expected to enter the environment may reasonably be expected to be nontoxic," have been incorporated into the extraordinary circumstances provision of § 25.21(a). Therefore, the categorical exclusion for IND's remains essentially unchanged. In the event FDA has reason to believe its action on an IND may significantly affect the environment, FDA will invoke the provision relating to "extraordinary circumstances" and require an EA. Therefore, the agency declines the suggestion to modify the categorical exclusion in § 25.31(e).

2. Foods, Food Additives, and Color Additives

31. Proposed § 25.32(b) provides for a categorical exclusion for FDA action on a request for exemption for investigational use of a food additive, if the food additive is intended to be used for clinical studies or research. One comment noted the absence of a discussion concerning the potential impact of the investigational use of food additives in the preamble to the proposal, despite the discussion about the potential environmental impact of investigational and clinical research for drugs. The comment recommended that FDA establish a maximum annual quantity for investigational uses of food additives allowed to be released to the environment.

The agency declines to establish additional criteria for the application of the categorical exclusion of the investigational use of food additives. FDA has not required that a formal application be submitted to the agency for the investigational use of a food additive. The investigational use of food additives is expected to be limited to small amounts needed in studies with laboratory animals under 21 CFR 170.17. Occasionally additives are tested in limited clinical trials under the control of institutional review boards. The program has functioned for 40 years with little investigational activity under 21 U.S.C. 348(i). Thus, the agency is not aware of any need to revise this exclusion to include a ceiling on the yearly amount of a substance that may be released into the environment. Furthermore, the comment provided no information on which to conclude that such a ceiling is justified.

32. One comment specifically supported the categorical exclusions in the proposed rule for food and color additives and generally recognized as safe (GRAS) substances. Another comment specifically supported the

categorical exclusions set forth in proposed § 25.32 (i), (k), and (r), but raised issues regarding the need for reform of the review process for food additive and GRAS petitions.

Reform of the review process for food additive and GRAS petitions is outside the scope of this rulemaking and will not be addressed here.

33. One comment, while generally supporting the categorical exclusions in proposed § 25.32 (i) and (j), requested that they be expanded to include all actions on components of food-contact materials, including actions on GRAS petitions, except where extraordinary circumstances exist. The comment asserted that compiling the information needed for EA's for food-packaging materials is unnecessary and unduly burdensome, that the costs of preparing EA's for these materials are significant, and that routine preparation of EA's for these actions results in an unnecessary expenditure of industry and agency resources. The comment requested that the agency not require EA's for actions on nonfunctional components of food-packaging materials because Federal, State, and local laws and regulations adequately control emissions to the environment at sites where these substances are used in the manufacture of food-packaging materials. The comment pointed out that the agency is proposing not to require information on the production of FDA-regulated substances based on its recognition that Federal, State, and local environmental laws and regulations adequately protect the environment at the production sites for those substances. The comment requested that the agency apply the same reasoning to conclude that EA's are no longer needed to assess the environmental impact of nonfunctional components of food-packaging materials that are used and enter the environment at the production sites of the packaging material. The comment also requested that EA's not be required for actions involving components of finished food-packaging material present at greater than 5 percent-by-weight because: (1) Most of these additives will replace other similar, already regulated additives and will not have any meaningful impact on the potential uses of the finished food-packaging material; and (2) adequate Federal, State, and local laws and regulations are in place to protect environments that may be affected by disposal of food-packaging material. The comment pointed out that "in certain rare situations, for example, in instances where the use of a new material may affect recycling streams, disposal of food-packaging materials prepared from a newly regulated

polymer could potentially have some effect on the environment." The comment suggested that in these instances it may be appropriate for the agency to require an EA and that proposed § 25.21 (Extraordinary circumstances) will provide the agency with the means to require EA's for these few situations.

FDA agrees that the new categorical exclusions in proposed § 25.32 (i) and (j) should be revised to include GRAS petitions. The agency also acknowledges that there are certain classes of nonfunctional components of food-packaging materials and certain classes of components of food-packaging material present at greater than 5 percent-by-weight of the finished food-packaging material that should be included under § 25.32(i). However, FDA does not agree that all classes of actions on substances intended for use as components of food-contact materials warrant categorical exclusion. Nor does the agency agree that compiling the information needed for EA's for food-packaging materials is unnecessary, unduly burdensome, and costly. The basis for the agency's decision on these classes of actions is explained below.

GRAS petitions: None of the petitions that the agency has reviewed while developing the categorical exclusions in § 25.32 (i) and (j) (including those it has reviewed since the proposal issued) were GRAS affirmation petitions for components of food-packaging material or components of food-contact surfaces of equipment or other repeat use food-contact articles. But, because the environmental information that would be needed under part 25 for a GRAS petition for these types of food-contact substances is identical to the information required for a food additive petition, the agency believes that its experience with food additive petitions is relevant to GRAS affirmation petitions and that any future GRAS affirmation petitions for these classes of actions can also be excluded. Therefore, FDA has revised proposed § 25.32(i) and (j) to include actions on GRAS affirmation petitions.

Nonfunctional components of food-packaging material: The agency does not believe it is appropriate to categorically exclude all actions on nonfunctional components of food-packaging material, as requested by the comment. To evaluate the request that FDA revise § 25.32(i) to further exclude from the requirements for EA actions on nonfunctional components of food-packaging materials, the agency reviewed 44 petitions for nonfunctional components of food-packaging

materials.¹ As a result of this review, the agency found that a number of these petitions warranted exclusion from the need for an EA, while others did not. The agency found that 13 of the petitions were for additives that remained with food-packaging materials used by consumers despite the fact that these additives did not function in the finished food-packaging material. As they pertained to use and disposal of nonfunctional components of food-packaging materials, the FONSI's for the agency's actions on these petitions were based on the following factors: (1) Only very small quantities, if any, of these additives were expected to enter the environment at sites where the additives were used in the manufacture of food-packaging materials; (2) only extremely low levels of substances, if any, could be expected to enter the environment as a result of disposal of food-packaging materials; and (3) virtually no change in the use of natural resources and energy would be expected because the additives would be replacing other, currently regulated, additives and would not affect the uses of the packaging materials to which they were added. These factors are the same as those upon which the agency bases its exclusion for actions on functional components of finished food-packaging materials. Therefore, the agency has decided that it is appropriate to revise proposed § 25.32(i) to include all components of food-packaging materials that remain with finished packaging through use by consumers and are present at less than 5 percent-by-weight, regardless of whether they perform a function in the finished package.

In its review of the remaining 31 petitions involving nonfunctional components of finished food-packaging material, the agency found that 5 petitions were for antimicrobial substances that are also regulated by EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as pesticides. In § 25.32(q) of the proposed rule, actions to approve a food additive petition or grant a request for exemption from regulation as a food additive under § 170.39 are categorically excluded when the substance that is the subject of the petition or request is registered by EPA under FIFRA for the same use requested in the petition or in the request for exemption.

Also among these 31 petitions were 6 petitions for substances that occur naturally in the environment. These petitions would be excluded from the

requirement to prepare an EA under the categorical exclusion in § 25.32(r) of the final rule.

The 20 remaining petitions involving nonfunctional components of finished food-packaging material were for additives that were not expected to remain with the finished article, but instead were expected to enter the environment at sites where they were used as processing aids in the manufacture of food-packaging materials and were neither antimicrobial substances nor naturally occurring substances. These types of additives are not intended to remain with the finished food-packaging materials which are used and disposed of by consumers throughout the United States. The results of environmental toxicity tests presented in some of these petitions showed that the additives had the potential to harm organisms in the environment present at or adjacent to the use sites. For 17 of these 20 petitions, FDA conducted an analysis of the environmental exposure levels of the additives at the use sites and compared these exposure levels to environmental toxicity information on the additives to determine the potential for significant impact. In some cases, the margin between environmental exposure levels and levels found to be toxic to organisms present in the receiving environment was very narrow. For the remaining three petitions, FDA relied upon adequate regulation of potential discharges to reach its environmental decision.

Under current part 25, FDA has required specific information about Federal, State, and local laws and regulations that are applicable to emissions at the site of production of the subject substances where the manufacturing operations are designed to provide maximum yield of the FDA-regulated article for commercial sale. FDA reviewed hundreds of submissions with this information before deciding to eliminate the requirements for its inclusion. However, the formats for EA's in current § 25.31a do not require information on emissions requirements at the sites where nonfunctional components of food-packaging materials are used to produce the finished article. A review of FDA's experience with EA's for most nonfunctional components of finished food-packaging materials that are expected to enter the localized use site environment (i.e., the finished food-packaging manufacturing facility) has revealed that analysis of exposure and environmental toxicity is necessary to determine the potential for significant impact. Based on this experience, therefore, the agency does not agree

with the comment that it can rely on other Federal, State, and local laws for protecting the environment to exclude actions on petitions for these nonfunctional components of food-packaging materials as was done to eliminate requirements for information on the sites of production of FDA-regulated articles.

Thus, the agency cannot establish an additional categorical exclusion for petitions for nonfunctional components of food-packaging that do not remain with food-packaging through use by consumers. The agency will provide specific guidance to petitioners for preparing EA's for those categories of petitions that will require EA preparation. The guidance for EA's involving nonfunctional components of food-packaging materials will focus on the relevant issues surrounding a proposed action and will take into consideration whether other laws and regulations adequately control potential environmental impacts or whether an action may threaten a violation of such laws and regulations as required by CEQ regulations (40 CFR 1508.27(b)(10)).

Components of Finished Food-packaging Material Present at Greater than 5 Percent-by-Weight: The comment requested a categorical exclusion for actions involving components of finished food-packaging material present at greater than 5 percent-by-weight, but did not provide any specific information showing that actions on petitions in this category do not individually or cumulatively have significant environmental effects. To evaluate this request, FDA reviewed 30 petitions for components of food-packaging materials present at greater than 5 percent.² The agency found that five of these petitions were for coatings or components of coatings for food-packaging materials. The FONSI's for the agency's actions on these petitions were based on the following factors: (1) Only extremely low levels of substances, if any, could be expected to enter the environment as a result of use and disposal of these coated food-packaging materials; and (2) virtually no change in the use of natural resources and energy would occur because the additives would be replacing other, currently regulated, additives and would not affect either the uses of the packaging materials to which they were added or the disposal technologies used for these materials. These factors are the same as those upon which the exclusion for actions on functional components of

¹ "Index of Petitions for Nonfunctional Components of Food-packaging Materials," (Docket No. 96N-0057).

² "Index of Petitions for Components of Food-packaging Materials Present at Greater than 5%," (Docket No. 96N-0057).

finished food-packaging materials present at less than 5 percent are based even though the components of the coatings may be present in the finished food-packaging material at greater than 5 percent-by-weight. Therefore, the agency is revising the exclusion in proposed § 25.32(i) to include actions on the components of coatings of finished food-packaging materials.

The agency's findings for the remaining 25 petitions support FDA's position that significant environmental effects may result from agency actions on components of finished food-packaging material present at greater than 5 percent-by-weight. Examples of petitions that required extensive analysis to determine the potential impact of food-packaging materials on solid waste management strategies include food additive petition (FAP) 6B3948 (Docket No. 86F-0341); FAP 7B3979 (Docket No. 86F-0508); FAP 8B4107 (Docket No. 88F-0404); FAP 1B4236 (Docket No. 91F-0198); and FAP 8B4110 (Docket No. 88F-0339). In some cases, the agency and the petitioners decided to include mitigating measures in the food additive regulations to avoid potentially significant environmental effects. In addition, the agency has not acted on FAP 7B3994, because it needs to consider further whether significant effects on solid waste management strategies may result (53 FR 47264 at 47267, November 22, 1988). Evaluation of these potential effects is being conducted along with an evaluation of the agency's proposed action to provide for the safe use of vinyl chloride polymers (51 FR 4177, February 3, 1986). The agency announced on November 22, 1988 (53 FR 47264), its intent to prepare an EIS on its actions on vinyl chloride and other chlorinated polymers. FDA continues to work on this statement.

This comment asserted that EA's are not needed for petitions for components of food-packaging materials because the effects of disposal of food-packaging materials by incineration or landfilling are subject to the control of laws, regulations, and government authorities directly concerned with the environment. FDA, based on its experience, agrees that the extremely low levels of substances that may leach from food-packaging materials disposed of in landfills are adequately controlled by EPA regulations in 40 CFR part 258. FDA is aware of laws and regulations governing the incineration of municipal solid waste, which include the incineration of food-packaging materials. However, there is potential for incineration of food-packaging

materials to threaten a violation of these laws and regulations. FDA will consider this potential effect under 40 CFR 1508.27(b)(10). For example, in its decision to prepare an EIS on its actions on vinyl chloride and other chlorinated polymers (53 FR 47264 at 47265, November 22, 1988), the agency found that the expected increase in hydrogen chloride emissions from incinerators may affect the ability of incinerator operators to comply with existing and anticipated emissions standards. This issue is still under agency review.

A number of the agency's actions on components of food-packaging materials present at greater than 5 percent-by-weight had potential for significant effects on the environment. The agency is unable, without specific information such as that provided in an EA, to distinguish which petitions for these actions may have potential for significant impact. Therefore, the agency will continue to require EA's for this category of petitions, with the exception of those petitions pertaining to components of coatings. The agency will develop and provide to petitioners specific guidance for preparing EA's for those categories of petitions that will require the preparation of EA's. The guidance for EA's involving components of packaging present at greater than 5 percent-by-weight will focus on the relevant issues surrounding a proposed action, and will take into consideration the extent to which other laws and regulations adequately control potential environmental impacts.

As a result of this analysis, proposed § 25.32, categorical exclusions for foods, food additives, and color additives, will be revised at paragraphs (i) and (j) to read as follows:

(i) Approval of a food additive petition, GRAS affirmation petition, or the granting of a request for exemption from regulation as a food additive under § 170.39 of this chapter, when the substance is present in finished food-packaging material at not greater than 5 percent-by-weight and is expected to remain with finished food-packaging material through use by consumers or when the substance is a component of a coating of a finished food-packaging material.

(j) Approval of a food additive petition, GRAS affirmation petition, or the granting of a request for exemption from regulation as a food additive under § 170.39 of this chapter, when the substance is to be used as a component of a food-contact surface of permanent or semipermanent equipment or of another food-contact article intended for repeated use.

Burden of compiling the information for EA's for food-packaging materials: As discussed above, for certain actions involving food-packaging materials, FDA will continue to require petitioners

to submit an EA. FDA does not agree that the information it requires the petitioner to submit in these EA's is unnecessary, nor does the agency believe the effort to provide such information is unduly burdensome. As FDA has stated above, it will provide guidance to industry regarding the focus of environmental documents. In addition, FDA has limited in the past and will continue to limit its requests for information to only the amount needed to assess the potential environmental impact of its actions. FDA recognizes that in some cases the information needed for EA's is not readily available or is not yet known to a petitioner. In such cases, the agency in the past has asked the petitioner to provide a best possible forecast or to use a conservative approach to analyze environmental effects. FDA will continue this approach, recognizing that in some cases there may be uncertainty about the potential for significant environmental impact of food-packaging materials.

In the preamble to the proposal (61 FR 14922 at 14935, 61 FR 19476 at 19489), FDA noted its calculation that the proposed changes in the environmental regulations would reduce the costs for both the regulated industry and for the agency. These reduced costs will result from, among other things, providing for categorical exclusions for additional classes of actions. To this end, the agency proposed and is now making final two exclusions that will apply to actions on food-packaging materials (§ 25.32 (i) and (j)). As explained above, these exclusions have been expanded in the final rule to include additional classes of actions. These changes are expected to further reduce the costs of preparing and reviewing environmental documents for food-packaging materials. The agency believes that the remaining actions on food-packaging materials that require EA's have the potential to result in significant environmental effects, and information in an EA is necessary for the agency to make decisions on these potential effects.

34. Proposed § 25.32(k) would categorically exclude actions to approve food additive, color additive, and GRAS affirmation petitions for substances added directly to food that are intended to remain in food through ingestion by consumers and that are not intended to replace macronutrients in foods. One comment claimed that FDA was proposing a 1 ppb environmental exposure threshold below which the exclusion applied, as was done for human drugs in proposed § 25.31(b). The comment requested that FDA establish a maximum annual quantity of

the food additive allowed to be released to the environment under this exclusion.

The agency declines to establish additional criteria for the exclusion under § 25.32(k) covering substances that are intended to remain in food through ingestion by consumers and are not intended to replace macronutrients in food. As explained in the preamble to the proposal (61 FR 14922 at 14928, 61 FR 19476 at 19482), the basis for this exclusion is FDA's experience reviewing 21 petitions in this class, all of which resulted in a FONSI. The FONSI's relied on one or more of the following scenarios: (1) The approval of the petition resulted in very low levels of the substances in either effluents and/or sewage sludge; (2) the substance was digested and/or metabolized by humans such that only the products of digestion and metabolism were expected to be excreted and those products were the same as (or very similar to) other products of digestion and metabolism resulting from human food; or (3) the substance was excreted largely intact but was rapidly degraded into nontoxic products. Based upon this review of petitions in this class, the agency found that it was not necessary to establish either an exposure threshold concentration or a maximum annual quantity of substances allowed to be released. Even in the three instances where it was necessary to compare the environmental exposure level of the substance with environmental toxicity data, there was a wide margin of safety. No information to support the establishment of either of these qualifying thresholds is provided in the comment. Therefore, the agency has no basis on which to revise § 25.32(k) to incorporate either an exposure threshold concentration or a maximum annual quantity that may be released.

35. An additional comment about the exclusion in proposed § 25.32(k) expressed concern about the potential for significant impacts on energy and natural resources resulting from the use and disposal of nonnutritive oils. This comment recommended that the proposed exclusion be withdrawn or that a ceiling be added that would require an EA where such substances enter the environment above a certain annual level.

The agency declines to amend the proposed exclusion as recommended. Actions on food additive petitions for nonnutritive oils or fat substitutes would not qualify for the categorical exclusion in § 25.32(k), because such substances are considered to be replacements for macronutrients. An EA submitted for a fat substitute would

include consideration of the impact on energy and natural resources resulting from the production (if appropriate), use, and disposal of such substances. Such considerations were part of FDA's action to approve the use of the fat substitute olestra (Docket No. 87F-0179).

36. Proposed § 25.32(m) would categorically exclude actions to prohibit or otherwise restrict or reduce the use of a substance in food, food packaging, or cosmetics. One comment supported this exclusion, but requested clarification regarding how FDA will consider under this exclusion impacts on the environment (to human well-being and on the environment itself) that are controversial.

As discussed in the preamble to the proposal (61 FR 14922 at 14929, 61 FR 19476 at 19483), the agency has found that this class of actions has not involved controversial issues with respect to potential impact on the physical environment. FDA's action to prohibit the use of CFC's is the only exception to this principle to date.

In most instances, the purpose of actions to restrict or withdraw approval of foods, food packaging, or cosmetics is to protect the public health. Potential impacts on human health, and any controversy surrounding such impacts, are fully considered in **Federal Register** documents (e.g., a preamble to a proposed or final rule restricting or withdrawing approval) supporting the action. See the response to comment 22, above. The appropriateness of an exclusion for a proposed action to restrict or eliminate the use of a substance in food, food-packaging, or cosmetics will depend on whether the action may involve extraordinary circumstances that would require evaluation through an EA or an EIS. Under proposed § 25.21, extraordinary circumstances include the degree to which the possible effects on the human environment are likely to be highly controversial, as provided in 40 CFR 1508.27(b)(4).

37. Proposed § 25.32(o) would categorically exclude actions to approve a food additive petition for the intended expression product(s) present in food derived from new plant varieties. One comment recommended that compounds that may be "hormone modulators" should not be included in this categorical exclusion.

FDA is not aware of any specific substances derived from new plant varieties that could potentially affect the endocrine system of other organisms. It is unlikely that FDA would receive a food additive petition for a substance derived from new plant varieties that

was intended to have a physiological effect on the human endocrine system. A substance derived from new plant varieties that is intended to have such an effect on the human endocrine system would be regulated by FDA as a drug. Thus, it is unlikely that a claim for categorical exclusion for a hormone modulator would be made under § 25.32(o) and FDA declines to modify § 25.32(o) to reflect such a scenario.

In the event FDA receives a food additive petition for a substance derived from new plant varieties that is known or suspected to have potential for affecting the endocrine system in humans, aquatic life, and/or wildlife, agency action on such a petition would generally be excluded under § 25.32(o). As described in the preamble to the proposed rule (61 FR 14922 at 14929-14930, 61 FR 19476 at 19483-19484), under § 25.32(o) environmental review of new plant varieties would be performed by the United States Department of Agriculture (USDA). Therefore, if USDA has granted a categorical exclusion or conducted an environmental review, NEPA review by FDA would be redundant and therefore, unnecessary.

38. In proposed § 25.32(q), actions to approve a food additive petition or grant a request for exemption from regulation as a food additive under § 170.39 are categorically excluded when the substance that is the subject of the petition or request is registered by EPA under FIFRA for the same use requested in the petition or in the request for exemption. One comment stated that the same information submitted to EPA for registration of pesticides under FIFRA should be encouraged for FDA submissions. The comment expressed concern about the lack of policy alignment between agencies regarding the level of risk and about the ability of FDA to meet deadlines due to its reliance on the review of data by another agency that may have different review priorities. The comment suggested that FDA "handle this proposed exclusion as a guideline policy rather than a categorical exclusion," or align interagency risk determination policies before allowing this exclusion.

FDA does not agree with the suggestion that the exclusion be handled as a guideline policy. As discussed in the preamble to the proposal (61 FR 14922 at 14930, 61 FR 19476 at 19484), FDA has found that the scope of EPA's review of the environmental risk of antimicrobial substances subject to pesticide registration under FIFRA encompasses FDA's review of the environmental risk

of these substances for food additive use under NEPA. In evaluating whether a food additive petition or request for exemption meets the categorical exclusion in § 25.32(q), FDA will ensure that the substance for which a petitioner seeks approval is identical to the substance that is registered as a pesticide under FIFRA. If the substance is registered as part of a formulation under FIFRA, FDA will ensure that it is approving the substance for use as part of that formulation registered under FIFRA. By "same use" the agency means that in a comparison of the food additive use to the pesticide use, the purpose of the use, any components used with the substance for the petitioned use, and the amount of the substance and the amounts of any components used with it are substantially identical. FDA has found that, when these antimicrobial substances are intended for the same use, its assessment of the environmental risk of antimicrobial substances is the same as EPA's assessment of the environmental risk of pesticides and, therefore, the food additive use will be subsumed under EPA's environmental review of the substance as a pesticide registered under FIFRA.

In addition to ensuring that the substance is identical to and for the same use as the registered pesticide, FDA will ensure that the label for the use of the substance as a food additive includes information related to the environmental effects, such as precautionary statements on environmental hazards, that is required on the label for the use of the substance as a registered pesticide under FIFRA. This will provide assurance that any adverse environmental effects from the use of the substance as a food additive have been addressed and are mitigated, as needed, to the same extent as any adverse environmental effects from the use of the substance as a pesticide registered under FIFRA.

In response to the comment that FDA may not be able to meet its deadlines because of its reliance on review of data by another agency, nothing in this final rule precludes a petitioner or requester from submitting an environmental assessment to FDA for review, despite the fact that the action may be eligible for a categorical exclusion under § 25.32(q). Moreover, establishing a categorical exclusion for an antimicrobial substance that is registered as a pesticide with EPA under FIFRA should not affect FDA's ability to meet its statutory deadlines for completing the review of food additive petitions that are eligible for an exclusion under § 25.32(q). In order for

a substance to be eligible for a § 25.32(q) categorical exclusion, the substance must be registered by EPA as a pesticide under FIFRA for the same use requested in the petition at the time the food additive petition is submitted to FDA. Antimicrobial substances that are not registered by EPA under FIFRA for the same use at the time the food additive petition is submitted to FDA would not be eligible for a categorical exclusion under § 25.32(q). Without the pesticide registration, FDA would not be able to determine whether the use is the same as that in the food additive petition or request for exemption and therefore eligible for a categorical exclusion.

As previously mentioned, the scope of environmental review for a pesticide registration, based on the agency's review of previous petitions, encompasses FDA's environmental review for the use of the substance as a food additive. Therefore, the agency does not anticipate that any additional environmental review would be required for a petitioned food additive use of a substance that is registered as a pesticide under FIFRA. However, if the substance is not registered as a pesticide under FIFRA or the environmental impacts resulting from the petitioned food additive use or request for exemption are not within the scope of EPA's environmental assessment performed for the pesticide registration, FDA's action on the substance would not warrant categorical exclusion under § 25.32(q), and instead, would require at least an EA under § 25.20.

3. Veterinary Drugs and Feed Additives

39. Proposed § 25.33(a) would categorically exclude action on an NADA, abbreviated application, or supplement to such applications, if the action does not increase the use of the drug. One comment pointed out that, in its categorical exclusion relating to actions that do not increase use, FDA uses the term "active moiety" when referring to human drugs in proposed § 25.31(a) and "drug" when referring to animal drugs in proposed § 25.33(a). The comment stated that the reason for the use of different terms was not apparent, and recommended that the term active moiety also be used when referring both to human drugs and animal drugs.

The agency does not agree that the term "active moiety" should be used in § 25.33(a) to describe the actions on animal drugs that are categorically excluded because for many animal drugs an explicit active moiety cannot be defined. For example, an animal drug may consist of biomass which is the

purified broth from fermentation manufacturing. In that case, the animal drug consists of a variety of components but an "active moiety" is not explicitly defined. If there is no increase in the use of an animal drug, it follows that there is no increase in the level of the substance in the environment and, consequently, no increase in any associated environmental effects.

40. One comment requested that proposed § 25.33(a) be revised to categorically exclude actions that do not increase the use and the concentration of the drug. The comment reasoned that when an animal drug is administered, the concentration of that drug in the environment, rather than the fact of "use," has the potential to raise environmental concerns.

The agency agrees that an increase in concentration has the potential to raise environmental concern but does not agree that the addition of the term "increase concentration" to the exclusion is necessary. The primary purpose of the categorical exclusion is to provide a simple method to identify for drug sponsors which actions obviously have no significant environmental impacts. An increase in use, such as an increase in dosage level, an increase in the duration of use, or the addition of a new indication obviously results in an increase in the environmental concentration. To help clarify what actions are categorically excluded under proposed § 25.33(a), the agency has defined in proposed § 25.5(b)(4) that "increased use" may occur if the drug is administered at higher dosage levels, for longer duration, or for different indications than were previously in effect, and if the drug is a new molecular entity. The term "use" is further defined to encompass disposal of FDA-related articles. Section 25.33(a) also lists specific examples of the actions that are excluded. Therefore, the agency believes that the use of the term "increased use," as defined in § 25.5(b)(4), along with the examples provided, best describes the criteria for categorical exclusion under proposed § 25.33(a).

41. In proposed § 25.33(a), change in sponsor is included as one of the types of actions covered by the categorical exclusion (§ 25.33(a)(5)). One comment requested that FDA reconsider the inclusion of actions relating to changes in drug sponsors in this categorical exclusion because such a change may result in manufacturing or process changes that could cause a difference in end product chemical profiles. The comment argued that differences in manufacturing practices may warrant further environmental evaluation.

The agency reconsidered the proposed categorical exclusion for changes in drug sponsor but decided to retain the exclusion in the final rule. A change in sponsor does not necessarily involve a change in the manufacturing or processing of a drug. In the event that a change in sponsor results in manufacturing or process changes, it is not likely that there will be a change in the end product that will affect the environmental impacts of the drug because a new sponsor must maintain the same quality, composition, and purity of the drug to assure that its safety and effectiveness are the same as the product approved for manufacture by a previous sponsor. Any change that would result in a change in the chemical profile of the end product would require a supplement to be filed with the agency. The need for environmental information would be evaluated by FDA in conjunction with agency action on that supplement. The exclusion in § 25.33(a) has been changed to clarify that actions listed "may" be excluded if the actions meet the criteria in the categorical exclusion.

42. In the preamble to FDA's proposed regulations (61 FR 14922 at 14931, 61 FR 19476 at 19485), FDA stated that proposed § 25.33(b) is being reserved for animal drugs "not otherwise excluded in § 25.33(a)." One comment expressed concern that this statement regarding § 25.33(b) may inadvertently create confusion about the actions on animal drugs exclusions in other paragraphs of proposed § 25.33, especially in proposed § 25.33(d)(5).

FDA can understand how the wording in the preamble (61 FR 14922 at 14931 and 14932, 61 FR 19476 at 19485 and 19486) could be confusing, but the regulations are explicit about what actions are categorically excluded. Actions that do not meet the criteria of § 25.33(a) may still be categorically excluded under § 25.33 (c) or (d), including § 25.33(d)(5). If the agency adopts criteria for excluding actions under § 25.33(b) as discussed in the preamble, this will add additional criteria for excluding actions, it will not restrict the application of other criteria to exclude actions.

43. One comment suggested that reserved § 25.33(b) should categorically exclude any action on a NADA, abbreviated application, or a supplement to such applications, that increases the use of a drug if the PEC in soil is less than the PNEC, based on a scientifically valid environmental test conducted with a representative soil organism. The comment noted that a relatively simple scientific explanation or calculation would be needed to

determine whether an action qualifies for such an exclusion. The comment defended the use of a scientific threshold or screening test for a categorical exclusion as appropriate, citing regulations issued by the Bureau of Indian Affairs (BIA), EPA, and the Federal Highway Administration (FHWA).

The agency declines to revise the proposed regulations as suggested. As explained above, the agency stated in the preamble to the proposal that it was reserving § 25.33(b) to provide for actions that increase the use of an animal drug when the agency determines a level at or below which the concentration of the substance in the environment does not significantly affect the environment. Criteria for this categorical exclusion would require a relatively simple calculation using limited available information. The proposed PEC to PNEC comparison represents more than a simple calculation or explanation. Ecotoxicity studies are performed, results are compared to expected environmental concentrations, and a conclusion is drawn (see the response to comment 26). The agency considers this activity to be an environmental risk assessment that is more appropriately provided as part of an EA.

The agency reviewed the BIA, EPA, and FHWA regulations cited in the comment. The BIA categorical exclusion refers to standards that are required by the Bureau of Land Management (BLM). To qualify for this categorical exclusion, an applicant merely states that it is in compliance with the BLM requirements. No scientific threshold or screening test is required. The EPA and FHWA citations refer to EPA and FHWA general categorical exclusion processes and do not include scientific explanations or calculations.

44. One comment addressed its statements to FDA's description, in the preamble to the proposal (61 FR 14922 at 14931, 61 FR 19476 at 19485), of the categorical exclusions established in proposed § 25.33 (a) and (b). The comment stated that the EIC, rather than the EEC, should be used to determine potential environmental impacts of veterinary drugs and feed additives. The comment argued that this will give more weight in determining potential exposures to "primary receptors" before environmental degradation or waste treatment. The comment also recommended that the evaluation should include potential human exposure, such as the potential exposure to children assisting in animal care or living in close proximity to family farm feedlots, at the EIC.

As explained above in response to comment 43 and in the preamble to the proposed rule (61 FR 14922 at 14931, 61 FR 19476 at 19485), § 25.33(a) categorically excludes action on an NADA, abbreviated application, or supplement to such applications, if the action does not increase the use of the drug. Proposed § 25.33(b) is reserved and would be for actions that increase the use of an animal drug if the agency determines a level at or below which the concentration of the substance in the environment does not significantly affect the environment.

The EEC is an appropriate measure to use in evaluating information in an EA to determine whether an environmental impact is expected. The EEC provides the most accurate means of determining the concentration of a substance to which organisms may be exposed. Due to various factors in the environment, e.g., dilution, binding to particulate matter, and volatility, the concentration of an introduced compound may change significantly before it comes into contact with organisms that may be harmed.

FDA addresses primary receptor issues, such as a child assisting in animal care or living in proximity to family farm animals, as public health issues under the act rather than through NEPA evaluation. See the response to comment 22, above.

45. Proposed § 25.33(d)(5) states that an action on a marketing application or supplement for an animal drug intended for therapeutic use under a prescription or veterinary order is categorically excluded and, therefore, ordinarily does not require an EA or an EIS. One comment contended that prescription animal drugs that are categorically excluded under proposed § 25.33(d)(5) could subsequently require an EA if they become available OTC. The comment assumes this is an unintended result and that grandfathering would be appropriate. The comment recommended that proposed § 25.33(d)(5) be revised to include a statement indicating that an animal drug that was once categorically excluded should not subsequently require an EA if it becomes available OTC.

The comment is correct in its assertion that a categorically excluded prescription animal drug could require an EA when the agency acts on an application to switch the drug to OTC availability. However, the comment incorrectly concludes that such a result is anomalous and unintended. As discussed in the preamble to the proposal (61 FR 14922 at 14932, 61 FR 19476 at 19486), the therapeutic use of an animal drug under a prescription by a veterinarian results in the drug being

administered to a limited number of animals for a limited amount of time. The agency's experience in reviewing EA's for these types of veterinary products indicates that this limited use results in no significant environmental impact. The limitations inherent in prescription use are not found in OTC use. Broader use and greater introduction of the drug into the environment may occur with OTC availability. Therefore, the agency believes that prescription to OTC switches of animal drugs warrant consideration through an EA. Grandfathering is not appropriate.

46. One comment stressed the importance of interpreting the term "therapeutic use" as it is used in the categorical exclusion for prescription veterinary drugs in proposed § 25.33(d)(5) independent of the percentage of the herd treated. The comment indicated that if prescription use were limited to single animal treatment, the section would cease to be an important measure to reduce the number of EA's.

Prescription animal drugs, by definition under the act, are limited to use under the professional supervision of a licensed veterinarian and, thus, are expected to be administered to a limited number of animals for a limited amount of time. Specifically, products intended for use by prescription require a veterinarian diagnosis of the disease or condition to be treated. The nature of this process limits the use of the prescription product and its introduction into the environment. Further, administration of the drug product by a veterinarian affords an added level of control over the use and disposal of the drug product. All veterinarians are trained on appropriate drug use procedures. Therefore, allowing a categorical exclusion under these circumstances is appropriate and the agency does not intend to interpret therapeutic use, as it pertains to proposed § 25.33(d)(5), based on the number or percentage of animals treated.

It is important to note that the agency's decision to propose this categorical exclusion of prescription animal drug products is primarily based upon its experience in reviewing EA's for these products. The EA's that comprise the bulk of agency experience in this area are for products used in terrestrial species. The agency has limited experience with reviewing drugs that will be used for the treatment of diseases in fish and other aquatic species. For this reason, the agency is revising proposed § 25.33(d)(5) to clarify that it applies only to terrestrial species.

The section has been revised to state, "Drugs intended for use under prescription or veterinarian's order for therapeutic use in terrestrial species."

47. One comment noted that the same experience that led the agency to categorically exclude prescription animal drugs under § 25.33(d)(5) could ultimately result in all animal drug products being excluded regardless of whether they are prescription or over the counter (OTC), subject to extraordinary circumstances.

FDA will not speculate on future categorical exclusions. The agency based its decision to categorically exclude prescription animal drugs intended for therapeutic use on its extensive experience in reviewing EA's for those products. As the agency gains experience in reviewing other classes of drug products, additional categorical exclusions may be proposed. In all instances, FDA will require an EA to be prepared for products that would ordinarily be categorically excluded if there are extraordinary circumstances, see § 25.21.

48. Proposed § 25.33(h) would categorically exclude the withdrawal of approval of a food additive petition that reduces or eliminates animal feed uses of a food additive. One comment questioned whether the disposal of nonnutritive oil in animal feed requires a food additive petition.

The inclusion of nonnutritive oils in animal feeds requires the submission of a food additive petition and the preparation of an EA. (See the response to comment 35, above.) The categorical exclusion for the withdrawal of approval of a food additive petition has no bearing on whether a food additive petition, and corresponding EA for the petition, would be required for the nonnutritive oil.

D. Subpart D—Preparation of Environmental Documents

49. Proposed part 25 regulations focus on the use and disposal from use of FDA-regulated articles, and do not routinely require submission of information regarding manufacturing sites or a certification of compliance with Federal, State, and local emission requirements. One comment recommended that manufacturing and production considerations continue to be included in the environmental evaluation process and suggested that FDA consider potential occupational exposures and worker safety. The comment also expressed concern that by basing some categorical exclusions, specifically § 25.31(b), on presumed toxicity of a substance disposed of after use, the agency "ignores the very

substantial environmental impacts that may arise from manufacture" of the product.

Another comment by the same author expressed particular concern about secondary and tertiary manufacturing processes involving food additives that may result in uncontrolled end products. The comment cited as an example a nonnutritive food grade oil that may be synthesized by a primary producer who then sells it to a secondary manufacturer for ingredient use in food product processing. The comment recommended that production of food additives, color additives, and GRAS substances not be included as a categorical exclusion and that the environmental impact of secondary or tertiary manufacturing be considered in an EA. Several related comments recommended that the production, processing, and disposal of nonnutritive oils, including the impact of liquid and solid oil components, the effect of processing on the form of the food additive entering the environment, and the potential nutritional impact of nonnutritive oils on microorganisms and invertebrates be included in EA's.

The agency has determined that its environmental evaluation process need not generally include a review of information on the manufacturing and production of FDA-regulated products, including food additives, color additives, and GRAS substances. This determination forms part of the basis for FDA's establishment of additional categorical exclusions for certain actions that currently require consideration of production sites in EA's and is the basis for FDA's decision that, for those actions requiring an EA, the EA will generally focus on potential impacts resulting from product use and disposal. Federal, State, and local environmental protection agencies are responsible for issuing regulations, permitting and licensing facilities, and enforcing compliance with those requirements that are necessary to ensure adequate protection of the environment from emissions resulting from production operations. Emergency response training and worker safety/training are under the purview of these agencies and/or the Occupational Safety and Health Administration (OSHA).

As discussed in the preamble to the proposed rule (61 FR 14922 at 14933, 61 FR 19476 at 19487), after reviewing hundreds of EA's that contained information regarding manufacturing sites, the agency found that FDA-regulated articles produced in compliance with applicable emission and occupational safety requirements will not significantly affect the

environment. However, if information available to the agency or the applicant establishes that a general or specific emission requirement issued by Federal, State, or local environmental agencies does not adequately address unique emission circumstances, and the emission may harm the environment, there would be sufficient grounds for FDA to request manufacturing information in an EA. Likewise, in accordance with CEQ regulations (40 CFR 1508.27(b)(10)), any action that threatens to violate a Federal, State, or local law or other requirement imposed for the protection of the environment would fall under § 25.21 (Extraordinary circumstances), and an EA would be required for the proposed action. Thus, although manufacturing site information will not routinely be requested, there may be specific circumstances that would require the submission of such information.

Concerning the comment about secondary and tertiary food additive production sites, FDA usually considers these facilities to be sites of use. The agency has found, with certain exceptions, that environmental introductions of food additives, color additives, and GRAS substances at secondary and tertiary production sites are minimal because these substances are typically meant to be incorporated into and function in food, food packaging, or food-contact equipment. Secondary direct food additives and nonfunctional components of food-packaging materials may, however, enter the environment at use sites because these additives are used as processing aids in the production of food and food-packaging materials, and are not intended to be present in the food or the finished packaging material. The agency did not propose a new categorical exclusion specifically for secondary direct additives, therefore, actions on these types of additives will generally require an EA. However, the agency notes that actions on certain secondary direct additives may qualify for exclusion under § 25.32 (j), (q), or (r), as revised, because they are used as components of the food-contact surface of permanent or semipermanent equipment or of another food-contact article intended for repeated use, are pesticides registered by EPA under FIFRA and subject to FDA's regulatory authority as food additives for the same use, or are substances that occur naturally in the environment. As discussed above in response to comment 33, the agency will continue to require EA's for certain actions involving nonfunctional components of

food-packaging materials. The agency will also require EA's for any normally excluded action if there are extraordinary circumstances suggesting that the action may have significant effects at use sites.

Regarding the example in the comment of a nonnutritive food oil, these actions do not qualify for exclusion under § 25.32(k), as revised, and require an EA because actions on these types of substances have the potential for significant environmental effects (see the responses to comments 35 and 48, above). The EA will take into consideration the potential effects raised in the comment, including introductions at all use and disposal sites (see, for example, the EA and FONSI for FDA's action on the fat substitute olestra (Docket No. 87F0179)).

50. Several comments suggested revisions to proposed § 25.40(a), which states: "The EA shall focus on relevant environmental issues and shall be a concise, objective, and well-balanced document that allows the public to understand the agency's decision." Two comments recommended the inclusion of a statement that the focus of the environmental review would be on the use and disposal of FDA-regulated articles, but not the manufacturing. One comment recommended substituting the following sentence: "The EA shall focus on relevant environmental issues relating to the use and disposal from use of FDA regulated articles and shall be a concise, objective, and well balanced document." thus eliminating the phrase that the EA shall be "a document that allows the public to understand the agency's decision." One comment requested additional language stating that manufacturing site information, including emission information, would not be required.

The EA formats in current part 25, which have been eliminated in the proposed rule, focus on an analysis of the use and disposal of FDA-regulated articles. To clarify the focus of EA's under the proposed regulations, FDA agrees with the suggestion to amend proposed § 25.40(a) to state that "The EA shall focus on relevant environmental issues relating to the use and disposal from use of FDA-regulated articles * * * ." Inclusion in the final regulation of a statement to the effect that emission information from production sites is not required in EA's would be contrary to FDA's position, as stated in the preamble to the proposed rule (61 FR 14922 at 14934, 61 FR 19476 at 19487 and 19488), that when information establishes that emission requirements promulgated by Federal, State, or local environmental protection

agencies do not address unique emission circumstances and the emissions may harm the environment, FDA will request manufacturing information in an EA.

The phrase included in the proposed regulations that an EA should be "a document that allows the public to understand the agency's decision" is consistent with CEQ environmental policies and objectives and will not be deleted. NEPA procedures must ensure that environmental information is available to public officials and citizens (40 CFR 1500.1(b)). Thus, among other things, environmental documents need to be written in plain language so that the public can readily understand them (see, e.g., § 1502.8).

51. Proposed § 25.40(a) states that EA's shall include a brief discussion of alternatives to the proposed action as described by section 102(2)(E) of NEPA. Proposed § 25.40(a) also states that if potentially adverse impacts on the environment are identified in the EA, the EA shall discuss any reasonable alternative course of action that offers less environmental risk or that is environmentally preferable to the proposed action. One comment stated that this requirement "would only require applicants or petitioners to discuss 'reasonable' alternatives where 'potentially adverse environmental impacts are identified,'" and, therefore, is inconsistent with 40 CFR 1508.9.

FDA does not believe there is an inconsistency between proposed §§ 25.40(a) and 1508.9. EA's are to be concise public documents to determine whether a more detailed analysis, an EIS, is required (§ 1508.9). A discussion of alternatives other than those which are "reasonable" is inconsistent with this overriding principle. Therefore, FDA is not amending § 25.40(a) in response to this comment.

52. One comment requested that proposed § 25.40(a) include a maximum page limit for EA documents.

Because the number or pages for any EA will vary in relation to the complexity of relevant environmental issues, and such flexibility should be permitted by the regulations, FDA declines to include in its regulation a page limit for EA's. CEQ regulations do not specify any limit on the number of pages in EA's. FDA suggested in the preamble (61 FR 14922 at 14934, 61 FR 19476 at 19488) that, as a general rule, an EA should normally be no more than 30 pages, not including test reports and data.

53. The last sentence of proposed § 25.40(a) allows for a tiered environmental testing scheme that would result in test termination when

sufficient data are available to suggest that no significant environmental impact will occur as a result of the potential agency action. One comment suggested that this sentence be changed to state that when results of the initial tier of testing indicate that testing may be stopped, the EA need only contain a certification which states that a PEC/PNEC calculation has been completed and the ratio of the PEC to PNEC is less than one.

The agency declines to include the suggested revision. Proposed § 25.40(a) describes general EA requirements for all FDA-regulated articles. While a tiered testing approach may be adopted by applicants and petitioners of all products regulated by the agency, the language recommended in the comment is limited to human drugs, biologics, and animal drugs. Thus, the inclusion of the suggested language in § 25.40(a) is not appropriate. Additionally, as discussed earlier in response to comment 26, if a PEC/PNEC ratio is used, FDA would need to review the underlying data that supports the PEC/PNEC ratio.

54. FDA has proposed to remove the EA and abbreviated EA formats and any reference to the formats currently found in § 25.31a and to provide appropriate formats in guidance documents. One comment emphasized that to the extent such guidance documents amend or revise informational requirements under NEPA, such requirements are impermissible unless the guidance documents are issued through notice and comment rulemaking under the Administrative Procedure Act (the APA) (5 U.S.C. 553), and the agency consults with CEQ to ensure that the FDA guidance is consistent with NEPA and CEQ requirements.

The APA (5 U.S.C. 553) does not require notice of interpretive rules, general statements of policy, or rules of agency organization, procedure, or practice except when notice is required by other statute. Guidance documents are issued by FDA to provide assistance to the regulated industry and interested parties by interpreting and clarifying requirements that have been imposed by statute or regulation. They reflect the agency's current thinking on the implementation of its regulatory scheme, and because they are not binding on industry or on the agency, they do not create requirements. Consequently, guidance documents are not subject to the notice and comment rulemaking provisions of the APA.

CEQ regulations (40 CFR 1507.3) encourage agencies to publish explanatory guidance for their own procedures and to revise them as

necessary to ensure full compliance with the purposes and provisions of NEPA. Use of guidances provides the agency with greater flexibility to interpret requirements under its NEPA procedures in a manner that responds to the evolving nature of environmental science and the needs of industry and interested parties. In the **Federal Register** of February 27, 1997, FDA announced its adoption of GGP's, which describes the agency's policies and procedures for the development, issuance, and use of guidance documents, including public input in the development of guidance and publication of a notice of availability. Any further development of guidance related to FDA's implementation of NEPA will be developed in accordance with these GGP's. Thus, although guidance documents that clarify the submission of environmental information to FDA are not required to undergo the notice and comment rulemaking procedures of the APA, such guidance documents are subject to public comment and input under the agency's GGP's. Until guidance documents are issued in accordance with the GGP's, applicants that need to submit an EA may follow the EA formats previously published by the agency or may contact the appropriate center for specific guidance on preparing the EA.

In the **Federal Register** of January 11, 1996 (61 FR 1031), FDA announced the availability of a guidance document entitled, "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements." That guidance was intended to assist industry by providing guidance on how to prepare EA's for submission to CDER under current part 25 as part of NDA's, antibiotic applications, abbreviated applications, and IND's. In preparing the "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements," CDER consulted with CEQ and gave CEQ an opportunity to review and comment on the guidance prior to its issuance. This guidance will be revised, as necessary, to ensure that the guidance is consistent with this final rule when it becomes effective. The agency intends to continue its working relationship with the CEQ in issuing additional guidance documents under the final rule.

55. Two comments requested that a general format for EA's be incorporated into proposed § 25.40(a). Both comments expressed concern that removal of the general format from part 25 may invite regulatory expansion, i.e.,

the opportunity for FDA to request more information.

As explained above and in the preamble to the proposal (61 FR 14922 at 14933, 61 FR 19476 at 19487), the agency, in consultation with CEQ, has decided that to the extent that EA formats are helpful, they are more appropriately placed in guidance documents. The formats included in former part 25 were developed to be applicable to all FDA-regulated articles. Due to the diverse nature of the products regulated by FDA, not all format items were relevant to each action. Consequently, some EA's contained unnecessary information and, in some instances, information needed to assess the environmental effects of an action was not initially submitted to the agency. Thus, the formats may be more appropriately included in guidance documents prepared by each center. Guidance documents will allow FDA to suggest EA formats that focus on important environmental issues relating to each type of product regulated by FDA and will assist the preparer in tailoring individual EA's to focus on environmental issues specific to the particular action.

56. Current § 25.31a establishes EA formats for proposed actions to approve food or color additives, drugs, biological products, animal drugs, and some medical devices, to affirm food substances as GRAS, and to grant requests for exemption from regulation as a food additive. One comment noted that in the prescribed EA format, an applicant or petitioner is required to identify the natural resources needed to produce, transport, use and/or dispose of a given amount of any product which is the subject of the action; to describe measures taken to avoid or mitigate potential adverse environmental impacts associated with the proposed action; and to describe in detail the environmental impact of all reasonable alternatives to the proposed action, including those that will enhance the quality of the environment and avoid some or all of the adverse environmental impacts of the proposed action (§ 25.31a(a)). The comment expressed concern that the proposed rule "completely eliminates" those obligations as they apply to marketing applications for paclitaxel derived from the Pacific yew.

Proposed § 25.21 will require an EA for any action, including one involving natural resources, that is ordinarily excluded if the action may have a significant effect on the environment. Proposed § 25.40(a) establishes that an EA shall include a brief discussion of the need for the proposed action,

alternatives to it, and environmental impacts of the proposed action and alternatives. If potentially adverse impacts on the environment are identified in the EA, the EA shall also discuss any alternative course of action that offers less environmental risk or that is environmentally preferable to the proposed action. The agency has determined that more specific information regarding the nature and scope of information that should be included in an EA will be provided in guidance documents rather than through regulatory requirements. Use of guidance documents will provide the agency with greater flexibility to implement NEPA in a manner that responds to the evolving nature of environmental science and the needs of industry and other interested parties. See the response to comment 54, above. As a result of this decision, topics to be analyzed in each EA will be discussed and clarified in guidance documents that will be issued by the center responsible for the underlying action. Such topics will include the use of natural resources in the proposed action (if relevant), and a description of measures that have been taken to avoid or mitigate adverse environmental impacts that may result from the proposed action.

With regard to marketing applications for drugs involving paclitaxel derived from the Pacific yew, FDA published a notice in the **Federal Register** (61 FR 58694), explaining the extent of environmental documentation that needs to be submitted to the agency for drug products containing paclitaxel. See the response to comment 15, above. Persons interested in the agency's application of NEPA requirements with regard to paclitaxel and the Pacific yew are encouraged to review that notice.

57. Proposed § 25.40(d) states that EA's may incorporate by reference information presented in other documents that are available to FDA and to the public. One comment recommended that this section be revised to clarify that other EA's for approved FDA-regulated articles may be incorporated by reference into an EA.

EA's that are available under the Freedom of Information Act are public information and therefore may be incorporated by reference into an EA to the extent that they are relevant to the action addressed in the EA. Information that is not publicly available but to which an applicant or petitioner has a right of reference or ownership may also be incorporated by that applicant or petitioner into an EA. In accordance with proposed § 25.51(a), however, such confidential information shall be

summarized in the EA to the extent possible. The agency does not find it necessary to revise the proposed regulation to further clarify this point.

58. Proposed § 25.40(e) states that the agency evaluates the information contained in an EA, along with any public input, to determine whether it is accurate and objective, whether the proposed action may significantly affect the quality of the human environment, and whether the agency should prepare a FONSI or EIS. One comment requested that this section be revised to define and restrict specific procedures in manufacturing and disposal to effectively prevent opportunities for some types of environmental release.

Defining and restricting specific procedures in manufacturing and disposal to prevent pollution are more appropriately handled by Federal, State, or local environmental protection agencies that have regulatory authority and more expertise in those matters. However, as part of FDA's NEPA review process, alternatives and mitigation measures are considered by FDA.

59. Proposed § 25.43 states that in cases where EIS's are required, the agency will prepare, at the time of its decision, a concise public record of decision. One comment asserted that this section should explicitly address the CEQ provisions governing limitations on actions during the NEPA process. CEQ regulations (40 CFR 1506.1(b)) require an agency to take appropriate action to ensure that the objectives and procedures of NEPA are achieved if the agency is aware that an applicant is about to take an action within the jurisdiction of the agency that will have adverse environmental impacts or will limit the choice of reasonable alternatives.

FDA is not required under 40 CFR 1507.3(b), and does not see any need, to explicitly include in its procedures specific language to implement 40 CFR 1506.1(b). Because an agency's procedures must supplement CEQ regulations, all CEQ regulations in 40 CFR parts 1500 through 1508 are incorporated by reference into FDA's policies and procedures implementing NEPA.

60. Proposed § 25.45 (Responsible agency official) states that the agency official identified in part 5 as being responsible for the underlying application or petition is responsible for preparing environmental documents. One comment suggested that § 25.45 be revised to require the responsible agency official to be available to review any questions arising from the preparation of an EA. Two comments recommended that part 5 be amended to

include a provision that establishes the Center Directors as the responsible officials for deciding the existence of extraordinary circumstances under proposed § 25.21 and prohibits redelegation of such authority. One of these comments also requested revisions to make it clear that any decision by the Center Director on the question of extraordinary circumstances constitutes final agency action.

FDA does not find it necessary to revise proposed § 25.45 to require the responsible agency official to be available to review questions arising from the preparation of an EA. The FDA official responsible for preparing environmental documents is available to review questions concerning environmental issues and to meet with interested parties (see, e.g., § 10.65 (21 CFR 10.65)). In proposed § 25.40, FDA specifically encourages interaction between the responsible agency official and those submitting EA's during the preparation of the environmental documents.

FDA also declines to amend part 5. Part 5 delegates to specific agency officials responsibility for taking particular actions on behalf of the agency. Responsibility for actions on petitions and applications is generally delegated to the Director or Deputy Director(s) of the center responsible for reviewing submissions relating to the FDA-regulated product for which an action is requested. Consistent with CEQ's policy that the disciplines of those who prepare environmental documents be appropriate to the scope and issues of the document, see e.g., 40 CFR 1502.6, the Center Directors delegate responsibility (e.g., authority to determine extraordinary circumstances and to mediate conflicts between reviewers and sponsors) to individuals within their organization who have specialized training and expertise to evaluate all relevant issues. Individuals in each center who have training and experience in environmental science and in implementing environmental statutes are responsible for determining the adequacy of EA's and claims for categorical exclusion and the existence of extraordinary circumstances. These individuals are expected to consult with their supervisors and other management officials as needed. Specific delegations of responsibility are available to the public through each center office.

Furthermore, each center has appeals procedures by which decisions of center personnel can be appealed to the Center Director. The Center Director's decision does not necessarily, however, constitute final agency action. A procedure for internal review of agency

decisions is established in § 10.75(a) (21 CFR 10.75(a)), which states that a decision of any FDA employee, other than the Commissioner, is subject to review by the employee's supervisor. Thus, the proposal that a Center Director's decision necessarily constitutes final agency action is contrary to FDA regulations and FDA does not believe that its regulations should be modified.

E. Subpart E—Public Participation and Notification of Environmental Documents

61. Proposed § 25.50(b) states that many actions performed by FDA are protected from disclosure by the act, the Trade Secret Act (the TSA) (18 U.S.C. 1905), and FDA regulations and "unless the existence of an application for human drugs * * * has been made publicly available, the release of the environmental document before approval of human drugs * * * is inconsistent with statutory requirements imposed on FDA." One comment stated that this provision conflicts with the requirements of NEPA and CEQ that mandate public involvement at the earliest possible time. The comment stated that FDA may not completely abandon NEPA's public participation provisions by broadly invoking protection under the TSA. The comment stated that at least for NDA's and ANDA's, FDA clearly has authority to release environmental documents following issuance of an approvable letter to the applicant. The comment cited two Federal court cases, *Flint Ridge Development Co. v. Scenic Rivers Association of Oklahoma et al.*, 426 U.S. 776 (1976) and *Concerned About Trident v. Rumsfeld*, 555 F.2d 817 (D.C. Cir. 1977), to support the proposition that exceptions to NEPA's requirements have been construed narrowly.

Proposed § 25.50(b) is consistent with NEPA and CEQ regulations. Section 102 of NEPA (42 U.S.C. 4332)

(D)irects that, to the fullest extent possible: (1) The policies, regulations, and public laws of the United States shall be interpreted and administered in accordance with the policies set forth in [NEPA], and (2) all agencies of the Federal government shall— * * * (C) include in every recommendation * * * for * * * major Federal action significantly affecting the quality of the human environment, a detailed statement by the responsible official on—(i) the environmental impact of the proposed action (emphasis added).

Section 102 of NEPA further requires copies of any such detailed statement and the comments and views of the appropriate Federal, State, and local agencies, which are authorized to

develop and enforce environmental standards, to be made available to the President, CEQ, and to the public as provided in 5 U.S.C. 552. CEQ regulations (40 CFR 1500.6) state that "the phrase 'to the fullest extent possible' in section 102 means that each agency of the Federal Government shall comply with that section unless existing law applicable to the agency's operations expressly prohibits or makes compliance impossible."

The TSA expressly prohibits any officer or employee of the United States from publishing, divulging, disclosing, or making known in any manner or to any extent not authorized by law any information which concerns or relates to trade secrets, processes, operations, styles of work, or apparatus, or to the identity, confidential statistical data, amount or source of any income, profits, losses, or expenditures of any person, firm, partnership, corporation, or association. The TSA covers trade secrets as well as confidential commercial or financial information. Therefore, FDA is prohibited from disclosing trade secrets and confidential commercial information except to the extent authorized by law.

Under section 301(j) of the act (21 U.S.C. 331(j)), FDA is authorized to disclose trade secret information only to the Secretary of the Department of Health and Human Services or officers or employees of the Department, courts when relevant in any judicial proceeding under the act, either House of Congress, or, to the extent of matter within its jurisdiction, any committee or its subcommittee or any joint committee of Congress or its subcommittee. FDA is not authorized to disclose trade secrets to any other parties.

The comment cited two cases. *Flint Ridge* stands for the proposition that the only time that a Federal agency can avoid compliance with NEPA under the "to the fullest extent possible" caveat is when a clear and unavoidable conflict in statutory authority exists, in which case NEPA must give way. In *Concerned About Trident*, the Court rejected the Department of Defense-Navy's attempt to exempt from the mandate of NEPA strategic military decisions made by the Department of Defense-Navy because the Navy pointed to no existing specific statutory authority prohibiting compliance with NEPA in that case or making such compliance impossible.

Proposed § 25.50(b) is consistent with NEPA's direction to implement its policies "to the fullest extent possible," as the case law has interpreted that phrase. In those instances in which the TSA and section 301(j) of the act prohibit FDA from disclosing

environmental information to the public, compliance with NEPA is impossible and NEPA must give way. FDA cannot disclose to the public environmental information prior to taking action to approve certain marketing applications. Thus, FDA does not contravene NEPA when it refuses to disclose information in such circumstances.

Furthermore, FDA's procedures comply with NEPA's requirements to implement NEPA to the fullest extent possible because the procedures require FDA to review and/or prepare environmental documentation for any major Federal action before taking the action unless the action meets criteria for categorical exclusion. Moreover, FDA's procedures specifically provide that information will be released to the public in accordance with NEPA when, and to the extent, permitted by the TSA and other laws governing FDA's operations. Clearly, FDA is not completely abandoning NEPA's public participation provisions. If FDA is not prohibited under the TSA and the act from disclosing specific environmental information before FDA takes action, FDA will disclose that environmental information at the earliest possible time before action is taken. To the extent that compliance with the TSA and the act make impossible disclosure of environmental information before action is taken, FDA will disclose environmental information after the action is taken to the extent permitted under the TSA and the act.

Finally, § 25.50 is also consistent with the requirement that environmental information be made available to the public as provided in the Freedom of Information Act (the FOIA) (5 U.S.C. 552). Although the FOIA requires an agency to make available to the public most information available to the agency, certain matters are exempt from disclosure. Specifically, the FOIA exempts from disclosure trade secrets and commercial or financial information that is obtained from a person and is privileged or confidential.

62. Proposed § 25.52(a) states that if an EIS is prepared for a drug, animal drug, biologic product, or device, it will become available to the public only at the time of the approval of the product. One comment asserted that this provision "cuts back significantly on one of the most fundamental requirements of NEPA and the CEQ regulations—the ability of the public to review and comment on proposed agency decisions." The comment stated that the proposal "constitutes a complete repeal of the agency's current NEPA regulations providing for public

involvement in the EIS process and, as such, it must be rejected."

The agency disagrees. Proposed § 25.52 does not repeal the agency's regulations providing for public involvement in the EIS process but merely clarifies that when there is a clear and unavoidable conflict between NEPA's public disclosure goals and other laws governing FDA's disclosure of information, FDA must follow the disclosure laws that govern its operations. As discussed in response 61 above, the agency is limited in its ability to disclose to the public information contained within certain marketing applications. The agency will generally make an EIS available to the public at the time of approval of the relevant drug, animal drug, biological product, or device (§ 25.52(a)) but, in instances where disclosure of an application has occurred, the agency will abide by its responsibility to make a diligent effort to involve the public while concurrently complying with its own disclosure requirements (§ 25.52(c)).

F. Subpart F—Other Requirements

63. Section 25.60 states that in accordance with Executive Order 12114, "Environmental Effects Abroad of Major Federal Actions," January 4, 1979, FDA will consider the environmental effects abroad of its potential actions. One comment claimed that under this provision, Executive Order 12114, not NEPA, would govern environmental impacts that may occur abroad as a result of FDA action. The comment stated that as a result, FDA's proposal would not govern environmental impacts associated with harvest of Pacific yew trees in Canada for paclitaxel marketed in the United States. The comment cited *Environmental Defense Fund v. Massey*, 986 F.2d 528 (D.C. Cir. 1993), stating that the Court of Appeals for the D.C. Circuit rejected the notion that NEPA only governs activities within the United States.

Executive Order 12114 and proposed § 25.60 (current § 25.50) have not changed since 1985. Executive Order 12114, "Environmental Effects Abroad of Major Federal Actions," represents the U.S. Government's "exclusive and complete determination of * * * actions to be taken by Federal agencies to further the purpose of the National Environmental Policy Act with respect to the environment outside the United States, its territories, and possessions." The agency issued current § 25.50 to implement this executive order. FDA requirements include the consideration of potential environmental effects of an action on a foreign nation, current

§ 25.50(a)(2) (proposed § 25.60(a)(2)). In the event the agency action would have a significant environmental effect on the foreign nation, the agency official will require additional environmental documentation, current § 25.50(c) (proposed § 25.60(c)).

In the case cited in the comment, *Environmental Defense Fund v. Massey*, 986 F.2d 528, 532 (D.C. Cir. 1993), the court held that the National Science Foundation must comply with NEPA before going forward with plans to incinerate food waste in Antarctica. The court expressly limited its decision to the unique circumstances of Antarctica, stating, "we do not decide today how NEPA might apply to actions in a case involving an actual sovereign." (*Massey*, at 537.) The court did not rule on the applicability of Executive Order 12114.

The comment's allegation that FDA's proposal would not govern the environmental impacts associated with the harvest of the Pacific yew in Canada for paclitaxel marketed in the United States is without basis. FDA is required to consider the environmental impacts of its actions either under NEPA or the Executive Order. Executive Order 12114 states if the responsible official determines that an action may have a significant environmental effect abroad, the responsible official shall prepare appropriate environmental documents. Additionally, as discussed in the response to comment 15, above, FDA issued a notice in the November 18, 1996, **Federal Register** explaining the environmental information to be submitted with marketing applications for drug products containing paclitaxel.

III. Conforming Amendments

The environmental regulations in part 25 are cited throughout FDA's regulations. Because FDA is revising part 25, the agency is taking this opportunity to make conforming amendments to 21 CFR parts 10, 20, 71, 101, 170, 171, 312, 314, 315, 511, 514, 570, 571, 601, 812, 813, and 814 to reflect revised part 25. These conforming amendments will ensure the accuracy and consistency of the regulations.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits

(including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities unless the rule is not expected to have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act (Pub. L. 104–4) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation). The following analysis demonstrates that this final rule is consistent with the principles set forth in the Executive Order and in these two statutes. The final rule is a significant but not an economically significant regulatory action under Executive Order 12866 and the rule does not impose any mandates on State, local, or tribal governments, or the private sector, that will result in an annual expenditure of \$100,000,000 or more.

Based on the approximate number of EA's that FDA currently receives each year and the resources needed to prepare them, the agency estimates that the reduced requirements for submitting EA's will result in an annual cost savings to industry of approximately \$15.7 million. Two letters received by FDA in response to the proposed rule commented that the rule would eliminate a majority of EA's that the respondents, or their members, have been required to submit in the past. These comments are consistent with the estimate presented here. The basis for this estimate is as follows:

Human Pharmaceuticals

Approximately 125 EA's related to human pharmaceuticals will be eliminated annually under the final rule. About one-half of these are abbreviated EA's; the remainder are full assessments. Based on industry estimates, FDA assumes that the average cost of preparing an abbreviated assessment was approximately \$40,000, while the average cost of a full assessment was approximately \$200,000. These assumptions yield a cost savings of about \$2.5 million for abbreviated EA's and \$12.5 million for full EA's, for a total savings to industry from the reduced requirements of EA's relating to human pharmaceuticals of approximately \$15 million per year.

Veterinary Products

The changes eliminate approximately 37 abbreviated EA's for veterinary products each year, at an industry-estimated average cost of approximately \$5,000 each. About 77 brief submissions, which currently require categorical exclusion criteria review, are also eliminated; these cost an industry-estimated \$300 each to prepare. Total cost savings to the veterinary products industry under the proposal are thus approximately \$208,000 per year.

Food Products

About 39 EA's per year received by the Center for Food Safety and Applied Nutrition (CFSAN) will be eliminated under the final rule. Approximately 30 of these would have been abbreviated EA's and 9 would have been full assessments under current rules. Based on industry estimates, FDA projects that the cost of producing most abbreviated EA's for CFSAN is approximately \$2,500 and the average cost of producing a full EA is approximately \$50,000. These assumptions imply an annual cost savings of approximately \$75,000 for abbreviated EA's and \$450,000 for full EA's, for a total annual savings to the foods industry of approximately \$525,000.

In addition to these savings to industry, the final rule will improve

FDA efficiency by eliminating agency review costs of approximately \$1 million per year.

As these regulations will not impose significant new costs on any firms, under the Regulatory Flexibility Act, 5 U.S.C. 605(b), the Commissioner certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

V. The Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). A description of these provisions is given below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: National Environmental Policy Act; Reporting Provisions.

Description: FDA has previously issued regulations that implement NEPA (part 25). This final rule calls for

applicants and petitioners to submit environmental information to FDA, in the form of EIS's, EA's, or claims for categorical exclusion, where appropriate. NEPA requires such reporting to enable FDA to take into account in its decisionmaking process the potential impact of agency actions on the environment.

This final rule will reduce the number of NEPA evaluations by providing for categorical exclusions for additional classes of actions that do not individually or cumulatively have a significant effect on the human environment and for which, therefore, neither an EIS nor an EA is required. FDA is also amending these regulations to ensure that the NEPA procedures are more concise and understandable to the public, and to reflect current FDA policy with respect to environmental considerations.

Individuals and organizations may submit comments on these burden estimates or on any other aspect of these information collection provisions, including suggestions for reducing the burden, and should direct them to the appropriate contact person listed at the beginning of this document.

Description of Respondents: Persons and businesses, including small businesses.

ESTIMATED ANNUAL REPORTING BURDEN

CFR section	No. of respondents	Annual frequency per response	Total annual responses	Hours per Responses	Total hours
25.15(a), (d)	455	11.82	5,376	7.94	42,685
25.40(a), (c)	455	.13	58	2832.93	164,310
Total	206,995

This estimate represents the total reporting burden for the amended regulations. The total reporting burden for the regulations in part 25 before the amendments was 710,987 hours; thus, the amended regulations will result in an estimated net decrease in burden of 503,992 hours, a reduction of more than 70 percent.

The information collection provisions in this final rule have been approved under OMB Control No. 0910-0332. This approval expires June 30, 1999. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

List of Subjects

21 CFR Part 10

Administrative practice and procedure, News media.

21 CFR Part 20

Confidential business information, Courts, Freedom of information, Government employees.

21 CFR Part 25

Environmental impact statements, Foreign relations, Reporting and recordkeeping requirements.

21 CFR Part 71

Administrative practice and procedure, Color additives, Confidential business information, Cosmetics, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 101

Food labeling, Nutrition, Reporting and recordkeeping requirements.

21 CFR Part 170

Administrative practice and procedure, Food additives, Reporting and recordkeeping requirements.

21 CFR Part 171

Administrative practice and procedure, Food additives.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business

information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 511

Animal drugs, Medical research, Reporting and recordkeeping requirements.

21 CFR Part 514

Administrative practice and procedure, Animal drugs, Confidential business information, Reporting and recordkeeping requirements.

21 CFR Part 570

Animal feeds, Animal foods, Food additives.

21 CFR Part 571

Administrative practice and procedure, Animal feeds, Animal foods, Food additives.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.

21 CFR Part 814

Administrative practice and procedure, Confidential business information, Medical devices, Medical research, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 10, 20, 25, 71, 101, 170, 171, 312, 314, 511, 514, 570, 571, 601, 812, and 814 are amended as follows:

PART 10—ADMINISTRATIVE PRACTICES AND PROCEDURES

1. The authority citation for 21 CFR part 10 continues to read as follows:

Authority: Secs. 201–903 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321–394); 21 U.S.C. 41–50, 141–149, 467f, 679, 821, 1034; secs. 2, 351, 354, 361 of the Public Health Service Act (42 U.S.C. 201, 262, 263b, 264); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461); 5 U.S.C. 551–558, 701–721; 28 U.S.C. 2112.

2. Section 10.30 is amended in paragraph (b) by revising item C to read as follows:

§ 10.30 Citizen petition.

* * * * *

(b) * * *

C. *Environmental impact.*

(A) claim for categorical exclusion under §§ 25.30, 25.31, 25.32, 25.33, or § 25.34 of this chapter or an environmental assessment under § 25.40 of this chapter.)

* * * * *

3. Section 10.40 is amended by revising paragraph (b)(1)(ix) to read as follows:

§ 10.40 Promulgation of regulations for the efficient enforcement of the law.

* * * * *

(b) * * *

(1) * * *

(ix) a reference to the existence or lack of need for an environmental impact statement under § 25.52 of this chapter; and

* * * * *

PART 20—PUBLIC INFORMATION

4. The authority citation for 21 CFR part 20 continues to read as follows:

Authority: Secs. 201–903 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321–393); secs. 301, 302, 303, 307, 310, 311, 351, 352, 354–360F, 361, 362, 1701–1706, 2101 of the Public Health Service Act (42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 263b–263n, 264, 265, 300u–5, 300aa–1); 5 U.S.C. 552; 18 U.S.C. 190; 19 U.S.C. 2531–2582; 21 U.S.C. 1401–1403.

5. Section 20.100 is amended by revising paragraph (c)(3) to read as follows:

§ 20.100 Applicability; cross-reference to other regulations.

* * * * *

(c) * * *

(3) Environmental assessments; finding of no significant impact, in § 25.51 of this chapter, or draft and final environmental impact statements, in § 25.52 of this chapter.

6. Part 25 is revised to read as follows:

PART 25—ENVIRONMENTAL IMPACT CONSIDERATIONS

Subpart A—General Provisions

Sec.

25.1 Purpose.

25.5 Terminology.

25.10 Policies and NEPA planning.

Subpart B—Agency Actions Requiring Environmental Consideration

25.15 General procedures.

25.16 Public health and safety emergencies.

25.20 Actions requiring preparation of an environmental assessment.

25.21 Extraordinary circumstances.

25.22 Actions requiring the preparation of an environmental impact statement.

Subpart C—Categorical Exclusions

25.30 General.

25.31 Human drugs and biologics.

25.32 Foods, food additives, and color additives.

25.33 Animal drugs.

25.34 Devices and electronic products.

Subpart D—Preparation of Environmental Documents

25.40 Environmental assessments.

25.41 Findings of no significant impact.

25.42 Environmental impact statements.

25.43 Records of decision.

25.44 Lead and cooperating agencies.

25.45 Responsible agency official.

Subpart E—Public Participation and Notification of Environmental Documents

25.50 General information.

25.51 Environmental assessments and findings of no significant impact.

25.52 Environmental impact statements.

Subpart F—Other Requirements

25.60 Environmental effects abroad of major agency actions.

Authority: Secs. 201–903 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321–393); secs. 351, 354–361 of the Public Health Service Act (42 U.S.C. 262, 263b–264); 42 U.S.C. 4321, 4331–4335; 40 CFR parts 1500–1508; E.O. 11514, 3 CFR 1966–1970, Comp., p. 902, as amended by E.O. 11991, 3 CFR 1977 Comp., p. 123. E.O. 12114, 3 CFR 1977 Comp., p. 123.

PART 25—ENVIRONMENTAL IMPACT CONSIDERATIONS

Subpart A—General Provisions

§ 25.1 Purpose.

The National Environmental Policy Act of 1969 (NEPA), as amended, directs that, to the fullest extent possible, the policies, regulations, and public laws of the United States shall be interpreted and administered in accordance with the policies set forth in NEPA. All agencies of the Federal Government shall comply with the procedures in section 102(2) of NEPA except where compliance would be inconsistent with other statutory requirements. The regulations in this part implement section 102(2) of NEPA in a manner that is consistent with FDA's authority under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. This part also supplements the regulations for implementing the procedural provisions of NEPA that were published by the Council on Environmental Quality (CEQ) in 40 CFR parts 1500 through 1508 and the procedures included in the "HHS General Administration Manual, part 30: Environmental Protection" (45 FR 76519 to 76534, November 19, 1980).

§ 25.5 Terminology.

(a) Definitions that apply to the terms used in this part are set forth in the CEQ regulations under 40 CFR part 1508. The terms and the sections of 40 CFR part 1508 in which they are defined follow:

- (1) Categorical exclusion (40 CFR 1508.4).
- (2) Cooperating agency (40 CFR 1508.5).
- (3) Cumulative impact (40 CFR 1508.7).
- (4) Effects (40 CFR 1508.8).
- (5) Environmental assessment (EA) (40 CFR 1508.9).
- (6) Environmental document (40 CFR 1508.10).
- (7) Environmental impact statement (EIS) (40 CFR 1508.11).
- (8) Federal agency (40 CFR 1508.12).
- (9) Finding of no significant impact (40 CFR 1508.13).
- (10) Human environment (40 CFR 1508.14).
- (11) Lead agency (40 CFR 1508.16).
- (12) Legislation (40 CFR 1508.17).
- (13) Major Federal action (40 CFR 1508.18).
- (14) Mitigation (40 CFR 1508.20).
- (15) NEPA process (40 CFR 1508.21).
- (16) Notice of intent (40 CFR 1508.22).
- (17) Proposal (40 CFR 1508.23).
- (18) Scope (40 CFR 1508.25).
- (19) Significantly (40 CFR 1508.27).

(b) The following terms are defined solely for the purpose of implementing the supplemental procedures provided by this part and are not necessarily applicable to any other statutory or regulatory requirements:

(1) *Abbreviated application* applies to an abbreviated new drug application, an abbreviated antibiotic application, and an abbreviated new animal drug application.

(2) *Active moiety* means 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.

(3) *Agency* means the Food and Drug Administration (FDA).

(4) *Increased use* of a drug or biologic product 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.

(5) *Responsible agency official* means the agency decisionmaker designated in part 5 of this chapter.

(c) The following acronyms are used in this part:

- (1) CEQ—Council on Environmental Quality.
- (2) CGMP—Current good manufacturing practice.

- (3) EA—Environmental assessment.
- (4) EIS—Environmental impact statement.
- (5) The act—Federal Food, Drug, and Cosmetic Act.
- (6) FIFRA—Federal Insecticide, Fungicide, and Rodenticide Act.
- (7) FONSI—Finding of no significant impact.
- (8) GLP—Good laboratory practice.
- (9) GRAS—Generally recognized as safe.
- (10) HACCP—Hazard analysis critical control point.
- (11) IDE—Investigational device exemption.
- (12) IND—Investigational new drug application.
- (13) INAD—Investigational new animal drug application.
- (14) NADA—New animal drug application.
- (15) NDA—New drug application.
- (16) NEPA—National Environmental Policy Act of 1969.
- (17) OTC—Over-the-counter.
- (18) PDP—Product development protocol.
- (19) PMA—Premarket approval application.

§ 25.10 Policies and NEPA planning.

(a) All FDA's policies and programs will be planned, developed, and implemented to achieve the policies declared by NEPA and required by CEQ's regulations to ensure responsible stewardship of the environment for present and future generations.

(b) Assessment of environmental factors continues throughout planning and is integrated with other program planning at the earliest possible time to ensure that planning and decisions reflect environmental values, to avoid delays later in the process, and to avoid potential conflicts.

(c) For actions initiated by the agency, the NEPA process will begin when the agency action under consideration is first identified. For actions initiated by applicants or petitioners, NEPA planning begins when FDA receives from an applicant or petitioner an EA or a claim that a categorical exclusion applies, or when FDA personnel consult with applicants or petitioners on the NEPA-related aspects of their requested actions. FDA may issue a public call for environmental data or otherwise consult with affected individuals or groups when a contemplated action in which it is or may be involved poses potential significant environmental effects.

(d) Environmental documents shall concentrate on timely and significant issues, not amass needless detail.

(e) If a proposed action for which an EIS will be prepared involves possible

environmental effects that are required to be considered under statutes or Executive Orders other than those referred to under "Authority" in this part, these effects shall be considered in the NEPA review, consistent with 40 CFR 1502.25 and the HHS General Administration Manual, part 30: Environmental Protection.

Subpart B—Agency Actions Requiring Environmental Consideration

§ 25.15 General procedures.

(a) All applications or petitions requesting agency action require the submission of an EA or a claim of categorical exclusion. A claim of categorical exclusion shall include a statement of compliance with the categorical exclusion criteria and shall state that to the applicant's knowledge, no extraordinary circumstances exist. Failure to submit an adequate EA for an application or petition requesting action by the agency of a type specified in § 25.20, unless the agency can determine that the action qualifies for exclusion under §§ 25.30, 25.31, 25.32, 25.33, or 25.34, is sufficient grounds for FDA to refuse to file or approve the application or petition. An EA 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 significantly affect the quality of the human environment.

(b) The responsible agency officials will evaluate the information contained in the EA to determine whether it is accurate and objective, whether the proposed action may significantly affect the quality of the human environment, and whether an EIS will be prepared. If significant effects requiring the preparation of an EIS are identified, FDA will prepare an EIS for the action in accordance with the procedures in subparts D and E of this part. If significant effects requiring the preparation of an EIS are not identified, resulting in a decision not to prepare an EIS, the responsible agency official will prepare a FONSI in accordance with § 25.41.

(c) Classes of actions that individually or cumulatively do not significantly affect the quality of the human environment ordinarily are excluded from the requirement to prepare an EA or an EIS. The classes of actions that qualify as categorical exclusions are set forth in §§ 25.30, 25.31, 25.32, 25.33, or 25.34.

(d) A person submitting an application or petition of a type subject to categorical exclusion under §§ 25.30,

25.31, 25.32, 25.33, or 25.34, or proposing to dispose of an article as provided in § 25.30(d) or 25.32(h), is not required to submit an EA if the person states that the action requested qualifies for a categorical exclusion, citing the particular categorical exclusion that is claimed, and states that to the applicant's knowledge, no extraordinary circumstances exist.

§ 25.16 Public health and safety emergencies.

There are certain regulatory actions that, because of their immediate importance to the public health or safety, may make full adherence to the procedural provisions of NEPA and CEQ's regulations impossible. For such actions, the responsible agency official shall consult with CEQ about alternative arrangements before the action is taken, or after the action is taken, if time does not permit prior consultation with CEQ.

§ 25.20 Actions requiring preparation of an environmental assessment.

Any proposed action of a type specified in this section ordinarily requires at least the preparation of an EA, unless it is an action in a specific class that qualifies for exclusion under §§ 25.30, 25.31, 25.32, 25.33, or 25.34:

(a) Major recommendations or reports made to Congress on proposals for legislation in instances where the agency has primary responsibility for the subject matter involved.

(b) Destruction or other disposition of articles condemned after seizure or whose distribution or use has been enjoined, unless categorically excluded in §§ 25.30(d) or 25.32(h).

(c) Destruction or other disposition of articles following detention or recall at agency request, unless categorically excluded in §§ 25.30(d) or 25.32(h).

(d) Disposition of FDA laboratory waste materials, unless categorically excluded in § 25.30(m).

(e) Intramural and extramural research supported in whole or in part through contracts, other agreements, or grants, unless categorically excluded in § 25.30 (e) or (f).

(f) Establishment by regulation of labeling requirements, a standard, or a monograph, unless categorically excluded in §§ 25.30(k) or 25.31 (a), (b), (c), (h), (i), or (j), or 25.32 (a) or (p).

(g) Issuance, amendment, and enforcement of FDA regulations, or an exemption or variance from FDA regulations, unless categorically excluded in § 25.30 (h), (i), or (j), or § 25.32 (e), (g), (n), or (p).

(h) Withdrawal of existing approvals of FDA-approved articles, unless categorically excluded in §§ 25.31 (d) or (k), 25.32(m), or 25.33 (g) or (h).

(i) Approval of food additive petitions and color additive petitions, approval of requests for exemptions for investigational use of food additives, and granting of requests for exemption from regulation as a food additive, unless categorically excluded in § 25.32 (b), (c), (i), (j), (k), (l), (o), (q), or (r).

(j) Establishment of a tolerance for unavoidable poisonous or deleterious substances in food or in packaging materials to be used for food.

(k) Affirmation of a food substance as GRAS for humans or animals, on FDA's initiative or in response to a petition, under parts 182, 184, 186, or 582 of this chapter and establishment or amendment of a regulation for a prior-sanctioned food ingredient, as defined in §§ 170.3(l) and 181.5(a) of this chapter, unless categorically excluded in § 25.32 (f), (k), or (r).

(l) Approval of NDA's, abbreviated applications, applications for marketing approval of a biologic product, supplements to such applications, and actions on IND's, unless categorically excluded in § 25.31 (a), (b), (c), (e), or (l).

(m) Approval of NADA's, abbreviated applications, supplements, and actions on INAD's, unless categorically excluded under § 25.33 (a), (c), (d), or (e).

(n) Approval of PMA's for medical devices, notices of completion of PDP's for medical devices, authorizations to commence clinical investigation under an approved PDP, or applications for an IDE, unless categorically excluded in § 25.34.

§ 25.21 Extraordinary circumstances.

As required under 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 (see 40 CFR 1508.27 for examples of significant impacts). Examples of such extraordinary circumstances include:

(a) Actions for which available data establish that, at the expected level of exposure, there is the potential for serious harm to the environment; and

(b) 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 Flora and Fauna to be endangered or threatened or wild flora or fauna that are entitled to special protection under some other Federal law.

§ 25.22 Actions requiring the preparation of an environmental impact statement.

(a) There are no categories of agency actions that routinely significantly affect the quality of the human environment and that therefore ordinarily require the preparation of an EIS.

(b) EIS's are prepared for agency actions 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.

Subpart C—Categorical Exclusions

§ 25.30 General.

The classes of actions listed in this section and §§ 25.31 through 25.34 are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:

(a) Routine administrative and management activities, including inspections, and issuance of field compliance programs, program circulars, or field investigative assignments.

(b) Recommendation for an enforcement action to be initiated in a Federal court.

(c) Agency requests for initiation of recalls.

(d) Destruction or disposition of any FDA-regulated article condemned after seizure or the distribution or use of which has been enjoined or following detention or recall at agency request if the method of destruction or disposition of the article, including packaging material, is in compliance with all Federal, State, and local requirements.

(e) Extramural contracts, other agreements, or grants for statistical and epidemiological studies, surveys and inventories, literature searches, and report and manual preparation, or any other studies that 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.

(f) Extramural contracts, other agreements, and grants for research for such purposes as to develop analytical methods or other test methodologies.

(g) Activities of voluntary Federal-State cooperative programs, including issuance of model regulations proposed for State adoption.

(h) Issuance, amendment, or revocation of procedural or administrative regulations and guidelines, including procedures for submission of applications for product development, testing and investigational use, and approval.

(i) Corrections and technical changes in regulations.

(j) Issuance of CGMP regulations, HACCP regulations, establishment standards, emergency permit control regulations, GLP regulations, and issuance or denial of permits, exemptions, variances, or stays under these regulations.

(k) Establishment or repeal by regulation of labeling requirements for marketed articles if there will be no increase in the existing levels of use or change in the intended uses of the product or its substitutes.

(l) Routine maintenance and minor construction activities such as:

(1) Repair to or replacement of equipment or structural components (e.g., door, roof, or window) of facilities controlled by FDA;

(2) Lease extensions, renewals, or succeeding leases;

(3) Construction or lease construction of 10,000 square feet or less of occupiable space;

(4) Relocation of employees into existing owned or currently leased space;

(5) Acquisition of 20,000 square feet or less of occupiable space in a structure that was substantially completed before the issuance of solicitation for offers; and

(6) Acquisition of between 20,000 square feet and 40,000 square feet of occupiable space if it constitutes less than 40 percent of the occupiable space in a structure that was substantially completed before the solicitation for offers.

(m) Disposal of low-level radioactive waste materials (as defined in the Nuclear Regulatory Commission regulations at 10 CFR 61.2) and chemical waste materials generated in the laboratories serviced by the contracts administered by FDA, if the waste is disposed of in compliance with all applicable Federal, State, and local requirements.

§ 25.31 Human drugs and biologics.

The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:

(a) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety.

(b) Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action 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.

(c) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

(d) Withdrawal of approval of an NDA or an abbreviated application.

(e) Action on an IND.

(f) Testing and certification of batches of an antibiotic or insulin.

(g) Testing and release by the Center for Biologics Evaluation and Research of lots or batches of a licensed biologic product.

(h) Issuance, revocation, or amendment of a monograph for an antibiotic drug.

(i) Establishment of bioequivalence requirements for a human drug or a comparability determination for a biologic product subject to licensing.

(j) Issuance, revocation, or amendment of a standard for a biologic product.

(k) Revocation of a license for a biologic product.

(l) Action on an application for marketing approval for marketing of a biologic product for transfusable human blood or blood components and plasma.

§ 25.32 Foods, food additives, and color additives.

The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:

(a) Issuance, amendment, or repeal of a food standard.

(b) Action on a request for exemption for investigational use of a food additive if the food additive to be shipped under the request is intended to be used for clinical studies or research.

(c) Approval of a color additive petition to change a provisionally listed color additive to permanent listing for use in food, drugs, devices, or cosmetics.

(d) Testing and certification of batches of a color additive.

(e) Issuance of an interim food additive regulation.

(f) Affirmation of a food substance as GRAS for humans or animals on FDA's initiative or in response to a petition, under parts 182, 184, 186, or 582 of this chapter, and establishment or amendment of a regulation for a prior-sanctioned food ingredient, as defined in §§ 170.3(l) and 181.5(a) of this

chapter, if the substance or food ingredient is already marketed in the United States for the proposed use.

(g) Issuance and enforcement of regulations relating to the control of communicable diseases or to interstate conveyance sanitation under parts 1240 and 1250 of this chapter.

(h) Approval of a request for diversion of adulterated or misbranded food for humans or animals to use as animal feeds.

(i) Approval of a food additive petition, GRAS affirmation petition, or the granting of a request for exemption from regulation as a food additive under § 170.39 of this chapter, when the substance is present in finished food-packaging material at not greater than 5 percent-by-weight and is expected to remain with finished food-packaging material through use by consumers or when the substance is a component of a coating of a finished food-packaging material.

(j) Approval of a food additive petition, GRAS affirmation petition, or the granting of a request for exemption from regulation as a food additive under § 170.39 of this chapter, when the substance is to be used as a component of a food-contact surface of permanent or semipermanent equipment or of another food-contact article intended for repeated use.

(k) Approval of a food additive, color additive, or GRAS petition for substances added directly to food that are intended to remain in food through ingestion by consumers and that are not intended to replace macronutrients in food.

(l) Approval of a petition for color additives used in contact lenses, sutures, filaments used as supporting haptics in intraocular lenses, bone cement, and in other FDA-regulated products having similarly low levels of use.

(m) Action to prohibit or otherwise restrict or reduce the use of a substance in food, food packaging, or cosmetics.

(n) Issuance, amendment, or revocation of a regulation pertaining to infant formulas.

(o) Approval of a food additive petition for the intended expression product(s) present in food derived from new plant varieties.

(p) Issuance, amendment, or revocation of a regulation in response to a reference amount petition as described in § 101.12(h) of this chapter, a nutrient content claim petition as described in § 101.69 of this chapter, a health claim petition as described in § 101.70 of this chapter, or a petition pertaining to the label declaration of ingredients as described in § 101.103 of this chapter.

(q) Approval of a food additive petition or the granting of a request for an exemption from regulation as a food additive under § 170.39 of this chapter for a substance registered by the Environmental Protection Agency under FIFRA for the same use requested in the petition.

(r) Approval of a food additive, color additive, or GRAS affirmation petition for a substance that occurs naturally in the environment, when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

§ 25.33 Animal drugs.

The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:

(a) Action on an NADA, abbreviated application, or a supplement to such applications, if the action does not increase the use of the drug. Actions to which this categorical exclusion applies may include:

(1) An animal drug to be marketed under the same conditions of approval as a previously approved animal drug;

(2) A combination of previously approved animal drugs;

(3) A new premix or other formulation of a previously approved animal drug;

(4) Changes specified in § 514.8 (a)(5), (a)(6), or (d) of this chapter;

(5) A change of sponsor;

(6) A previously approved animal drug to be contained in medicated feed blocks under § 510.455 of this chapter or as a liquid feed supplement under § 558.5 of this chapter; or

(7) Approval of a drug for use in animal feeds if such drug has been approved under § 514.2 or 514.9 of this chapter for other uses.

(b) [Reserved]

(c) Action on an NADA, abbreviated application, or a supplement to such applications, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

(d) Action on an NADA, abbreviated application, or a supplement to such applications, for:

(1) Drugs intended for use in nonfood animals;

(2) Anesthetics, both local and general, that are individually administered;

(3) Nonsystemic topical and ophthalmic animal drugs;

(4) Drugs for minor species, including wildlife and endangered species, when

the drug has been previously approved for use in another or the same species where similar animal management practices are used; and

(5) Drugs intended for use under prescription or veterinarian's order for therapeutic use in terrestrial species.

(e) Action on an INAD.

(f) Action on an application submitted under section 512(m) of the act.

(g) Withdrawal of approval of an NADA or an abbreviated NADA.

(h) Withdrawal of approval of a food additive petition that reduces or eliminates animal feed uses of a food additive.

§ 25.34 Devices and electronic products.

The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:

(a) Action on a device premarket notification submission under subpart E of part 807 of this chapter.

(b) Classification or reclassification of a device under part 860 of this chapter.

(c) Issuance, amendment, or repeal of a standard for a class II medical device or an electronic product, and issuance of exemptions or variances from such a standard.

(d) Approval of a PMA or a notice of completion of a PDP or amended or supplemental applications or notices for a class III medical device if the device is of the same type and for the same use as a previously approved device.

(e) Changes in the PMA or a notice of completion of a PDP for a class III medical device that do not require submission of an amended or supplemental application or notice.

(f) Issuance of a restricted device regulation if it will not result in increases in the existing levels of use or changes in the intended uses of the product or its substitutes.

(g) Action on an application for an IDE or an authorization to commence a clinical investigation under an approved PDP.

(h) Issuance of a regulation exempting from preemption a requirement of a State or political subdivision concerning a device, or a denial of an application for such exemption.

Subpart D—Preparation of Environmental Documents

§ 25.40 Environmental assessments.

(a) As defined by CEQ in 40 CFR 1508.9, an EA is a concise public document that serves to provide sufficient evidence and analysis for an agency to determine whether to prepare an EIS or a FONSI. The EA shall include brief discussions of the need for the

proposal, of alternatives as required by section 102(2)(E) of NEPA, of the environmental impacts of the proposed action and alternatives, and a listing of agencies and persons consulted. An EA shall be prepared for each action not categorically excluded in §§ 25.30, 25.31, 25.32, 25.33, or 25.34. The EA shall focus on relevant environmental issues relating to the use and disposal from use of FDA-regulated articles and shall be a concise, objective, and well-balanced document that allows the public to understand the agency's decision. If potentially adverse environmental impacts are identified for an action or a group of related actions, the EA shall discuss any reasonable alternative course of action that offers less environmental risk or that is environmentally preferable to the proposed action. The use of a scientifically justified tiered testing approach, in which testing may be stopped when the results suggest that no significant impact will occur, is an acceptable approach.

(b) Generally, FDA requires an applicant to prepare an EA and make necessary corrections to it. Ultimately, FDA is responsible for the scope and content of EA's and may include additional information in environmental documents when warranted.

(c) Information concerning the nature and scope of information that an applicant or petitioner shall submit in an EA may be obtained from the center or other office of the agency having responsibility for the action that is the subject of the environmental evaluation. Applicants and petitioners are encouraged to submit proposed protocols for environmental studies for technical review by agency staff. Applicants and petitioners also are encouraged to consult applicable FDA EA guidance documents, which provide additional advice on how to comply with FDA regulations.

(d) Consistent with 40 CFR 1500.4(j) and 1502.21, EA's may incorporate by reference information presented in other documents that are available to FDA and to the public.

(e) The agency evaluates the information contained in an EA and any public input to determine whether it is accurate and objective, whether the proposed action may significantly affect the quality of the human environment, and whether an EIS or a FONSI will be prepared. The responsible agency official designated in part 5 of this chapter as responsible for the underlying action examines the environmental risks of the proposed action and the alternative courses of action, selects a course of action, and

ensures that any necessary mitigating measures are implemented as a condition for approving the selected course of action.

§ 25.41 Findings of no significant impact.

(a) As defined by the CEQ regulations (40 CFR 1508.13), a FONSI is a document prepared by a Federal agency stating briefly why an action, not otherwise excluded, will not significantly affect the human environment and for which, therefore, an EIS will not be prepared. A FONSI includes the EA or a summary of it and a reference to any other related environmental documents.

(b) The agency official(s) responsible for approving the FONSI will sign the document, thereby establishing that the official(s) approve(s) the conclusion not to prepare an EIS for the action under consideration.

§ 25.42 Environmental impact statements.

(a) As defined by CEQ regulations (40 CFR 1508.11) and section 102(2)(C) of NEPA, an EIS should be a clear, concise, and detailed written statement describing:

- (1) The environmental impacts of a proposed action;
- (2) Any adverse effects that cannot be avoided if the action is implemented;
- (3) Alternatives to the action;
- (4) The relationship between local short-term uses of the environment and the maintenance and enhancement of long-term productivity; and
- (5) Any irreversible and irretrievable commitments of resources that would be involved in the proposed action should it be implemented.

(b) The CEQ regulations (40 CFR 1501.7 and part 1502) describe the process for determining the scope of an EIS and provide detailed requirements for the preparation of draft and final EIS's. CEQ format and procedures for preparing EIS shall be followed.

(c) Under the conditions prescribed in 40 CFR 1502.9, the agency will prepare a supplement for a draft or final EIS and introduce the supplement into the administrative record.

§ 25.43 Records of decision.

(a) In cases requiring environmental impact statements, at the time of its decision, the agency shall prepare a concise public record of decision.

(b) The record of decision shall:

- (1) State what the decision was;
- (2) Identify and discuss alternatives considered by the agency in reaching its decision;

(3) State whether all practicable means to avoid or minimize environmental harm have been adopted, and if not, why not; and

(4) Summarize the program for monitoring and enforcing the practicable means adopted to avoid or minimize the environmental harm.

§ 25.44 Lead and cooperating agencies.

For actions requiring the preparation of an EIS, FDA and other affected Federal agencies will agree which will be the lead agency and which will be the cooperating agencies. The responsibilities of lead agencies and cooperating agencies are described in the CEQ regulations (40 CFR 1501.5 and 1501.6, respectively). If an action affects more than one center within FDA, the Commissioner of Food and Drugs will designate one of these units to be responsible for coordinating the preparation of any required environmental documentation.

§ 25.45 Responsible agency official.

(a) The person designated in part 5 of this chapter as the responsible agency official for the underlying action is responsible for preparing environmental documents or ensuring that they are prepared.

(b) The responsible agency official will weigh any environmental impacts of each alternative course of action, including possible mitigation measures, and will balance environmental impacts with the agency's objectives in choosing an appropriate course of action. The weighing of any environmental impacts of alternatives in selecting a final course of action will be reflected in the agency's record of formal decisionmaking as required by 40 CFR 1505.2.

Subpart E—Public Participation and Notification of Environmental Documents

§ 25.50 General information.

(a) To the extent actions are not protected from disclosure by existing law applicable to the agency's operation, FDA will involve the public in preparing and implementing its NEPA procedures and will provide public notice of NEPA-related hearings, public meetings, and the availability of environmental documents.

(b) Many FDA actions involving investigations, review, and approval of applications, and premarket notifications for human drugs, animal drugs, biologic products, and devices are protected from disclosure under the Trade Secret Act, 18 U.S.C. 1905, and 301(j) of the act. These actions are also protected from disclosure under FDA's regulations including part 20, §§ 312.130(a), 314.430(b), 514.11(b), 514.12(a), 601.50(a), 601.51(a),

807.95(b), 812.38(a), and 814.9(b) of this chapter. Even the existence of applications for human drugs, animal drugs, biologic products, and devices is protected from disclosure under these regulations. Therefore, unless the existence of applications for human drugs, animal drugs, biologic products, or premarket notification for devices has been made publicly available, the release of the environmental document before approval of human drugs, animal drugs, biologic products, and devices is inconsistent with statutory requirements imposed on FDA. Appropriate environmental documents, comments, and responses will be included in the administrative record to the extent allowed by applicable laws.

§ 25.51 Environmental assessments and findings of no significant impact.

(a) Data and information that are protected from disclosure by 18 U.S.C. 1905 or 21 U.S.C. 331(j) or 360j(c) shall not be included in the portion of environmental documents that is made public. When such data and information are pertinent to the environmental review of a proposed action, an applicant or petitioner shall submit such data and information separately in a confidential section and shall summarize the confidential data and information in the EA to the extent possible.

(b) FONSI's and EA's will be available to the public in accordance with 40 CFR 1506.6 as follows:

(1) When the proposed action is the subject of a notice of proposed rulemaking or a notice of filing published in the **Federal Register**, the notice shall state that no EIS is necessary and that the FONSI and the EA are available for public inspection at FDA's Dockets Management Branch. If the responsible agency official is unable to complete environmental consideration of the proposed action before a notice of filing of a food or color additive petition is required to be published under the act, and if the subsequent environmental analysis leads to the conclusion that no EIS is necessary, the final regulation rather than the notice of filing shall state that no EIS is necessary and that the FONSI and the EA are available upon request and filed in FDA's Dockets Management Branch.

(2) For actions for which notice is not published in the **Federal Register**, the FONSI and the EA shall be made available to the public upon request according to the procedures in 40 CFR 1506.6.

(3) For a limited number of actions, the agency may make the FONSI and EA

available for public review (including review by State and areawide information clearinghouses) for 30 days before the agency makes its final determination whether to prepare an EIS and before the action may begin, as described in 40 CFR 1501.4(e). This procedure will be followed when the proposed action is, or is closely similar to, one that normally requires an EIS or when the proposed action is one without precedent.

§ 25.52 Environmental impact statements.

(a) If FDA determines that an EIS is necessary for an action involving investigations or approvals for drugs, animal drugs, biologic products, or devices, an EIS will be prepared but will become available only at the time of the approval of the product. Disclosure will be made in accordance with 40 CFR 1506.6 and part 20 of this chapter. The EIS will in all other respects conform to the requirements for EIS's as specified in 40 CFR part 1502 and 1506.6(f).

(b) Comments on the EIS may be submitted after the approval of the drug, animal drug, biologic product, or device. Those comments can form the basis for the agency to consider beginning an action to withdraw the approval of applications for a drug, animal drug, or biologic product, or to withdraw premarket notifications or premarket approval applications for devices.

(c) In those cases where the existence of applications and premarket notifications for drugs, animal drugs, biologic products, or devices has already been disclosed before the agency approves the action, the agency will make diligent effort (40 CFR 1506.6) to involve the public in preparing and implementing the NEPA procedures for EIS's while following its own disclosure requirements including those listed in part 20, §§ 312.130(b), 314.430(d), 514.11(d), 514.12(b), 601.51(d), 807.95(e), 812.38(b), and 814.9(d) of this chapter.

(d) Draft and final EIS's, comments, and responses will be included in the administrative record and will be available from the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

Subpart F—Other Requirements

§ 25.60 Environmental effects abroad of major agency actions.

(a) In accordance with Executive Order 12114, "Environmental Effects Abroad of Major Federal Actions" of January 4, 1979 (44 FR 1957, January 9, 1979), the responsible agency official, in

analyzing actions under his or her program, shall consider the environmental effects abroad, including whether the actions involve:

(1) Potential environmental effects on the global commons and areas outside the jurisdiction of any nation, e.g., oceans and the upper atmosphere.

(2) Potential environmental effects on a foreign nation not participating with or otherwise involved in an FDA activity.

(3) The export of products (or emissions) that in the United States are prohibited or strictly regulated because their effects on the environment create a serious public health risk.

(4) Potential environmental effects on natural and ecological resources of global importance designated under the Executive Order.

(b) Before deciding on any action falling into the categories specified in paragraph (a) of this section, the responsible agency official shall determine, in accordance with section 2-3 of the Executive Order, whether such actions may have a significant environmental effect abroad.

(c) If the responsible agency official determines that an action may have a significant environmental effect abroad, the responsible agency official shall determine, in accordance with section 2-4(a) and (b) of the Executive Order, whether the subject action calls for:

- (1) An EIS;
- (2) A bilateral or multilateral environmental study; or
- (3) A concise environmental review.

(d) In preparing environmental documents under this subpart, the responsible official shall:

(1) Determine, as provided in section 2-5 of the Executive Order, whether proposed actions are subject to the exemptions, exclusions, and modification in contents, timing, and availability of documents.

(2) Coordinate all communications with foreign governments concerning environmental agreements and other arrangements in implementing the Executive Order.

PART 71—COLOR ADDITIVE PETITIONS

7. The authority citation for 21 CFR part 71 continues to read as follows:

Authority: Secs. 201, 402, 409, 501, 505, 506, 507, 510, 512-516, 518-520, 601, 701, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 342, 348, 351, 355, 356, 357, 360, 360b-360f, 360h-360j, 361, 371, 379e, 381); secs. 215, 351 of the Public Health Service Act (42 U.S.C. 216, 262).

8. Section 71.1 is amended in paragraph (c) by revising item J to read as follows:

§ 71.1 Petitions.

* * * * *

(c) * * *

J. The petitioner is required to submit either a claim for categorical exclusion under § 25.30 or 25.32 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

PART 101—FOOD LABELING

9. The authority citation for 21 CFR part 101 continues to read as follows:

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 371).

10. Section 101.12 is amended by revising paragraph (h)(12) to read as follows:

§ 101.12 Reference amounts customarily consumed per eating occasion.

* * * * *

(h) * * *

(12) A claim for categorical exclusion under § 25.30 or 25.32 of this chapter or an environmental assessment under § 25.40 of this chapter; and

* * * * *

11. Section 101.69 is amended by revising paragraph (h), item E of paragraph (m)(1), item C of paragraph (n)(1), and item C of paragraph (o)(1) to read as follows:

§ 101.69 Petitions for nutrient content claims.

* * * * *

(h) All petitions submitted under this section shall include either a claim for a categorical exclusion under § 25.30 or 25.32 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

(m) * * *

(1) * * *

E. The petitioner is required to submit either a claim for categorical exclusion under § 25.30 or § 25.32 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

(n) * * *

(1) * * *

C. The petitioner is required to submit either a claim for categorical exclusion under § 25.30 or § 25.32 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

(o) * * *

(1) * * *

C. The petitioner is required to submit either a claim for categorical exclusion under § 25.30 or § 25.32 of this chapter or an environmental assessment under § 25.40 of this chapter.

12. Section 101.70 is amended in paragraph (f) by revising item F to read as follows:

§ 101.70 Petitions for health claims.

* * * * *

(f) * * *

F. The petitioner is required to submit either a claim for categorical exclusion under § 25.30 or § 25.32 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

PART 170—FOOD ADDITIVES

13. The authority citation for 21 CFR part 170 continues to read as follows:

Authority: Secs. 201, 401, 402, 408, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 341, 342, 346a, 348, 371).

14. Section 170.35 is amended by revising paragraph (c)(1)(viii) to read as follows:

§ 170.35 Affirmation of generally recognized as safe (GRAS) status.

* * * * *

(c) * * *

(1) * * *

(viii) A claim for categorical exclusion under § 25.30 or § 25.32 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

15. Section 170.39 is amended by revising the second sentence in paragraph (c)(6) and the seventh sentence in paragraph (e) to read as follows:

§ 170.39 Threshold of regulation for substances used in food-contact articles.

* * * * *

(c) * * *

(6) * * * The request should contain either a claim for categorical exclusion as specified in § 25.32 of this chapter or an environmental assessment as specified in § 25.40 of this chapter.

* * * * *

(e) * * * For actions requiring an environmental assessment, the agency's finding of no significant impact and the evidence supporting that finding, contained in the petitioner's environmental assessment, also will be available for public inspection at the Dockets Management Branch in accordance with § 25.51(b)(2) of this chapter.

* * * * *

PART 171—FOOD ADDITIVE PETITIONS

16. The authority citation for 21 CFR part 171 continues to read as follows:

Authority: Secs. 201, 402, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 342, 348, 371).

17. Section 171.1 is amended in paragraph (c) by revising item H to read as follows:

§ 171.1 Petitions.

* * * * *

(c) * * *

H. The petitioner is required to submit either a claim for categorical exclusion under § 25.30 or § 25.32 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

18. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec. 351 of the Public Health Service Act (42 U.S.C. 262).

19. Section 312.23 is amended by revising paragraph (a)(7)(iv)(e) to read as follows:

§ 312.23 IND content and format.

(a) * * *

(7) * * *

(iv) * * *

(E) Environmental analysis requirements. A claim for categorical exclusion under § 25.30 or 25.31 or an environmental assessment under § 25.40.

* * * * *

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

20. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

21. Section 314.50 is amended by revising paragraph (d)(1)(iii) to read as follows:

§ 314.50 Content and format of an application.

* * * * *

(d) * * *

(1) * * *

(iii) Environmental impact. The application is required to contain either

a claim for categorical exclusion under § 25.30 or 25.31 of this chapter or an environmental assessment under § 25.40 of this chapter.

22. Section 314.101 is amended by revising paragraph (d)(4) to read as follows:

§ 314.101 Filing an application and an abbreviated antibiotic application and receiving an abbreviated new drug application.

* * * * *

(d) * * *

(4) The applicant fails to submit a complete environmental assessment, which addresses each of the items specified in the applicable format under § 25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.30 or § 25.31 of this chapter.

* * * * *

PART 511—NEW ANIMAL DRUGS FOR INVESTIGATIONAL USE

23. The authority citation for 21 CFR part 511 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 512, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 360b, 371).

24. Section 511.1 is amended by revising paragraph (b)(10) to read as follows:

§ 511.1 New animal drugs for investigational use exempt from section 512(a) of the act.

* * * * *

(b) * * *

(10) The sponsor shall submit either a claim for categorical exclusion under § 25.30 or § 25.33 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

PART 514—NEW ANIMAL DRUG APPLICATIONS

25. The authority citation for 21 CFR part 514 continues to read as follows:

Authority: Secs. 501, 502, 512, 701, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 352, 360b, 371, 379e, 381).

26. Section 514.1 is amended by revising paragraph (b)(14) to read as follows:

§ 514.1 Applications.

* * * * *

(b) * * *

(14) Environmental assessment. The applicant is required to submit either a claim for categorical exclusion under § 25.30 or § 25.33 of this chapter or an

environmental assessment under § 25.40 of this chapter.

* * * * *

27. Section 514.8 is amended by revising the fourth sentence of paragraph (a)(1) to read as follows:

§ 514.8 Supplemental new animal drug applications.

(a)(1) * * * A supplemental application shall be accompanied by either a claim for categorical exclusion under § 25.30 or § 25.33 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

28. Section 514.110 is amended by revising paragraph (b)(10) to read as follows:

§ 514.110 Reasons for refusing to file applications.

* * * * *

(b) * * *

(10) The applicant fails to submit a complete environmental assessment under § 25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.30 or § 25.33 of this chapter.

* * * * *

29. Section 514.111 is amended by revising paragraph (a)(9) to read as follows:

§ 514.111 Refusal to approve an application.

(a) * * *

(9) The applicant fails to submit an adequate environmental assessment under § 25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.30 or § 25.33 of this chapter.

* * * * *

PART 570—FOOD ADDITIVES

30. The authority citation for 21 CFR part 570 continues to read as follows:

Authority: Secs. 201, 401, 402, 408, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 341, 342, 346a, 348, 371).

31. Section 570.35 is amended by revising paragraph (c)(1)(viii) to read as follows:

§ 570.35 Affirmation of generally recognized as safe (GRAS) status.

* * * * *

(c) * * *

(viii) A claim for categorical exclusion under § 25.30 or 25.32 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

PART 571—FOOD ADDITIVE PETITIONS

32. The authority citation for 21 CFR part 571 continues to read as follows:

Authority: Secs. 201, 402, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 342, 348, 371); sec. 301 of the Public Health Service Act (42 U.S.C. 241).

33. Section 571.1 is amended in paragraph (c) by revising item H to read as follows:

§ 571.1 Petitions.

* * * * *

(c) * * *

H. The petitioner is required to submit either a claim for categorical exclusion under § 25.30 or § 25.32 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

PART 601—LICENSING

34. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381); secs. 215, 301, 351, 352 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461).

35. Section 601.2 is amended by revising the third sentence in paragraph (a) and the second sentence in paragraph (c)(2) to read as follows:

§ 601.2 Applications for establishment and product licenses; procedures for filing.

(a) * * * The applicant shall also include either a claim for categorical exclusion under § 25.30 or 25.31 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

(c) * * *

(2) * * * The applicant shall also include either a claim for categorical exclusion under § 25.30 or 25.31 of this chapter or an environmental assessment under § 25.40 of this chapter.

* * * * *

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

36. The authority citation for 21 CFR part 812 continues to read as follows:

Authority: Secs. 301, 501, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701, 702, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331, 351, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371, 372, 374, 379e, 381); secs. 215, 301, 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b–263n).

37. Section 812.20 is amended by revising paragraph (b)(9) to read as follows:

§ 812.20 Application.

* * * * *

(b) * * *

(9) A claim for categorical exclusion under § 25.30 or 25.34 or an environmental assessment under § 25.40.

* * * * *

PART 814—PREMARKET APPROVAL OF MEDICAL DEVICES

38. The authority citation for 21 CFR part 814 continues to read as follows:

Authority: Secs. 501, 502, 503, 510, 513–520, 701, 702, 703, 704, 705, 721, 708, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 352, 353, 360, 360c–360j, 371, 372, 373, 374, 375, 379e, 381).

39. Section 814.20 is amended by revising paragraph (b)(11) to read as follows:

§ 814.20 Application.

* * * * *

(b) * * *

(11) An environmental assessment under § 25.20(n) prepared in the applicable format in § 25.40, unless the action qualifies for exclusion under § 25.30 or § 25.34. If the applicant believes that the action qualifies for exclusion, the PMA shall under § 25.15(a) and (d) provide information that establishes to FDA's satisfaction that the action requested is included within the excluded category and meets the criteria for the applicable exclusion.

* * * * *

Dated: May 9, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

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