NRSP-7 Five-year Review
1998 - 2003

National Research Support Project-7

A National Agricultural Program to Provide Data for the Safe and Effective Use of Drugs in Minor Species

NRSP-7 Review
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Executive Summary

Report of Five-year Review
1998-2003

NRSP-7 – Minor Use Animal Drug Program

W. W. Saylor, S. A. Brown and S. W. Jack
December 23, 2003

This is the second review of the NRSP-7 Minor Use Animal Drug Program since it was separated from the IR-4 program. The program was last reviewed in 1997. Dr. John Babish serves as the National Coordinator for NRSP-7 program activities. He works closely with the four Regional Coordinators: Dr. Paul Bowser (New York AES), Dr. Art Craigmill (California AES), Dr. Ronald Griffith (Iowa AES) and Dr. Alistair Webb (Florida AES). These five constitute the voting members of the Technical Committee. Most of the work of the program is conducted at the Regional Coordinators' institutions. Other non-voting members of the Technical committee include FDA liaison Dr. Meg Oeller, Chair of the Administrative Advisors Dr. Donald Robertson (Kansas AES) and USDA/CSREES Representative Dr. Larry Miller.

NRSP-7 projects are initiated by a formal Animal Drug Request (ADR) submitted to a Regional Drug Coordinator. The ADR's are forwarded to FDA/CVM for comments. Contact is made with the appropriate pharmaceutical company to determine the willingness of the sponsor to seek approval for use of the drug in the minor species. Pending favorable initial review by both FDA/CVM and the pharmaceutical sponsor, the ADR will be discussed at the next scheduled meeting of the Technical Committee. ADR's are prioritized by the Technical Committee based upon prospects for success, anticipated cost, importance to the animal industry and the pharmaceutical company's commitment. Once an ADR is accepted as a research project, the Technical Committee develops a study protocol in consort with FDA/CVM, conducts the research, and submits the data generated for development of a Public Master File and drug approval.

For the 5-year period of this review, NSRP-7 is responsible for a total of five PMF/drug approvals. Federal expenditures for the period of $550,000 to $588,000 per year for a total of $2.825 million represent an average Federal expenditure of $565,000 per drug approved. Total investment for the period was $3.95 million, including $1.125 million (40%) in nonfederal funds, and represents an average from all sources of $790,000 per PMF. Even with the increased cost per drug approval in recent years, the NRSP-7 program continues to demonstrate remarkable efficiency and cost effectiveness. Compared to an average investment of the pharmaceutical industry of $2 to $8 million for adding a label claim to a existing veterinary drug, information generated for additional label claims by the NRPS-7 program costs only approximately 10 to 40% of

pharmaceutical industry costs.

The Review Committee was impressed with the remarkably efficient productivity of the NRSP-7 program over its 21-year existence. The Committee made several specific recommendations for improvement in the programs effectiveness. A summary of some of those suggestions follows here:

- The Technical Committee should seek active participation of stakeholders as *ad hoc* members of the Technical Committee.
- While the focus of the program should continue to be food- and fiber-producing minor species, the Review Team strongly urges the Technical Committee to expand the mission of the program to include agriculturally important "ornamental species" (e.g., tropical fish species).
- The Technical Committee should consider organizing the program into regional "Centers of Excellence" for conducting the program's research.
- The Technical Committee together with the Administrative Advisors should develop a long-term strategy for providing funding to the program.
- The Technical Committee should modify and simplify the Animal Drug Prioritization Form and the prioritization process.
- The Technical Committee is encouraged to conduct several areas of research in parallel, rather than in series, in order to reduce the time of a given drug in the approval process.

The Review Team concludes that NRSP-7 program provides an excellent example of how a relatively small investment of public funds can be leveraged to provide highly effective, efficient outcomes that have significant economic impact and benefit to animal well-being and public safety.

The review team, consisting of Drs. Scott A. Brown, Pfizer Animal Health, Sherman W. Jack, Mississippi State University, and William W. Saylor, University of Delaware and team leader, submits the following consensus report on the review of the NRSP-7 project.

Introduction

The **mission of NRSP-7**, the USDA Minor Use Animal Drug Program is:

- to identify animal drug needs for minor species and minor uses in major species,
- to generate and disseminate data for safe and effective therapeutic applications, and
- to facilitate FDA/CVM approvals for drugs identified as a priority for a minor species or minor use.

To accomplish these goals, NRSP-7 functions through the coordination of efforts among animal producers, pharmaceutical manufacturers, FDA/CVM, USDA/Cooperative State Research, Education, and Extension Service, universities, State Agricultural Experiment Stations and Veterinary Medical Colleges throughout the country.

The NRSP-7 program was last reviewed in 1997. To meet the mandated review requirements of federally-supported projects, the Administrator of USDA/CSREES appointed a review team composed of representatives of Land Grant Universities, the pharmaceutical industry and aquaculture stakeholders to conduct the 2003 review.

The **review committee's charge** was to examine:

- accomplishments of the program,
- current organizational structure,
- program operations, and
- future programmatic direction.

The Review Team found the NRSP-7 program to be a highly effective program operating in an area of critical and competing needs. Review Team recommendations offer a mechanism to enhance the interactions between the regional coordinators, stakeholders and FDA/CVM. Additionally, the Review Team recommendations suggest incorporation of additional metrics of productivity to convey the true efficiency and stakeholder responsiveness of the program.

The Review Team met at the NRSP-7 Western Regional Laboratories, University of California, Davis, CA on August 19th and 20th, 2003. This consensus document is forwarded to CSREES Administrator and NRSP-7 staff for their consideration.

NRSP-7 Accomplishments and Successes

In 1976, the Food and Drug Administration (FDA) initiated an extensive study of the minor use of animal drugs through the efforts of a minor use/minor species drug committee. This committee, comprised of representatives of the FDA's then Bureau of Veterinary Medicine and Bureau of Foods, the U.S. Department of Agriculture (USDA), the pharmaceutical industry, and animal producer groups identified the scope of the problem as a lack of approved drugs for (1) diseases of minor species; and (2) the principle minor diseases of major species. The committee identified the principal diseases for which drugs were not available in the minor species. The committee also recognized that the livestock industry in the United States relies heavily on the judicious

use of drugs for the prevention and treatment of diseases in food animals. Without these drugs, animal suffering and mortality would greatly increase, as would the cost of producing animal-derived food products. However, before a drug can be marketed for use in a food animal species, it must be shown to be safe to the human consumer of the animal-derived food, and safe and efficacious in the target animal.

In 1982, the IR-4 Animal Drug Program was established as part of the overall IR-4 Minor Use Pesticide Management Program. Since that time the animal portion established itself as a national means of securing approved drugs and as a conduit between the animal industries and the FDA. In 1992, IR-4 Administrative Advisors recommended that with the change from Interregional Projects (IR's) to National Research Support Projects (NRSP's), as well as the experience gained under the reorganized IR-4 Project, that the two programs (pesticide and animal) be separated into two projects. In 1993, NRSP-7 was thus created as the Minor Use Animal Drug Program.

Prior to the Minor Animal Drug Approval Program, the FDA had approved the use of drugs for minor species as follows: none for rabbits, one for ducks and pheasants (none for other game birds), two for food fish, four for goats and twenty-one for sheep. Minor and specialty use needs have continued to accumulate, leaving the producer of these species without the drugs necessary for disease prevention and control. More than 100 drugs have been identified as urgently in need of approval for minor species. The Minor Use Animal Drug Program has received over 320 Animal Drug Requests submitted by researcher investigators at federal, state, and university laboratories, veterinarians, and animal industry personnel for approval of a specific drug for the control of a certain disease in an animal industry.

Since the first drug approval in 1984 under the former IR-4 program, NRSP-7 has been responsible for generating 30 Public Master File (PMF) publications in the *Federal Register*, an average of 1.4 per year during its 22 years of funding. These Public Master Files have supported FDA approval for 23 products. A total of $9,116,000 has been granted through Federal funding and an additional 41 percent, on average, has been obtained through nonfederal funds during the term of the NRSP-7 program. The average total expenditure per completed research for a drug approval or publication of a Public Master File was $398,000. Average federal expenditures per completed research for a drug approval or publication of a Public Master File was $304,000.

For the 5-year period of this review, NSRP-7 is responsible for a total of five PMF/drug approvals. Federal expenditures for the period of $550,000 to $588,000 per year for a total of $2.825 million represent an average Federal expenditure of $565,000 per drug approved. Total investment for the period was $3.95 million, including $1.125 million (40%) in nonfederal funds, and represents an average from all sources of $790,000 per PMF. This increase in cost per approval over the average for the entire NRSP-7 history is in line with the increases realized by the pharmaceutical industry as a whole for drug approval. Reasons for the increased approval costs for all parties include the higher standard of study conduct and reporting expected by FDA/CVM, increased cost of improved analytical methods and the associated equipment, and the cost of performing bridging assays for more thorough analytical method validation.

Even with the increased cost per drug approval in recent years, the NRSP-7 program continues to demonstrate remarkable efficiency and cost effectiveness. Compared to an average investment of the pharmaceutical industry of $2 to $8 million

for adding a label claim to a existing veterinary drug, information generated for additional label claims by the NRPS-7 program costs only approximately 10 to 40% of pharmaceutical industry costs.

In addition to formal submissions for PMF approval, NRSP-7 has provided information on therapeutics in minor species use through 11 peer-reviewed publications, three papers in press, and a number of presentations at workshops and national and international professional and stakeholders meetings. Two PhD dissertations have come from research activities supported in part by NRSP-7. The Technical Committee is to be commended for the development of the NRSP-7 web site as a communication tool for dissemination of information generated by the program. The site provides for the submission of Animal Drug Requests (ADR's), operational information and monitoring of project progress by Technical Committee members, access to the MUMS (Minor Use Minor Species) program and links to a variety of stakeholders' websites. The use of the Internet to optimize communications with stakeholders and program participants continues to improve in this rapidly changing medium.

Current Organizational Structure

NRSP-7 is composed of a Technical Committee and four Administrative Advisors. The Administrative Advisors are Experiment Station Directors, one from each region of the US, who provide liaison between the Directors of the State Agricultural Experiment Stations, USDA/CSREES, FDA/CVM, various animal organizations, and others coordinating the efforts of this program. The Administrative Advisors establish and set policy consistent with the mission of the program, and provide advice on budget, and administrative matters relating to the program.

The Technical Committee is composed of: the National Animal Drug Coordinator, who serves as chair of the committee; Regional Animal Drug Coordinator from each of four regions; the chair of the Administrative Advisory Committee (non-voting); the USDA/CSREES representative (non-voting); and the FDA/CVM representative to NRSP-7 (non-voting). The Technical Committee conducts the affairs of NRSP-7 Minor Use Animal Drug Program, including such matters as prioritizing projects, planning workshops, and funding and overseeing the progress of individual drug projects.

In addition to the Technical Committee, the FDA/CVM has a Minor Use Animal Drug Committee that meets with the Technical Committee once a year at one of the semi-annual meetings of the Technical Committee. The FDA Committee consists of representatives from the Division of Therapeutic Drugs for Food Animals, Antimicrobial Drugs Branch, Methods Validation, Analytical Branch and Wildlife Drugs Branch, and the Environmental Sciences Staff.

The National Animal Drug Coordinator is salaried on a part-time basis and maintains an office. The Regional Animal Drug Coordinators are not compensated by salary except for secretarial or technical assistance. Several undergraduate and graduate students funded through other programs work in the Regional Coordinators' laboratories and contribute the success of the NRSP-7 program.

The current organization structure provides for effective management of NRSP-7 program operations. The following **recommendation** is made to further improve organizational structure:

- The Technical Committee should seek active participation of stakeholders as *ad hoc* members of the Technical Committee. This is the one group whose participation is most obviously lacking in the program, and whose advice and voice could be the most influential in advancing the mission of NRSP-7, particularly in seeking additional funding for the program. This should not be done one stakeholder at a time, but as a group in order to develop a common purpose among the minor use/minor species stakeholders.

Program Operation

The Technical Committee meets twice each year to conduct the business of the program. Routinely the fall meeting is held in Rockville, MD with members of FDA/CVM staff in attendance. The spring meeting is usually held in conjunction with a visit to a minor use species stakeholder facility, the site of which rotates from region to region.

Projects are initiated by the submission of an Animal Drug Request (ADR - available on the NRPS-7 website) to a Regional Animal Drug Coordinator. The ADR's are forwarded to FDA/CVM to request comments regarding the extent of the data required for drug approval (e.g. efficacy, target animal safety, residue depletion, and/or environmental assessment studies). Contact is made with the appropriate pharmaceutical company to determine the willingness of the sponsor to seek approval for use of the drug in the minor species. Pending favorable initial review by both FDA/CVM and the pharmaceutical sponsor, the ADR will be discussed at the next scheduled meeting of the Technical Committee. Using the ADR Prioritization Form (available on-line), a decision will be made whether or not to accept the project and, if so, the priority with which the project should move forward. Currently, only drugs or compounds intended for the prevention or treatment of diseases or for reproductive management in food- and/or fiber-producing species are considered for funding. Regional Coordinators will determine: 1) what kind and how much work has been done on the compound; 2) the approval requirements; 3) data collection capabilities available at the leader laboratory, at other NRSP-7 laboratories, and at other laboratories in the region; 4) the level of funding required to complete the work; 5) whether an appropriate field research program is underway that will provide samples for analysis; and then will, if appropriate, initiate negotiations for financial support that may be needed for performance of necessary work at other universities, federal agencies or private organizations. Once an ADR is accepted as a research project, study protocols are developed and reviewed by FDA/CVM and modified as necessary. All research projects are conducted in accordance with FDA's Good Laboratory Practices regulations.

While the current program operations have been successful in producing remarkable results with limited funding, the Review Team makes the following **recommendations** that could improve operational efficiency of the program.

- While the focus of the program should continue to be food- and fiber-producing minor species, the Review Team strongly urges the Technical Committee to expand the mission of the program to include agriculturally important "ornamental species" (e.g., tropical fish species). The size of the ornamental industries and their contributions to the economy, particularly in some regions, dictate that consideration should be given to including their needs in the scope of the program.
- Stakeholders should be invited to be active non-voting participants in at least one of the semi-annual meetings. The nature of the participation could be *ad hoc*, that

is, inviting representatives from different stakeholder groups to meetings on a rotating basis, without representation from a single or specific group "assigned" to the committee. The Review Team sees this as a critical step to the future of the program. It is suggested that the spring meeting provide the venue for this stakeholder participation, and that the meeting take place within the Washington, DC area to provide the opportunity for the participating stakeholders to visit key legislators on behalf of NRSP-7.

- The Technical Committee should consider conducting quarterly meetings electronically (e.g., web-conferencing) or by conference call to discuss new ADR's and make decisions on their fate. This approach would accelerate the movement of ADR's into the program queue, or remove it from the list of potential projects.
- The Technical Committee should consider organizing the program into regional "Centers of Excellence" for conducting the program's research. While it is important to recognize that each laboratory may have areas of research specialization and the associated facilities and equipment (i.e., for aquaculture research), the program should be organized to minimize redundancies, especially in high-end equipment. Areas of specialization could include bioanalytical capabilities, informatics, and in-life activities. Development of centers would optimize the use of the limited resources of the program, help focus program activities, and enable closer monitoring of project progress.
- The Review Team recognizes the backlog of projects in the program and the workload required to complete active research projects. However, the operational procedures currently employed encourage delays in moving drugs through the process to final approval. There appears to be little sense of urgency in moving projects forward. Acting on ADR's and providing research updates on a semi-annual basis permit some projects to languish for long periods of time. Implementation of quarterly Technical Committee meetings will aid speeding the prioritization process. The "RUSTI" mechanism on the NRSP-7 website will be an important asset for monitoring project progress. Both should be used to enhance the accountability and productivity of the program.

Funding

The Minor Use Animal Drug Program is funded primarily through the USDA Special Grants program, administered by CSREES in cooperation with the NRSP-7 Technical Committee. Currently there are no "off-the-top" Regional Research funds allocated to the Minor Use Program, the only NSRP that does not receive "off the top" Regional Research funds. The program receives significant "in-kind" support from a number of sources including the institutions (State Experiment Stations, Schools of Veterinary Medicine, Federal Laboratories) where the regional coordinators are housed, animal producer groups, and pharmaceutical companies. Total funds infused into the program for the last five-year period totaled $9,116,000. In general, the funds are allocated equally among the four regional laboratories after an allotment has been provided to the national Coordinator for salary and office maintenance costs.

Since the last review, the National Coordinator has spent considerable energy and time meeting with the Experiment Station Directors at their regional association meetings to improve the visibility of the program and to solicit support of the directors through "off-the-top'" funding for the program. Although the regional and national importance of the NRSP-7 program would suggest the appropriateness of additional funding by the regional directors, the efforts have been met with moderate interest on

the part of the directors and "off-the-top" funding has not been forthcoming. It is unlikely that it will. These responses are not surprising in light of the current economic situation faced by universities, level CSREES formula (Hatch) funds distributed to Experiment Stations, and a continued increase in demands by stakeholders.

Over the past several years, several meetings have been held with the Administrator of CSREES to request his/her support for increased funding by the agency through the Special Grants program. Those soliciting support on behalf of NRSP-7 have included the Chair of the Administrative Advisors, The chair of the last Review Team, liaisons from the Animal Health Institute and the AVMA, and representative from several stakeholder producer groups. These efforts have met with limited success, particularly in light of the nature of the requests - up to a doubling of the current funding level.

The Review Team makes the following **recommendations** about future funding of the program:

- Because it is unlikely that additional funding can be realized through the regional "off-the-top" funding mechanism, the National Coordinator should limit his activities in this direction. Within the life of the Minor Use Animal Drug Program, no "off-the-top" funding has been provided to any new program put in place. Hence it is most unlikely that NRPS-7 will garner support from this funding mechanism.
- The Technical Committee together with the Administrative Advisors, should develop a long-term strategy for providing funding to the program. Past attempts at increases CSREES agency funding have been minimally successful, and probably are not the most effective focus for increased support. Stakeholders must be a significant part of any new initiative. It is suggested that, as part of the stakeholder participation in semi-annual meetings, they are asked to contact and, where feasible, visit appropriate legislators on behalf of the program.
- The proposed MUMS program, once instituted and funded, should be viewed as a potential source of additional funding for NRSP-7. The expertise, facilities and track record of the Regional Coordinators should make them very competitive for new funding from this new program.
- A consortium of MUMS stakeholders should be viewed as a source of capital funding, particularly for equipment that might support an array of projects of interest to a broad set of stakeholders. This necessitates the NRSP-7 leaders to coalesce a heretofore-disparate set of stakeholders, each with different and individual requests, into a cohesive group interested in working together to provide the infrastructure that would benefit the entire array of stakeholders.

Project Management

The NRSP-7 program has historically managed projects by evaluating the ADR's, implementation of the Animal Drug Prioritization Form, and managing activities through various phases of the data-gathering process in a linear fashion (i.e., without progressing the projects along on multiple fronts simultaneously). While this has resulted in a very budget-conscious programmatic approach, the Review Team makes the following **recommendations** to enhance efficiency of the process:

- Modify and simplify the Animal Drug Prioritization Form and the prioritization process. The Team reviewed the form and worked through the prioritization process

and found it to be confusing and cumbersome, particularly the "Product Status Code" assignment and the implications of the code for the future of the drug.

- Contact the originators of ADR's once a decision on the prioritization has been made, if the originator is outside the NRSP-7 group (e.g., a stakeholder, a pharmaceutical sponsor, etc.). It is important for those providing ADR submissions to the program to learn early of the fate of the request.
- Conduct several areas of research in parallel, rather than in series, in order to reduce the time for a given drug in the approval process. In particular, focus on ways to reduce the time needed for the most time-consuming segment of the program (often the analytical method development/validation and human food safety studies). In addition, in instances where additional resources may shorten the timeline for completion of the studies, consideration should be given to shifting resources to the rate-limited activity.
- The stages of activity could be more carefully monitored not only during the semi-annual Technical Committee meetings, but also in the recommended more frequent teleconferences or web-conferences. Languishing tasks can then be managed more aggressively by the Technical Committee. Furthermore, a process whereby languishing tasks are followed up by the National Coordinator may prompt more diligent attention than what might otherwise occur.
- A more rigorous approach to seeking completion of the project through to FDA approval and labeling should allow fewer projects to culminate in the Public Master File. This would include more aggressive efforts with the pharmaceutical industry to complete the administrative tasks of label changes and NADA submission.

Informatics

The development of the NRSP-7 website provides an outstanding mechanism for communication of the Technical Committee within itself and with NRSP-7 stakeholders and participants. The “RUSTI” program has the potential for significantly improved internal tracking of project progress. The Review Team makes the following **recommendations** to further enhance the effectiveness of the website:

- The Technical Committee is encouraged to post PDF versions of publications and/or dissertations that have been supported through NRSP-7 funds as well as links to other appropriate pages (partners, producer and/or pharmaceutical company websites). Existing brochures and any newly developed media information packages should likewise be posted here.
- The Technical Committee is encouraged to consider using the website as a mechanism to “survey” stakeholders’ opinions about the effectiveness of the NRSP-7 program.

Outreach

Several recommendations have already been made regarding the need for the Technical Committee to more actively seek stakeholder participation in its activities. This form of outreach is viewed as critical by the Review Team for the future success of the program, particularly in terms of future funding opportunities. The Review Committee makes the following specific **recommendation** for outreach not only to stakeholder groups but also to congressional members and staff:

- The Technical Committee is encouraged to organize and host a “MUMS Night on Capitol Hill.” This event is viewed as an annual opportunity to invite legislators and staff to an informal evening organized to inform them of current activity and

to raise their awareness of the needs for increased, more consistent funding. Ideally, such an event could be scheduled during the spring NRSP-7 meeting when congressional budget discussions are underway, and at a time that the stakeholder groups would be attending the NRSP-7 semi-annual meeting in the Washington area.