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**Comments related to the
"Request for Comments on Development of Options to
Encourage Animal Drug Approvals for Minor Species
and for Minor Uses"
Docket No. 97N-027 Federal Register Vol. 62 No. 120
June 23, 1997**

97N-0217

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97N-0217

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**COMMENTS RELATED TO THE "REQUEST FOR COMMENTS ON
DEVELOPMENT OF OPTIONS TO ENCOURAGE ANIMAL DRUG APPROVALS FOR
MINOR SPECIES AND FOR MINOR USES" DOCKET NO. 97N-027
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Proposed Legislation to Stimulate Availability

Legislation is proposed to increase the incentive for researchers and sponsors, and manufacturers to conduct research to generate the safety and effectiveness data needed for the approval of animal drugs intended for minor uses and minor species (MUMS).

Minor use of an animal drug is defined as any use in a major species for a disease, condition, or alteration of physiologic/somatologic function that rarely occurs or occurs in limited geographical areas, or any use in a minor species, which does not provide the economic return on investment required to attract the money to conduct the research.

Minor species are defined as any species other than major species. Major species include cattle, swine, chickens, dogs, and cats. Sheep, turkeys and horses are intentionally deleted from the major species list.

Sponsor-manufacturers have been responsive to practitioners in need of MUMS drugs by making approved drugs available, providing advice on protocol development, and in some cases, by sharing information in their FDA Veterinary Master Files. Understandably, such sponsors have not been enthusiastic in expending the substantial resources necessary for MUMS research and development to either add labeling indications to existing drugs or to develop new chemical entities for such use. Additional legislation will be needed to expand the incentives available to encourage researchers and manufacturers to support the development of new MUMS drugs and to support the development of information on cross species use of animal drugs or human drugs.

Legislation is therefore recommended to provide for FDA designation of "designated MUMS drug status." Such legislation would clarify the drugs, sponsors, and indications for use that qualify for special treatment to encourage availability for treatment of minor use-minor species. Entry to the process would be initiated through sponsor's requests to FDA to receive designation of a veterinary drug as a minor use-minor species drug.

One approach proposed is similar to that developed via the Orphan Drug Act of 1983, contained in sections 525 through 528 of the Food, Drug and Cosmetic Act and implementing regulations in 21 CFR 316. Although there are significant differences between orphan drugs and MUMS drugs, the success of the orphan products development program can provide valuable insights for development of MUMS drugs. The following insights on the program may be gained from information provided by the Office of Orphan Products Development. In the 15 years prior to the Orphan Drug Act, fewer than one drug per year for rare diseases or conditions were granted approval by the Agency. In the 13 years since enactment, 675 drugs have been designated as orphan drugs, and 148 of these have progressed to New Drug Application (NDA) Approval by

the FDA. Sponsors who have achieved marketing approval for orphan drugs in the U.S. cite the seven-year period of orphan drug exclusive marketing as the most important incentive that stimulated them to devote the resources to pursue NDA approval. Other provisions of the act, i.e., tax credits, protocol assistance, and grants for clinical studies on orphan drugs, were also deemed by sponsors to be important incentives. A review of the approved drugs, however, demonstrates that very few orphan drugs without the potential for some profit to small companies have progressed to approval.

A two-tiered approach of incentives is established to stimulate the availability of MUMS drugs based on the priority of need, and the importance of the drug for the indication and species identified. This approach recognizes that the real orphans of the MUMS drugs will need special incentives and other programs to encourage development.

The two categories are "High priority MUMS drugs," and "Secondary priority MUMS drugs." When MUMS designation for a drug is requested by a sponsor, only that sponsor will be entitled to designated MUMS drug status for the drug. FDA may also act in the absence of a sponsor's application to designate a drug or class of drugs as "MUMS drugs in need of development" to further encourage sponsorship of studies and development of such drugs.

HIGH PRIORITY MUMS DRUGS:

1. Application Requirements

Sponsors seeking the extensive incentives conferred by high priority "designated MUMS drug status" will submit documentation to the FDA in a request for high-priority designation of a MUMS drug adequate to demonstrate all of the following:

a. That the drug is intended for treatment of a disease, condition, or alteration of a physiologic or somatologic function for a MUMS. Conditions and functions may include non-disease states and productivity considerations such as fertility enhancement, increasing lactation and fibre yield, and increasing aquaculture yields.

b. Financial projections on costs and anticipated income from sales to demonstrate that the intended MUMS indication occurs so infrequently that the sponsor has no hope of recovering within a five-year period after New Animal Drug Application (NADA) approval, the costs of research and development for such diseases or conditions, or

Evidence that the drug is intended for diseases or conditions for which existing marketed drugs are not available or if they are available, a description of why they are inadequate to treat the disease or condition.

c. Evidence of a promising scientific rationale for effectiveness, documented when possible by scientific literature to constitute an important advance in therapy for the MUMS condition, or for a broad class of MUMS conditions and species.

d. Documentation that the drug is for life-threatening or otherwise serious disease or condition in the target species, and/or has the potential for significant impact on human health or human food economics for the species targeted.

2. Legislative Incentives Needed for Designated High-Priority MUMS Drugs

For drugs designated by FDA as "High-Priority MUMS Drugs," appropriate incentives will include:

a. Establishment of an Office of Minor Use Minor Species (MUMS) and appropriation of the funds to professionally staff such an office in the Center for Veterinary Medicine, FDA. The office would have the responsibility and authority to implement legislative provisions such as exclusivity, protocol assistance, and performance as a desk officer-liaison for the development of MUMS. Additionally the office would act as an internal ombudsman for MUMS development within FDA, would develop innovative programs to identify promising human drugs for MUMS use, and would promote, develop and coordinate communications and cooperative industry, professional, and consumer efforts.

b. Beginning upon the date of approval of an NADA for such drug for a MUMS indication for which the sponsor received MUMS designation status, the FDA will not approve an NADA for another sponsor for the same drug for the same indication, for a period of ten years. FDA may approve a second drug if the agency determines that the sponsor cannot make the drug available. Sponsors may consent to allow a second sponsor to obtain approval of the same drug for the same use.

c. Authorization and appropriation by Congress of a significant war chest (\$10 million) and additional FTE staff adequate to implement a program whereby FDA can finance field studies and development of such drugs under contractual arrangement with research institutions or drug sponsors/manufacturers. After approval, contractual arrangements for manufacturing and distribution of the product may be initiated with a drug manufacturer similar to the Salk-Swiftwater contract with the U.S. Army. Additionally, requests for applications announced for the NRSP-7 program will provide that sponsors of drugs receiving designated high-priority MUMS status will be given preferred status for review and funding.

d. The sponsor holding designated high-priority MUMS status for a drug will be entitled upon the date of obtaining NADA approval to a tax credit equal to 100% of the cost of research and development and such expenses as are necessary to make the drug available. Such tax credits will be applicable prospectively or retrospectively for up to ten years after NADA approval.

e. FDA will request legislative authority to establish a "Conditional NADA Approval" when High-priority MUMS drugs are considered to be:

experiences related to improving efficacy of the drug as used, are made on a systematic basis to FDA.

FDA may make a determination that a need exists to answer remaining questions about risks and benefits after such time as the drug has progressed to conditional NADA approval. In such cases, FDA may require a commitment from the sponsor of such drug to make reports to FDA and /or to initiate post-marketing studies to fill in additional information as FDA determines will be needed from experience with the drug related to the drug's risks, benefits, profile of appropriate use, and applicability to other species. Non-compliance by the sponsor with reporting or the conduct of follow-up studies required will constitute cause for removal of MUMS drug exclusivity status when such status has been granted to the sponsor. Conditionally approved NADAs will be required to include labeling that specifies the specific exemptions that were provided to allow conditional approval of the drug.

SECONDARY PRIORITY MUMS DRUGS:

1. Application Requirements

Sponsors seeking the incentives that confer to secondary priority MUMS drugs will submit a description of the drug, and sufficient documentation to the agency to demonstrate:

- a. That the drug is intended for treatment of a disease or condition for a MUMS.

period of five years. FDA may approve a second drug if the agency determines that the sponsor cannot make the drug available. Sponsors may consent to allow a second sponsor to obtain approval of the same drug for the same use.

b. The sponsor of such drug will be entitled upon the date of obtaining NADA approval to a tax credit equal to 100% of the cost of research and development to obtain an NADA and make the drug available to practitioners. Such credit may be applied forward or backward in time for a period of ten years after approval.

c. The sponsor/manufacture of such drug will be accorded authority to include reference to the specific designated MUMS uses of the drug in its label and instructions for use, subject to FDA guidelines to be developed on such references.

d. If such drugs are already approved for use in humans or in major species, FDA will request sponsors of the approved drugs to share data in public master files (PMFs), when applicable, with sponsors of designated MUMS indications for these drugs.

**NON-LEGISLATIVE AGENCY OPTIONS (FDA, AND JOINT FDA/ USDA)
FOR STIMULATING THE DEVELOPMENT OF MUMS**

1. Establishment of MUMS Species Desk Officer

Establishment of species-specific MUMS desk officers in USDA and FDA who have the responsibility for development, coordination and oversight of all incentives and development projects within the agency for MUMS species. Desk officers will be established for all species and will perform the following functions:

- a. Evaluation of reports received on MUMS drug use over a period of time to determine applicability of cross species use.
- b. Interaction with species-specific interest groups including farmers, producers, researchers, veterinary clinics and hospitals with high exposure to and interest in such species and conditions.
- c. Coordination of interactions and support to activities by “lead researcher-practitioners,” and suggesting program priorities to NRSP-7 administrators regarding special focus of research funds.
- d. Encouraging and jointly sponsoring special technology or consensus conferences with animal science professionals and others to address problems, opportunities, and drug development needs. Feeding information on special needs on drug development to decision makers in the FDA and USDA

No additional appropriations will be requested for initiation of the program. Results will be evaluated on the first years experience and accomplishments, and a request for appropriated funds will be made based on plans desk officers experience with programs that need financial support.

2. Technology Assessment Program for MUMS

FDA will initiate technology assessment programs, such as annual workshops, in which focus groups will be held to encourage the presentation of scientific information to be profiled against common drug use and diagnostic therapeutic practices for the target MUMS. Scientific researchers as well as practitioners, wildlife management specialists, zookeepers, breeders, etc., will provide testimony on the special problems and disease conditions in specific species. Species-specific conferences will be conducted over this period during which consensus will be sought regarding the priority problems to be addressed, and special incentives or other programs that are needed to stimulate the availability of drugs for such species. A primary focus of this activity will be to transfer drug treatments, toxicity, and technologies from the human sector to the animal-use sector. Another focus will be to develop consensus on where the problems are

and what is needed regarding federal, professional, industry and interest group efforts to jointly resolve the problems impeding development. The CVM will submit a plan for such programs and request appropriations of funds to support such activities beginning in Fiscal year 1998.

3. Availability and Access to Information in PMFs and VMFs.

When designated priority MUMS drugs are in Investigational New Animal Drug (INAD) status for another species or are already approved for use in another species, FDA will proactively request sponsors/manufacturers of these drugs to open their VMFs to allow reference by sponsors of designated MUMS uses for such drugs. In many cases MUMS sponsors may benefit by the capability of referring to but not directly viewing such files. Sponsors of approved INADs and NADAs will be encouraged when appropriate by FDA to share data on effectiveness, safety, and residue chemistry, via use of the PMF or by other means directly with sponsors of such drugs for MUMS indications. Experience gained by veterinary practitioners and submitted in reports on Veterinary Feed Directive use will be made available to MUMS-use sponsors when possible.

4. Reference and Labeling on Unapproved Uses

Upon adequate demonstration to FDA of the animal safety of a designated high-priority MUMS drug, the sponsor/manufacturer of such drugs will be accorded authority to include reference to the designated MUMS unapproved use of the drug in its labeling and instructions for use, subject to FDA guidelines to be developed on such references. Such labeling will be regulated under INAD regulations and a central repository or PMF will be established, whereby reports of field studies, case experiences, adverse reactions, and residue experience may be posted and made available to all end users of the drug. Information accumulated in this file may be used to justify changes in the regulatory status and NADA approval for the drug.

5. Relief from Safety Requirements

A study will be initiated to determine the feasibility and potential effect of legislation or other actions within existing FDA and USDA authority to relieve sponsors of designated high-priority MUMS drugs of the responsibility for research to demonstrate human safety related to NADA approval of drugs for such conditions when it is determined to be in the national interest to expedite availability of the drug. For such MUMS drugs that are adequately demonstrated via NADA to be safe and effective for the disease or condition in the target species, the U.S. Government will initiate and fund such human safety studies as are deemed necessary. Alternatively, the government may provide for 100% tax credits to sponsors to provide additional evidence to demonstrate human food safety of drug residues or effects. This will relieve marginally capitalized but committed sponsors of the unfair burden of proving food safety.

6. "Lead Researcher-Practitioner" Program

In recognition that the most needy MUMS conditions may not have any drugs currently identified or proposed for research, FDA and USDA will jointly establish a lead researcher-practitioner program.

a. Identifying leaders for high-priority MUMS indications

This program will encourage practitioner-researchers to assume responsibility and leadership roles in all aspects related to a specific MUMS indication for a minor species. This program will be initiated by recognition of high-priority MUMS diseases or conditions for which drugs are not available, practitioner and treatment expertise is lacking, or no sponsor has expressed interest in any drug that has promise for the condition. In rare cases when a drug is identified for such conditions, FDA may designate the drug as a non-sponsored high-priority MUMS drug.

b. Federal Register announcement of MUMS in need of lead researcher-practitioners.

FDA and USDA will announce a list of species and indications in the Federal Register that are in need of lead researchers-practitioners, and also identify promising drugs for any of these conditions that FDA has designated in the absence of sponsorship as high-priority MUMS drugs. Veterinary research organizations, industry sponsors, and veterinary medical schools will be individually invited to establish at least one lead researcher- practitioner to address a listed MUMS condition.

Although no funds will be specifically targeted for this program, FDA and USDA will maintain and widely publish the lead researcher-practitioner list for referral of cases for treatment or participation in research. It is anticipated that the nationwide status and prestige associated with lead researcher-practitioner status for a MUMS will act as a potent incentive and may even allow for some competition between qualified applicants.

c. Qualifications for lead researcher-practitioner status for MUMS conditions will require:

1. Demonstration of education and experience that qualifies them to conduct research and treat animals with the targeted MUMS condition.
2. Location in an institution, organization, or geographic area in which sufficient numbers of target animals are found on feedlots, farms, research facilities, or other evidence of exceptional capability to access such animals.
3. Availability of the facilities for maintenance, treatment or diagnosis within the institutional affiliation, with a history of compliance with appropriate governmental regulations.
4. Past experience within the proposed institution conducting veterinary medical research or providing treatment for the target or similar MUMS.

d. Once named as lead researcher-practitioners, the requirement to maintain U.S. government recognition of the approbation will be:

1. demonstration that sufficient numbers of target MUMS animals have been diagnosed or treated by the lead researcher-practitioner.

2. demonstration of accomplishments in-vitro or in-vivo assessing chemical compounds or approved drugs with pharmacological promise for the MUMS condition.

3. initiation of controlled animal studies on MUMS afflicted with the target disease or condition. D.V.M. and V.M.D. and Ph.D. dissertations will also be encouraged to address aspects such as strategic approaches to treatment of the diseases or to perform needed controlled field studies on MUMS drugs and conditions. These studies may be on any aspect of the requirements for NADA approval such as evaluation of pharmacokinetics, animal and human toxicity, dose-ranging evaluations, assessment of residue retention and depletion, and establishment of a scientific basis for withdrawal time requirements.

4. over the long term, publication in juried veterinary medical journals of studies conducted in the target MUMS and demonstration that the lead researcher-practitioner is being acknowledged throughout the U.S. as a center for referral, central repository for information, consultation, and advice in the diagnosis or treatment of the target MUMS condition. Also over the long term, accomplishments will be expected regarding encouragement of manufacturers to initiate studies on drugs identified to have promise for these MUMS conditions.

6. Continuation of education, experience, ethical behavior, maintenance of facilities, and compliance with appropriate regulations after lead researcher-practitioner status was attained.

7. Leadership in annual meetings, technology assessment or consensus development conferences sponsored by FDA, USDA or other groups on subjects related to the MUMS condition.

At the end of the first year of the program, the agencies will evaluate the impact of the program and request that Congress provide funds needed to expand successful initiatives.

7. Acceptance of Foreign Studies

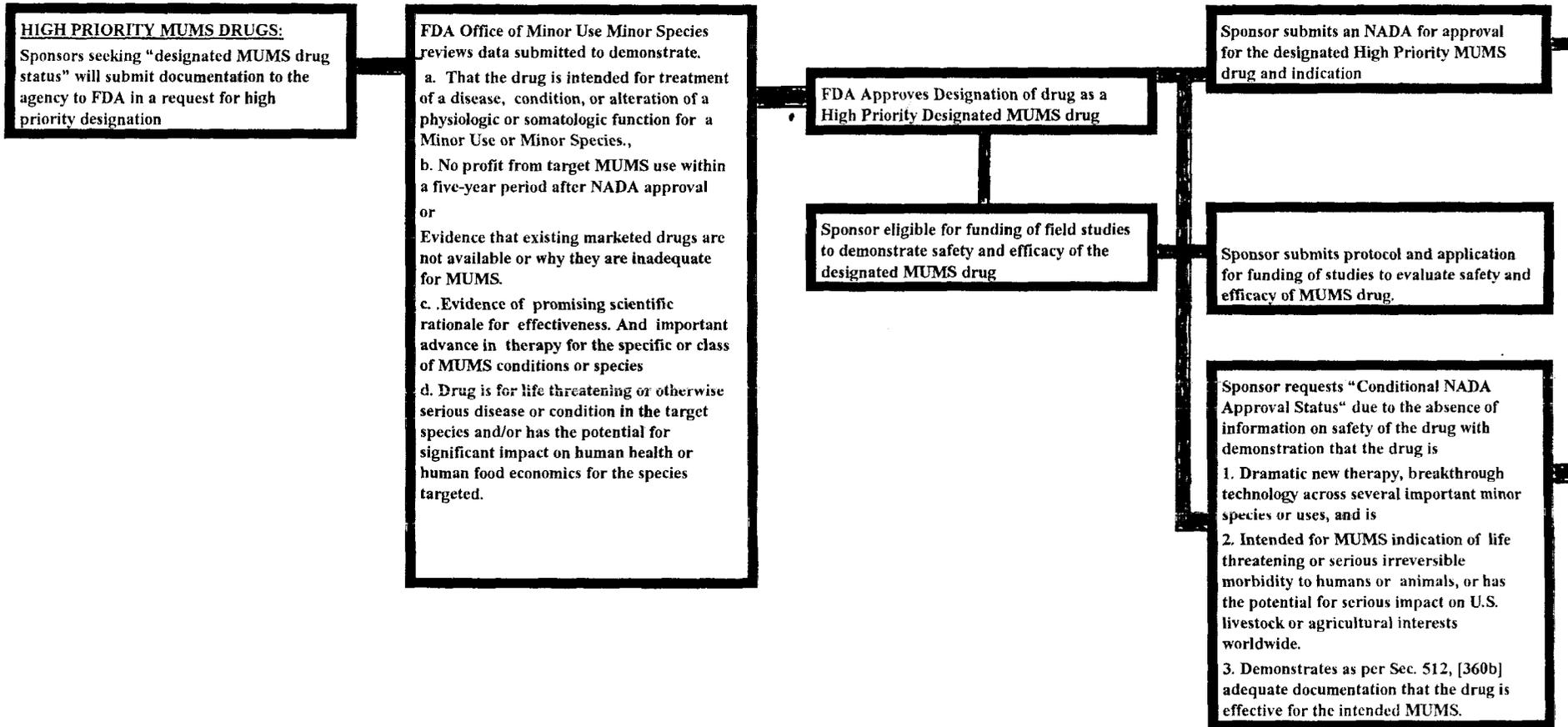
FDA will provide for increased acceptance of foreign data from studies in support of NADA applications on MUMS drugs, provided such studies are designed and conducted under rigorously controlled protocols that conform to practices expected of such data derived from U.S. conducted studies. Such studies must be performed by qualified investigators, and must be conducted in accordance with ethical principles acceptable to the world community. Studies meeting these criteria may be utilized to support NADA approval in the U.S. of such drug for the MUMS indication when the sponsor has provided documentation to the FDA to prove conformance with above listed requirements. FDA will develop a guideline to assist sponsors in evaluating prospective or retrospective studies conducted at foreign research sites as related to requirements for design and control of INAD and NADA studies.

8. Establishment of a Pilot Animal MUMS Traditional Medicine Assessment Program in the USDA or FDA

Congress would fund a pilot program in one or more priority MUMS species to:

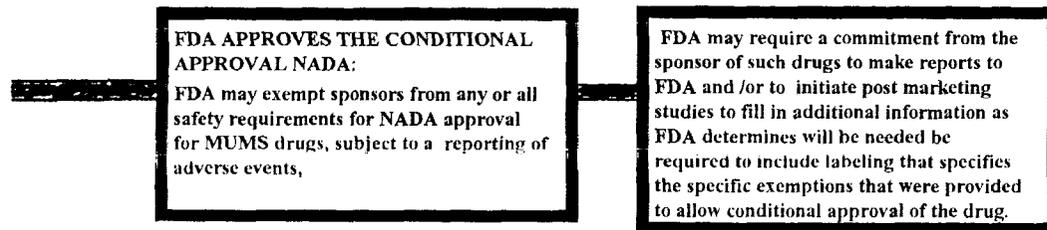
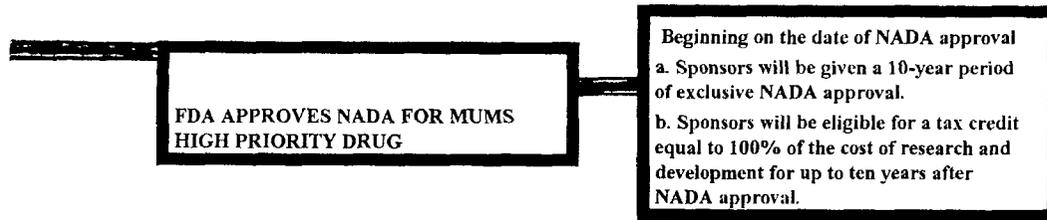
- a. review the world wide literature regarding the use of approved drugs in third world countries, as well as unapproved tropical medicines, herbs, nostrums, natural substances, tribal medicines, and other treatments related to diseases or conditions in such species.
- b. refer knowledge gained on such uses for the review by scientists qualified to assess the promise of such substances and practices for MUMS conditions.
- c. to encourage sponsors to develop and make promising drug substances available that have a pharmaceutical quality sufficient to meet research standards for field trials.
- d. promote the development of INADs and NADAs on such substances.
- e. evaluate the results obtained in the pilot program related to application of the effort to other MUMS. The agency will make recommendations and make requests for resources from Congress related to expansion of the program based on experience with the pilot program.

FLOW CHART FOR DESIGNATION OF HIGH PRIORITY MUMS DRUGS



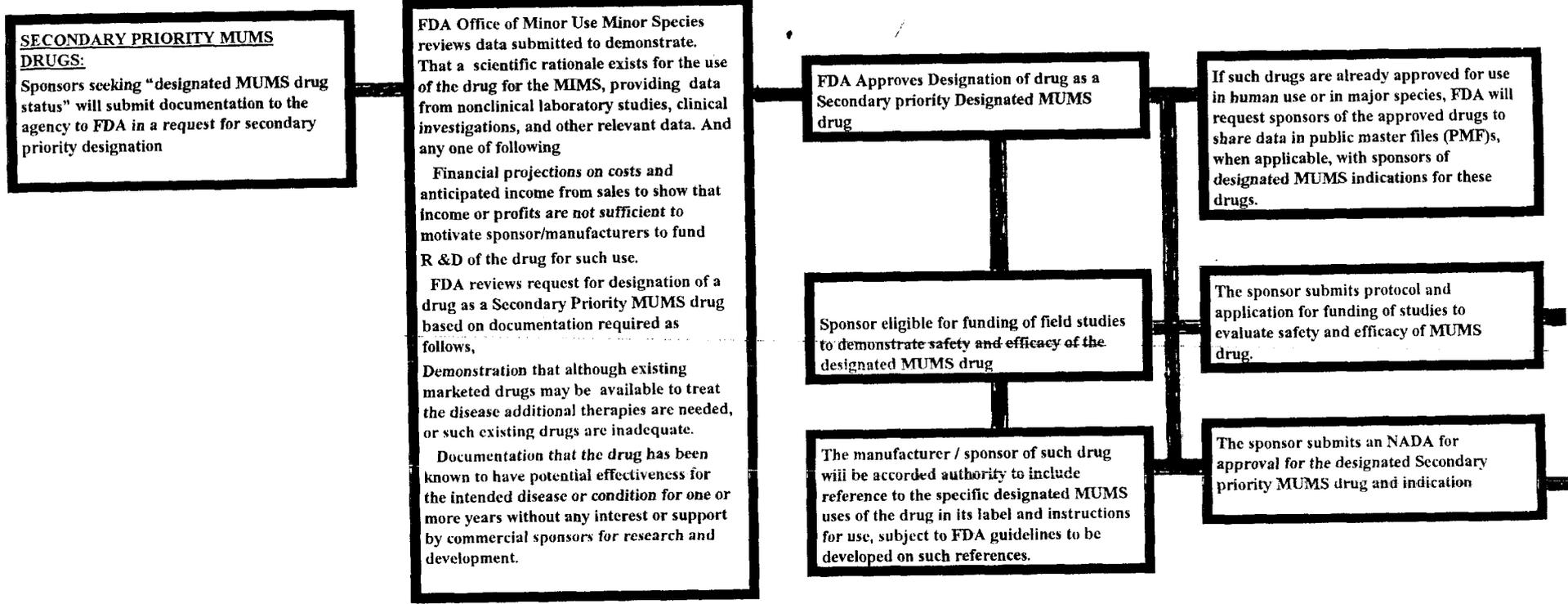
11(a)

FLOW CHART FOR DESIGNATION OF HIGH PRIORITY MUMS DRUGS (CONT)



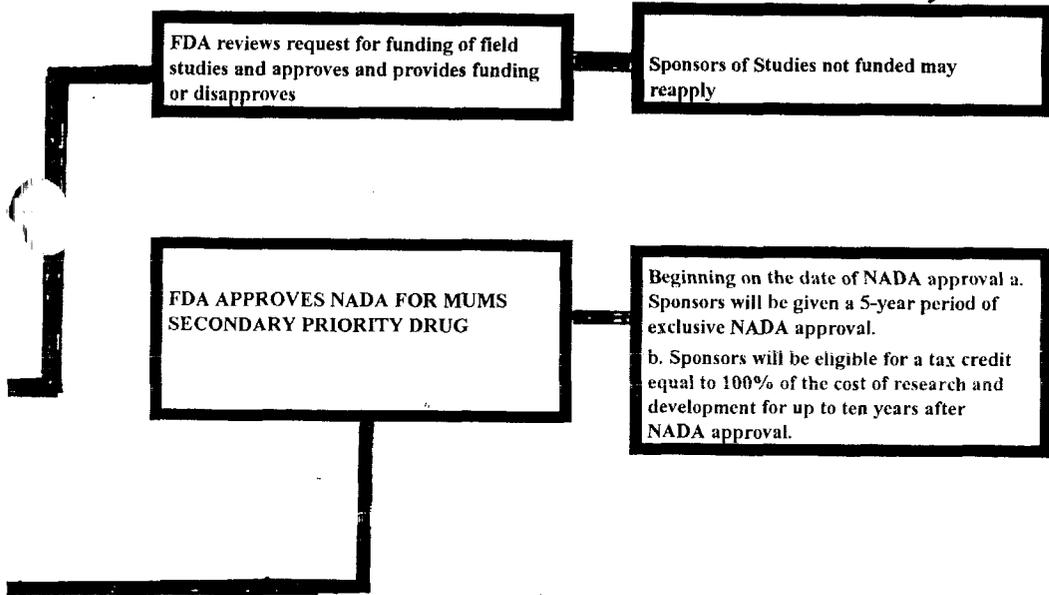
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FLOW CHART FOR DESIGNATION OF SECONDARY PRIORITY MUMS DRUGS



12 (a)

FLOW CHART FOR DESIGNATION OF SECONDARY PRIORITY MUMS DRUGS (CONT.)



12 (b)



Memorandum

Date . July 1, 1997

From Associate Director, Policy and Regulation, HFV-6

Subject Comments for Adding to a Docket

To Docket Management Branch, HFA-305
Attn.: Jennie Butler

Please put the attached document on Docket No. 97N-0217.



G.A. Mitchell, D.V.M.

Mr. Emery Sturniolo was hired by CVM to read the June 23 Federal Register (FR) Request for Comment on minor uses and minor species and to write a paper describing his thoughts from reading the FR questions. Mr. Sturniolo has a Masters degree in Public Administration and is a former FDA employee. When he was an FDA employee, he assisted in the drafting of policy, procedures, guidelines, and proposed and final regulations for the implementation of the Orphan Drug Act of 1983.