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IMPACT OF GOVERNMENT REGULATIONS ON DEVELOPMENT OF CHEMICALS USED IN ANIMAL PRODUCTION

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Report No. 85
October 1980

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FOREWORD

As the Nation enters a period of increasing financial stress, due in part to government actions, including those taken by regulatory agencies, members of the public are becoming increasingly aware that the cost-benefit concept has application to government regulations. Regulations have benefits, but they also have costs. Through education regarding such matters, society will hopefully be enabled to adopt a position in which the benefits are well in excess of the costs.

Because of a desire to increase the general level of understanding regarding the impacts of government regulations on the development of agricultural chemicals, the executive committee of the Council for Agricultural Science and Technology (CAST) authorized the distribution of a mail ballot to members of the board of directors in November 1978 to determine whether a task force should be established to prepare a report dealing with the impacts. The board approved, and the task force was promptly established. The task force included expertise in agricultural economics, agronomy, animal science, dairy science, entomology, meat science, nematology, plant pathology, poultry science, range management, sociology, soil science, toxicology, and weed science.

This report, the first of two prepared by the task force, deals primarily with regulation of animal drugs and nutritional supplements and to a minor extent with pesticides used in animal production. The second report will address the regulation of chemical pesticides used in agriculture and forestry.

The first draft of this report was reviewed by a subcommittee of the task force at a special meeting, and a revised version was sent to the headquarters office for editing. Editing was done by Dr. T. C. Byerly with assistance from the headquarters office, and the edited version was returned to the task force and the CAST executive committee for review and comment. A revised version was then returned to the same groups for further comments before the final version was reproduced for publication.

On behalf of CAST, I thank members of the task force and all the others who gave of their time and talents to prepare this report as a contribution of the scientific community to public understanding. Thanks are due also to the employers of task force members who made the time of their employees available at no cost to CAST. And finally, thanks are due to members of CAST. The unrestricted contributions they have made in support of the work of CAST have financed the report.

This report is being distributed to the Agriculture Committees of Congress, the U.S. Department of Agriculture, the Food and Drug Administration, the media, and institutional members of CAST. Individual members may receive a copy on request.

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Charles A. Black
Executive Vice President
Council for Agricultural
Science and Technology

PREFACE

This is a report of the Council for Agricultural Science and Technology (CAST) task force on the Impact of Government Regulation on the Development of Agricultural Chemicals. The task force has organized and focused its efforts in two areas: (a) the effects of regulation on innovation in chemicals for use in animal production and (b) the effects of regulation on innovation in development of plant protection chemicals. The task force decided fairly early in its deliberations not to include a consideration of regulation and innovation in fertilizers.

This report has been prepared by the task force subcommittee on Animal Production Chemicals. It has been read and approved by the entire membership of the task force.

The task force held meetings on January 29 and 30, 1979, in Washington, D.C., and in Atlanta on April 17 and 18, 1979. The two subcommittees each held additional meetings to discuss and revise their findings. The task force held discussions with staff members of the Food and Drug Administration (Bureau of Foods and Bureau of Veterinary Medicine), the Environmental Protection Agency, the USDA Food Safety and Quality Service, the National Agricultural Chemicals Association, the American Feed Manufacturers Association, the Animal Health Institute, the Fertilizer Institute, and the Environmental Defense Fund. Consultations were held with individual government, industry, and university scientists by individual task force members. The task force has appreciated the interest and cooperation of the representatives of government, industry, public interest groups, and individual scientists who have made the report possible. Any errors or misinterpretations of the information incorporated in this report are, however, the task force's own responsibility.

The Subcommittee on Chemicals Used in Animal Production included Charles A. Lassiter (Chairman), Gerald A. Carlson, Edward C. Naber, Albert M. Pearson, Duane E. Ullrey, and Robert J. Weir. The Subcommittee on Chemical Pesticides for Crop and Forest Uses included Eldon I. Zehr (Chairman), Samuel R. Aldrich, Thomas Allen, Arnold P. Appleby, Gerald A. Carlson, Don A. Dillman, David Graham, Ronald J. Kuhr, John D. Radewald, and Robert J. Weir.

Vernon W. Ruttan
Task Force Chairman

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SUMMARY

Extensive progress has been made over the last several decades to satisfy the national concern for the health and safety of consumers of animal products. This progress, however, has not been made without costs in terms of reduced productivity of scientific and technical effort devoted to research on, and development of, chemicals for animal production. The decline in research and development productivity has certain unfavorable implications for the future in terms of animal production and cost of animal products to consumers. The principal concerns discussed in this report regarding the system of regulation, the direction in which it is moving, and its consequences may be summarized in the following four points. Some of these concerns are shared also by certain members of the Food and Drug Administration.

- The share of sales devoted to research and development in the animal drug industry appears to have declined since the mid-1970s. The percentage of research and development expenditures devoted to innovation has declined. The costs of developing and testing new animal drugs have risen sharply. The productivity of research and development effort in the animal drug industry has declined. If taken individually, these trends might not appear to be a source of undue concern. Taken together, they imply a less healthy environment for technical advance in the animal drug industry currently than in the past.

- The data requirements for clearing new chemicals are now extensive and are expensive to fulfill, and the process of obtaining clearance is at times unduly prolonged. A clear implication of two case studies presented in this report is that only a part of the delay in obtaining clearance is due to scientific or technical considerations. Major causes of delay include the failure of the Food and Drug Administration to publish the procedures required for clearing new drugs; complex, imprecise protocols for new animal drug applications; step-by-step consideration of the information submitted; and requests for supplemental information.

- The Food and Drug Administration's proposed "sensitivity of method" document does not adequately discriminate between compounds that merit extensive testing and those that do not. The result may be misallocated scientific resources and deterred development of useful chemicals of limited market potential. The document also proposes the use of models which would confound the interpretation of research findings and in some instances would lead to incorrect conclusions.

- The regulatory procedures employed by the Food and Drug Administration discourage the development of both major drugs for minor species and minor drugs for major species of animals. The logical consequence is a direction of research and development in animal health, nutrition, and production toward the major species, and possibly also the concentration of effort on a limited range of products. The ultimate effect could be a failure to utilize effectively the available chemical and genetic potential that will be needed as new sources of productivity in the future.

OVERVIEW

Chemicals are important factors in the production of meat, milk, and eggs. Their use assures more abundant supplies at lower prices to consumers. Food products of animal origin provide about 65 percent of the protein we consume, in forms we prefer.

Through regulatory action, the Food and Drug Administration (FDA) and other federal, state. and local agencies assure the safety and wholesomeness of these foods. Chemicals must be approved for use, and food products from livestock and poultry are monitored for residues of drugs and pesticides as a safety precaution. Residues hazardous to human health are found only infrequently. Regulatory actions are taken to eliminate violative products and their causes. Such actions include the withdrawal of approved drugs found unsafe under conditions of use.

Safe and effective new chemicals are needed to increase animal productivity. New products result from innovative research and development (R&D) carried on in the laboratories of industry sponsors, and in those of public and private research agencies. Publicly supported R&D in agriculture is estimated to yield an annual return to the public of more than 35%. The return to industry and, hence, the stimulus to develop new products, is determined by market returns and costs of product development and marketing. The animal drug industry spent funds equal to 10 to 13.6 percent of annual sales for R&D during the 1965-1978 period.

The number of new animal drugs approved from 1965 through 1967 was 10; only 5 were approved from 1975 through 1977. The cost per new drug, in deflated dollars, increased from $13.8 million in 1965-1967 to $36.4 million in 1975-1977.

Uses of new animal drugs (NADs) and other feed additives for the production of animals and animal food products that move in interstate commerce are subject to approval by FDA under the provisions of the Federal Food, Drug, and Cosmetics Act (FFDCA). States and local agencies may regulate uses for animals and animal products within their respective jurisdictions.

Requirements for approving new drugs and other feed additives are complex and imprecise. In some instances, several years elapse between the time of application and FDA action approving the proposed use. The process of approving new animal drugs could be accelerated and made more efficient if the information to be required were clearly specified in writing at the beginning of the process and if some allowance were made for the changes in requirements that are introduced after the manufacturer has committed resources to obtaining the information specified initially. Changes in requirements may result, not only from new developments in regulations, but also from differences in interpretations and personal views as new FDA personnel become involved in the approval process. Other

factors contributing to delay and increasing costs include requirements for establishing safety and efficacy, and for developing and validating methods for quantitative assay of residues and metabolites.

FDA receives New Animal Drug Applications (NADAs), petitions for affirmation of GRAS (generally regarded as safe) status of substances which will become food components, and feed additive petitions. All require information as to the chemical nature of the substance; the safety of the intended use for the health of humans and other animals; the efficacy of the substance for the intended use; and the availability of sensitive, quantitative methods for determining residues in food. NADAs and food additive petitions require environmental impact analyses under the National Environmental Policy Act, administered by the Environmental Protection Agency.

FDA regulations provide that if the FDA Commissioner finds no grounds for denying approval within 180 days after a NADA has been filed, or 90 days after an application has been made for approval of feed containing new animal drugs, the applicant shall be notified that the application is approvable. Ninety days after filing, food additive petitions must be approved, denied, or extended for not more than 180 days.

Despite these provisions, approval has sometimes required much longer. In one instance described in detail, more than 28 months elapsed between application and approval of NADAs for the feed use of one antibiotic drug. A supplemental NADA providing for extended use of the antibiotic to market weight of the recipient animal required 38 months for approval.

Costs associated with approval for use of the nutrient selenium as a feed additive have exceeded 1 million dollars. A case study of the selenium issue shows that requests to FDA for GRAS status for this nutrient, essential for all animals, was requested in 1970; the first feed additive regulation became effective in 1974. Selenium addition to cattle and sheep feeds was not approved until 1979. Losses due to selenium deficiency in cattle and sheep were estimated to exceed $500 million in 1975. There is still no approval for use of selenium in diets of hens producing eggs for human consumption.

The potential market for minor drugs for major species and of all drugs for minor species is currently insufficient to justify the cost of obtaining information required for their approval. Nonproprietary chemicals similarly have too limited a profit potential to justify the costs of obtaining approval for their use.

FDA is cognizant of, and responsive to, needs and opportunities for reduction in cost of approval which do not reduce assurance of safety to human health. Changes in regulations by FDA to make application protocols more concise and exact might reduce the time and cost imposed on applicants without diminishing assurance to consumers of the safety of animal food products.

Publicly funded R&D might provide the data necessary for NADAs for minor drugs, drugs for minor species, and nonproprietary chemicals. In terms of increased supply and variety of foods of animal origin at less cost, the return to the public would likely be high.

A BVM "Medicated Feed Task Force" has recommended that animal drug regulation concentrate on preventing introduction into the human food supply of drug residues harmful to human health. The task force recommended that drugs be classified into risk categories. Drugs posing very small risk might require no regulation. Drugs posing potential residue risk to human health (e.g., carcinogens) would require regulation. Adoption by FDA of the Medicated Feed Task Force proposals could reduce costs associated with NADAs.

Also under consideration by FDA is a "Sensitivity of Method" document. The proposals in this document do not adequately discriminate between compounds that merit extensive testing and those that do not. The result may be misallocated scientific resources and deterred development of useful chemicals of limited market potential. The document also proposes the use of models which would confound the interpretation of research findings and in some instances would lead to incorrect conclusions.

INTRODUCTION

Prior to the mid-1920s, technical progress in American agriculture was directed primarily to the achievement of increases in output per worker through advances in mechanical technology. During the last half century, advances in mechanical technology have been complemented by new biological and chemical technologies directed to increasing output per unit of land, water, and animal resources. Agricultural research and development associated with the technologies has a very high annual return in relation to its cost (Evenson et al., 1979).

Use of chemicals in animal production plays an important role in a livestock industry that provides eggs, milk, and meat to the human diet. Food products of animal origin provide about 65 percent of the protein we consume, in forms we prefer. Drugs are utilized by the producer of animal products to prevent and control various diseases of livestock and poultry, thus enhancing the general well-being of the animal and improving the efficiency of feed conversion. Pesticides are used to control external parasites. The native supplies of essential nutrients in the plant products used for animal feed are supplemented by additional sources used as feed additives to provide adequate nutrition. As a result of the beneficial effects of these chemicals, the animal producer is able to reduce significantly the cost of production, thus contributing to the economic welfare of the producer and providing the consumer with lower cost animal products.

Since the early 1960s, the implications of the new biological and chemical technologies for the health and safety of agricultural producers and consumers and for the quality of the environment have been of heightened concern. The result has been the emergence of new laws and regulations to achieve more effective social control over the development and use of biological and chemical technologies. Regulations to assure the safety of animal products have evolved piecemeal and involve effort by several governmental agencies.

Both the drive for *technical innovation* leading to improvement in the productive capacity of plants and animals and the drive for *institutional innovation* resulting in constraints on the development and use of the new technologies have been generated by powerful economic and social forces. Increasing scarcity of land and water resources, reflected in rising agricultural land values and rising costs of land improvement, is continuing to create a strong need for yield-increasing technologies in agriculture--for higher output per acre. The rising value that society is placing on health and the rising demand for environmental quality have led to a demand for effective social controls over the development and use of new technology.

This report attempts to assess the impact of the new regulatory regimes that have emerged in recent years on innovation in chemical technologies useful in animal production. This is only a small part of the broader issues referred to in the preceding paragraph. The report is dedicated, however, to the proposition that it is in the interest of society to develop a set of institutions to manage the new scientific and technical potential opened up by advances in the application of biological and chemical technology on agricultural production in a manner that permits us to satisfy both the need for advances in agricultural productivity and our concerns for the health and safety of agricultural producers and consumers. It is in the further interest of society that both of these objectives be accomplished in a manner consistent with a good quality environment.

UNIQUENESS OF ANIMALS IN SAFETY OF FOOD SUPPLY

It is a common misconception that all drugs and environmental contaminants fed to food animals are passed *in toto* to humans. The fact is that animals generally pass on only a part, and in some instances almost none, of these substances in the food products that they generate; this provides a unique protective mechanism, a matter that has received little recognition. The problems from contamination have usually been recognized in animals before they became apparent in the human population and have provided a safeguard that is not available in plant products that are consumed directly by humans. An example of this was seen in the recent accidental mixing of polybrominated biphenyls (PBBs) into the rations of farm animals in Michigan, where the problem first became apparent in the animal population (Selikoff et al., 1978). Although deaths were reported in dairy cattle, there was no clear evidence of health problems in the human population (Selikoff et al., 1978). PBB studies by Fries et al. (1978), Durst et al. (1978), and Willett and Durst (1978) have indicated the effectiveness of cattle in filtering PBBs out of the food supply, whether it be milk or meat.

Similarly, aflatoxins were first observed in poultry being fed naturally contaminated feeds (Sargent et al., 1961; DeIongh et al., 1962), and later in other species (Allcroft and Roberts, 1968; Keyl and Booth, 1971; Armbrecht et al., 1971). Polan et al. (1971) have shown that only 0.17 to 0.30 percent of the aflatoxin intake could be recovered from the milk of dairy cows. Furtado (1979) has recently demonstrated that retention of aflatoxins in the tissues of the pig amounted to only 0.015 and 0.005 percent of the ingested amounts of aflatoxins B_1 and B_2, respectively. Thus, animals provide a unique and effective filter, as well as a warning of contamination, that has helped humans by either filtering out part of the contaminants or by causing signs of toxicity in the exposed animal population that have aided in recognition of the problem. This protective mechanism was not present in an incident in India in which 106 humans died from eating corn containing aflatoxin that had been produced by the mold, *Aspergillus flavus* (Krishnamachari et al., 1975). The Food and Drug Administration has established "action levels" for aflatoxins and PBBs in feed and food to assure safety (Food and Drug Administration, 1978).[1]

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[1] Action levels represent the limit at or above which FDA will take legal action against a product to remove it from the market.

COMPLEXITY OF THE REGULATORY SYSTEM

The evolution of feed safety requirements through a series of Congressional legislative actions has resulted in involvement of several independent government agencies and the development of several independent sets of regulations governing different aspects of approval for the use of chemical technologies and enforcement of safety requirements for animal products. Consequently, the process of gaining approval for new chemical technologies is often confusing.

Animal products are supervised by four different federal agencies, namely, the Food Safety and Quality Service (FSQS) of the U.S. Department of Agriculture, the Bureau of Foods (BF) in the Food and Drug Administration (FDA), the Bureau of Veterinary Medicine (BVM) also in FDA, and the Environmental Protection Agency (EPA) as well as state agencies (under the Public Health Services Act). Feeds entering interstate commerce are regulated by FDA. States also regulate feeds under state laws. The primary responsibility of FSQS is surveillance and enforcement of regulations to assure that the meat and poultry inspection programs meet standards for food safety and quality. Although FSQS has little input into developing standards for safety, it has primary responsibility for enforcing standards for residues, once they have been adopted. BVM has administrative responsibility for approving new drugs and other feed additives, with regard to both efficacy and animal safety. BF is charged with scientific review of the data on human food safety and, thus, has responsibility for approving drugs and other feed additives leaving residues that enter the human food supply. EPA has the responsibility for approving pesticides utilized primarily for controlling external parasites that could result in residues in animal products. Separate approvals for a new chemical technology thus may be required from more than one agency, and regulations related to animal products must ultimately be enforced by still another agency, FSQS.

The agencies themselves have recognized that the separation of responsibilities has resulted in problems of approving new products for use with food-producing animals. Thus, the Interagency Liaison Group, which is composed of the directors of the several agencies, has been formed to coordinate and clarify the roles of the respective agencies in order to eliminate unnecessary duplication in requirements and functions.

PRODUCTIVITY OF ANIMAL DRUG INNOVATION

The regulatory system has been amazingly effective in assuring a safe and nutritious supply of animal products for human diets. Nonetheless, the cumbersome nature of the system has certain unfavorable impacts on development of new chemical technologies, the consequence of which is not immediately apparent to members of the public.

Research and Development (R&D) expenditures by the animal drug industry expanded in real terms until 1974. This long-term expansion resulted in approval of many valuable compounds. However, the numbers of new compounds approved have declined in recent years. This section examines research productivity of the animal drug industry for the past 15 years and discusses alternative explanations for the recent decrease in animal drug innovation.

Since 1965 the Animal Health Institute (AHI) has compiled information from member companies on their sales, research and development expenditures, and number of new compounds approved. This information is shown in Table 1 for the period 1965 to 1978. An accounting firm is utilized to maintain the confidentiality of the information.

The sales figures for the AHI members are shown in Column 1. There appears to be a steady increase in undeflated industry sales. The annual growth rate has been about 9.4 percent (Column 2) including price increases. Only in recent years has AHI compiled unit prices for representative animal health products. Figures for 1975 and 1976 (not shown) indicate stable prices relative to consumer prices and other agricultural production costs (Animal Health Institute, 1978, p. 22).

Research and development expenditures in nominal and deflated terms are shown in Columns 3 and 4, respectively. Though undeflated R&D expenditures have risen for the industry, the deflated figures in Column 4 show no increases in these investments after 1974. There appears to have been a period of R&D expansion until 1971 and then a relatively constant investment level thereafter. The ratio of R&D expenditures to sales (Column 5) appears to have risen, peaked in 1971, and declined slightly in recent years.

Companies were asked to give the proportion of their R&D expenditures devoted to innovative activities. Though this information is sketchy, it does show a decline in the early 1970s and stability in recent years (Column 6).

The last two columns give a measure of the output of the research and development efforts. Column 7 is the number of new drug entities approved for use in each year, and Column 8 is the total number of animal species for which the new compounds were registered. Although there is considerable year-to-year variability in new compounds registered, moving averages show a reduction in new compounds registered in recent years. Selecting beginning, mid, and ending three-year periods, for example, one finds that the average annual number of new compounds was 2.3, 3.3, and 1.0, respectively.

A more complete measure of productivity, used in several evaluations of the pharmaceutical industry (Baily, 1972; Grabowski, Vernon, and Thomas, 1978), is R&D expenditures per new product. For the 1965-1967, 1970-1972, and 1975-1977 periods these expenditures were $13.8, $16.9, and $36.4 million, respectively. Again, there appears to be a decrease in productivity in the most recent period.

There are several possible explanations for the apparent decline in research productivity in the ani-

Table 1. Animal Drug Research and Development[a]

Year	AHI member sales ($ million)	Sales annual growth (percent)	AHI R & D ($ million)	AHI R & D deflated[b] ($ million)	Total R & D ÷ total sales	Percent of R & D innovative (percent)	New drugs approved (number)	New use registrations[d] (number)
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
1964							1	
1965	267.5		26.7	35.0	10.0		2	2
1966	300.6	12.3	31.5	40.6	10.5		4	4+M[c]
1967	322.4	7.2	38.6	48.9	11.9		3	3
1968	310.5	-3.7	41.1	49.7	13.2		6	6
1969	336.0	8.2	44.3	50.9	13.2		4	7
1970	387.9	15.4	50.7	55.2	13.1	86	5	5
1971	415.4	7.1	55.9	58.2	13.6	83	3	4
1972	459.2	10.5	55.6	55.6	12.1	81	2	2
1973	517.9	12.8	62.8	59.3	12.1	81	5	5
1974	564.8	9.0	73.4	63.1	13.0	78	0	0
1975	583.8	3.4	77.2	60.7	13.2		4	4
1976	689.9	18.2	84.3	63.1	12.2		1	1
1977	741.9	7.5	90.9	58.2	12.3	80	0	0
1978[e]	912.0	22.9					2	
Mean		9.4						

[a] From annual surveys by Ernst and Ernst for the Animal Health Institute (AHI).

[b] Column 3 divided by the GNP deflator (1972 = 100).

[c] Four separate-use compounds plus one compound with multiple uses.

[d] New entity registrations by species of animal.

[e] Preliminary data.

mal drug industry. The *depletion argument* is that over time there is a reduction of the possible stock of effective compounds so that each additional new drug becomes more and more costly to discover and develop. Baily (1972) found this effect to be important in the human drug industry. Grabowski, Vernon, and Thomas (1978) developed the method of using drug discoveries in other countries to test the level of depletion. The Animal Health Institute's observation that seven compounds available in other countries cannot be used in the United States indicates that the depletion effect may not explain the reduction in animal drug registrations in the United States. More adequate data suitable for statistical analysis are needed to test the depletion hypothesis against other explanations.

The *regulatory stringency argument* is that testing requirements for safety and efficacy approval by the Food and Drug Administration are suppressing innovative activity. The effects of regulatory stringency may take the form of delays in approval, increase in expenditures for tests, shifting of expenditures from innovative to noninnovative activities, or a combination of these. Also, threat of, or actual removal of, compounds from the market may induce reductions in innovative R&D expenditures.

There is little information on regulatory timing and expenditures for tests. Column 6 in Table 1 shows only that the share of R&D expenditures for innovative activities has declined. This may be an inaccurate measure because definitions of "innovative" activities are not fully consistent among firms and may tend to exaggerate the impact of regulations. However, it is well known that there is about a 4- to 5-year delay from adjustments in R&D to the time of submission of new compounds for FDA approval. The reductions in approvals do coincide with innovative reductions 4 to 5 years earlier (1970-73 R&D shifts and 1974-77 reductions).

Increasing testing costs can arise from both increased regulatory stringency and general price increases in performing tests. Table 2 shows the changes in costs to perform various safety tests necessary for both pesticide and animal drug registration. Note that the most precipitous increase in testing costs came not during the period of rapid inflation of 1974-1975 but rather in the 1976-1978 period. Pathologists and toxicologists are required to carry out the testing of pesticides and drugs, and training for these professions requires considerable time. The 43 percent increase in average salary of pathologists and the 23 percent increase in average salary of toxicologists between 1977 and 1979 suggests that the increased testing required has increased the demand for such specialists and the salaries they receive. Explanations of the type of regulatory actions that may induce changes in R&D investments are discussed in other sections of the report.

A *final possible reason* for decreasing animal drug innovation is that the demand for new animal drugs may have decreased. A decrease in demand for new animal drugs might reflect decreased demand for animal products, improvement in animal health, or a shift to nondrug approaches to animal health care. The recent rapid rise in the total sales value of animal health drugs (Table 1, Column 1) in the absence of drug price increases, mentioned earlier, appears to indicate a rapidly expanding market for existing drugs. Therefore, the expanding demand for drugs should be encouraging more R&D activity.

Table 2. Cost Trends per Toxicological Study and Testing Industry Wage Rates[a]

Year	Costs in thousands of dollars				
	Subchronic rat test	Chronic mouse test	Chronic rat test	Annual pathologist salary	Annual toxicologist salary
1973	10	30	50		
1974	11	35	65		
1975	12	45	72		
1976	14	55	80		
1977	20	60	120	28	22
1978	50	150	230		
1979	70	220	295	40	27

[a] Based on a survey of four private toxicological companies by Litton Bionetics. The salaries in the last two columns are for beginning, board-certified veterinary pathologists and for beginning professional toxicologists with a Ph.D. degree.

CLEARANCE OF NEW ANIMAL DRUG APPLICATIONS

The clearance procedures for new animal drugs are very complex and are poorly understood. Some procedures suggested by FDA are not explicit. This section outlines our understanding of the overall procedure involved and presents a case history of one antibiotic that was submitted for clearance in 1972 and did not receive final clearance until 1978. In addition, the regulation of essential nutrient additions to animal feeds is addressed since in many cases these also must receive FDA clearance for their use.

Figure 1 presents a flow chart which illustrates our understanding of the critical steps required in developing a new animal drug application (NADA), including the involvement of FDA. The flow chart shows the various tests required to gain approval, with time allowed for review and approval by FDA.

The actual NADA is made in triplicate on Form FD 356V (4/78), Attachment 1, and is submitted by the manufacturer to BVM as explained in the instructions on the form. Briefly, the application requires: (1) identification; (2) a table of contents and summary; (3) labeling information in detail; (4) components and composition information; (5) information on manufacturing methods, facilities, and controls; (6) samples of the new animal drug; (7) information on analytical methods for residues; (8) evidence establishing its safety and effectiveness; (9) information on compliance of new animal drugs subject to section 512 (n) of the act; (10) an environmental impact analysis; and (11) confidentiality of data in a new animal drug application.

A copy of the Internal Bureau of Foods Processing of Animal Drug Petitions, Attachment 2, explains the petition flow process within BF and how coordination is achieved with BVM. It points out how the application is logged in and how its movement is followed, along with a record of the number of days lapsed at each work station. The document also points out that, before BF can recommend approval of a new animal drug to BVM, concurrence is required from the Division of Chemistry and Physics (DCH), the Division of Toxicology (DT), and the Associate Director for Sciences (SCI). The responsibilities of each of these groups are explained in the document.

By statute, FDA is required to respond to the applicant within 180 days of submission of the NADA, informing the applicant that the application is approved or the reasons it is not approved. FDA frequently does not respond within the 180-day period; in fact, the usual response period is reported to be from about 7 months to more than 12 months. A new 180-day response period (plus any delay in responding) goes into effect each time FDA requests additional information. Thus, the time required for action can be extended 6 months or more at a time over an extended period.

Figure 2 shows a drug company's schedule for a NADA submission for clearance of a cattle feed premix, with times required to obtain the necessary data for each step in the clearance process. The study began January 15, 1975, with the final submission for NADA clearance being submitted in the second quarter of 1977. More than 2 years would be required to carry out all of the necessary tests. This example allows only a minimum of time to make all required tests and to prepare the data for submission. After the NADA has been submitted, FDA has 180 days to respond and, as already indicated, may take longer. If additional testing or information is required, FDA has an additional 180 days to respond. The requests for additional testing or information make NADA applications a "moving target" since regulations and requirements for clearance may change after the original submission; this is disconcerting to the applicant, and it discourages NADA submissions from the standpoint of both cost and uncertainty.

An actual case history with dates of submission of, and responses to, a NADA for an antibiotic to be administered in the feed is outlined in Figure 3. Four NADAs covering two dosage forms and two indications of use were submitted by the manufacturer between June 16, 1972, and July 31, 1972. BVM transmitted preliminary oral comments on all four NADAs to the manufacturer on November 30, 1972. Formal review by BVM was completed, and written comments were sent to the manufacturer, on

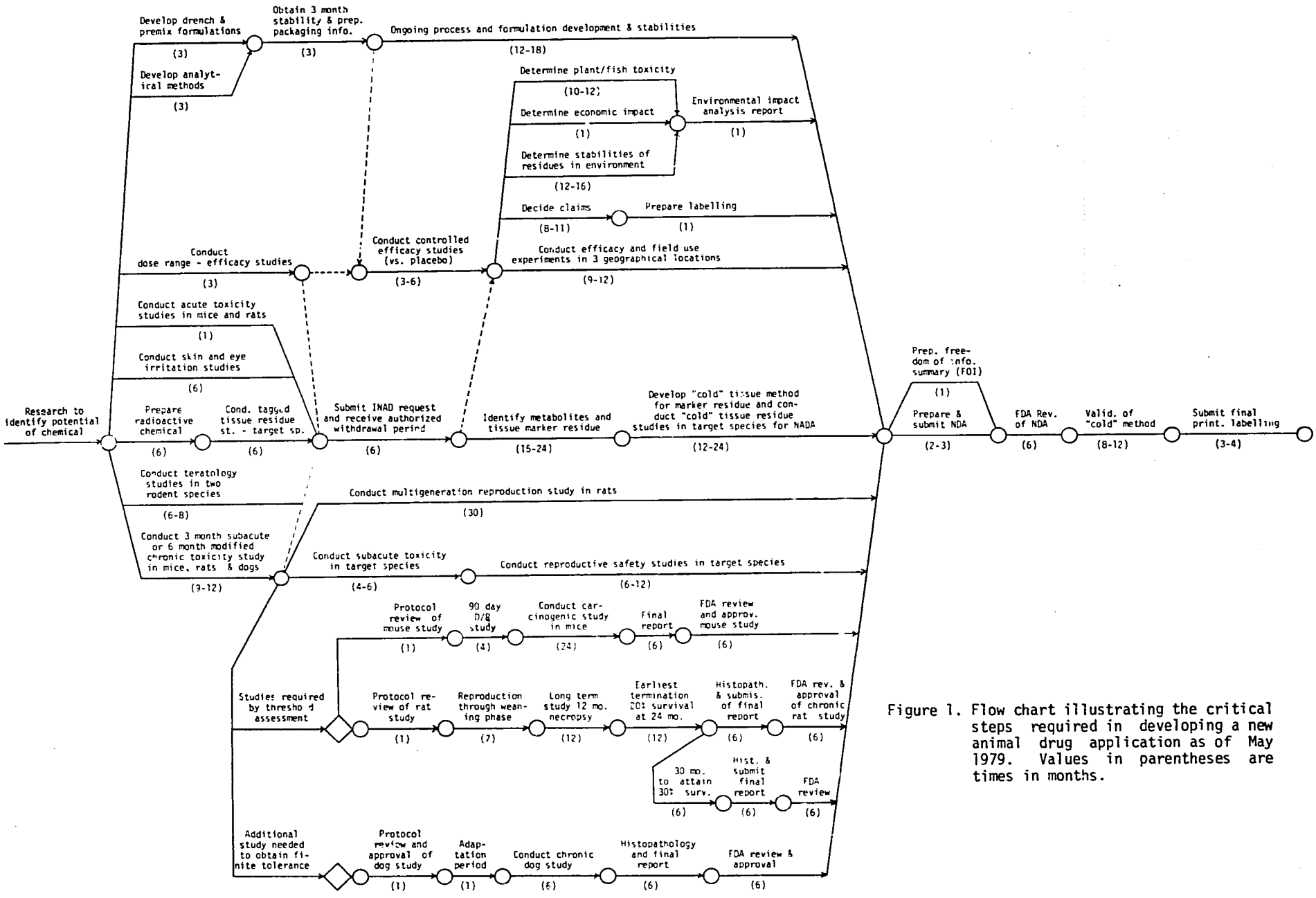

Figure 1. Flow chart illustrating the critical steps required in developing a new animal drug application as of May 1979. Values in parentheses are times in months.

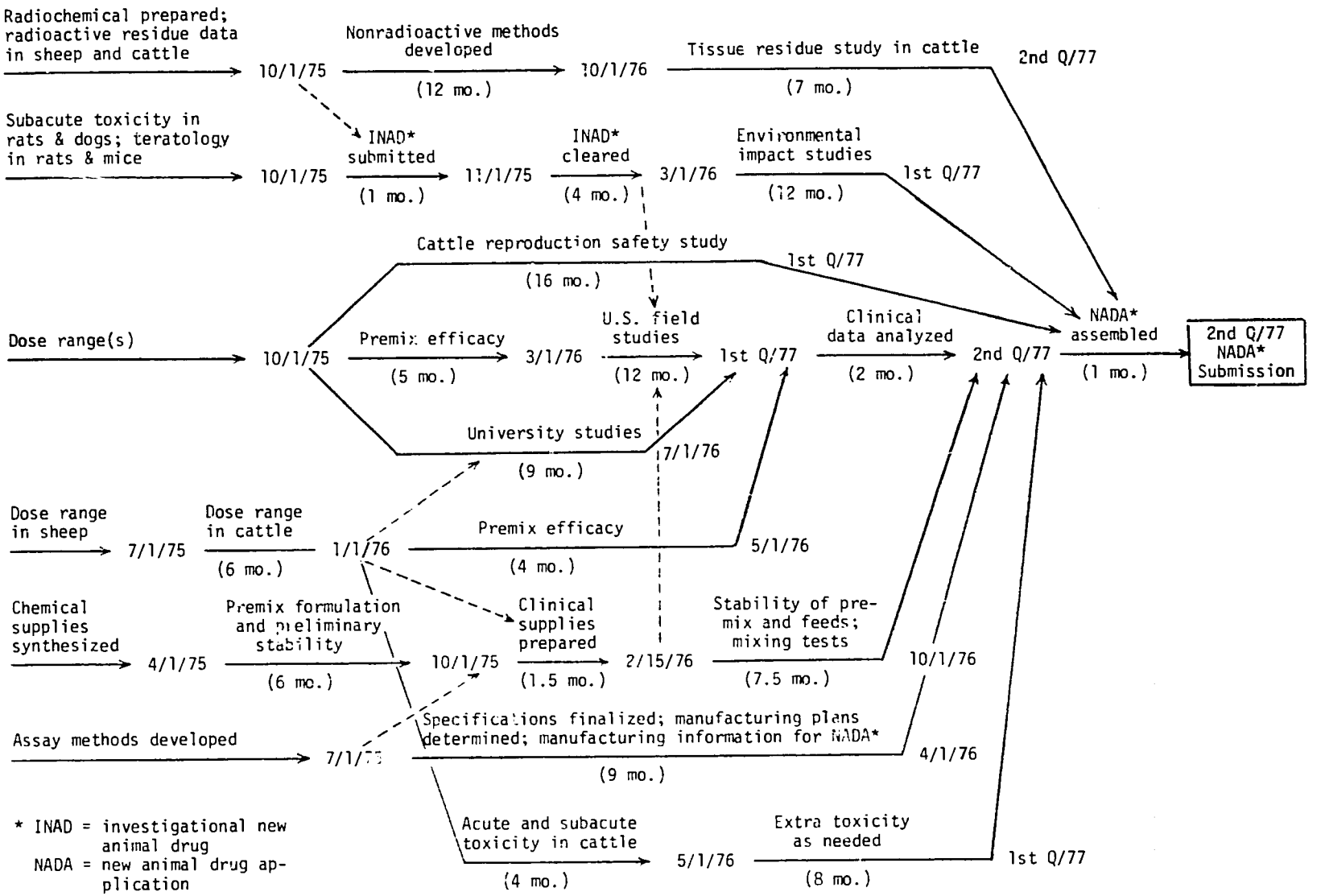

Figure 2. A drug manufacturer's plan of action with estimated times for obtaining and processing various parts of the information required to obtain approval from the Food and Drug Administration for sale of the dosage form (premix) of an anthelmintic drug for cattle. The premix is intended for sale to feed manufacturers.

Figure 3. A Chronology of the Submission and Review of New Animal Drug Applications for an Antibiotic Proposed for Use in Animal Feeds at Two Levels of Dosage and With Two Indications of Use

1.	Four NADAs covering two dosage forms and two indications of use were initially submitted by the manufacturer	6/16/72 6/19/72 7/28/72 7/31/72
2.	Preliminary oral comments were received by the manufacturer from BVM concerning all NADAs submitted	11/30/72
3.	Formal review by BVM was completed, and final additional comments from BVM were received by letter by the manufacturer	2/06/73
4.	Manufacturer submitted a reply to FDA answering questions raised as the result of the 2/6/73 review	3/01/73
5.	BVM advised the manufacturer that a range of doses for one of the claims would not be acceptable	4/10/73
6.	Manufacturer withdrew claim for the range of doses and submitted a request for one dose level	4/12/73
7.	Review of original submissions and all amendments submitted through 4/12/73 was completed, and additional comments were received from BVM by the manufacturer	6/11/73
8.	BVM requested that the four NADAs be consolidated into two NADAs	7/22/74
9.	BVM advised that the two NADAs were approvable and requested final printed labeling	9/19/74
10.	Final printed labeling was submitted by the manufacturer	9/27/74
11.	Federal Register notice approving NADAs was published	12/17/74
12.	Supplemental NADA providing for use of product to market weight was submitted to BVM by the manufacturer	7/14/75
13.	Reply received by the manufacturer from BVM advising that until additional safety data were received and reviewed no comments would be forthcoming and the application was considered withdrawn	7/31/75
14.	Manufacturer resubmitted supplemental application to BVM requesting extension of claims to market weight	1/28/76
15.	Manufacturer received letter from FDA notifying that BF had completed review of safety data and that there was no objection to extension of the claim to market weight	7/27/76
16.	Label revisions, Environmental Impact Analysis Report, and Freedom of Information Summary consistent with guidelines effective July 31, 1976, were requested by BVM	10/27/76
17.	Manufacturer hand-delivered revised Freedom of Information Summary, Environmental Impact Analysis Report, and final printed labeling and packaging information to BVM	11/24/76
18.	BVM advised the manufacturer that BF scientists had decided to modify data requirements for this class of drugs to establish adequately the conditions of safe use	1/31/77
19.	Manufacturer forwarded a request to BVM for approval of supplementary applications with a commitment on the part of the manufacturer to complete the modified requirements	2/09/77
20.	BVM advised the manufacturer that data requirements considered necessary to affirm safe use must be met prior to approval, since the supplemental applications constituted a risk of increased human exposure	2/18/77
21.	Manufacturer submitted required additional safety data, revised Freedom of Information Summary, and amended Environmental Impact Analysis Report	1/24/78
22.	FDA requested more detail in Freedom of Information Summary	3/01/78
23.	Manufacturer submitted revised Freedom of Information Summary	3/28/78
24.	Manufacturer met with FDA officials to review questions regarding additional safety data submitted	3/30/78
25.	Review was completed; request for final labeling was received by the manufacturer	8/02/78
26.	Manufacturer submitted final labeling	8/14/78
27.	Federal Register notice of supplemental clearance was published by FDA	9/19/78

February 6, 1973. The response time varied from 190 days for the last NADA submitted to 235 days for the earliest one.

On March 1, 1973, the manufacturer replied to questions raised by BVM. BVM promptly advised the manufacturer on April 10, 1973, that the range of dosages prescribed in one of the claims was not acceptable. On April 12, 1973, the manufacturer withdrew the claim on a range of dosages and submitted a request for a single dose level.

BVM reviewed the original submissions and all amendments previously submitted by the manufacturer and, on June 11, 1973, sent additional comments to the manufacturer. On July 22, 1974--over a year later--BVM requested that the four NADAs be consolidated into two NADAs. The manufacturer complied with the request. On September 19, 1974, BVM advised the manufacturer that the two NADAs were approvable and requested final printed labeling, which was submitted on September 27, 1974. Then on December 17, 1974, a notice of approval of the two NADAs was published in the *Federal Register*.

BVM then asked for verification of the usefulness of the product in feeding animals to market weight. Verification was supplied by the manufacturer on July 14, 1975. On July 31, 1975, BVM advised the manufacturer that additional safety data were needed and that until they were received and reviewed, the application would be considered withdrawn.

The manufacturer obtained supporting data for the safety of the antibiotic and resubmitted a supplemental application to BVM on January 28, 1976, requesting extension of claims to market weight. On July 27, 1976, the manufacturer received a letter from FDA indicating that BF had completed a review of the safety data and concluded that there was no objection to extension of the claim for the use of the product to market weight. On October 27, 1976, BVM requested label revisions, an Environmental Impact Analysis Report, and a Freedom of Information Summary consistent with the guidelines for July 31, 1976. These documents were hand-delivered to BVM on November 24, 1976.

On January 31, 1977, the manufacturer received a reply from BVM stating that BF scientists had decided to modify the data requirements for this class of drugs to establish more adequately the conditions for safe use. The manufacturer forwarded a request to BVM on February 9, 1977, for approval of supplementary applications with a commitment on the part of the manufacturer to complete the modified requirements. A reply from BVM was received by the manufacturer February 18, 1977, stating that the data requirements showing the product to be safe must be submitted prior to approval for supplementary use, since the supplemental applications constituted a risk of increased human exposure.

The manufacturer submitted the required additional safety data, a revised Freedom of Information Summary, and an amended Environmental Impact Analysis Report on January 24, 1978. On March 1, 1978, FDA requested more details in the Freedom of Information Summary; these were submitted by the manufacturer on March 28, 1978.

On March 30, 1978, representatives of the manufacturer met with FDA officials and reviewed questions on the additional safety data submitted. The FDA review was completed and a request for final labeling was received by the manufacturer on August 2, 1978. Final labeling was submitted to FDA on August 14, 1978. On September 19, 1978, a notice of supplemental clearance for broad usage of the antibiotic was published in the *Federal Register*.

The chronology of the review process outlined in Figure 3 points out the difficulties encountered in obtaining clearance of one antibiotic. Although two of four original NADAs were approved in 2 years and 4 to 5 months from the original submission dates, this was only for limited usage. An additional 3 years and 2 months were required to obtain clearance for broad usage of the product. The step-by-step documentation outlined herein clearly illustrates that the approval process for new animal drugs is slow, confusing, and frustrating. In spite of the voluminous amount of data and information required in the original NADA, the clearance procedure required a great deal of additional supporting information before approval. FDA seemingly considered only one step at a time instead of indicating in one communication all the points on which added information or data were needed.

The process of approving new animal drugs could be accelerated and made more efficient if the information to be required were clearly specified in writing at the beginning of the process and if some allowance were made for the changes in requirements that are introduced after the manufacturer has committed resources to obtaining the information specified initially. Changes in requirements may result, not only from new developments in regulations, but also from differences in interpretations and personal views as new FDA personnel become involved in the approval process.

REGULATION OF ESSENTIAL NUTRIENT ADDITIONS TO ANIMAL DIETS

Essential nutrients are substances which must be present in the diet of an animal because they cannot be synthesized by the animal's own tissues or, in ruminants, by microbial symbionts in the gastrointestinal tract. When these nutrients are missing from the diet or are present in less than required amounts, animal health is adversely affected. This illness may be expressed in a variety of ways, depending upon the function of the nutrient and the degree of its deficiency. Sometimes a marginal deficiency may be detected only by examining the activity of certain blood enzymes or by determining the concentration of the nutrient in certain tissues. There may be no clinical signs; and only when a secondary stressor, such as inclement weather, is superimposed, is the deficiency overtly expressed. Some nutrient deficiencies result in skin lesions, impaired locomotion, diminished vision, or nerve dysfunction. Growth may slow, and reproduction may cease. The ultimate deficiency sign is death.

The essentiality of a substance as a nutrient and the amount of an essential nutrient required are natural phenomena. The phenomena can be elucidated by experimentation, but they are not subject to human laws or regulations.

The Federal Food, Drug and Cosmetic Act, as amended (Food and Drug Administration, 1979a), does not include a definition of essential nutrients for animals. The term "animal feed" has been interpreted by FDA to include this class of substances, and the official position of BVM relative to regulation of nutrients in animal feeds was outlined in the BVM Policy and Procedures Manual published in 1976. While many of these regulations appear reasonable in intent, they are couched in terms that allow arbitrary application. For example, one section reads "Vitamins and minerals may be present in premixes intended for use in non-medicated animal feed, and in animal feed itself provided . . . there is an established need for each nutrient in the target animal; that it is present at levels consistent with recognized nutritional needs in a stable and biologically available form; that recognized safe levels are not exceeded unless otherwise cleared; and that the feed is not otherwise adulterated or misbranded." Established need has generally been based on definition of quantitative requirements for the target animal by the Committee on Animal Nutrition (CAN) of the National Academy of Sciences - National Research Council. Since quantitative nutrient requirements are not usually defined by CAN unless published scientific data are considered adequate, the BVM staff has the option of concluding that, in the absence of a quantitative nutrient requirement set by CAN, there is no established need, despite clear evidence of a qualitative requirement.

An additional complication is introduced by interactions of nutrients that modify quantitative requirements, *e.g.*, the well-known increase in the need for zinc in the diet of swine when dietary calcium concentrations are increased. Such interactions demand flexibility in the levels of nutrients permitted in diets so that they can be truly "in accordance with good manufacturing or feeding practice," as stated in the Code of Federal Regulations for general purpose food additives (21 CFR § 582.1005 et seq.).

Other environmental factors also may modify the need for supplemental nutrients. Moldy corn fed to swine sometimes contains antivitamin K substances which result in fatal hemorrhages in young pigs at the time of castration. Supplemental vitamin K will prevent the problem, but CAN has only recently established a quantitative requirement for this nutrient,

and strict interpretation of BVM regulations would deter addition of vitamin K to the feed.

Since essential nutrient additions to animal diets are regulated as food additives or through qualification for the generally recognized as safe (GRAS) list, individuals who wish to fortify animal diets with nutrients recently recognized (since 1958) as essential must file a petition with FDA, proposing issuance of a regulation prescribing the conditions under which such additives may be safely used. Since essential nutrients are not optional additives to diets which are demonstrably deficient, restrictions on their use pose a dilemma. If essential nutrients are not added to animal diets which are known to be deficient, illness and death may be expected. If unapproved nutrients are added to such diets, one may be in violation of FDA regulations.

To gain FDA approval of nutrient additions is not a simple matter. Nutrients are seldom in proprietary form, and individual companies are loathe to make the financial commitment necessary to gain FDA approval for their use. This problem has caused difficulties as animal production systems have changed, leading to deficiencies of certain nutrients--such as selenium--which previously were of little concern.

Selenium was established as an essential nutrient in 1957, and extensive areas of the United States have been determined to be selenium-deficient. Since the amount of selenium needed in the diet tends to be inversely related to vitamin E intake, the use of pasture (normally containing high concentrations of vitamin E), or of other high vitamin E feeds, masked all but the more severe selenium deficiencies. However, dramatic reductions in the use of pasture for livestock have taken place over the past 20 years, markedly decreasing vitamin E consumption. Feeds for chickens, turkeys, and swine contain fewer ingredients that supply vitamin E from natural sources than they did earlier. As a consequence, selenium-vitamin E deficiency has increased.

United States Department of Agriculture (USDA) statistical summaries for 1970 indicated that approximately 65 percent of the laying hens, 55 percent of the broilers, and 50 percent of the turkeys were produced in selenium-deficient states. Economic losses to poultry producers associated with lack of approval for addition of inorganic selenium to poultry diets were calculated by FDA staff members to be in excess of $27 million annually (Food and Drug Administration, 1974). Selenium deficiency was calculated to be causing annual losses of about $55 million to the swine industry.

The first petition to FDA for GRAS status for selenium was filed in 1970 (see Attachment 3). GRAS status was denied. Petitions for food additive approval were then filed. After many man-years of research by agricultural experiment station scientists, approval for selenium as a food additive was granted in 1974. In the meantime, economic losses in the swine and poultry industry had accumulated to an estimated $328 million.

Previously, white muscle disease (selenium-vitamin E deficiency) had been diagnosed in lambs and calves in 30 of the 50 states (Wolf et al., 1963). Despite the discovery in 1958 that selenium would protect against this disease in young ruminants, it was still not legal to supplement deficient ruminant diets in 1975. USDA agricultural statistics for that year showed that approximately 51 percent of the beef cattle, 69 percent of the dairy cattle, and 31 percent of the sheep were produced in selenium-deficient states. Total losses from selenium-vitamin E deficiency during 1975 to producers of these three species were estimated to be nearly $545 million (Selenium for Ruminants Task Force, 1976).

In 1975 a Selenium for Ruminants Task Force, involving scientists from nine universities, was formed specifically to gather information which might satisfy the regulatory requirements of FDA. On January 29, 1979, approval for supplementing ruminant diets with selenium was granted.

Twenty-two years have passed since the essential nature of selenium was discovered. This period includes 12 years during which the efforts of large numbers of scientists were directed specifically toward gaining FDA approval for selenium supplements to food animal diets. This task is still not complete, since FDA has not approved selenium supplements for hens producing eggs for human consumption. This omission is not based on concern for human health since the literature (Arnold et al., 1972, 1973; Cantor and Scott, 1974; Combs and Scott, 1977; Latshaw, 1975; Ort and Latshaw, 1978; Thapar et al., 1969) contains adequate evidence of the safety of the practice. Rather, approval has not been granted because an appropriate petition has not yet passed through the regulatory protocol. The research costs related to meeting regulatory requirements for selenium cannot be precisely estimated. The specific projects involving the Selenium for Ruminants Task Force were budgeted at $173,124 for a 1-year period. It would be conservative to suggest that the effort expended so far in meeting regulatory requirements for selenium has cost over a million dollars. The inability to supplement demonstrably deficient diets during this period has cost hundreds of millions.

PROSPECTS FOR REGULATORY CHANGE IN ANIMAL DRUGS AND NUTRIENTS

The food and drug laws in the United States have undergone considerable change since 1906. A number of persons are now advocating that the time is ripe for changes in regulations to avoid stagnation of research on new drugs, to ease the burden and costs of regulation, and to focus on issues of safety in the food supply. For example, the Scientific Committee, Food Safety Council (1978), has published a proposed "System for Food Safety Assessment." The proposed system regards a substance as safe if it presents a socially acceptable risk of an unfavorable effect at levels of consumption that are experienced by high consumers of food in which the substance occurs.

Clearance for the use of a chemical substance in animal feeds requires that a food additive petition be filed unless the substance in question can be generally regarded as safe (GRAS). For a substance to be approved as GRAS, its safety must be well documented in the scientific literature. Approval of a petition for use of a chemical substance as a food additive requires documentation as to its safety and efficacy,

but it need not be documented in the scientific literature. In some instances, it appears to be easier to obtain approval as a food additive than it is to gain approval as GRAS.

A clear and distinct protocol for submitting and approving requests for both GRAS and food additives would assist the industry in obtaining approvals and would also reduce its criticism of the regulations. It could also reduce the regulatory burden connected with reviewing and approving petitions.

Several recent documents indicate the existence of concern within FDA for the problems of regulating animal drugs. The first such document is the report and recommendations of the Medicated Feed Task Force entitled "Second Generation of Medicated Feeds." This internal document recommends orienting the medicated feed program to maximize public health protection. Questions of animal safety and drug efficacy would be less important to regulation while human health risk potential would become the key issue according to the recommendations in the report. The authors conclude that human safety is the proper departure point for determining whether a drug used in animal feed is a "new animal drug" and therefore subject to rigorous control under FFDCA. This approach would probably be accepted by most persons.

Many problems exist with the current medicated feed program. Those cited in the FDA report include: (1) regulations do not effectively focus on problems related to human health, (2) administration of the current program generates unnecessary paper work and expends staff time without relevance to public health protection, (3) good manufacturing practices are not assured since many applications for drug use are made by drug companies for feed manufacturers who do not have adequate equipment to prepare feeds from concentrated drug premixes, (4) obligations to inspect the large number of medicated feed firms cannot be met or carried out adequately due to lack of resources and due to lack of guidance and training of FDA field staff and cooperating state personnel, and (5) violations are not adequately dealt with under current regulation.

If the recommendations of the Medicated Feed Task Force were adopted and implemented, regulations would concentrate on preventing harmful drug residues from being introduced into the human food supply. Under the proposal, all drugs would be classified according to the degree of risk they present to humans from drug residues in food. A system for classifying drugs into risk categories is proposed in the document. Where there is no risk or the risk is very small, the drug would not be subject to regulatory control. Where the risk of residues is potentially significant, as in the case of carcinogens, approval of medicated feed applications by FDA would contribute to proper use of the drug in feeds. In this way, FDA resources at the preclearance level could be used more effectively to maximize human health protection. The surveillance and compliance aspects of the program would also be directed to those drugs for which the risk of residues is potentially significant to human health.

The Medicated Feed Task Force estimates that implementation of the recommendations would eventually result in 50 percent fewer submissions of Medicated Feed Applications (Form FD-1800). In addition, the Task Force recommends that new drug applications be simplified with emphasis on label reviews; that feed mill inspections be limited to firms requiring new drug approvals; that the state contract program for regulation of medicated feeds be revitalized; and that a comprehensive training program be established for FDA and state personnel involved in the new regulatory program.

The second document, containing proposed rules on "Criteria and Procedures for Evaluating Assays for Carcinogenic Residues in Food-Producing Animals," was published in the *Federal Register*, volume 44, number 55, pages 17070 to 17114, Tuesday, March 20, 1979. This proposal would set requirements for safety testing of animal drugs, food additives, and color additives and for analytical methods to detect residues of these substances in meat, milk, and eggs. Since each method has a limit to its sensitivity, no method can ascertain absolutely that no residue is present. Hence, rules are proposed in this sensitivity of method (SOM) document to ensure that any residues escaping detection by an approved method do not pose a significant risk of cancer to humans. "No significant risk" is defined as a level of residue that would have a probability of causing no more than one cancer in a million lifetimes.

An examination by FDA of the effect of the SOM threshold assessment scoring system on currently approved drugs would be of value to all concerned as a basis for perspective. The SOM appears to broaden the process of drug approval and to bring within purview many compounds that are unlikely to have carcinogenic potential. A threshold procedure that does not discriminate between compounds that merit extensive testing and those that do not would result in misallocation of scientific resources and would deter development of useful animal drugs of limited market potential. In addition, the "use factor" proposed as a part of the scoring system focuses on the number of animals potentially treated rather than on the amount of edible tissue consumed. (Each American annually consumes, on the average, about 17 chickens and 20 percent of a beef carcass, but the carcass weights involved are about 48 and 120 pounds, respectively.)

The SOM also proposes that residue limits be based on concentrations in the "edible tissue that is the most efficient accumulator of residues." Since kidney and liver are frequently the "most efficient accumulators" but are consumed in much smaller amounts than muscle, this proposal does not realistically deal with potential human exposure.

Another reservation concerning the SOM document is that it proposes to estimate potential carcinogenicity by linear extrapolation from doses observed to be carcinogenic to zero. There is serious doubt that the linear extrapolation model and the one-hit theory of carcinogenesis involved in this extrapolation are appropriate for all compounds, particularly those that are normally produced in the body.

To restrict drug evaluation to the rigid system proposed would be valuable in the sense that everyone would know what was involved and could proceed accordingly. On the other hand, the system proposed is not now scientifically validated, and its adoption as a regulation would have the effect of inhibiting scientific advances and of directing scientific work along lines that may eventually be found inappropriate.

Moreover, it is a violation of statistical principles to deny that a single animal might occasionally fall beyond the ninety-ninth percentile relative to residues of substances normally produced in the body. For such animals to be judged in violation of federal regulation would be inconsistent with the statistical principle that, in a population of animals, one animal in 100 would normally be expected to fall in this position. This violation of statistical principles is

not ameliorated by the requirement that 450 to 500 animals be used in each experimental group (p. 17098). Such a requirement would be extremely difficult to comply with if the target animals were cattle.

Problems associated with clearance of drugs of limited use (minor drugs or use of drugs for minor species) are apparently receiving some consideration by FDA. A major problem here is that there is too little economic incentive for companies to clear drugs for use when the potential market for them is restricted to a small volume because they are not frequently used or their use is for a minor species of animal, such as rabbits, ducks, or sheep. In such cases, the investment in providing required preclearance information on the drug may exceed projected profits from the sale of the drug. Satisfactory rules and regulations are needed for these situations in which the drugs are of significant value to agricultural producers even if those producers are limited in number. One possibility is for a reduction in requirements for preclearance of major drugs for minor species.

Recently a third document entitled "Safety and Effectiveness Data Supporting the Approval of Minor Use New Animal Drugs" was published in the *Federal Register*, part 3, for Friday, July 20, 1979. This proposal speaks to rule changes that would make it possible to extrapolate data from one species to another species in the support of applications for the use of new drugs in minor species of animals. Adoption of this proposal would probably stimulate drug applications for use in minor species where they are now absent.

Another possibility is the adoption of a "temporary clearance" device to permit the use of animal health and nutrient chemicals after preliminary data appear promising but before the bank of data required for the present permanent "clearance" has been fully accumulated and approved. After further experience, including monitoring, such a product could then be given regular clearance if no adverse affects are observed. If problems occur, the temporary clearance could be revoked without any new authority. This procedure would greatly speed the process of approval and would increase the availability of drugs and other feed additives for use in minor species.

One of the problems in the minor species area is the fact that a species classed as minor from a drug-use standpoint may be classified as major by FSQS; sheep are a case in point. Thus, although BVM might relax its testing requirements for new chemicals, FSQS and BF consider sheep a major species and are as inflexible in their residue requirements as they are for a major drug-use species. This viewpoint is justified on the basis that sheep are a part of the food supply. Thus, an attempt to make it easier to obtain approval of chemicals for a minor species could conceivably be no advantage at all, and in some instances could actually lead to additional problems.

Clearance of a minor drug for a major species is another matter. In this case, the most feasible way to expedite clearance appears to be to accept less rigorous pretesting requirements. Whether or not adequate pretesting could be done with scaled-down requirements probably would require scientific judgment. For each compound that might potentially be involved, data concerning toxicity, carcinogenicity, teratogenicity, etc. would need to be considered.

It seems unlikely that ways will be found to stimulate drug clearance applications from manufacturers for use of minor drugs in minor species. This last case might best be handled by a combination of one of the possibilities mentioned previously with sponsorship of the costs of preclearance testing by a government agency, state experiment station, or agricultural industry organization. FDA has not yet published proposals to deal with the minor drug, minor species problem.

Obtaining clearance for nonpatented or nonproprietary products is another major problem. Because all companies can sell them, there is insufficient incentive for any one company to undertake the expense required to obtain clearance. As a consequence, such products are almost eliminated from the market. A similar situation prevails with products on which the patents have expired. Many such former proprietary products with a long history of usefulness are discontinued because there is insufficient economic incentive for any one company to carry out the additional research needed to obtain clearance on the basis of current data requirements. This seeming dilemma and the societal loss it entails might be resolved by a combination of change in data requirements with a means to provide certain protection for companies that invested the resources needed to clear the products.

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ATTACHMENT 1
NEW ANIMAL DRUG APPLICATION

Form FD 356V (4/78)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

NEW ANIMAL DRUG APPLICATION *(Drugs for Animal Use)*

(Title 21, CFR § 514)

FOR FDA USE ONLY
NADA NO.
DATE RECEIVED:

NAME OF APPLICANT

ADDRESS *(Street Number, City, and Zip Code)*

FDA DRUG REGISTRATION NO. | DATE:

TYPE OF SUBMISSION *(Check one)*

- ☐ ORIGINAL APPLICATION *(CFR 514.1(a))*
- ☐ AMENDMENT TO AN UNAPPROVED ORIGINAL APPLICATION *(CFR 514.6)*
- ☐ AMENDMENT TO AN UNAPPROVED SUPPLEMENT TO AN APPROVED APPLICATION *(CFR 514.6)*
- ☐ SUPPLEMENT TO AN APPROVED APPLICATION *(CFR 514.8 (a))*
- ☐ SPECIAL NEW ANIMAL DRUG APPLICATION SUPPLEMENT - CHANGES BEING EFFECTED *(CFR 514.8 (a))*

CHEMICAL NAME *(In cases of multi-component drug mixtures a continuation sheet must be attached)*

GENERIC NAME:

PROPRIETARY NAME:

INSTRUCTIONS FOR PREPARING AND SUBMITTING THE NEW ANIMAL DRUG APPLICATION

i. Assemble and bind three identical copies of the submission.
ii. Identify each front cover with the name of the applicant, the proprietary name, if available, the name of the new animal drug and the dosage form.
iii. Use separate pages for each numbered heading consistent with subparagraph (1) through (11) of this Application form. Number the pages of the new animal drug application. Each copy should bear the same page numbering.
iv. Each copy of an original new animal drug application shall contain three complete sets of labeling.
v. Submit separate applications for each different dosage form of the drug proposed. Repeating in each application basic information pertinent to all dosage forms is unnecessary if reference is made to the application containing such information. Such references should be made by volume and page. Include in each application information applicable to the specific dosage form, such as labeling, composition, stability data, efficacy data, method of manufacture and investigational new animal drug application number.
vi. Forward amendments, supplements, reports and other correspondence submitted after the original application in the above format. Identify the submission with the assigned NADA number. If the submission is a supplemental application, full information shall be provided on each proposed change concerning any statement made in the approved application.
vii. Submit to: Food and Drug Administration
Bureau of Veterinary Medicine *(HFV-16)*
5600 Fishers Lane
Rockville, MD 20857

The undersigned submits this application for a new animal drug pursuant to section 512(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that the labeling and advertising for the new animal drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application and if the article is a prescription new animal drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the new animal drug will also contain, in the same language and emphasis, information for its use including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant hazards, contraindications, side effects, and precautions contained in the labeling which is part of this application in accordance with 21 CFR 201.105. It is understood that all representations in this application apply to the drug produced until changes are made in conformity with § 514.8. It is further understood that new animal drugs as defined in § 510.3, intended for use in the manufacture of animal feeds in any State will be shipped only to persons who may receive such drugs in accordance with § 510.7. The undersigned certifies, that the methods, facilities, and controls described under item 5 of this application conform to the current good manufacturing practice regulations in 21 CFR PART 200.

No new animal drug application may be processed unless a completed application form has been received (21 CFR 514.1).

SIGNATURE OF APPLICANT *(Responsible official or Authorized Agent)*	TITLE OF AUTHORITY	DATE SUBMITTED

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official, if the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001)

Enter the estimated time (manhours) to prepare this application. *(Include typing, photocopy and assembly only)*	Original Copy	
	Duplicate/Triplicate Copies	
	TOTAL (manhours)	

The following information, described in 21 CFR 514, shall constitute the requirements of this application:

1. **Identification.** Whether the submission is an original or supplemental application; the name and address of the applicant; the date of the application; the trade name(s) (if one has been proposed) and chemical name(s) of the new animal drug. Upon receipt, the application will be assigned an NADA number, which shall be used for all correspondence with respect to the application.

2. **Table of Contents and Summary.** The application shall be organized in a cohesive fashion, shall contain a table of contents which identifies the data and other material submitted, and shall contain a well-organized summary and evaluation of the data in the following form:
   i. Chemistry:
      a. Chemical structural formula or description for any new animal drug substance.
      b. Relationship to other chemically or pharmacologically related drugs.
      c. Description of dosage form and quantitative composition.
   ii. Scientific rationale and purpose the new animal drug is to serve:
      a. Clinical purpose.
      b. Highlights of laboratory studies: The reasons why certain types of studies were done or omitted as related to the proposed conditions of use and to information already known about this class of compounds. Emphasize any unusual particularly significant pharmacological effects or toxicological findings.
      c. Highlights of clinical studies: The rationale of the clinical study plan showing why types of studies were done, amended, or omitted as related to laboratory studies and prior clinical experience.
      d. Conclusions: A short statement of conclusions combining the major points of effectiveness and safety as they relate to the use of the new animal drug.
      e. List of references. References to pertinent information including information contained in files of the Food and Drug Administration as provided in 21 CFR 511.1.

3. **Labeling.** Three copies of each piece of all labeling to be used for the article (total of 9).
   i. All labeling should be identified to show its position on, or the manner in which it is to accompany the market package.
   ii. Labeling for nonprescription new animal drugs should include adequate directions for use by the layman under all conditions of use for which the new animal drug is intended, recommended, or suggested in any of the labeling or advertising sponsored by the applicant.
   iii. Labeling for prescription veterinary drugs should bear adequate information for use under which veterinarians can use the new animal drug safely and for the purposes for which it is intended, including those purposes for which it is to be advertised or represented, in accord with 21 CFR 201.105
   iv. All labeling for prescription or nonprescription new animal drugs shall be submitted with any necessary use restrictions prominently and conspicuously displayed.
   v. Labeling for new animal drugs intended for use in the manufacture of medicated feeds shall include:
      a. Specimens of labeling to be used for such new animal drug with adequate directions for the manufacture and use of finished feeds for all conditions for which the new animal drug is intended, recommended, or suggested in any of the labeling, including advertising, sponsored by the applicant.
      b. Specimens of all labeling representative of those proposed to be used for finished feeds manufactured from the new animal drug.
   vi. Draft labeling may be submitted for preliminary consideration of an application. Final printed labeling will ordinarily be required prior to approval of an application. Proposed advertising for veterinary prescription drugs may be submitted for comment or approval.

4. **Components and Composition.** A complete list of all articles used for production of the new animal drug including a full list of the composition of each article:
   i. A full list of the articles used as components of the new animal drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new animal drug and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each component should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary name is used it should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed component may be specified.
   ii. A full statement of the composition of the new animal drug. The statement shall set forth the name and amount of each ingredient whether active or not, contained in a stated quantity of the new animal drug in the form in which it is to be distributed (for example, amount per tablet or milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variation may be specified.
   iii. If it is a new animal drug produced by fermentation:
      a. Source and type of microorganism used to produce the new animal drug.
      b. Composition of media used to produce the new animal drug.
      c. Type of precursor used, if any, to guide or enhance production of the antibiotic during fermentation.
      d. Name and composition of preservative, if any, used in the broth.
      e. A complete description of the extraction and purification processes including the names and compositions of the solvents, precipitants, ion exchange resins, emulsifiers, and all other agents used.
      f. If the new animal drug is produced by a catalytic hydrogenation process (such as tetracycline from chlortetracycline) a complete description of each chemical reaction with graphic formulas used to produce the new animal drug, including the names of the catalyst used, how it is removed, and how the new animal drug is extracted and purified.

5. **Manufacturing Methods, Facilities, and Controls.** A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the new animal drug. This description should include full information with respect to any new animal drug in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing, and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the new animal drug, and the following:
   i. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new animal drug, he shall: Identify each person who will perform any part of such operations and designate the part; and provide a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls he will use in his part of the operation. The statement shall include a commitment that no change will be made without prior approval by the Food and Drug Administration, unless permitted under 21 CFR 514.8.
   ii. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the new animal drug has the identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.
   iii. A description of the physical facilities, including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.
   iv. The methods used in the synthesis, extraction, isolation, or purification of any new animal drug. When the specifications and controls applied to such new animal drugs are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperature, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the new animal drug may be specified. A flow sheet and indicated equations should be submitted when needed to explain the process.
   v. Precautions to insure proper identity, strength, quality, and purity of the raw materials, whether active or not, including:
      a. The specifications for acceptance and methods of testing for each lot of raw material.
      b. A statement as to whether or not each lot of raw material is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.
   vi. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new animal drug, including:
      a. The method of preparation of the master formula records and individual batch records and the manner in which these records are used.
      b. The number of individuals checking weight or volume of each individual ingredient entering into each batch of the new animal drug.
      c. A statement as to whether or not the total weight or volume of

each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

d. The precautions used in checking the actual package yield produced from a batch of the new animal drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

e. The precautions used to assure that each lot of the new animal drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

f. Any special precautions used in the operations.

vii. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the new animal drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components.

a. A description of practicable methods of analysis of adequate sensitivity to determine the amount of the new animal drug in its final dosage form including finished feeds and in drinking water should also be included. Methods should be included for any premix or other intermediate mix for such drugs. Where two or more active ingredients are included, methods should be quantitative and specific for each active ingredient.

b. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

viii. An explanation of the exact significance of any batch control numbers used in the manufacturing, processing, packaging, and labeling of the new animal drug, including such control numbers that may appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

ix. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

x. A complete description of, and data derived from, studies of the stability of the new animal drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or planned. Stability data should be submitted for any new animal drug, for the finished dosage form of the new animal drug in the container in which it is to be marketed, including any proposed multiple-dose container, and, if it is to be put into solution at the time of dispensing, for the solution prepared as directed. If the data indicate that an expiration date is needed to preserve the identity, strength, quality, and purity of the new animal drug until it is used, the applicant shall propose such expiration date. If no expiration date is proposed the applicant must justify its absence.

xi. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product. An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the new animal drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.

xii. The methods, facilities, and controls described under item 5 of this application conform to the current good manufacturing practice regulations in 21 CFR 200.

xiii. An analysis of the environmental impact of the manufacturing process(es) of the article that is the subject of the requested action as specified under 21 CFR 25.1(g).

Include:

(1) An identification of pollutants expected to be emitted;

(2) A citation of applicable Federal, state, and local emission requirements; and,

(3) A certification that such emission complies with said requirements. Where there are no applicable Federal, state or local emission requirements, citation and certification shall be made to appropriate industry, advisory, or voluntary standards acceptable to the agency.

6. **Samples.** Samples of the new animal drug and articles used as components and information concerning them may be requested by the Bureau of Veterinary Medicine as follows:

i. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new animal drug application to which it relates. Included are:

a. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new animal drug and other assayed components of the finished new animal drug.

b. A representative sample or samples of each strength of the finished dosage form proposed in the application and employed in the clinical investigations and a representative sample or samples of each new animal drug from the batch(es) employed in the production of such dosage form.

c. A representative sample or samples of finished market packages of each strength of the dosage form of the new animal drug prepared for initial marketing and, if any such sample is not from a representative commercial-scale production batch, such a sample from a representative commercial-scale production batch, and a representative sample or samples of each new animal drug from the batch(es) employed in the production of such dosage form, provided that in the case of new animal drugs marketed in large packages the sample should contain only three times a sufficient quantity of the new animal drug to allow for performing the control tests for drug identity and assays.

ii. The following information shall be included for the samples when requested:

a. For each sample submitted, full information regarding its identity and the origin of any new animal drug contained therein (including a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays.

b. For any reference standard submitted, a complete description of its preparation and the results of all laboratory tests on it, if the test methods used differed from those described in the application, full details of the methods employed in obtaining the reporting results.

7. **Analytical Methods for Residues.** Applications for new animal drugs shall include a description of practicable methods for determining the quantity, if any, of such drug in or on food, and any substance formed in or on food because of its use, and the proposed tolerance or withdrawal period or other use restrictions for such drug if any tolerance or withdrawal period or other use restrictions are required in order to assure that the proposed use of such drug will be safe. When data or other adequate information establish that it is not reasonable to expect the new animal drug to become a component of food, assay methodology is not required.

i. The kind of information required by this subdivision may include: Complete experimental protocols for determining drug residue levels in the edible products, and the length of time required for residues to be eliminated from such products following the drug's use; residue studies conducted under appropriate (consistent with the proposed usage) conditions of dosage, time, and route of administration to show levels, if any of the drug and/or its metabolites in test animals during and upon cessation of treatment and at intervals thereafter in order to establish a disappearance curve; if the drug is to be used in combination with other drugs, possible effects of interaction demonstrated by the appropriate disappearance curve or depletion patterns after drug withdrawal under appropriate (consistent with proposed usage) conditions of dosage time, and route of administration; if the drug is given in the feed or water, appropriate consumption records of the medicated feed or water and appropriate performance data in the treated animal; if the drug is to be used in more than one species, drug residue studies or appropriate metabolic studies conducted for each species that is food-producing. To provide these data, a sufficient number of birds or animals should be used at each sample interval. Appropriate use of labeled compounds (e.g. radioactive tracers) may be utilized to establish metabolism and depletion curves. Drug residue levels ordinarily should be determined in muscle, liver, kidney, and fat and where applicable, in skin, milk, and eggs (yolk and egg white).

As a part of the metabolic studies, levels of the drug or metabolite should be determined in blood where feasible. Samples may be combined where necessary. Where residues are suspected or known to be present in litter from treated animals, it may be necessary to include data with respect to such residues becoming components of other agricultural commodities because of use of litter from treated animals.

ii. If such new animal drug is one which has been shown to induce cancer when ingested by man or animal or after other tests which are appropriate for the evaluation of the safety of such drug and the Secretary is requested to find that, under the conditions of use specified in the proposed labeling and reasonably certain to be followed in practice, such drug will not adversely affect the animals for which it is intended and that no residue of such drug will be found in any edible portion of such animals, after slaughter or in any food yielded by or derived from the animal, methods of analysis shall be submitted in such form as to be suitable for publication in the Federal Register.

8. **Evidence to establish safety and effectiveness.**

i. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the new animal drug is safe and effective for use as suggested in the proposed labeling.

ii. An application may be refused unless it includes substantial evidence, consisting of adequate and well-controlled investigations, including field investigation, by experts qualified by scientific training and experience to evaluate the effectiveness of the new animal drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the new animal drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

iii. An application may be refused unless it contains detailed reports of the investigations, including studies made on laboratory animals, in which the purpose, methods and results obtained are clearly set forth of acute, subacute, and chronic toxicity, and unless it contains appropriate clinical laboratory results related to safety and efficacy. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the raw data are available in the application.

iv. All information pertinent to an evaluation of the safety and effectiveness of the new animal drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, both favorable and unfavorable, involving the new animal drug that is the subject of the application, and related new animal drugs shall be submitted. An adequate summary may be acceptable in lieu of a reprint of a published report that only supports other data submitted. Include any evaluation of the safety or effectiveness of the new animal drug that has been made by the applicants veterinary or medical department, expert committee, or consultants.

v. If the new animal drug is a combination of previously investigated or marketed new animal drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components, shall be submitted. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted to the Food and Drug Administration by the applicant; with written authorization, information may also be incorporated from the material that another applicant has on file with the Food and Drug Administration. Each ingredient designated as active in any new animal drug combination must make a contribution to the effect in the manner claimed or suggested in the labeling, and, if in the absence of express labeling claims of advantages for the combination such a product purports to be better than either component alone, it must be established that the new animal drug has that purported effectiveness.

vi. An application shall include a complete list of the names and post office addresses of all investigators who received the new animal drug. This may be incorporated in whole or in part by reference to information submitted under the provisions of 21 CFR 511.1.

vii. Explain any omission of reports from any investigator to whom the investigational new animal drug has been made available. The unexplained omission of any reports of investigations made with the new animal drug by the applicant or submitted to him by an investigator or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources that would bias an evaluation of the safety of the new animal drug or its effectiveness in use, constitutes grounds for the refusal or withdrawal of the approval of an application.

9. **New animal drugs subject to section 512(n) of the act.** If the application is for a new animal drug subject to the certification provisions of section 512(n) of the act and the drug is included in regulations promulgated under section 507 of the act, the applicant may be exempted from the submission of some of the information required by subparagraph (8) of this paragraph if the application includes data adequate to prove that the new animal drug is comparable to the new animal drug for which certification has been previously provided.

10. Environmental Impact Analysis Report. The applicant is required to submit an environment impact analysis report analyzing the environmental impact of the ultimate use or consumption of the new animal drug pursuant to 21 CFR 25.1.

11. **Confidentiality of Data And Information In A New Animal Drug Application.** The availability for public disclosure of any record in the NADA file shall be handled in accordance with the provisions of 21 CFR 514.11.

i. After approval has been published in the Federal Register certain data and information (as indicated in 21 CFR 514.11(e)) in the NADA file are immediately available for public disclosure unless extraordinary circumstances are shown. This information shall be known as a Freedom Of Information (FOI) Summary.

Preparation of the FOI Summary shall be by the applicant according to guidelines specified by the agency.

ATTACHMENT 2

INTERNAL BUREAU OF FOODS PROCESSING OF ANIMAL DRUG PETITIONS

INTERNAL BUREAU OF FOODS PROCESSING OF ANIMAL DRUG PETITIONS

(INADS, NADAs, and Master Files)

Petition Flow Process

1. The petition flow within the Bureau of Foods is depicted in Exhibit A.

2. A special messenger daily delivers new submissions and returns reviews between the Bureau of Veterinary Medicine (BVM) (Dr. Kingma's office) and the Bureau of Foods (BF) (Ms. Perez's office).

3. A new record-keeping and tracking system has been partially implemented by the Bureaus and should be fully operational in fiscal year 1977. The new system is expected to substantially reduce the clerical staff time now spent in recording information, improve the quality of the information recorded, and allow for more frequent reporting of status to the appropriate managers.

In the new system, preprinted record materials are attached to each petition in BVM, and the information is filled in by the BVM reviewer before submission to BF. The preprinted material includes two master cards and a tear-sheet with multiple stubs (See Exhibit B).[1] One of the master cards is permanently attached to the petition, and information is entered by various reviewers en route. The second master card becomes the BF master log maintained in the Office of the Associate Director for Sciences (SCI). The tear sheet stubs are used by each work station in BF to record a petition movement within the Bureau. For each movement, a stub with the petition number is initialed, dated, and the mail symbol of the unit to which the petition has been delivered is recorded. The stub is sent to SCI for attachment to a master card showing the current location of that petition.

The central log records not only the movement but also the number of days lapsed in each work station and the cumulative number of days in BF. Each month a listing is sent to each manager giving the petitions outstanding in his work unit, the number of days in his unit, and the total number of days the petition has been in BF.

4. Although the central processing records for BF are maintained in SCI, the master subject files are maintained in the Division of Toxicology by specially trained staff. These include a BF correspondence file for each petition and a cross-indexing system of drugs, sponsors and identification numbers. All petition jackets are returned to BVM after review. Therefore, the subject files are often relied upon for

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[1] Not included.

information in subsequent reviews to avoid recalling jackets unless necessary. Bureau staff are currently considering needs for scientific data storage and retrieval in BF and the possibilities of acquiring a computer terminal for the BF reviewers for direct access to the BVM computer information file.

5. All petitions are carried between work stations, avoiding the regular mail delivery, to assure no delays and to maintain security. In addition, all offices of the staff involved with petition review are locked at night to maintain security.

6. The initial routing of a petition submission is determined at the time of logging in SCI based on the information supplied with the petition by the BVM reviewer.

The Scientific Review Process

Before BF recommends approval of a new animal drug to BVM, concurrence is always required from the Division of Chemistry and Physics (DCH), the Division of Toxicology (DT), and the Associate Director for Sciences (SCI).

1. DCH has responsi ility for evaluation of the following:

   A. Adequacy of the residue information and determination of the withdrawal period.

   B. Adequacy of the proposed regulatory method of analysis for residues.

   C. Adequacy of information on the metabolism of the drug (in conjunction with DT).

When the proposed regulatory method and residue data involve a microbiological assay, e.g. for an antibiotic, BVM has responsibility for the adequacy of these data. However, DCH in conjunction with DT considers the question of drug metabolism and the assignment of conditions for the assay which include the target tissue, compounds to be measured, and the required lower limit of measurement.

The DCH team leader for animal drug review assigns a primary reviewer for each petition. On completion of the review, a response is prepared to the Assistant Director for Petition Review in DT. A rough draft of the response is reviewed with the DCH team leader and the Chief of the Residue Analysis and Method Investigation Branch (RAMIB) before final typing. Frequently, the reviewers in the unit will exchange

and critique each other's reviews to take advantage of the various expertises within the review unit. Another advantage of this practice is to provide general familiarity with the petition by more than one reviewer, so that in the absence of the primary reviewer, another staff member is available to handle questions.

Occasionally, a rough draft is discussed with a reviewer in DT, when questions of mutual interest need to be clarified before a conclusion is reached. This most frequently occurs in recommendations for granting a withdrawal period for INAD use or in the review of metabolism data where decisions involve both toxicology and chemistry judgments.

Following the supervisory approval of the team leader and Chief of the RAMIB, the response is returned to the primary reviewer, typed in final form, signed by the reviewer, and transmitted to DT.

2. DT is responsible for the following:

   A. Adequacy of the toxicology data.

   B. Assignment of the "safe" level of residue or tolerance, or alternatively, assignment of the lower limit of measurement required for the regulatory method of analysis for residues to assure food safety.

   C. Overall responsibility to determine when all requirements on food safety have been satisfied.

DT shares responsibility with DCH to determine the adequacy of the metabolism data.

When DT determines the "safe" level of residue, DCH recommends a withdrawal period based on the residue data. In the case of an INAD where the human safety data are incomplete for NADA approval, judgments on withdrawal for investigational use are made jointly considering the limitations in both the chemistry and toxicology information.

DT has responsibility for preparing the BF response to BVM. Accordingly, the response is from the DT reviewer, through the DT Assistant Director for Petition Review and the Associate Director for Sciences to the BVM reviewer.

The rough draft of the response is reviewed by the DT team leader before final typing. When the response to BVM is completed in DT and signed by the reviewer and supervisors, it is transmitted to SCI.

3. The BF program manager for animal drugs provides a policy review for the Bureau and has delegated authority to sign off all responses for SCI. Any petition which involves the setting of a new precedent or major deviation from usual policy will be referred to the Associate Director for Sciences for his approval. Following approval in SCI, the response is transmitted to BVM.

4. Any reviewer has the option of requesting consultation or special review of particular data by a subject matter expert in the Bureau. For example, in DCH this may be a mass spectrometry expert, a polymer chemist, a heavy metals analytical specialist, a pesticide chemist, etc. In DT, it may be a specialist in teratology, mutagenesis, neuropharmacology, etc., or a request may be made of the Division of Pathology for a special review.

Statistical analysis is always conducted on the data from a method validation trial. The DCH and DT reviewers may request special statistical review by the Division of Mathematics on any data where they feel it is advisable before a conclusion is reached.

Some petitions raise questions about an area of microbiology or questions of the nutritional integrity of food from drug-treated animals. Therefore, a review or consultation with appropriate staff in the Division of Microbiology or the Divisions of Nutrition and Consumer Services may be sought.

Each assigned reviewer in DCH and DT has the responsibility to alert his supervisors and the BF program manager when a petition raises policy issues or administrative and legal questions that need to be resolved prior to completing the BF recommendation. Arrangements can then be made to resolve these issues while the scientific review proceeds concurrently.

5. In any complex scientific area, there will on occasion be differences of scientific opinion among the staff. The procedures in BF for resolving such differences utilize the line organization authority. For example, when a reviewer in DCH and a reviewer in DT have a difference of opinion which is not resolved in joint conference with the respective team leaders, the issue is reviewed first by the next line supervisors and ultimately is reviewed by the respective Division Directors, if necessary. The Associate Director for Sciences may or may not initially participate in a Division Director's review.

Generally, Division Directors are not involved in a given petition review unless controversy arises. Therefore, it is requested that when a drug sponsor opposes the conclusions reached by the Bureau on a human safety question and plans to appeal the decision to the Director

of the Bureau of Foods, that the matter first be brought to the attention of the BF program manager so that arrangements can be made for a briefing on the issue to the Division Directors and the Associate Director for Sciences for their consideration.

Informal exchange of ideas and information is encouraged between the reviewers in BF and BVM. When a major disagreement occurs between the two Bureaus which can not be resolved by the reviewers, the BF program manager arranges for a BF re-evaluation of the issue by the line managers. If a major policy issue is involved, the matter may be placed on the agenda for the regularly held joint BVM-BF Director and staff meetings or presented to the Working Group on Animal Drugs, chaired by the Deputy Commissioner.

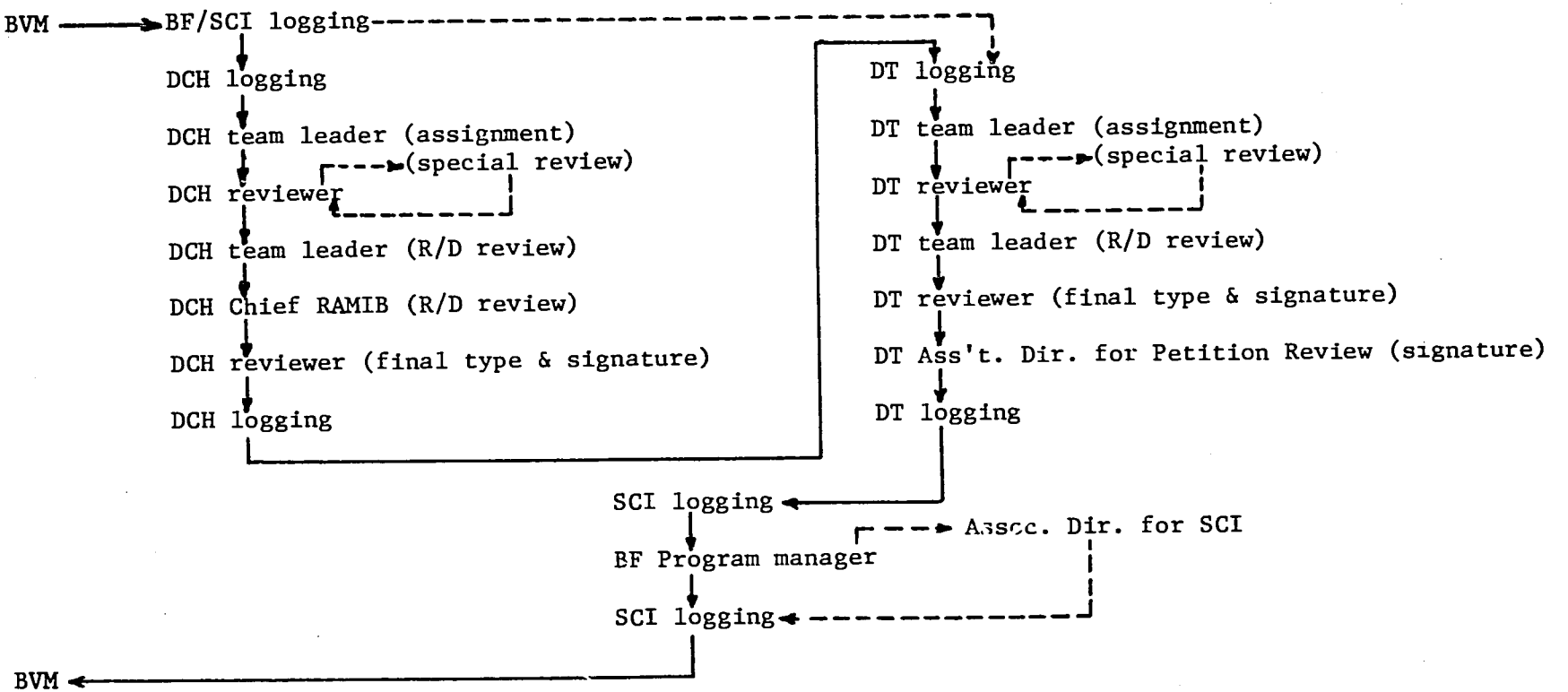
Petition Assignments and Priority

The assignment of primary reviewers for each petition in DCH and DT by the team leaders is based primarily on current workload for each reviewer and past experience or expertise with the particular type of drug. Whenever possible, continuity on sequential submissions is maintained with the original reviewer, although workload consideration and training of reviewers may affect the assignment decisions.

Petitions are handled on a priority basis by date of receipt by the reviewer, unless there is a valid reason mutually agreed upon by BVM and BF management. Because each reviewer at any time will have a number of petitions assigned, he may elect while conducting an extensive review of one petition or awaiting additional information, to handle a relatively short submission out of sequence. For this reason, reviews of protocols or INADs may be completed while an extensive review of a new NADA with prior data of receipt, is in progress. The review of data submitted to Master Files or in Drug Experience Reports are generally given lower priority than INAD and NADA submissions, unless the data are critical to a pending NADA and INAD approval.

In addition to the above guidelines, the Bureau managers utilize the monthly status reports on outstanding petitions to focus on priority.

Petition Flow Process in the Bureau of Foods, Exhibit A.



Bureau of Veterinary Medicine (BVM)
Bureau of Foods (BF)
Office of the Associate Director for Sciences (SCI)
Division of Chemistry and Physics (DCH)
Division of Toxicology (DT)
Residue Analysis and Methods Investigation Branch (RAMIB)
Rough Draft (R/D)
———— represents usual route
– – – – – represents alternative route

ATTACHMENT 3

REGULATION OF ESSENTIAL NUTRIENT ADDITIONS TO ANIMAL DIETS

D. E. Ullrey[1]

The Federal Food, Drug, and Cosmetic Act as amended (FDA, 1979a) does not include a definition of essential nutrients for animals. The term "animal feed" has been interpreted to include this class of substances, and essential nutrient additions to animal diets have been regulated as food additives or through qualification for the GRAS (generally recognized as safe) list. This position requires that individuals who wish to fortify animal diets with nutrients recently recognized (since 1958) as essential must file a petition with the Food and Drug Administration (FDA), proposing issuance of a regulation prescribing the conditions under which such additives may be safely used. Since nutrients are not usually proprietary substances, individual companies are loathe to make the financial investments necessary to gain FDA approval for their use. This problem has caused particular difficulties as animal production systems have changed, leading to deficiencies of certain nutrients-such as selenium - which previously were of little concern.

Selenium — A Model Case

Selenium is a semimetal which is very similar to sulfur in its chemical properties. It exists in soil as basic ferric selenite, calcium selenate, elemental selenium, and organic compounds derived from plant and microbial tissue. Its availability for uptake by plants is greater in alkaline soils than in acid soils, and certain plants accumulate the element in quantities which are toxic to animals which eat them. Much of the early interest in selenium among nutritionists concerned this very issue. Marco Polo referred in his journals to "...a poisonous plant...which if eaten by (horses) has the effect of causing the hoofs...to drop off" (Polo, 1926). In 1857, Dr. T. C. Madison, a U.S. Army surgeon at Fort Randall, Nebraska Territory, described similar signs in horses which he attributed to "alkali disease" (Madison, 1860). Selenium was identified as the toxic principle by scientists from the U.S. Department of Agriculture and the South Dakota and Wyoming State Agricultural Experiment Stations through a series of studies begun in 1929 (Franke, 1934). Not until 1957 (Schwarz and Foltz, 1957; Patterson et al., 1957; Scott et al., 1957; Stokstad et al., 1957) was the role of selenium as an essential nutrient established. Kubota et al. (1967) subsequently determined that the selenium-deficient areas of the United States are much larger than those areas which are selenium-toxic.

Deficient diets result in a number of signs that can be prevented by supplemental selenium. These include liver necrosis (Schwarz and Foltz, 1957; Eggert et al., 1957), exudative diathesis (Patterson et al., 1957), and myopathy (white muscle disease) (Muth et al., 1958; Hogue, 1958; Hartley and Grant, 1961). Species in which deficiency signs have been demonstrated include mice, rats, guinea pigs, rabbits, chickens, turkeys, quail, swine, sheep, cattle, horses, dogs, deer, and squirrel monkeys. Growth responses to selenium supplements have been reported in children with kwashiorkor (Schwarz, 1967; Majaj and Hopkins, 1966). In 1973, workers at the University of Wisconsin established that selenium is an integral part of the enzyme glutathione peroxidase, which functions importantly in protecting cell membranes against peroxidative damage (Rotruck et al., 1973). This enzyme is present in the tissues of all higher animals, including humans.

Selenium Deficiency On Farms

Dramatic changes have been made in the management of food animals over the past 20 years. Most poultry, swine, dairy cattle, and finishing beef cattle are now raised with limited use of pasture. This change, plus less use of other green forages, has decreased intakes of vitamin E. Since the need for selenium is related to the dietary supply of vitamin E, animals raised under intensive management in selenium-deficient areas frequently exhibit deficiency signs when not supplemented with selenium and vitamin E (National Research Council, 1971).

Michigan State University scientists first diagnosed the deficiency in commercial swine herds in Michigan in 1967 (Michel et al., 1969). Since other diseases bear some resemblance to this deficiency, it is likely that the deficiency was present, but undiagnosed, much earlier (Trapp et al., 1970). Sudden-death losses were common in pigs shortly after weaning, and controlled studies suggested that mortality ranged from 15 to 20 percent, while deficiency lesions were present in 25 percent or more. Impaired reproductive efficiency was also evident (Ullrey, 1974).

Similar practical problems were reported in commercial turkey flocks in southwestern Ohio in 1964 (Scott et al., 1965). Poor growth, increased mortality, and gizzard myopathy were seen in young poults. In the presence of vitamin E, a selenium requirement of 0.18 ppm was established. In 1967, Thompson and Scott showed that even when generous amounts of vitamin E were present, selenium was still essential for the chick and quail, and a year later (Thompson and Scott, 1968) these Cornell scientists recommended that poultry feeds which were not supplemented with a stable form of vitamin E should contain selenium at a concentration of at least 0.15 ppm, a figure which was 0.1 ppm greater than most commercial poultry feeds in that region.

Petition For GRAS Status For Selenium

The increasing incidence of selenium deficiency in the nation's herds and flocks during the 1960s stimulated the American Feed Manufacturers Association (AFMA) to petition FDA for GRAS status for selenium, so that supplements might be legally added to animal diets. The petition was prepared by the AFMA Director of Feed Control and Nutrition and was submitted March 9, 1970. Supplements to the petition were provided on March 31, April 21, May 11, May 18, May 21, and Octo-

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ber 1, 1970. On September 23, 1970, the Director of the FDA Bureau of Veterinary Medicine (BVM) acknowledged receipt of the petition and several of the supplemental submissions. The BVM Director concluded that GRAS status had not been established and proposed in this and a subsequent letter (dated November 24, 1970) that studies should be conducted with target species to establish whether selenium supplements would increase selenium concentrations in edible tissues of animals which were not initially deficient. This proposal was based on the 1962 Drug Amendments (Public Law 87-781) of the Federal Food, Drug, and Cosmetic Act (FDA, 1979a) which required that chemicals used in feed for food-producing animals must not adversely affect the animals nor result in a residue in products used for human food if the chemicals posed a carcinogenic risk.[2]

The AFMA Director of Feed Control and Nutrition replied to the BVM Director on December 21, 1970, by submitting published data on (1) ranges of selenium levels in typical turkey, chicken, and swine feeds, (2) normal background levels of selenium in tissues of poultry and swine, (3) the effect of recommended selenium supplements in poultry and swine diets on human selenium intakes, and (4) tissue selenium levels in poultry and swine fed practical diets supplemented with selenium. Since comparable data were not available for ruminants, the original petition was amended to include only poultry and swine. However, the petitioners reaffirmed their belief that this submission satisfied the existing and proposed GRAS criteria (FDA, 1970). The official notice of filing of the petition was published in the Federal Register Thursday, June 17, 1971 (FDA, 1971), although the GRAS issue was replaced by a proposal to establish a food additive regulation governing "...the safe use, as a nutrient, of selenium from sodium selenite or sodium selenate in the feed of chickens, turkeys, and swine...."

Food Additive Regulation For Selenium For Swine And Poultry

During the period that the AFMA petition was being developed and for some years afterward, a number of researchers were conducting controlled studies to develop data for submission to FDA. Since selenium was not an approved food additive, these studies were conducted under "investigation of new animal drug" (INAD) numbers issued by FDA. Regulatory activity was also coordinated with the Meat and Poultry Inspection Service of USDA. Experimental animals fed supplemental selenium could not be used for human food, and their carcasses or products were denatured and destroyed. After sufficient data were acquired to satisfy FDA and USDA of the safety of the practice, human food use was permitted after a 60-day selenium withdrawal.

On April 19, 1973, a Draft Environmental Impact Statement (FDA, 1973a) was published by FDA in compliance with the requirements of the National Environmental Policy Act. A proposed food additive regulation was published 8 days later (FDA, 1973b). By the end of the comment period (June 26, 1973), the FDA Hearing Clerk had received 19 comments on the environmental impact statement and 143 comments on the regulation. Of the 143 comments, 65 were from private citizens, 40 from feed and associated industries, 12 from trade associations, and 26 from university scientists. Responses were judged 73 in favor, 68 opposed and 2 noncommital. Of the 40 feed and related industry comments, 38 favored selenium supplements, one was opposed, and one was noncommital. All 12 trade association comments favored the proposal, as did 22 of the 26 university comments; 3 were opposed, and one was noncommital. One of the 65 comments from private citizens was in favor, while the remainder were opposed.

After the submission of further data, and deliberation by FDA, the availability of the Final Environmental Impact Statement--Selenium in Animal Feeds was announced in the Federal Register on Tuesday, January 8, 1974 (FDA, 1974b). The final food additive regulation was also published that day (FDA, 1974a). It took effect on February 7, 1974, 17 years after the discovery of the essential nature of selenium, and 4 years after submission of the original petition to FDA. {Parenthetically, New Zealand's Governor-General authorized selenium supplementation under medical or veterinary prescription in 1959 (Governor-General, 1959)}.

Food Additive Regulation For Selenium For Ruminants

Despite the discovery in 1958 (Muth et al., 1958; Hogue, 1958) that selenium would protect against white muscle disease in young ruminants, and the generally recognized benefit of injectable vitamin E-selenium preparations for young lambs and calves, it was still not legal to supplement deficient ruminant diets in 1975. On August 29, 1975, the Assistant Director of the Ohio Agricultural Research and Development Center, Wooster, wrote to a number of agricultural experiment station directors and animal science department chairmen, enlisting their support in establishing a Selenium for Ruminant Animals Task Force. Initial members of the Task Force included scientists from Purdue University, Virginia Polytechnic Institute and State University, University of Illinois, Ohio Agricultural Research and Development Center, Oregon State University, and Michigan State University. Their efforts were coordinated by the Assistant Director of the Ohio Agricultural Research and Development Center in consultation with the AFMA Director of Feed Control and Nutrition and a representative of FDA-BVM.

The Task Force held its first meeting at the O'Hare Hilton in Chicago on October 23 and 24, 1975. The previously designated scientists were present, plus representatives from the University of Florida and the University of Missouri. A representative from the University of Wisconsin joined the Task Force later. This group assumed responsibility for assembling published information and developing new data in the preparation of a supplemental food additive petition to permit the addition of selenium as sodium selenite or selenate to the diets of sheep and cattle at a level of 0.1 ppm. Some research was already underway. Additional research was initiated, and preparation of the petition began immediately.

The Task Force found that evidence of selenium-responsive disease in the field was overwhelming; ac-

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[2] Six published studies (National Research Council, 1976) have examined the issue of selenium as a carcinogen. Three studies alleged that this element was carcinogenic, while three drew the opposite conclusion. A critical evaluation of these six trials revealed significant errors in experimental design, unusually high levels of selenium and/or infectious disease in the three studies in which carcinogenicity was indicated. The remaining three studies, which were well controlled investigations, found no evidence of carcinogenic activity. Scientists in FDA and the National Cancer Institute concluded that "judicious administration of selenium derivatives to domestic animals would not constitute a carcinogenic risk" (FDA, 1973b).

cording to one survey (Wolf et al., 1963), white muscle disease had been diagnosed in lambs and calves in 30 of the 50 United States. Agricultural statistics showed that approximately 51 percent of the beef cattle, 69 percent of the dairy cattle, and 31 percent of the sheep produced in 1975 in the United States were produced in selenium-deficient states. Economic losses to livestock producers were associated with death losses, impaired reproductive efficiency, and, in some cases, reduced growth, feed efficiency, and production of milk and wool. Total losses during 1975 to producers of beef cattle, dairy cattle, and sheep were estimated to be nearly $545 million (Selenium for Ruminants Task Force, 1976).

On March 31, 1977, the first edition of the supplemental petition was submitted to FDA. Subsequent editions ultimately included the following sections:

(1) Indications of selenium-responsive disease in the field, including reports from veterinary diagnostic laboratories.
(2) Justification for adding selenium to the diets of ruminants.
(3) Selenium content of grains and forages in relation to the selenium requirements of ruminants.
(4) Safety of selenium when fed at a level of 0.1 ppm to cattle and sheep.
(5) Analytical methods for selenium.
(6) Proposed methods of feeding selenium to sheep, dairy cattle, and beef cattle.
(7) Research data from Task Force members.
(8) Estimate of effects on human health from consumption of tissue from ruminants consuming feed containing selenium at 0.1 ppm.
(9) Environmental and economic impact analysis.

On Tuesday, March 21, 1978 (FDA, 1978a), an amendment to the selenium regulation was published, permitting supplementation of the diet of ewes and ewes with lambs up to 8 weeks of age. Notice was given in the Federal Register on April 7, 1978 (FDA, 1978b), that a food additive petition had been filed by AFMA (for the Task Force) proposing that the use of supplemental selenium be extended to diets of sheep and of beef and dairy cattle. A further amendment was published on Friday, January 26, 1979 (FDA, 1979b), including beef, dairy cattle, and all ages and sexes of sheep. The final regulation thus included the following features:

Selenium (as sodium selenite or selenate) may be added to feed as follows:

(1) Poultry
  (a) In complete feed of growing chickens up to 16 weeks of age at a level not to exceed 0.1 ppm.
  (b) In complete feed of turkeys at a level not to exceed 0.2 ppm.
(2) Swine
  (a) In complete feed at a level not to exceed 0.1 ppm.
(3) Sheep
  (a) In complete feed at a level not to exceed 0.1 ppm.
  (b) In a feed supplement for limit feeding at a level not to exceed an intake of 0.23 mg/head/day.
  (c) Up to 30 ppm in a salt-mineral mixture for free-choice feeding at a rate not to exceed an intake of 0.23 mg/head/day.
(4) Beef cattle
  (a) In complete feed at a level not to exceed 0.1 ppm.
  (b) In a feed supplement for limit feeding at a level not to exceed an intake of 1 mg/head/day.
  (c) Up to 20 ppm in a salt-mineral mixture for free-choice feeding at a rate not to exceed an intake of 1 mg/head/day.
(5) Dairy cattle
  (a) In complete feed at a level not to exceed 0.1 ppm.

Epilogue

It has taken 22 years from the discovery of the essential nature of selenium to gain approval from FDA to add this nutrient to the diets of certain poultry, swine, sheep, and cattle. This period includes 12 years during which the efforts of large numbers of scientists were directed specifically toward this goal. The research cost cannot be precisely estimated, but the specific projects involving the Selenium for Ruminants Task Force were budgeted at $173,124[3] for a 1-year period in 1976 and 1977 (Johnston, 1976). It would certainly be conservative to suggest that the effort expended so far in meeting regulatory requirements for selenium has cost over a million dollars. The inability to supplement demonstrably deficient diets during this period has cost hundreds of millions. Further effort is still needed and is continuing, since addition of selenium to diets for laying hens producing eggs for human consumption has not yet been approved by FDA.

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[3] This amount includes some costs of graduate assistants and technical assistance but not the salaries of senior scientists.

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