NEW ANIMAL DRUG DETERMINATION

I. Purpose:

A. To provide a ready guide to CVM personnel in determining when a drug constitutes a new animal drug (NAD) as defined under the Federal Food, Drug, and Cosmetic Act (FFDCA).

B. To provide guidance to review personnel seeking expert testimony in support of NAD charges.

II. Statutory Authority:

Unless already thoroughly familiar with them, the scientific review officer or consumer safety officer should study the sections of the acts and regulations listed below prior to undertaking NAD enforcement work.

A. Federal Food, Drug, and Cosmetic Act (FFDCA):

1. 201(v) - defines a new animal drug.

2. 201(g) - defines a drug.

3. 201(f) - defines a food.

4. 201(w) - defines an animal feed.

5. 201(s) - defines a food additive.

6. 201(p) - defines a new drug.

7. 201(q) - defines a pesticide.

8. 501(a)(5) and 501(a)(6) - state that a new animal drug or a feed containing a new animal drug shall be deemed to be adulterated if it is unsafe within the meaning of Section 512. That is, it is not the subject of

an approved new animal drug application (NADA) or is not exempt under the investigational provisions. (There are other adulteration charges which can be brought against a drug or a device per 501.)

9. 502(a) - a drug or device shall be deemed to be misbranded if its labeling is false or misleading in any particular.

10. 502(f)(1) - a drug or device shall be deemed to be misbranded unless its labeling bears adequate directions for use.

11. 512 - establishes for NADAs the requirements and the conditions of submission, review, approval, withdrawal, etc. A new animal drug is adulterated if not in compliance with this section.

12. 402(a)(2)(C) - establishes that a food is adulterated if it contains an unapproved new animal drug unless exempt in accordance with the investigational provisions of Section 512.

B. Title 21 of the Code of Federal Regulations:

1. 21 CFR 310.3(g) - defines a new drug substance.

2. 21 CFR 510.3 - clarifies the definition of a new animal drug.

3. 21 CFR 510.4 - exempts veterinary biologics which are in full compliance with the requirements of the Federal Animal Virus, Serum, Toxin Act, and attendant regulations from the requirements of 512 of FFDCA.

C. Federal Animal Virus, Serum, and Toxin Act (AVSTA):

1. 9 CFR (Subchapter E) 101.2(w) - the term biological products, sometimes referred to as biologics, biologicals, or products, shall mean all viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live micro-organisms, killed micro-organisms, and the antigenic or immunizing components of micro-organisms intended for use in the diagnosis, treatment, or prevention of diseases of animals.

D. Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA):

1. "2(u) - The term 'pesticide', means (1) any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, and (2) any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant: Provided. That the term 'pesticide, shall not include any article (1)(a) that is a new animal drug, within the meaning of Section 201(v) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(v) or (b) that has been determined by the Secretary of Health and Human Services not to be a new animal drug by a regulation establishing conditions of use for the article, or (2) that is an animal feed within the meaning of Section 201(w) of such Act (21 U.S.C. 321(w)) bearing or containing an article covered by clause (1) of this proviso."

III. Jurisdiction:

A. USDA - Under authority of the VSTA of March 4, 1913, USDA controls veterinary biologics. FDA can still exercise jurisdiction over these products in accordance with 501(a)(5) and 512 of the FFDCA if they do not comply with the VSTA, and has done so in the past at the request of USDA. (Other sections of 501 and 502 of the FFDCA are also applicable to biologics.) The regulations covering veterinary biologics may be found in Title 9 of the CFR.

B. EPA - Pesticides are regulated by EPA under the Federal Environmental Pesticides Control Act (FEPCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Title 40 of the CFR contains the regulations under which pesticide programs operate.

FDA regulates pesticide residues in animal feeds in accordance with tolerances published under 40 CFR 186. The Memorandum of Agreement (MOA) between EPA and FDA should be studied to delineate regulatory control of products which may be considered both pesticides and drugs.

C. FDA - The FDA operates under the FFDCA and regulations published in Title 21 of the CFR. To be subject to FDA jurisdiction, products must be either drugs, foods, devices, colors, or cosmetics (human) introduced into or delivered for introduction into interstate commerce.

IV. New Animal Drug - Exemptions:

Under certain conditions, drugs may be legally introduced in interstate commerce despite the fact that they do not meet the stated requirements of 201(v), 510(a)(5) and 512 of FFDCA regarding new animal drug approval.

A. Grandfather Clause:

1. Food and Drug Act of 1938 - This revision of the Act provided that any drug which was marketed prior to June 25, 1938, could continue to be marketed without approval provided no significant alterations in formulation or labeling had occurred since that time. That is, such a drug would not be considered a new drug (which was, at that time, defined to include animal drugs).

2. Kefauver-Harris Amendments of 1962 - These amendments to the Act became effective as of October 10, 1962, and required that drugs be proven to be "effective" for their intended uses-implied or stated. These amendments also contained a "Grandfather" clause which provided that drugs, commercially marketed in the United States prior to October 9, 1962, and after June 25, 1938, which were not approved drugs and not considered new drugs should not be considered new drugs under the new amendments provided the products had not significantly changed labeling or formulation. That is, such products were exempted from the efficacy requirements of the amended Act.

3. Animal Drug Amendments of 1968 - Animal Drugs placed on the market on or after October 10, 1962, must be shown to be safe and effective for their intended uses in accordance with the 1968 Animal Drug Amendments to the Act. The October 9, 1962 "Grandfather" clause was specifically applied to animal drugs with the adoption of these amendments.

4. Limits of the "Grandfather" Clause - The exemptions noted above apply only to new animal status (201(v) and 501(a)(5)). Grandfathered articles may still be considered violative under other sections of the Act, particularly 502(f)(1) or 502(a).

B. Not- New Drug Status Opinions - Revoked - The "Grandfather" clauses noted above potentially apply to any animal drug placed on the market prior to October 10, 1962. The exemptions are very strictly interpreted and the burden of proof of exemption is on the manufacturer. By

FEDERAL REGISTER publication May 28, 1968, the Commissioner stated that any prior opinions to the effect that an article is "not a new drug" or is "no longer a new drug" were revoked.

Any evidence a regulated firm submits in the form of prior correspondence stating that a product was not a new animal drug should be viewed in this light. Unless a product is specifically proven to be "grandfathered," it should be evaluated in accordance with current scientific knowledge despite previous opinions that it is an "old drug."

V. Factors Determining Drug Status:

Before a product can be determined to be a new animal drug, it must first be established to be within the jurisdiction of FDA as a drug defined by 201(g). Such evaluations are not always clear-cut and should include the following considerations:

A. Drug as Defined by 201(g) - Note particularly in 201(g)(1)(c) the parenthetical statement "(other than food)." Because of this phrase, many oral vitamin/mineral, etc., products with stated or implied claims to improve growth promotion or increase feed efficiency are difficult to proceed against as drugs and misbranded food charges should be considered in such cases. The ultimate determining factor may be subtle implications in promotional material involving therapeutics. In making the decision, it should be borne in mind that support of a new animal drug charge places less burden of proof on FDA than does a misbranded food charge.

B. Device as Defined by 201(h) - Note the similarity of the definitions of drug and device. The major difference lies in whether the product under consideration achieves its principle intended effects through chemical action on or within the body or through being metabolized. Do not think of device in the narrow sense of a "machine" or "mechanical contrivance"; a spray-on bandage may be a device.

C. Jurisdictional Consideration - While certain products meet the definition of a drug, they also meet the definition of products (such as biologics or pesticides) regulated by other agencies and the regulation of such may have been deferred to those agencies by inter-agency agreement. See particularly 21 CFR 510.4 and the 1973 EPA/FDA Memorandum of Agreement.

VI. Factors Affecting New Animal Drug Status:

The definition of a new animal drug bears the phrase “not generally recognized, among experts . . . ." That phrase obviously leaves a great deal of room for interpretation relative to any specific product being reviewed and ultimately may have to be interpreted by the courts in specific cases.

Several such recent interpretations should prove helpful to CVM reviewers. The factors affecting NAD determinations can generally be divided into two classes, (1) scientific--involving indications and formulations, and (2) legal--involving availability of expert witnesses.

A. Precedent Cases and Interpretation of "General Recognition" - The Supreme Court provided an interpretation of "general recognition" in the cases of Bentex Pharmaceuticals and Hynson, Westcott and Dunning, Inc., which establishes that general recognition of safety and effectiveness must be based on substantial evidence derived from adequate and well-controlled studies. Furthermore, to serve as a basis for general recognition by experts, such data must be publicly available. In essence, this means that general recognition must be based on the same kind of data necessary to support NADA approval and that the data must be published. These principles were extended to animal drugs in the cases of Naremco, Inc. and Mastikure Products, Inc. Few animal drugs meet these criteria and therefore most are considered by CVM to be new animal drugs.

B. Both Scientific and Legal Criteria Must be Met - In the final analysis, even though CVM determines a product to be a new animal drug in accordance with the precedents above and the scientific criteria below, unless expert witnesses can be obtained to support that opinion, the product is, for all practical purposes, not a new animal drug. (See also Section 8(i) of this guide.)

C. Scientific Criteria - At least four major considerations must be addressed by medical reviewers considering the new animal drug status of a product: indications for use, dosage forms and formulations, combinations of drugs, and "grandfather" status.

1. Indications for Use:

This involves all aspects of labeling and promotional material

where claims are either stated or implied. These include not only the direct claims made for the product but also the name of the product, the proportion of each ingredient, the dosage form and formulation, route and duration of administration, species for which intended, Rx or OTC status, and such other factors. Note particularly the additional safety issues involved with products intended for food-animal use. Due to the scarcity of published data on individual product depletion rates, virtually all products for food-animal use will be NAD by CVM scientific criteria.

2. Dosage Form and Formulation:

It is important to note that CVM is responsible for reviewing and approving products. Similar formulations should not be assumed to be similarly bioavailable. The amount of proof needed to satisfy CVM that two products are bioequivalent varies depending on the nature of the product. Tablets, particularly enteric-coated tablets, may be the most suspect class and inhalation anesthetics and true solutions for I.V. use the least suspect. In the latter cases, demonstrations of chemical equivalency are usually accepted as sufficient. Products in these two classes are less likely to be an NAD as defined by 201(v) than tablet formulations, for example. Topical preparations, oral powders and suspensions, and parenteral suspensions fall somewhere in between. The likelihood of a product being generally recognized as safe and effective based on pub lished data derived from well-controlled studies, is inversely proportional to the potential for differences in bioavailability.

3. Combination Products:

The principles established in the CVM combination drug policy are derived, in part, from the NAS/NRC drug efficacy reviews and are generally accepted by the scientific community. Thus, they are applicable to NAD determinations and data essentially meeting the requirements of that policy would have to be available in the scientific literature to form a basis for general recognition of safety and efficacy. For this reason, virtually all combination products will be new animal drugs by CVM criteria.

4. Grandfather Exemption:

As noted previously, certain products which were marketed prior to October 1962 may be exempt from NAD status under very specific conditions. If there is reason to believe that a product may be grandfathered, the Administrative File of the manufacturer should be obtained and past labeling and formulations reviewed to determine whether any changes have occurred. Such changes may void the exemption. The exemption applies only to identical products with identical labeling marketed before 1938 and/or 1962.

D. Legal (Expert Witness) Criteria:

The testimony of non-government experts is generally necessary to support a contested regulatory action based on a new animal drug charge. The primary issue will be lack of general recognition of safety and efficacy (and frequently Grandfather status). Experts should be advised that the principle established by the precedent cases is that such recognition must be based on data derived from adequate and well-controlled studies. Within these general parameters experts should be selected as follows:

1. Number of Experts Needed:

This is variable to some extent but should generally not be less than two. It is not necessary to call all known experts to court to establish general recognition, only a representative number (usually two or three) so that even if contested by the defendant's experts, a significant difference in scientific opinion can be demonstrated. Such a difference of opinion would be enough to establish lack of general recognition of safety and efficacy.

2. Kind of Expert Needed:

Generally the expertise chosen will directly relate to the most significant areas of lack of general recognition. For example, Board Certified Toxicologists if safety is a primary issue, Board Certified Dermatologists if the efficacy of a topical product is of primary concern, etc. In some cases, it will be necessary to obtain a mixture of expertise to properly support the case. Such determinations should be discussed with the consumer safety officer and the attorney assigned to the case. Preferably experts

should be located close to the geographical location of the trial but expertise should not be sacrificed to achieve this objective.

3. How to Identify Experts:

The names of experts may be obtained from the literature pertaining to particular products or scientific concerns involved in the case. Additionally, the Divisions of Surveillance and Compliance maintain files of the curriculum vitae of experts previously contacted. The AVMA Directory lists Board Certified veterinarians, and other scientific and professional organizations publish membership rosters which frequently contain biographical data on individual members. Once one expert is contacted, he/she can usually supply the names of several others who are considered particularly competent in certain areas.

VII. The Causes of New Animal Drug Determinations:

There are three major reasons why CVM personnel are called upon to make NAD determinations:

A. Submission of an NADA by a Sponsoring Firm:

The fact that this calls for an NAD determination is frequently overlooked. If there is any doubt in a reviewer's mind regarding the lack of general recognition of safety and efficacy of a product, and particularly, if no other similar products are the subjects of approved NADAs, personnel in the Division of Surveillance should be contacted to determine the current NAD status of the product. (See also Sections 8(i) and 8(j) of this guide.)

B. Request for Label and Formulation Review either Directly by Firms or by FDA Personnel.

C. Support for Proposed Regulatory Letter, Citation, Seizure, Injunction or Prosecution.

VIII. Procedures for New Animal Drug Determinations:

While every case is different and therefore no specific guidance can be provided which will apply in all cases, some general guidelines to assist CVM reviewers in making NAD determinations follow:

A. Basic Product Information Needed:

Before definitive NAD determinations can be made, complete labeling and associated promotional material, complete formulation and the marketing history of the product must be available to the reviewer. The former must be submitted either by the firm or collected and submitted by FDA personnel. The marketing history can be established by establishment inspection reports located in the Administrative Files.

B. Primary Reference Sources:

Veterinary and human texts serve as the first source of information on a product since general recognition should be reflected in the discussions and recommendations of such texts. Each ingredient in a formulation, as well as the total combination, should be researched. Older reference texts are valuable for this purpose and should be retained by CVM.

C. Basic Reference Findings:

Any indication of toxicity or lack of efficacy of any ingredient in a product should be documented and the reference cited. Any recommendation for use based on another literature reference should be recorded for future reference. Record the inability to find any references at all in the appropriate general texts.

D. In-Depth Literature Search:

In those cases where some references to the use of a product are made which are purportedly based on data, and no convincing documentation of lack of safety or efficacy can be found, a complete literature search is in order before a decision is rendered.

E. Consultation with Experts:

In some cases, a complete literature search will demonstrate some data (probably generic in nature) and perhaps a generally positive view of the safety and efficacy of the drug substance in question. Under these circumstances, a reviewer is advised to contact several experts and elicit their opinion prior to making an NAD determination. If the opinion is to be rendered in support of a regulatory action, this should definitely be accomplished. Document these opinions thoroughly.

F. Informal Opinions:

New animal drug opinions may bear on the necessity for new animal drug approval, and on possible regulatory action. Therefore, as noted above, new animal drug opinions must be given more careful consideration than can be afforded in formulating informal verbal opinions. Further, informal new animal drug opinions based on an incomplete consideration of the data may be at variance with a position already adopted by another Division in the Center, thus serving as a source of confusion and possible embarrassment. No verbal opinions will be given to inquirers by any CVM personnel as to whether an animal drug is a new animal drug, and if so, as to our regulatory posture concerning the drug. All such request must be made in writing, and routed to the Division of Compliance, which has the responsibility for providing advisory opinions as to the status of drugs under the Food, Drug, and Cosmetic Act. It is only in this way that we can be assured of a written record that reflects the institutional views of the Center and the Food and Drug Administration.

G. Responsibility for NAD Opinion:

Division of Compliance (DC) will rely on the opinion of the Division of Surveillance (DS) which, in turn, may consult with other Divisions, as needed, concerning the medical basis for the new animal drug status of an animal drug. If DS advises that a product is an NAD and may not be marketed without approval, they will give firm assurance to DC that the testimony of experts can be obtained, should it be necessary to support a legal action. In addition, DS will comment as to the following:

1. Whether the drug is intrinsically an NAD because of its chemical composition, or merely because of its labeling directions for use or for the purpose for which it is intended.

2. Whether the article can be relabeled or reformulated in any way so that it may be marketed without the need for an approved NADA.

H. Class Actions:

A number of products have been determined to be NAD on a class basis in accordance with the criteria noted above. For example: articles sterilized by radiation; timed-release drugs; radioactive drugs; microencapsulated drugs; medicated blocks; medicated liquid feed supplements; antibiotic, nitrofuran and sulfonamide drugs in the feed of animals (subtherapeutic uses); and

antibiotics, nitrofurans and sulfonamides for use in food- producing animals by whatever means of administration. Many of these determinations are the subjects of statements of policy now published in Title 21 of the CFR.

I. Lack of Expert Testimony to Back CVM Position:

In the event that a product is determined to be NAD on the basis of CVM scientific criteria, but expert testimony to support its lack of general recognition of safety and/or efficacy is not available, and a response to the manufacturer is required, it is appropriate to inform the involved manufacturer that an NADA is not required to support marketing at the present time but that such may be needed in the future.

If the situation noted above applies to a class of products, then manufacturers who voluntarily submit NADAs for products in the class should be informed that such applications are not presently required but may be in the future; and that no regulatory action based on a 501(a)(5) or 501(a)(6) charge is contemplated against either the manufacturer's product or competitive products (provided they are appropriately labeled for generally recommended indications at generally recommended doses, etc.).

If the sponsor still wishes to get an NADA approved for the product, it should be accepted and reviewed as rigorously as any other NADA.

J. Need for Unpublished Data to Support NAD:

It is important to note that any NADA, which is recommended for approval, must bear some unpublished data generated using the product being approved (or bear a demonstration of bioequivalence to a product supported by such data); otherwise approval may constitute an affirmation of general recognition of safety and efficacy. If CVM experts can review published data submitted with the application and conclude it supports the safety and efficacy of the product, then so can any expert and the product may not be a new animal drug. If it is not a new animal drug by CVM standards, then an NADA is not needed for the product, and the manufacturer should be so informed. A possible exception to this would be a case in which a firm generated new data and then published it prior to NADA approval (an unexpected occurrence). In this case, it could be argued that the product was a new animal drug in accordance with 201(v)(2) because it had not been used to a material extent or for a material time.

IX. Expert Witnesses:

Before any contact with an expert witness, the CVM representative should be familiar with the product, with the law pertaining to the situation, and with the general literature (or lack thereof). If litigation is imminent, know where the case will be held and approximately when the trial will occur.

A. Initial Contact:

The following points should be discussed in a logical process (a list of potential questions to be asked the expert is available as an appendix to the more detailed CVM training document on NAD determinations):

1. Inform the expert that FDA is contemplating (or involved in) regulatory action regarding the unapproved use of a particular product or products.

2. Explain that the reviewer is unable to find data to support the safety and efficacy of the product in question.

3. Discuss the intended uses of the product and determine the expert's experience with the product, with FDA, and with court testimony, in general, and his familiarity with the literature on the drug product.

4. Determine whether the expert is aware of any controlled studies on the drug substance and on the product.

5. Determine whether the expert believes the product to be generally recognized as safe and effective based on data derived from adequate and well-controlled studies in the published literature.

6. Obtain a current curriculum vitae from the expert.

7. Obtain suggestions for other potential witnesses, particularly if the expert is supportive but unavailable for the particular trial date.

8. Confirm all telephone conversations with a follow-up letter to the expert thanking him/her for the time expended.

9. Record the amount of time taken in consultation prior to a contested regulatory action, and if it is significant, report it together with a recommendation for compensation of the expert to: Director, Division of Compliance, HFV-230.

B. Documenting Services of Expert:

Prepare a memorandum informing the Consumer Safety Officer (CSO), HFV-230, who has been assigned to the case, the name of any expert who has agreed to represent FDA and who will potentially spend time reviewing labels and/or literature in support of the case. This must be done immediately so that the appropriate documents can be initiated to compensate the expert for his/her time. Any significant amounts of time the expert spends in telephone conversations with a CVM reviewer should also be documented and sent forward to the same CSO.

C. Follow Up:

Following the conclusion of the case, by whatever means, write the involved experts thanking them for their services and time and informing them of the outcome.