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Requirements of the FDA for the environmental assessment of animal health products*

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Abstract

Under the National Environmental Policy Act, the Center for Veterinary Medicine (the Center) at the Food and Drug Administration (FDA) assesses the potential environmental impact of a wide variety of animal health products. The FDA considers the manufacture, use, and disposal of these products. Environmental assessments of some products, for example, products that may cause indirect or secondary effects or products used in aquaculture, are particularly challenging. For actions not categorically excluded, sponsors of animal drug products must prepare either complete or abbreviated environmental assessments (EAs), depending upon the nature of the requested action. Complete EAs must address potential impacts caused by manufacture, use, and disposal of the product. Data from environmental testing are used in the development of complete EAs. Good Laboratory Practice (GLP) regulations and inspections are used to ensure the accuracy and data integrity of environmental information submitted for EAs. Potential impacts from manufacture of the product must be considered in both complete and abbreviated EAs. Good Manufacturing Practice (GMP) inspections are used to verify manufacturing information provided in environmental assessments. Efficient development of complete EAs requires making use of the tiered testing system, starting the environmental assessment early in the drug approval process, and communicating with the FDA Center for Veterinary Medicine when questions arise.

1. Introduction

The objective of this paper is to present an overview of the environmental assessment procedures used by the Food and Drug Administration (FDA) in its regulation of animal health products. Because of the limited time available, we can only summarize the specific requirements for these environmental assess ments. However, we hope that this presentation will leave the reader with an

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understanding of the need for environmental assessment of animal health products, the basic components of the two types of environmental assessments most commonly prepared for the FDA, what is expected from environmental testing, and some of the relatively simple things one can do to save time and resources in the preparation and review of environmental assessments submitted to FDA's Center for Veterinary Medicine (Center). If one is new to developing environmental assessments for the FDA and in need of more detailed information, the FDA Environmental Assessment Technical Assistance Handbook (Handbook) [1] will be a helpful reference. It is available from the National Technical Information Service (NTIS).

2. Types of animal health products regulated by the FDA

Animal health products include a wide variety of substances. For example, there are antibacterial agents, produced by chemical synthesis and fermentation, and antiprotozoal agents, used especially in poultry and swine. In addition, antiparasitic/anthelmintic agents are used to control the many roundworms, filaria, warbles, nematodes, and copepods that infect domesticated birds, mammals and fish. Also, there are production drugs, e.g., drugs given for the purpose of increasing the rate of weight gain, feed efficiency, milk production, or carcass leanness. These latter products may be antibacterial agents or other chemicals administered continuously. Probiotics, i.e., cultures of microbes administered orally to animals to prevent disease or increase production, are generally considered to be animal drugs or food additives, depending on the claims of the individual products. Nutritional additives and feed ingredients, including yeasts, and silage inoculants, are regulated by FDA as food additives. In some cases, transgenic animals may be considered to be or to contain animal drugs, e.g., animals modified to produce animal drugs in their milk and animals modified to express additional hormones and growth factors for the purpose of increasing production efficiency. Jurisdiction over transgenic animals and plants is still being sorted out, however, among FDA, the Department of Agriculture, and the Environmental Protection Agency.

The Center considers drugs for many types of animals, and the management procedures used for them are varied. Non-food animals include dogs, cats, horses, foxes, aquarium and bait fish, zoo animals, mink, and chinchillas. Food animals include cattle, poultry, swine, finfish, crawfish, mollusks, shrimp, reindeer, bison, sheep, rabbits, goats, and bear. The type of environmental introductions of drug residues that may occur through use in these animals varies from small and controlled to large and uncontrolled.

3. Environmental impacts of animal health products

The National Environmental Policy Act (NEPA) [2] requires that Federal agencies include in decisionmaking an objective consideration of the potential

environmental impacts associated with each contemplated action. Included are actions sponsored by applicants, such as requests for approval of new animal drug applications and food additive petitions. The procedures governing NEPA reviews at the FDA are found in the Council on Environmental Quality Regulations [3] and in FDA implementing procedures [4]. The current version of FDA's NEPA regulations appears in Title 21 of the Code of Federal Regulations (CFR) in Part 25.

One may wonder why new animal drug approvals are included as actions requiring consideration of potential environmental impacts. Many people find it hard to imagine the possible environmental consequences of animal drug use. Like pesticides, animal drugs are bioactive by design and their spectrum of bioactivity is often much broader than the intended pest organism. The chemical classes of substances used as animal drugs include products that have registered uses as pesticides, such as organophosphate chemicals, avermectins, and certain antibiotics. There is also a much wider range of chemicals in use: b-agonists, hormones, quinolones, ionophores, aniline dyes, and synthetic and fermentation antibacterial agents. The listing of nearly all the approved animal drug and food additive products is found in 21 CFR §§ 500–599.

Under NEPA, the agency is also responsible for considering not only the direct environmental effects, but also the indirect and secondary environmental effects of its actions. Therefore, impact assessment must go further than a prediction of the direct effects of bioactive residues on exposed communities. Ecological perturbations, changes in land use patterns, resource allocation issues, effects on biogeochemical cycles, greenhouse gas emissions, and effects on biodiversity or endangered and otherwise protected species and habitats must be considered. Here, methodology for predicting impacts is often absent, and the predictions are fraught with uncertainty. The potential impacts appear large, but the probability of their occurrence seems small. Methodology for assessing these impacts has been developed as the cases present themselves, sometimes before product approval and sometimes, painfully, after product marketing. This is a new field, and we are learning and using our experience as it develops. For this reason, the environmental issues addressed in pre-market reviews are slowly expanding to take into account the impacts that may have become evident only in a post-approval situation. The first example is a case in which an animal health product has already triggered a review of indirect effects.

3.1 Famphur, avian toxicity, and the Endangered Species Act

In 1986, the Fish and Wildlife Service (FWS) brought to the Center's attention a situation concerning bird deaths and the use of an animal drug. Some of the birds being reported as dead were protected under the Endangered Species Act [5]. An organophosphate, famphur, formulated as an external "pour-on" product for cattle, was implicated in the death of magpies and in the secondary poisoning of red-tailed hawks. The product is poured on the centerline of the backs of cattle. A portion of the drug is then absorbed systemically, killing lice

and warbles that are infesting the cattle. A well-controlled field study conducted by Dr. Charles Henny of the FWS confirmed [6] that famphur pour-on also killed magpies and raptors, with deaths occurring for up to 82 days after the cattle were treated. Magpies were consuming contaminated cattle hair, being poisoned, and then being preyed upon by hawks, who were also being poisoned. A tertiary poisoning of a great-horned owl was reported. Dead and dying bald eagles consuming the carcass of a treated cow were added to the list [7]. By 1989, other cases of poisoning were reported, some apparently due to intentional baiting, for geese, ducks, red-wing blackbirds, grackles, crows, sandhill cranes and red-tailed hawks in Georgia and West Virginia [8].

The Center is currently going through the procedures under the Endangered Species Act to receive a biological opinion from the FWS [9, 10]. The final biological opinion will be released to the public for comment. When jeopardy is established, procedures will have to be developed to reduce or eliminate the threat to endangered species and probably also to birds protected under the Migratory Bird Treaty Act [11]. Other organophosphate pour-on products already being marketed will also undergo a similar review. Now that the Center is aware of the potential problem, pre-market environmental reviews of pour-on products of all chemical classes include a consideration of avian toxicity.

The second example concerns the use of selenium as an animal feed supplement. Although no environmental harm has been demonstrated from the use of this product, there is sufficient concern to warrant an attempt by the Center to gather more information.

3.2 Selenium supplementation and biogeochemical cycles

Selenium is a required element for most, if not all, animal life. Agricultural soils in much of the United States yield crops that are nutritionally deficient in selenium. The diets of domestic livestock and poultry are primarily derived from these crops. Supplementation of animal feeds with selenium, as sodium selenite, has been an approved practice since 1973 [12]. The selenium fed to animals is not entirely retained in their bodies, but is excreted in their wastes. These wastes are often added to agricultural soils as fertilizer. Thus, there is an opportunity for selenium to accumulate in soil or to be leached out of soil and carried in runoff from amended soils and feedlots.

Selenium is present in the environment in many valence states and salts, as well as in biomethylated and aminated organic forms. The bioavailability and mobility of selenium in the environment is therefore affected by factors such as pH, redox potential, microbial activity, rainfall, and the presence of organic matter [13]. These factors, in combination with the presence of geological sources of selenium and irrigation practices, have caused serious environmental impacts at Kesterson Reservoir in California [14]. Other drainages in the Western U.S. may also be affected [15]. To date, selenium derived from the manure of supplemented animals has not been shown to be a factor in the environmental problems that have been observed.

The question for the Center is: "Does selenium supplementation of animals result in wastes that may cause selenium-related environmental impacts?" To answer this question, a better understanding of the selenium biogeochemical cycle and an improved ability to predictively model the effects of selenium for various local conditions will be required. Unfortunately, it is difficult to interpret the information contained in the large number of site specific and laboratory-based scientific papers that are being published and to relate the information to the specific needs of the Center. FDA held a public hearing on August 25, 1992, to give interested persons an opportunity to present relevant scientific data concerning environmental introductions, fate, and effects of selenium compounds.

The last example demonstrates the challenges we are facing in developing environmental assessments for one rapidly growing food animal industry, the aquaculture industry.

3.3 Aquaculture

The intensive rearing of various fish and shellfish for food is becoming big business. As an example, production of farm-raised catfish in the United States rose from 5.7 million pounds in 1970 to more than 360 million pounds in 1990 [16]. Acreage of catfish ponds in Mississippi alone exceeded 100,000 in 1991 [17]. The net pen rearing of salmon (as another example) is concentrated in the Pacific Northwest and New England. Freshwater salmonids are being reared wherever the water is cold enough. Salmonid hatchery operations are set up as environmental mitigations for the habitat lost to dam projects. The list of species being used in aquaculture operations ranges from mollusks to crustaceans to a great variety of freshwater and marine finfish.

Most aquaculture operations are intensive, high density monocultures. Like their terrestrial equivalent, poultry, intensively grown fish are susceptible to disease epidemics. Much of the industry, as it is currently managed, depends upon the availability of effective antimicrobials and other bioactive chemicals to control disease organisms and parasites. The drug products are often used prophylactically. Because fish are extremely susceptible to handling stress, anesthetics and other chemicals are needed when the fish are handled or transported. Other drugs are used as markers for population studies of fish that are released to the wild for part of their life cycles.

Medicated feeds and other drug formulations may be added directly to the water when fish are treated. These formulations and excreted residues usually enter a water resource, and have the potential to degrade the resource to the extent that other uses may be precluded. Water quality goals for the receiving waters may not be achievable. When the Center reviews the environmental impact of aquaculture products, we try to determine whether they will cause changes in water quality that could cause significant environmental impacts on downstream ecosystems or would cause public health concerns.

In the case of aquaculture products, the fact that FDA has approved an aquaculture drug does not mean that, environmentally, it is suitable for use in

every situation. When waste treatment or waste reduction procedures are feasible for a drug product, we try to describe the procedures in the environmental assessment and, as appropriate, on the product label.

4. Requirements for the environmental assessment of animal health products

It is useful to keep in mind that the term environmental assessment is often used to refer to a process. It is also one type of document that is used to relate to the public the information obtained during the process. At the Center for Veterinary Medicine, the purpose of the process of environmental assessment is to determine whether there may be environmental impacts from the manufacturing, use, and disposal of an animal health product. For actions not categorically excluded, the most common type of environmental document prepared for Center decisions is the environmental assessment (EA). The EA, whether it is prepared by an applicant or by the FDA, must be an objective analysis of the potential environmental impacts of the action, including mitigation measures that are possible to avoid or reduce any expected impacts.

Two kinds of environmental assessments are prepared for the Center, depending upon the nature of the requested action: (1) complete environmental assessments, for the types of actions (e.g., requests for approval of new chemical entities to be used in a food-producing species) that require a review of the potential environmental impacts caused by the product's manufacturing and use, and (2) abbreviated environmental assessments, for the types of actions requiring only a review of the potential environmental impacts caused by the manufacture of the product. The development of a complete environmental assessment is a dynamic process, often requiring frequent feedback from the Center as it progresses. It may take considerable time to develop. For this reason, and for others that will be explained later, we recommend that sponsors begin the environmental assessment early in the approval process.

It is in the development of a complete environmental assessment that data from environmental testing are most often used. The results of this testing are eventually synthesized into a reasonable, objective assessment of the potential for an action to cause significant environmental impacts. The public document (usually an EA) that results is an environmental impact prediction that consists of an exposure assessment integrated with ecotoxicity data [18]. Remember that the complete environmental assessment must take both manufacturing and use of the product into account.

4.1 Determination of impacts due to use of animal health products

Before a testing plan is developed, the sponsor should estimate (most common) or measure the potential environmental introductions of bioactive residues of the drug product. This estimation is made with consideration given to

the metabolism of the drug or food additive by the target animal and the waste management procedures expected to be used for each class of animal that will be given the product. If adequate environmental fate data are not available, appropriate environmental fate screening tests are conducted in the laboratory to evaluate the potential for transformations and environmental mobility of the residues. An exposure assessment is prepared from these data, and an appropriate suite of screening tests for environmental effects is selected. Generally, the effects tests are single species toxicity tests on aquatic or terrestrial organisms. By comparing the results of the screening tests with the expected exposures, an environmental impact or hazard determination can be prepared [1].

We recommend the use of a tiered testing system to gather appropriate testing data for a particular case. The tier arrangement that we recommend includes (1) chemical characterization, (2) analysis of the environmental introductions of the chemical and/or its metabolites, (3) analysis of the environmental fate of the chemical and/or its metabolites, and (4) analysis of the environmental effects of the chemical and/or its bioactive metabolites. For more details of this system, refer to Matheson [18].

For a tiered testing approach to work efficiently, it is necessary to analyze the tiers sequentially. Therefore, it is important to begin environmental testing early in the investigational phase of developing animal drugs. At the Center, we encourage the submission of environmental testing plans and protocols for review. This allows applicants to have some assurance that the Center agrees with the scientific approach being taken. Applicants can thereby benefit from the mistakes of others and have a relatively unpressured scientific interchange with the environmental staff reviewers who will eventually review the study results.

Many of the scientific methods needed to develop the supporting data are contained in the FDA Environmental Assessment Technical Assistance Handbook [1], available from the National Technical Information Service. The Handbook also contains general environmental assessment guidance.

Whenever possible, the FDA testing protocols are consistent with those recommended by the U.S. Environmental Protection Agency (EPA), the American Society for Testing and Materials (ASTM), and the Organization for Economic Cooperation and Development (OECD). FDA can thus avoid unnecessary duplication of environmental testing. Environmental testing that has already been performed often will not have to be repeated under a different protocol as applicants move from one regulatory agency to another and from one country to another for approvals of the same chemical substance. FDA encourages applicants to include in their environmental documents data submitted to other regulatory agencies, such as EPA.

4.2 Data integrity

Requiring applicants to gather environmental data is acceptable under the National Environmental Policy Act only if: (1) the agency (FDA) can verify the accuracy of the information provided and (2) the agency makes its own

evaluation of the environmental issues and takes responsibility for the scope and content of the environmental assessment.

The predictions in an environmental assessment must be objective, that is, based upon data gathered and reported in such a way that the agency can confirm the accuracy and validity of the test. Because of the rules concerning privacy, FDA is the sole federal agency responsible for verifying the information used in predicting the potential environmental impacts of drug substances. FDA takes the review of data very seriously.

The agency uses Good Laboratory Practice regulations [19] to ensure the accuracy and data integrity of environmental information submitted for animal drug applications. FDA inspects laboratories conducting environmental tests and audits the data in the laboratory records against the information submitted.

Applicants are not permitted to pick and choose among completed environmental studies to decide which ones to submit. They are required to submit any environmental information, regardless of its quality. The applicant is encouraged, however, to explain whatever methodological or data limitations are perceived in each study.

Complete EAs must also document impacts due to the manufacture of products. Because the documentation required is the same as that for abbreviated EAs, we will discuss it in the context of development of an abbreviated EA.

4.3 Documentation of impacts due to manufacture of animal health products

Abbreviated environmental assessments are required for lower volume products used in a dispersed fashion, including drugs intended for non-food animals, some uses under a veterinarian's orders, and for topical, ophthalmic, or anesthetic use. Alternate manufacturing sites and generic products are also included in this category. Abbreviated environmental assessments document potential impacts from manufacturing only.

All actions that involve manufacture of an animal health product at a new site or by a new procedure are reviewed for their potential impact at that site. Occupational safety, handling of hazardous wastes, air emissions, waste water, solid wastes, and biocontainment requirements are all considered, as appropriate to the manufacturing process. These must also be discussed in a complete EA.

You might ask whether the EPA, Occupational Safety and Health Administration (OSHA), State, and local governments regulate these emissions. The answer is yes, but only after manufacture has begun. FDA reviews the products prior to manufacture and marketing. In the case of unapproved animal drug applications, the Center is normally barred from disclosure of the applications to persons outside the Department of Health and Human Services until the application is approved. So, for example, the FDA cannot routinely consult on the specifics of undisclosed pending applications with the EPA, OSHA or the States. Additionally, the EPA is proscribed from regulating FDA-regulated products under the Toxic Substances Control Act [20] or the Federal, Insecticide,

Fungicide and Rodenticide Act [21]. This makes the FDA the sole federal agency reviewing and predicting the environmental impacts (including occupational) of animal drug substances before their introduction into the environment.

Whenever possible, we encourage applicants to approach the various regulatory groups controlling emissions permits and to ensure that the manufacture of the new product will be in compliance with requirements. This is not always possible for new chemical entities. But if it is, FDA can rely on a manufacturer's identification of the pollutants expected to be emitted, a discussion of the pollution controls exercised, and an identification and signed certification of compliance with Federal, State, and local emissions requirements. The inclusion in EAs of Material Safety Data Sheets (MSDSs) and emissions permits is encouraged as evidence of compliance with OSHA, EPA, and state and local requirements. We also assess data that support the MSDS. We have found that this checking serves a valuable purpose in assuring that all product sponsors have planned for safety in the workplace and for properly treated wastes.

Foreign manufacturing must also be addressed under the FDA environmental regulations. It is a common and incorrect assumption that, because a product is manufactured in a foreign country, no environmental review of that aspect of the application is required. Under Executive Order 12114, "Environmental Effects Abroad of Major Federal Actions," [22] and the corresponding FDA environmental regulations at 21 CFR 25.50, the requirement is established for evaluation of the impact of agency actions on the global commons and on foreign countries. The preferred method for addressing the potential environmental impacts of foreign manufacturers is to cite the emissions requirements that apply at the foreign locale, determine the effect of the new or additional manufacturing activity on those requirements, and certify compliance with the foreign emissions requirements.

FDA uses Good Manufacturing Practice (GMP) inspections both domestically and abroad before approving new manufacturing sites [23–26]. The inspection is an opportunity to verify the information provided in environmental assessments relating to emissions controls and permits, workplace safety measures, and environmental monitoring. The FDA investigator determines whether equipment and controls described in the EA are in place, are validated to operate at the stated standards, and that they are operating and maintained. There should be standard operating procedures for equipment, workplace monitoring, spill cleanup, and for accidental environmental releases. The various emissions permits should be available and up to date. Material Safety Data Sheets should be available for employees. The investigator's report is evaluated prior to any agency action to approve an application.

4.4 Public participation in environmental assessment of animal health products

If the FDA finds after reviewing the EA that an action is not expected to cause significant environmental impacts, it prepares a finding of no significant

impact (FONSI). In this case, both the FONSI and the EA are released to the public at the first opportunity. (The existence of some types of applications is held confidential until they become approvable.) The environmental assessment for a food additive petition is available as soon as it is filed. The public participates in the decisionmaking by reviewing these NEPA documents and providing comments concerning environmental impacts overlooked, inadequately defined, or not properly considered. If the evidence in the EA indicates the action is expected to cause significant impacts, FDA will prepare an environmental impact statement.

4.5 Suggestions for more efficient development and review of environmental assessments

Following is a list of suggestions, taken from our experience, that will improve the efficiency of the development of environmental assessments for animal drug products.

1. Recognize that the environmental assessment of each product will be unique. Make use of the tiered testing approach in your planning.

2. Include environmental screening information in the data sets that you use to decide among candidate products. Integrate environmental data acquisition into the investigational stages of drug development. Starting environmental considerations late means incomplete submissions, problems that are difficult to correct, and delays. Environmental considerations are not an add-on item to be tackled after most of the rest of the investigation of the proposed product is completed.

3. Submit protocols or environmental testing plans for review when you have questions over specific methodology or the direction your environmental testing should take.

4. Provide signed certifications of compliance with pollution and occupational requirements for all manufacturing sites and sign the EA. Where manufacturing sites are contract sites controlled by other firms, environmental information for that firm may be provided in a master file or provided to the sponsor for inclusion in the EA. This is also true for foreign manufacturing sites.

5. Provide a Material Safety Data Sheet (MSDS) for the bulk new drug substance. FDA has two interests in obtaining an MSDS for the new drug substance. First, an adequate MSDS is an indication of compliance with OSHA requirements. Second, FDA must provide the MSDS to its own chemists when they are asked to analyze samples collected during inspections.

6. Provide sufficient details in test reporting. Frequently omitted, but necessary, information includes thorough reporting of test methodology, unexpected changes in experimental methods after protocol approval, and unexplained deviations from methods in the Environmental Assessment Technical Assistance Handbook. Refer to the appropriate Technical Assistance Documents in the Handbook for a list of items that we consider to be minimal for sufficient reporting. A frequent deviation from methods is reduction of replication to

the point that the experimental design and its results cannot be analyzed statistically.

7. Pay attention to quality control and proofreading of EAs. Have someone ensure that EAs are complete. It is not unusual for us to receive EAs with pages or entire sections missing. Remember that EAs are public display documents.

8. Consistently differentiate confidential from non-confidential information. EAs should contain no protected trade secret or business information, except as a confidential appendix. Confidential information that must be used in considering environmental impacts of a product should be summarized in a Freedom of Information Act format and included in the display portion of the EA.

References

1 U.S. Food and Drug Administration, Environmental Assessment Technical Assistance Handbook, NTIS Pub. No. P87-175345, Springfield, VA, 1987.
2 National Environmental Policy Act, 42 U.S.C. §§ 4321–4261, Washington, DC, 1982.
3 Council on Environmental Quality Regulations, 40 CFR §§ 1500–1508, Washington, DC, 1988.
4 U.S. Food and Drug Administration, National Environmental Policy Act; Policies and Procedures; Final Rule, 50 FR 16635–16669, 21 CFR § 25, Washington, DC, 1985.
5 Endangered Species Act, 16 U.S.C. 1531 et seq., Washington, DC, 1982.
6 C.J. Henny, L.J. Blus, E.J. Kolbe and R.E. Fitzer, Organophosphate insecticide (famphur) topically applied to cattle kills magpies and hawks, J. Wildlife Manage., 49(3) (1985) 648–658.
7 C.J. Henny, L.J. Blus, E.J. Kolbe and R.E. Fitzer, Case histories of bald eagles and other raptors killed by organophosphorus insecticides topically applied to livestock, J. Wildlife Dis., 23 (1987) 292–295.
8 D.H. White, L.E. Hayes and P.B. Bush, Case histories of wild birds killed intentionally with famphur in Georgia and West Virginia, J. Wildlife Dis., 25(2) (1989) 184–188.
9 U.S. Fish and Wildlife Service, Regulations of Department of Interior, Interagency cooperation — Endangered Species Act of 1973, as amended, 50 CFR § 402, Washington, DC, 1986.
10 U.S. Fish and Wildlife Service, Regulations of the Department of Interior, Listing endangered and threatened species and designating critical habitat, 50 CFR § 424, Washington, DC, 1984.
11 Migratory Bird Treaty Act, 16 U.S.C. 703 et seq., Washington, DC, 1974.
12 U.S. Food and Drug Administration, Food additives permitted in feed and drinking water of animals — Selenium, 21 CFR 573.920, Washington, DC, 1973.
13 U.S. Food and Drug Administration, Selenium; Environmental Impact; Opportunity to Comment, 54 FR 29019–29025, Washington, DC, 1989.
14 T.S. Presser and H.M. Ohlendorf, Biogeochemical cycling of selenium in the San Joaquin Valley, California, USA, Environ. Manage., 11 (1987) 805.
15 M.A. Sylvester, J.P. Deason, H.R. Feltz and R.A. Engberg, Preliminary results of the Department of Interior's irrigation drainage studies, In: R.C. Severson, S.E. Fisher and L.P. Gough (Eds.), Proc. of the 1990 Billings Land Reclamation Symp. on Selenium in Arid and Semiarid Environments, Western United States, U.S. Geological Survey Circ. 1064, Washington, DC, 1991.

16 R.H. Brown, Catfish now considered major menu item, Feedstuffs, 63(40) (1991) 10.
17 R.H. Brown, Mississippi adds catfish pond acreage, Feedstuffs, 63(40) (1991) 10.
18 J.C. Matheson, III, The nuts and bolts of preparing an environmental assessment, Fd. Drug Cosmetic Law J., 43(6) (1988) 831–841.
19 U.S. Food and Drug Administration, Good laboratory practice for nonclinical laboratory studies, 21 CFR § 58, Washington, DC, 1978.
20 Toxic Substances Control Act, 15 U.S.C. §§ 2601–2654, Washington, DC, 1982.
21 Federal Insecticide, Fungicide and Rodenticide Act, 7 U.S.C. 136–136y, Washington, DC, 1982.
22 President of the United States, Environmental effects abroad of major federal actions, Executive Order 12114, 44 FR 1957, Washington, DC, 1977.
23 U.S. Food and Drug Administration, Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs; general, 21 CFR § 210, Washington, DC, 1978.
24 U.S. Food and Drug Administration, Current good manufacturing practice for finished pharmaceuticals, 21 CFR § 211, Washington, DC, 1978.
25 U.S. Food and Drug Administration, Current good manufacturing practice for medicated feeds, 21 CFR § 225, Washington, DC, 1976.
26 U.S. Food and Drug Administration, Current good manufacturing practice for Type A medicated articles, 21 CFR § 226, Washington, DC, 1975.