Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products

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Guidance for Industry

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This guidance represents the Food and Drug Administration's (FDA's or Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance using the contact information on the title page of this guidance.

I. INTRODUCTION

We, FDA, are issuing this guidance to provide you, investigational new drug application (IND) sponsors and applicants for a biologics license application (BLA) or a supplement to a BLA (BLA supplement), with recommendations on considerations when assessing whether to submit an Environmental Assessment (EA) for gene therapies, vectored vaccines, and related recombinant viral or microbial products (GTVVs).[1] This guidance also contains recommendations as to what information should be included in an EA and what you can expect once an EA is filed. This guidance finalizes the draft guidance of the same title dated June 2014. This guidance also supplements the guidance entitled "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications" dated July 1998, (July 27, 1998, 63 FR 40127) (1998 Guidance) and supersedes the recommendations for GTVVs in section IV.B.1 "Assessing Toxicity to Environmental Organisms" in the 1998 Guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Cellular, Tissue and Gene Therapies (OCTGT) in FDA's Center for Biologics Evaluation and Research (CBER) in consultation with the Office of Vaccines Research and Review (OVRR), CBER. Both OCTGT and OVRR review the IND submissions and BLA applications or supplements for GTVVs.

II. BACKGROUND

The National Environmental Policy Act of 1969 (NEPA) (42 U.S.C. § 4321, et. seq.) requires all federal agencies to assess the environmental impacts of their actions and to ensure that the interested and affected public is informed of the environmental analyses. The Council on Environmental Quality (CEQ) is responsible for overseeing federal efforts to comply with NEPA. The CEQ regulations, which are binding on FDA, establish procedures for implementing NEPA and can be found under Title 40 of the Code of Federal Regulations (CFR) Parts 1500 through 1508.

FDA has adopted procedures to supplement the CEQ regulations. FDA's NEPA policies and procedures can be found under 21 CFR Part 25. These regulations specify that all applications requesting agency action (e.g., INDs, BLAs, and supplements to BLAs) must be accompanied by either an EA or a claim of categorical exclusion (21 CFR 25.15(a)).

In 1997, FDA amended its NEPA regulations to, among other things, increase the efficiency of the Agency's implementation of NEPA and to reduce the number of NEPA evaluations by providing for categorical exclusions for additional classes of actions that had been identified as normally not having a significant impact, individually or cumulatively, on the quality of the environment and for which, therefore, neither an environmental impact statement (EIS) nor an EA is required.[2] Note that the 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 environment (21 CFR 25.21 and 25.31).

Failure to submit an adequate EA for an application requesting action by the agency, unless the Agency can determine that the requested action qualifies for categorical exclusion, is sufficient grounds for FDA to refuse to file an application or to withhold approval for an application (21 CFR 25.15(a)). The Agency evaluates the information contained in an EA to determine whether the preparation of an EIS is necessary (21 CFR 25.15(b)). If the proposed action will not significantly affect the quality of the environment, then the Agency will instead prepare a finding of no significant impact (FONSI) (21 CFR 25.15(b)).

III. SCOPE

This guidance describes what to consider when determining whether you are required to submit an EA for your IND, BLA, or BLA supplement for a GTVV, or whether your submission qualifies for categorical exclusion under 21 CFR 25.31. Additionally, for those INDs, BLAs, or BLA supplements for GTVVs for which an EA is required, this guidance provides information on the content and format of the EA submission. The EA should focus on relevant environmental issues relating to the FDA-regulated article. FDA considers the environmental impacts of its actions as an integral part of its regulatory process and the effects of FDA-

[2] National Environmental Policy Act; Revision of Policies and Procedures, (Final Rule) (62 FR 40570, July 29, 1997).

regulated products on humans and public health are routinely assessed by the Agency during the review process under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHS Act) and therefore, do not need to be addressed in an EA.[3]

Note that CBER does not take action on Master Files (MFs) (i.e., it does not approve or disapprove submissions to a MF). Therefore, NEPA does not apply to MFs, and neither an EA nor a claim of categorical exclusion need be submitted for a MF. However, if an EA is required to be submitted for a particular IND, BLA, or BLA supplement, certain information that is included in a MF may be needed to address the relevant environmental issue(s).[4] Additionally, FDA may consider information that is included in a MF in the context of determining whether a particular IND, BLA, or BLA supplement qualifies for categorical exclusion.

The scope of this guidance includes EA considerations (i.e., whether or not an EA is required to be submitted) for INDs, BLAs, and BLA supplements for gene therapies[5] and vectored vaccines for infectious disease indications.[6] This guidance also includes EA considerations for INDs, BLAs, and BLA supplements for related viruses and microbes that were generated using recombinant DNA technology (e.g., a virus/microbe with an attenuation created by a point mutation or gene deletion). EA considerations for INDs, BLAs, and BLA supplements for live-attenuated viral or microbial vaccines created by traditional methods such as serial passaging and recombinant protein based vaccines are not within the scope of this guidance.

IV. HOW DO YOU DECIDE WHETHER AN EA IS NEEDED?

All applications requesting agency action (e.g., INDs, and BLAs) must be accompanied by either an EA or a claim of categorical exclusion (21 CFR 25.15(a)). As discussed above, certain classes of actions are subject to categorical exclusion and, therefore, ordinarily do not require the

[3] Although actions that affect public health or safety are recognized to have the potential to significantly affect the quality of the human environment (40 CFR 1508.27(b)(2), 40 CFR 1508.8(b)), NEPA's authority is intended to supplement other statutory responsibilities of the agency, such as those under the FD&C Act and PHS Act. Note that under the regulations implementing NEPA (40 CFR Part 1500), the term "human environment" must be interpreted comprehensively to include the natural and physical environment and the relationship of people with that environment (40 CFR 1508.14) (see also the definition of "effects" in 40 CFR 1508.8).

[4] For more information on how an EA should reference information in a MF, see section IV.F of 1998 Guidance.

[5] Gene therapies are defined in the FDA guidance document entitled, "Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events" dated November 2006 as "[p]roducts that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells in vivo or transferred to cells ex vivo prior to administration to the recipient." This guidance is available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm.

[6] For purposes of this guidance, a vectored vaccine is one that uses a virus or microbe (typically a bacterium), or a DNA plasmid to introduce DNA/RNA encoding for antigens to cells of the body. "Vector" refers to the virus, microbe, or DNA plasmid used as the carrier.

preparation of an EA because, as a class, the Agency has determined that these actions, individually or cumulatively, do not significantly affect the quality of the environment (21 CFR 25.15(c)). Examples of submissions that are ordinarily categorically excluded include the following:

1. BLAs and BLA supplements, if FDA's action on the submission does not increase the use of the active moiety (21 CFR 25.31(a)).
2. BLAs and BLA supplements for substances that occur naturally in the environment when FDA's action on the submission does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment (21 CFR 25.31(c)).
3. INDs (21 CFR 25.31(e)).

For submissions that are subject to categorical exclusion under 21 CFR 25.31, you are not required to submit an EA if you state that the action requested (e.g., action on an IND or BLA) qualifies for categorical exclusion, cite the particular categorical exclusion that is claimed, and state that to your knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)). Ordinarily, you do not need to provide data to support a claim that the action requested qualifies for categorical exclusion. However, the Agency will request additional data if needed to establish to its satisfaction that the criteria for categorical exclusion have been met. As discussed in more detail below, if the Agency concludes that a product is not categorically excluded because of an extraordinary circumstance, you will need to submit an EA (21 CFR 25.21).

A. IND Applications

A request for agency action on an IND is ordinarily categorically excluded from the requirement to submit an EA (21 CFR 25.31(e)), unless extraordinary circumstances indicate that the specific proposed agency action may significantly affect the quality of the environment (see 21 CFR 25.21 and section IV.C. of this document). FDA believes that, in most cases, agency action on an IND for a clinical study using a GTVV will not significantly affect the quality of the environment because, in brief, these clinical trials are closely monitored and are limited to a designated study group.[7] However, if there are extraordinary circumstances that indicate that agency action on an IND may significantly affect the quality of the environment, then the categorical exclusion will not apply and the Agency will require preparation and submission of an EA (21 CFR 25.21).

[7] Note that this has consistently been the Agency's experience. For example, in the preamble to the Final Rule, FDA stated in relevant part, "…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."(62 FR 40570 at 40578) In addition, the preamble to the Final Rule went on to state, "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." Id. at 40579.

A sponsor wishing to claim a categorical exclusion for a request for agency action on an IND must include a claim in the environmental analysis section (21 CFR 312.23(a)(7)(iv)(e)) of the IND application. In the claim for categorical exclusion, a sponsor must state that the action requested qualifies for a categorical exclusion, cite the particular categorical exclusion that is claimed, and state that to his/her knowledge no extraordinary circumstances exist (21 CFR 25.15(d)). To comply, we recommend that the following statement be included in the environmental analysis section of the IND:

> *We are claiming a categorical exclusion under 21 CFR 25.31(e), and therefore have not prepared an environmental assessment. The agency action we are requesting complies with the categorical exclusion criteria. Furthermore, we are not aware of any extraordinary circumstances that would require the preparation of an environmental assessment.*

B. Licensing Applications

Section 25.31(c) provides a categorical exclusion for FDA approval of a BLA for substances that "occur naturally in the environment when FDA's action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment."[8]

1. Applications for GTVVs that FDA does not consider "occur[ring] naturally in the environment" for purposes of 21 CFR 25.31(c).

   In determining whether a GTVV is a substance that "occur[s] naturally in the environment" for purposes of 21 CFR 25.31(c), FDA considers whether or not the GTVV includes functional protein-coding sequences from a different genus. Specifically, a GTVV that includes functional protein-coding sequences from a genus that is different from the organism that is expressing the sequences is not considered to "occur naturally in the environment" under 21 CFR 25.31(c). In contrast, a GTVV that includes functional protein-coding sequences from one or more species within a single genus is considered to "occur naturally in the environment" under the regulation.[9] Accordingly, FDA considers most GTVVs to be substances that do not "occur naturally in the environment" because most GTVVs include functional protein-coding sequences from a different genus. Therefore, applications requesting agency action for GTVVs that

[8] BLAs may also be eligible for categorical exclusion under 21 CFR 25.31(a).

[9] This regulatory interpretation of "occur naturally in the environment" is informed, in part, by the definition of "new organism" in the 1986 "Coordinated Framework for Regulation of Biotechnology" issued by the Executive Office of the President, Office of Science and Technology Policy (OSTP Notice). The OSTP Notice defines "new organism" to mean an organism that is "deliberately formed to contain an intergeneric combination of genetic material; excluded are those that have resulted from the addition of intergeneric materials that is [sic] well-characterized and contains only non-coding regulatory regions such as operators, promoters, origins of replication, terminators and ribosome binding regions." See "Coordinated Framework for Regulation of Biotechnology," 51 FR 23302 (June 26, 1986).

are engineered to express one or more proteins from a different genus should include an EA because FDA would not consider the criteria for a claim of categorical exclusion to be met (See 21 CFR 25.15 and 25.31(c)). Examples of such GTVVs include a plasmid vaccine expressing a viral envelope protein, or a viral vector expressing a human enzyme.

2. Applications for GTVVs that are generally considered to "occur naturally in the environment" for purposes of 21 CFR 25.31(c).

FDA generally considers GTVVs that fall into the categories described under sections a. and d. below to be substances that are "occur naturally in the environment" for purposes of 21 CFR 25.31(c). Accordingly, applications for such GTVVs may be eligible for a categorical exclusion under 21 CFR 25.31(c). To claim a categorical exclusion under 21 CFR 25.31(c) and comply with the general provisions for filing a BLA, we recommend that the following statement be included in the environmental analysis section of the licensing application:

> *We are claiming a categorical exclusion under 21 CFR 25.31(c) from the need to prepare an environmental assessment. The agency action we are requesting complies with the categorical exclusion criteria. Furthermore, we are not aware of any extraordinary circumstances that would require the preparation of an environmental assessment.*

a. FDA generally considers GTVVs that contain functional protein-coding sequences from one or more species within a *single* genus to "occur naturally in the environment" for purposes of 21 CFR 25.31(c).[10] For example, reassortant viruses involving combinations of genetic material from more than one species within the same genus could be eligible for the 21 CFR 25.31(c) categorical exclusion. Such reassortant viruses are typically considered naturally occurring as long as they do not contain sequences from more than one genus, regardless of whether they were created by traditional co-infection methods or using recombinant DNA technology.

b. FDA generally considers GTVVs that differ from a wild-type substance only in attenuating point mutations or deletions to be substances that "occur naturally in the environment" for purposes of 21 CFR 25.31(c) because such mutations can occur

[10] See footnote 9, *supra*.

as natural variants during replication/propagation.[11] Reasons for introducing these changes to a wild-type substance may include the following:

- To reduce virulence.
- To restrict the ability of the product to replicate in humans (i.e., inhibit virion assembly by altering the structural elements of the virus particle).

c. FDA generally considers GTVVs that have been killed or inactivated by undergoing a specific manufacturing step designed to eliminate their ability to replicate to be substances that "occur naturally in the environment" because they are not viable and are degraded into substances that occur naturally in the environment.[12]

There are a number of methods for inactivating biological products that preserve functionality (e.g., a formaldehyde inactivated virus preparation may retain sufficient immunogenicity for use as a vaccine). In these situations, to demonstrate that your product should be considered to "occur naturally in the environment" under 21 CFR 25.31(c), you should demonstrate that the product is inactivated and unable to replicate through process validation and/or lot release testing and maintained through effective quality control procedures. The Agency will carefully review these methods for compliance with good manufacturing practices.

d. FDA generally considers GTVVs that consist of genetically-modified human cells to be substances that "occur naturally in the environment" for purposes of 21 CFR 25.31(c) because these cells have stringent nutritional requirements for survival and replication and are therefore not viable in the environment and are degraded into naturally occurring substances.

C. Extraordinary Circumstances

As provided in 21 CFR 25.21 and 40 CFR 1508.4, FDA will require an EA for an action that would ordinarily be categorically excluded if extraordinary circumstances exist that may "significantly"[13] affect the quality of the environment (21 CFR 25.21).

[11] For similar reasons, FDA has long considered live-attenuated viral or bacterial vaccines created by traditional methods such as serial passaging to "occur naturally in the environment" for purposes of 21 CFR 25.31(c).
[12] This is consistent with the text in the preamble to the Final Rule, which stated "Living and dead cells and organisms regulated by the agency may also be considered for categorical exclusion under this provision [proposed 21 CFR 25.31(c)] if the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment." (62 FR 40570 at 40578).
[13] The term "significantly" is defined under 40 CFR 1508.27.

Extraordinary circumstances may exist at both the investigational and marketing phases; however, the Agency anticipates that relatively few submissions for GTVVs will present extraordinary circumstances that may significantly affect the quality of the environment at either the investigational or the marketing phase.

In assessing whether your GTVV product presents extraordinary circumstances that may "significantly" affect the quality of the environment, CBER recommends that you focus on the following elements of the "significantly" definition (40 CFR 1508.27), which have the greatest potential to apply:

1. The degree to which the effects of the GTVV on the quality of the environment are likely to be highly controversial (40 CFR 1508.27(b)(4)).

2. The degree to which the possible effects of the GTVV on the human environment are highly uncertain or involve unique or unknown risks (40 CFR 1508.27(b)(5)).

3. The degree to which the GTVV may adversely affect an endangered or threatened species or its habitat that has been determined to be critical under the Endangered Species Act of 1973 (40 CFR 1508.27(b)(9)).

4. Whether the effects of the GTVV on the environment threaten a violation of Federal, State, or local law or requirements imposed for the protection of the environment (40 CFR 1508.27(b)(10)).

V. WHAT INFORMATION SHOULD BE INCLUDED IN YOUR EA?

The format of EA submissions for INDs, BLAs, and BLA supplements for GTVVs should follow the 1998 Guidance, as well as provide the additional information recommended below in this guidance for the following four sections: "Identification of Substances Subject to Proposed Action"; "Identifying and Assessing Potential Environmental Effects"; "Mitigation Measures"; and "Alternatives to the Proposed Action."

A. Identification of Substances Subject to the Proposed Action

We recommend that EAs for GTVVs include a description of substances subject to the proposed action and a description of the potential metabolites, degradants, or byproducts released into the environment.

If a product becomes degraded after administration, the environmental effects identified in section V.B. of this document might include only those related to the degradation products released. For example, in the case of a replication-deficient viral vector administered by intramuscular injection, data to demonstrate the release of vector DNA

into the environment (detectable by PCR at the injection site and/or in excreta), and the absence of release of intact virus (detectable by infectivity assays), may justify consideration of the environmental effects of only vector DNA in the EA.

You should also identify known and potential variants of the GTVVs released into the environment. We recommend that you submit experimental data to characterize theoretical or observed variants that have greater potential environmental risk than the GTVV. For example, GTVVs may be designed to be replication defective and yet a low level of replication competent product may be present as an impurity. Upon administration, this replication competent impurity may cause an active infection in the patient or study participant capable of disseminating to others and causing disease or injury to susceptible individuals or populations. When the GTVVs are themselves capable of replicating, natural selection may lead to the development of variants that have a selective advantage. These variants may arise during manufacture or after product administration because of mutations, replication errors, or recombination events.

B. Identifying and Assessing Potential Environmental Effects

This section should identify environmental effects associated with the proposed action. Assessment of the magnitude and likelihood of each environmental effect should be presented, and a conclusion should be given regarding the overall risk to the environment. We recommend that you consult with the Agency during early development about what types of supporting data will be needed in an EA at the time of BLA submission. When addressing the environmental issues associated with a GTVV, you should follow the following recommendations. We have developed these recommendations specifically for GTVVs, and you should follow these in lieu of those that are outlined in the 1998 Guidance in section IV.B.1. entitled, "Assessing Toxicity to Environmental Organisms."

1. Identifying potential environmental effects

To identify potential environmental effects, you should consider the following:

a. Phenotypic attributes of the parental strain and/or vector:

i. Is the strain or vector virulent, pathogenic, or known to be associated with animal, plant or microbial toxicities?
ii. Is there an understanding of the environmental distribution, host range, and tropism?
iii. Are there substrates that may limit growth or reproduction?
iv. Is the strain or vector susceptible to control by antibiotics, antivirals, or biocides?
v. What is known regarding the genetic stability and prevalence of gene exchange in natural populations of the strain or vector?

vi. What is known about the stability of the strain or vector in the environment and is the strain capable of survival under adverse conditions (spores, dormancy, etc.)?

b. Environment into which the GTVV may be introduced:

i. Does the product have traits that may give it a selective advantage over natural organisms?
ii. Would susceptible species be exposed?
iii. Does the environment provide limited or reduced capacity for growth or reproduction?
iv. Are species or strains closely related to the product present in the environment that may be affected?
v. Can dispersal be naturally controlled by barriers in the environment?
vi. What is known about the effectiveness of monitoring and mitigation plans?

c. Attributes of the genetic alteration:

i. Does the alteration affect the ability of the product to replicate?
ii. What effects could transgene expression or exposure have outside of the target population?
iii. What is known about the genetic stability of the altered sequence?

2. Assessing the magnitude of potential environmental effects

The magnitude of environmental effects refers to the severity of consequences ranging from those that are negligible and self-limiting to those that would be severe, having serious effects or leading to long term, permanent harmful consequences. The magnitude of an effect will vary depending on the components released into the environment and organisms exposed. Estimates of magnitude are based both on events known to occur and those that may be reasonably foreseeable.

For degraded components released after administration, there may be no significant environmental effects. Partially degraded components may be further degraded in the environment, eventually reaching a point where they are indistinguishable from those occurring naturally (e.g., when DNA sequences from GTVVs are degraded into naturally occurring sequences and nucleotides).

It may be possible for partially-degraded components of GTVVs to retain a level of detectable biological activity. For example, a super-coiled plasmid may still retain the ability to transfer genetic material (such as antibiotic resistance genes) to other bacteria even after limited degradation. Therefore, the persistence of

antibiotic resistance genes in the environment should be considered. Although the likelihood of this event may be low (discussed in section V.B.3. of this document), the impact of the event may be significant if, after a rare transfer event, the antibiotic resistance gene could spread to environmental organisms and potentially compromise existing treatments.

When estimating the magnitude of the effect, sponsors/applicants should consider populations that might be particularly susceptible to uptake or infection. For example, a clinical trial involving administration of a live, attenuated recombinant poxvirus in an immune-competent study population may cause mild localized skin reactions and limited environmental release. The EA should take into consideration the potential to cause disease and injury in susceptible organisms (e.g., household pets or species in the environment) in which it may cause infection.

Genetic instability should also be considered when estimating the magnitude of an effect. Mutation, reversion, recombination, and reassortment may alter the magnitude of an effect. For example, replication deficient adenoviruses are manufactured in cell substrates that can complement the replication deficiency. This may cause a low level of replication competent adenovirus (RCA) to form as a result of recombination between the vector genome and the cellular genome. Even though RCA levels are carefully monitored and controlled,[14] you should consider the potential magnitude of environmental release of a replication competent adenovirus carrying a transgene.

3. Estimates of likelihood of environmental effects

Estimates of likelihood are to be based both on events known to occur and those that may be reasonably foreseeable.

For example, if biologically active (e.g., capable of transduction and/or replication) GTVVs are released, you should consider the likelihood of infection, persistence, or colonization. This would include an assessment of factors involved in tropism, host range and selection pressures, which may make survival more or less likely.

The likelihood of environmental effects may be assessed experimentally, including:

[14] As discussed in the FDA guidance entitled, "Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)" dated April 2008, FDA recommends less than 1 RCA per dose or $3x10^{10}$ viral particle. Available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072587.htm.

a. Amount of GTVVs and their metabolites released from patients into the environment.
b. Environmental decay and half-life measurements.
c. Frequency of uptake by susceptible species and estimates of infectious dose.
d. Measurement of "fitness" - how well GTVVs compete against other similar organisms in the environment.
e. Mutation or reversion to virulence rates.

Obtaining experimental data to address these issues (if needed) may require considerable time and planning. We recommend that you consult with the Agency during early-phase trials about what types of supporting data will be needed in an EA at the time of BLA submission.

4. How to evaluate the overall environmental risk

Based on the previous sections (section V.B.1. through 3, of this guidance document), an evaluation of the overall environmental risk should be given. To estimate the environmental risk, the magnitude of each environmental effect is combined with the likelihood of the effect occurring. The risk may be described in qualitative terms ranging from high, moderate, and low to negligible.

C. Mitigation Measures

This section should describe any measures taken to avoid or mitigate the overall environmental risk and may include procedures to inactivate, contain, limit exposure, or monitor release of a product. You should state if no environmental effects have been identified.

Procedures can be implemented to decrease environmental risk, in most cases by reducing likelihood of exposure. Some examples of mitigation measures are:

1. Requirement for hygienic measures and waste treatment.
2. Handling GTVVs under appropriate biocontainment.
3. Minimizing patient contact with susceptible populations or species.
4. Control measures to minimize aerosol formation.

D. Alternatives to the Proposed Action

If potentially adverse environmental impacts are identified for an action or a group of related actions, the EA must "discuss any reasonable alternative course of action that offers less environmental risk or that is environmentally preferable to the proposed action" (21 CFR 25.40(a)). Measures may be proposed to mitigate individual effects and depending on the adequacy of these measures, they may lower the overall risk level (see also section V.B.4. of this document).

VI. WHAT SHOULD YOU EXPECT AFTER FILING YOUR EA?

A. Agency Action

The Agency evaluates the information contained in an EA and any public input to determine whether it is accurate and objective and to determine whether the proposed action may significantly affect the quality of the environment, and whether an EIS or a FONSI is necessary. After evaluating the environmental risks associated with the proposed action and the alternatives, the Agency will select a course of action and ensure that any necessary mitigating measures are implemented as a condition for approving the course of action (21 CFR 25.40(e)). 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 environment, an EIS will be prepared (21 CFR 25.22(b)). Otherwise, the Agency will prepare a FONSI (21 CFR 25.41).

B. Environmental Impact Statement

If FDA determines that an EIS is necessary, an EIS will be prepared and become available at the time the product is approved (21 CFR 25.52). An EIS must provide full and fair discussion of these impacts, and must inform decision makers and the public of the reasonable alternatives that would avoid or minimize adverse impacts or enhance the quality of the environment (40 CFR 1502.1). In the event that an EIS is required for a GTVV, the nature or complexity of the product will direct which agencies will work with FDA to prepare the EIS. The responsibilities of FDA and other agencies are set forth in 40 CFR Part 1501.

C. Finding of No Significant Impact

A FONSI is a public document prepared by the Agency stating briefly why an action, not otherwise excluded, will not significantly affect the 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 environmental documents (21 CFR 25.41(a)).

VII. REFERENCES

1. FDA Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications, July 1998, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070561.pdf.

2. Coordinated Framework for Regulation of Biotechnology, June 26, 1986, 51 FR 23302, http://www.aphis.usda.gov/brs/fedregister/coordinated_framework.pdf.