National Research Support Project 7
(NRSP-7)

A National Agricultural Program for Minor Use Animal Drugs

Renewal

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NRSP007: A National Agricultural Program for Minor Use Animal Drugs

Duration:	October 2014 to September 30, 2015
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Statement Of Issues And Justification

Globalization of food markets has allowed countries with less stringent animal drug approval requirements to dominate U.S. sheep, goat, farmed shrimp and fish, venison, honey and game bird production industries. At the same time, the growing concern in the U.S. over antibiotic resistance in human health and the use of antibiotics in food producing animals threatens to eliminate or severely curtail antimicrobial use in veterinary medicine. In April of 2013, the Center for Disease Control and Prevention (CDC) released their report entitled, "Antibiotic Resistance Threats in the United States 2013". With respect to the issue of antibiotic use in food animals, the CDC report concluded "*Because of the link between antibiotic use in food-producing animals and the occurrence of antibiotic-resistant infections in humans, antibiotics should be used in food-producing animals only under veterinary oversight and only to manage and treat infectious diseases, not to promote growth*." Since the release of this report, efforts have grown to sharply eliminate any use of antibiotics in animals without veterinary oversight. There appears little doubt that the next several years will introduce a new era of antimicrobial use in veterinary medicine. This movement may, in the end, assist NRSP-7 by curtailing unsupervised use of antibiotics in minor species production. Thus, our stakeholders will not have the unrestricted availability of antibiotics and become even more dependent on the Program.

The Minor Use Animal Drug Program is the only national program designed and organized to address the issues of the prudent use of antibiotics, anthelmintics and production drugs in minor species of food- and fiber-producing animals. Until 2006 NRSP-7 was consistently funded through as a line item in the Federal Budget at $588,000 per year. Due to the elimination of earmarks by Congress, the Program lost direct Congressional funding in 2007 and 2008. Federal support resumed in 2009 and 2010, but has been provided through Hatch funding by the SAES at a 70% level over the last four years. Overall, Hatch funding has supplied less than 40% of the operating budget of the Program, with all of these funds directly supporting research. While appreciated, the current level of support, with additional cuts through sequestration and increasing costs of research, is insufficient to maintain the NRSP-7 as a viable, robust national program.

Over the next year, the Program will pursue additional funding support from the Minor Use Minor Species Program of the FDA/Center for Veterinary Medicine and developers of organic or natural alternatives to antimicrobial and pesticide use in food animals. Additionally, USDA/NIFA has been exploring ways to consolidate related programs. This has been successfully implemented for a subset of programs related to plant protection, and task forces are currently working toward consolidation of selected water programs. Early-phase discussions concerning possible consolidation of animal protection and production programs, including NRSP-7, are now underway. Stakeholders will also be engaged to further Congressional interest in tighter control of antimicrobial use in food animals through NRSP-7 research. Additionally, the Program will continue communications with the IR-4 Pesticide program liaison Dr. Malamud-Roam to further assess critical pesticide approvals for animals. These efforts, we believe, will assist the Program to be federally funded once again. If sustainable funding cannot be obtained, however, consideration will be given to termination of the Program.

Prerequisite Criteria: Mission

Broadly stated, National Research Support Projects (NRSPs) are created to conduct activities that enable other important research efforts. Examples of NRSP activities might include collection of data that are widely used by other research groups and efforts, development of databases, or development of critical technologies. In accordance with the focus of NRSPs, the missions of the NRSP-7 Minor Use Animal Drug Program are:

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

Minor uses include minor species (all species except dogs, cats, horses, cattle, swine, chickens, and turkeys), while minor uses in major species are those that occur infrequently or in limited geographical locations. The primary emphasis of the Program is on food-and/or fiber- (hair, wool, fur, feathers or hide) producing minor species with a secondary interest in non-food animals such as bees and tropical fish.

To accomplish these goals, NRSP-7 functions through the coordination of efforts among animal producers, pharmaceutical manufacturers, Food and Drug Administration/Center for Veterinary Medicine, United States Department of Agriculture/Cooperative State Research, Education, and Extension Service, universities, State Agricultural Experiment Stations and veterinary medical colleges throughout the country.

Prerequisite Criteria: How does this NRSP pertain to a national issue?

Globalization of food markets has allowed countries with less stringent animal drug approval requirements to dominate our sheep, goat, rabbits, farmed shrimp and fish, venison, honey and game bird production industries. One-third of the lamb and 82% of venison consumed in the US comes from Australia and New Zealand. Nearly 90% of the commercially farmed shrimp are imported. Additionally, two-thirds of the honey consumed in the US is imported and half of that honey comes from China. In order to complete with these countries, American producers are forced to use therapeutics not approved in minor species.

The economic impact of minor animal species agriculture in the United States is great, but at risk. THE United States gross annual farm gate income from production of specialty animal species has been estimated by producer groups at over $4.8 billion. Further, these farm gate revenues produce an economic stimulus to the US Gross Domestic Product estimated at another $37 billion. Table 1 provides a break down of theses national figures by state. Lack of approved drugs for these producers is seriously threatening the growth and long-term viability of these collective industries and the security of our food supply. While the cumulative contribution of minor species to agricultural income is great, the return to pharmaceutical companies for research on therapeutics for this category, by species is small and generally unprofitable.

Because of this substantial investment in time and resources, pharmaceutical companies must be assured that the drug will have a reasonable potential for profit. Therefore most drug approvals are sought only for those animal species that are produced in sufficient numbers to support large volume sales, specifically cattle, swine, chickens and turkeys. There is little economic incentive for pharmaceutical firms to generate data necessary to seek FDA/CVM approval of drugs in minor species; hence, very few drugs are available for management of diseases in these minor species. Inequities in drug availability represent serious management

and economic problems for producers for minor species. Today, more than half of all commercially led pharmaceutical R&D in the veterinary medical field is focused on developing products for companion animals, and the emphasis on this sector is likely to increase in coming years, as companion animals live longer, and more diseases of old age are diagnosed and treated[2].

TABLE 1.
ECONOMIC IMPACT OF MINOR ANIMAL SPECIES BY STATE AS OF 2013

INDUSTRY	LEADING STATES	US FARM GATE VALUE [$M]	US ECONOMIC IMPACT [$M]
Game Bird	TX, NC, PA, KS, WI, NY, IL, SD, FL, MN, IA, GA, MS, IN & AL.	$897	$5,401
Rabbits	CA, GA, OH, PA, & TX	$21.6	$898
Honey Bees	ND, CA, SD, FL, MT, MN, TX, & WI.	$166	$17,284
Cervid	TX, PA, OH, FL, LA, IA, & KS	$966 (farming) $817 (hunting)	$3,241
Meat Goats	TX, TN, CA, GA, OK, NC, KY, MO, FL, & AL	$187 $205 (breeding)	$1,123
Dairy Goats	TX, OH, NY, PA, WI, WA, IN, CA, MD, MN, MI, FL, & KS.	$63.0 $16.0 (export)	$474
Sheep	TX, CA, WY & CO	$810	$4,861
Catfish/Aquaculture	**Catfish** MS, AK, AL, & LA **Trout** WA, WI, PA, ID, NC, OR, NY, CA, & CO	Catfish $518 Trout $94.6	$3,111 $172
	Total =	**$4,761**	**$36,564**

The Food and Drug Administration/Center for Veterinary Medicine (FDA/CVM) has been aware that veterinarians and livestock producers were using unapproved drugs for minor species without the safeguards that approved drugs carry. Additionally, little peer-reviewed literature existed to provide veterinarians with sufficient information for rationale extra-label use. Such unapproved drug use could not only cause detrimental effects to the animals being treated, but could also lead to the persistence of drug residues in animal products intended for human consumption. Efforts were and continue to be necessary provide US animal producers with safe and effective means to compete in a global market, while assuring US consumers a safe and wholesome food supply.

In 1976, the FDA/CVM 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. In summary, private sponsors had supported approvals for the use of minor use drugs 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 producers of these species without the drugs necessary for disease prevention and control. A definite need has been established for approval of minor use veterinary drugs and the scope of the problem was defined. This need was also affirmed by various grower organizations.

Additionally, the committee recognized that the livestock industry in the United States relies heavily on the judicious use of drugs for the 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.

The process of generating the safety and efficacy data necessary for FDA/CVM approval of a drug is costly and time-consuming. In 1999, it was estimated that the cost to a pharmaceutical company for research necessary to obtain FDA/CVM approval for a new drug exceeded $20 million, and required 8 to 10 years of concentrated research effort [1]. More recently, issues relating to (1) escalating costs in the development of analytical methods, (2) concerns over antimicrobial resistance in human medicine, and (3) increased environmental testing have increased veterinary drug approval costs dramatically[2]. Drug approvals are generally species and disease specific and additional label claims also come with considerable added expense. Pharmaceutical company estimates place the cost of simply adding a label claim to an FDA/CVM approved drug at $10 to $25 million[3, 4].

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 has been established as a national means of securing approved drugs and as a conduit between the animal industries and the FDA/CVM.

In December 1990, the USDA/CSRS requested a peer review of the IR-4 program, including both the pesticide portion and the minor use animal component. A reorganization of the minor use animal drug section was one of the recommendations of the Review Team. This Change was carried out with the development of a separate Minor Use Animal Drug Technical Committee that reported to the IR-4 Administrative Advisors.

In 1992, IR-4 Administrative Advisors recommended that with the change from interregional Projects (IRs) to National Research Support Projects (NRSPs), 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.

Congress has considered bills to promote drug availability for minor species and for minor uses in major species. The Animal Medicinal Drug Uses Clarification Act of 1994 [AMDUCA] and the Animal Drug Approval Act [ADAA] have expanded “extra label” uses for minor species. The limitations imposed by AMDUCA on extra-label drug use in feeds, however, proved to be a major problem to aquaculture and game bird industries and a guidance document has outlined conditions where limited extra-label use of approved formulations will be permitted under conditions of a valid veterinarian-client-patient relationship. The Minor Use Animal Drug Program is the only organized State/Federal effort to address the inadequate number of FDA/CVM approved drugs available for minor-use species and has been responsible for nearly all of the progress made in the approval of minor-use/minor-species drugs.

The advantages of doing the work as a multistate project - There are two critical advantages for organizing the Minor Use Animal Drug Program as a multistate project. First, farm production of minor species represents a highly fragmented industry. Of the eight or so farming industries that focus on the production of minor species, none represent more than ten states in the US. To cite only two examples, catfish farming is concentrated in Mississippi, Arkansas, Alabama and Louisiana, while deer farms comprise significant farm revenues in Texas, Pennsylvania and Ohio. Over the 31 years of the Program, Land Grant institutions represented by the four Regional Coordinators have developed significant expertise in addressing the issues of regional producers. These same institutions have also dedicated facilities and personnel to meet the Good Laboratory Practices regulations (CFR 21.58).

Second, FDA/CVM approval of drugs requires performing clinical field trials in several geographical locations throughout the US. The rationale behind this requirement is that climate and other environmental conditions as well as possible differences in husbandry may affect the efficacy of any particular drug regimen. Coordinating these field trials spread throughout the US is most cost-effective through the multistate project approach. Our Regional Coordinators have worked closely together during the life of the Program to facilitate such work. Projects such as our ivermectin cattle tick study in Texas is currently run through both Iowa State University and the University of Florida. Such coordination uses the ruminant expertise of Iowa State veterinarians with the analytical capabilities of the University of Florida.

Thus, only a multistate project could possibly address the needs of such a widespread collection of industries and Federal regulations in a cost-effective manner.

What the likely impacts will be from successfully competing the work - Since its inception in 1983, the Minor Use Animal Drug Program has been responsible for generating 52 New Animal Drug Applications, an average of 1.6 per year. Further, the Program has supplied supplemental data to the US Fish and Wildlife Services in support of 21 New Animal Drug Applications. Together these applications have supported FDACVM approval for 73 drugs for use in minor food species.

From inception, regional coordinators have published 206 peer-reviewed articles relating to the use of therapeutic drugs in minor species. Such publications benefit stakeholders by providing veterinarians with the necessary information to allow the extra-label use of these drugs on minor species.

NRSP-7 was established and is still needed today because there are insufficient financial incentives for the veterinary pharmaceutical industry to invest in minor species. Additionally, there are potential liability issues from animal injury in minor species that may create unfavorable risk-reward relationships for pharmaceutical companies that add these species to established label claims. NRSP-7 develops the data to support the drug approval process and eventually the addition of the minor species to the label claim. In doing so, NRSP-7 helps to improve the international competitiveness of US agriculture. As the veterinary pharmaceutical industry continues to undergo worldwide consolidation, the resources devoted to minor species and minor uses continue to diminish. This makes the role of NRSP-7 increasingly critical for maintaining the efficient and competitive production of these minor species and minor uses in the US.

Through a productive MUADP/NRSP-7, producers and veterinarians will continue to have the necessary information to prevent disease-related losses, to reduce pain and suffering in important species, and avoid contamination of our foods with drug residues.

Rationale: Priority Established by ESCOP/ESS

The seven ESCOP National Priorities include: (1) Develop new and more competitive crop products and new uses for diverse crops and novel plant species; (2) Develop new products and new uses for animals; (3) Reduce the risks of local and global climatic change on food, fiber, and fuel production; (4) Provide the information and knowledge needed to further improve environmental stewardship; (5) Improve the economic return to agricultural producers; (6) Strengthen our communities and families and (7) Ensure improved food safety and health through agricultural and food systems.

NRSP-7 research addresses three of the seven ESCOP Roadmap Challenges, including Challenge 2, Challenge 5, and Challenge 7. The primary contribution of NRSP-7 is to ***Ensure improved food safety and health through agricultural and food systems*** *(Challenge 7)***.** Concern over drug residues in our food supply has grown exponentially over the last 10 years.

Food producers and veterinarians are under pressure to limit the use of antimicrobials in food animals and employ more prudent oversight over even therapeutic uses. Prior to the initiation of the Program in 1982, private sponsors had supported approvals for the use of minor use drugs 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. A majority of these approvals represented outdated drugs with insufficient data on the post-treatment residue levels as well as efficacy. In the 31 years of the Program, data supplied by multistate research provided for the modification of 52 label claims to include minor species, an overall average of 1.6 per year. Included in these approvals were one for rabbits, nine for game birds, 16 for fish, lobster and shrimp, 15 for meat and dairy goats, eight for bison and reindeer, one for foxes and two for honey bees.

In addition to adding minor species to label claims, the Program works to ensure food safety through the publication of data on the pharmacokinetics, safety and effectiveness of modern drugs in minor species. Extra-label use of drugs by veterinarians, requires knowledge of the pharmacokinetics, tissue distribution, and sensitivity of the animal to support the decision to treat with an unapproved therapeutic. Regional coordinators in the Program have published 206 peer-reviewed articles supporting veterinarians in their decision to use drugs in an extra-label use manner. This information is also supplied to the FARAD program for online access to veterinarians (http://www.farad.org).

Thus, the linkage to human health includes improving the quality and safety of food, addressing issues of zoonotic diseases that threaten both animal and human health, and assuring safe and efficacious animal health products that do not adversely affect human health.

Additionally, with respect to (*ESCOP Roadmap Challenge 5)*, ***Improve competitiveness and profitability/economic return to the producer in agriculture***, NRSP-7 serves as a critical support component of minor species production systems in the US. Economic survival of these minor species producers depends upon their ability to treat diseases with approved drugs and the knowledge that such treatment will not harm the species or incur illegal drug residues. Production units or farms for minor species typically operate on thin margins. Economic success or even survival depends on optimal health of the crop. Limiting disease with approved therapeutics allows producers to treat animals with confidence and assurance that the dose selected will perform as intended and will not result in illegal contamination.

The study of ivermectin medicated feed blocks for Cattle Fever Ticks by NRSP-7 is another example in which the program supports improved competitiveness in agriculture. Treatment of cattle within the 852-square mile quarantine zone that runs along the Mexico-Texas border with ivermectin-treated molasses blocks was identified as a minor use in a major species through the efforts of NRSP-7. Additionally, the experience of the Program with the analysis of ivermectin and the drug approval process has enabled NRSP-7 to establish pivotal efficacy and safety data and await only the cooperation of the manufacturers to put the newly documented products to use in the quarantine zone. Since most other treatment options have failed, without these new ivermectin/molasses blocks in use, the entire U.S. cattle industry is at risk if Cattle Tick Fever returns to the United State (www.angusbeefbulletin.com/extra/2008/dec08/images/.../**texas_tick**.pdf).

The work on the FDA/CVM approval for progesterone implants for estrus synchronization in sheep by NRSP-7 has enabled sheep farmers to begin producing lambs throughout the year. This in turn allows the producer to supply animals to the market at times other than peak “natural” breeding periods, improving US sheep farming competitiveness in the US and foreign markets.

NRSP-7 also assists to ***Develop new products and new uses for animals*** *(Challenge 2).* Without NRSP-7, the introduction of many new animal species would not be possible since they

are generally high value specialty animals with few, if any, approved therapeutics. The work on the development of the ivermectin/molasses blocks described in the context of Challenge 5 is also consistent with Challenge 2 and is discussed in more detail above. Other options for the containment of the Cattle Fever Tick have failed to contain the tick in the quarantine zone or result in illegal drug residues.

Rationale: Relevance to Stakeholders

Animal producers are the primary stakeholders in the NRSP-7 program, but pharmaceutical companies may be considered significant stakeholders as well. Other groups with interest in minor animal drug use include veterinarians and regulators. The active participation of animal producers and pharmaceutical companies is essential for the success of the program. However, to one degree or another, NRSP-7 involves all stakeholders. NRSP-7 producer stakeholders are represented by the following 58 organizations in 10 categories: American Association of Wildlife Veterinarians, American Association of Zoo Veterinarians, American Farm Bureau, American Feed Industry Association, American Pet Product Manufacturers Association, Inc., American Rabbit Breeders Association, American Sheep Industry Association, American Veterinary Medical Association, Animal Health Institute, Animal Drug Alliance, Arkansas Bait and Ornamental Fish Growers Association, Catfish Farmers of America, Center for Veterinary Medicine, Florida Tropical Fish Farms Association, Inc., Food Animal Concerns Trust, International Association of Aquatic Animal Medicine, International Association of Fish and Wildlife Agencies, North American Deer Farmers Association, North American Gamebird Association, Inc., National Pork Producers Council, National Cattlemen's Beef Association, National Fisheries Institute, National Turkey Federation, Pacific Coast Shellfish Growers Association, and the National Aquaculture Association.

By category, stakeholders include:

- **Agencies** – Fish and Wildlife Service, and Animal and Plant Health Inspection Service, and FDA Center for Veterinary Medicine.
- **Aquaculture**: Marine Fish Dealers, American Tilapia Association, U.S. Trout Farmers Association, American Fisheries Society, World Aquaculture Society, Aquaculture Network Information Center, and Catfish Planet.
- **Bees**: International Bee Research Association, Iowa State Entomology Index: Beekeeping, and Beekeeper's Home Pages Internet Resources.
- **Caprine**: American Dairy Goat Association.
- **Game Birds**: Mississippi State Game Bird Management, Pheasants Forever, Quail World, and North American Gamebird Assiation.
- **Institutions**: Auburn University (aquaculture and fisheries), Cornell University (aquaculture), Minnesota (avian), and Texas AMU (poultry science).
- **Lagamorphs**: American Rabbit Breeders Association.
- **Ratites**: American Emu Association and The American Ostrich Association.
- **Reptiles**: The Gator Hole and Crocodilian Internet Resources.
- **Ungulates**: Alpaca Registry, National Bison Association, The White-Tailed Deer Farmer's Network, North American Deer Farmers Association, Deer Hunting Net, and North American Elk Breeders Association.

These stakeholders provide input to NRSP-7 as to their individual drug needs and support through the contribution of animals, facilities for drug testing, commercial drugs, data, and analytical methodology.

Stakeholder needs – Veterinary medicine has a key role in protecting the health and productivity of several billion farm animals worldwide, ensuring the quality of the food they yield, and in

protecting the health of approximately one billion companion animals. But despite the large number of animals treated with veterinary pharmaceuticals, the human healthcare market is about 35 times larger than the combined market for all non-human species, which had a global value in 2012 of $21.1 billion. This figure can be divided among three main modalities: veterinary pharmaceuticals, biologicals and medicated feed additives (MFAs). 63% of the $21.1 billion veterinary health market in 2011 is accounted for by pharmaceuticals ($13.3 billion), 25% by biologicals ($5.27 billion) and 12% by medicinal feed additives ($2.5 billion). Food animal healthcare comprised $12.45 billion of the total 2011 market; companion animal healthcare comprised $8.64 billion (http://finance.yahoo.com/news/global-veterinary-health-products-market-193000008.html). Moreover, this animal market is dominated by a large number of products that generate small revenues, and so the balance between the amount of R&D investment required relative to the likely return on this investment is a particularly crucial issue in veterinary drug development.

Minor species represent an excellent example of this diverse market. Agricultural production of fish, game birds, sheep, goats, ratites bees and deer in the United States is critically important to numerous regional economies in the United States. This diverse aggregation of minor species represents approximately $4.8 billion in state and local US farm revenues annually. Additionally, processing and export of minor species food and fiber products represents an additional $36.6 billion of revenue. Individually, however, these minor species represent drug markets too small to provide a sufficient return on the high cost of developing a new drug application.

Prior to NRSP-7, the FDA/CVM 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 (most of which have been withdrawn). Minor and specialty use needs have continued to accumulate, leaving the producer of these species without the drugs necessary for disease prevention and control. The Minor Use Animal Drug Program has received 352 Animal Drug Requests submitted by animal producers, 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. Of these requests, more than 40 have been identified as priority projects for NRSP-7.

Measuring stakeholder use – Animal produces who use unapproved drugs for the treatment of livestock face the liability of illegal drug residues as well as the risk of ineffective dosages. Before the Minor Use Animal Drug Program, these producers had little choice, but to use unapproved drugs when faced with outbreak situations. Without these drugs, animal suffering and mortality would greatly increase, as would the cost of producing animal-derived food products. The FDA/CVM is aware that veterinarians and livestock producers were using unapproved drugs without the safeguards that approved drugs carry. Because there is widespread use of unapproved drugs in minor species and the level of use is small, approval of drugs for the minor use needs does not generally result in a measurable increase in sales to the pharmaceutical company. Thus, it is not possible to achieve a measure of stakeholder use of NRSP-7 data and drug approvals through increases in drug sales. One major exception to this situation is in the area of aquaculture. Increases in sales and usage of NRSP-7 developed drug approvals can be monitored through medicated feed records and pharmaceutical company shipment records.

The current development of valid metrics to measure stakeholder use of NRSP-7 information involve more use of the NRSP-7 website. Surveys, technical conferences with various partner groups can be conducted through the internet. Other avenues to increase information on stakeholder use include inviting stakeholder representatives to technical committee meetings,

providing closer contact during monthly conference calls between semi-annual technical committee meetings.

Objectives and Projected Outcomes

The objectives of NRSP-7 are:

1. Identify the animal drug needs for minor species and minor uses in major species.
2. Generate and disseminate data for the safe, effective, and legal use of drugs intended for use in minor animal species.
3. Facilitate FDA/CVM approvals of drugs for minor species and minor uses.

Objective 1 - Identify the animal drug needs for minor species and minor uses in major species

Critical and emerging needs are identified by the Minor Use Animal Drug Program Technical Committee based on information obtained from stakeholders represented by animal industry groups and producer organizations, scientific and professional groups, literature surveillance, and research originating within the program. To further refine specific project objectives, contacts are made with key, knowledgeable representatives from producer organizations, scientific and professional groups, government agencies, and pharmaceutical companies. Identification of producer group workshops and symposia proceedings are also used to gather information about priority needs and emerging issues.

Highest priority are given to research projects that address drugs or compounds that are required to prevent or treat disease, or for reproductive management. Drugs intended for the prevention or treatment of disease or for the modification of specific physiological functions in minor species, or to treat or prevent minor diseases in major food animal species are selected over drug requests for nonfood animals.

Specifically, a system has been devised to review, evaluate and recommend the feasibility of each animal drug clearance proposal submitted. When a proposal is accepted, the necessary data will be obtained, compiled and submitted to FDA/CVM for establishment of a public master file, which will lead to the approval of the drug.

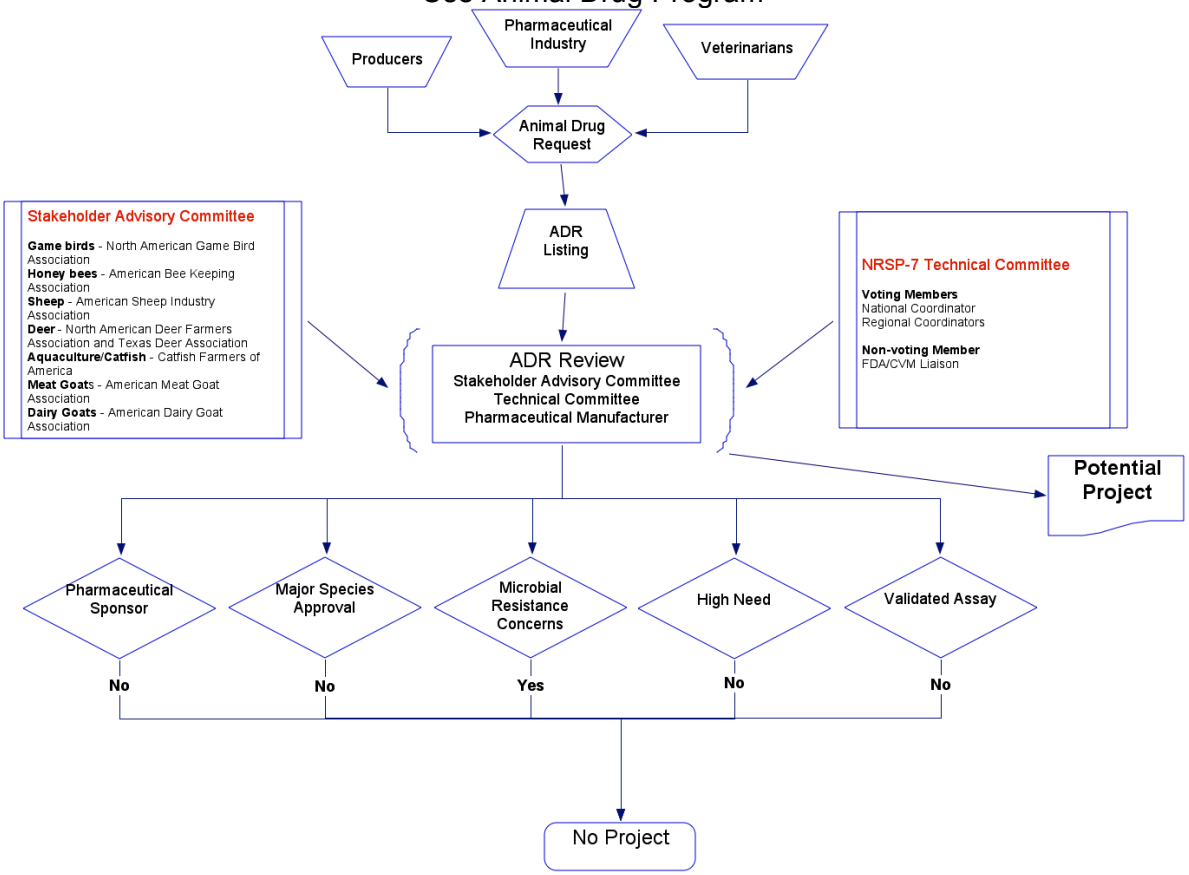
The process for selection of drugs for testing in NRSP-7 is represented schematically in Figure 1. Filing of an Animal Drug Request (ADR) form by any group or individual associated with specialty animal production initiates the process. Representatives of such groups include, animal producers or their representative organizations, pharmaceutical manufacturers, university faculty and veterinarians. An example of the information requested for an ADR is provided in Appendix A. This ADR request form can be submitted online at www.NRSP7.org or through any of the four Regional Drug Coordinators, the National Coordinator, and FDA/CVM liaison. Once received, the ADR is assigned a unique ADR number and included in the master ADR listing maintained at FDA/CVM, the National Coordinator's headquarters and at www.NRSP7.org.

During the spring annual meeting the NRSP-7 Technical Committee and representatives of the Stakeholder Advisory Committee (SAC) review the current projects and consider new ADR for funding. Each newly received ADR is then evaluated by the Technical Committee and SAC according to established criteria that include (1) availability of a pharmaceutical manufacturing sponsor, (2) major species approval, (3) microbial resistance concerns, (4) significance to the animal industry, (5) cost of developing the necessary data, and (6) food safety implications. ADR requests that meet these criteria are considered as potential projects.

Specific regional coordinators are assigned follow-up of all potential projects generally decided by regional expertise. Further concerns regarding the potential project are then addressed including: (1) the identification of researchers and research facilities, (2) development of FDA/CVM approved protocols with reasonable numbers of animals, and (3) scheduling. Monthly

conference calls of regional coordinators, administrative advisors, FDA/CVM and USDA/CSREES liaisons provide continued follow-up of potential project progress.

Figure 1.
Flow Chart Outlining The Process For Selection Of Drugs For Testing In The NRSP-7 Minor Use Animal Drug Program



Regional Coordinators determine: (1) what kind and how much work has been done on the compounds selected for study, (2) the approval requirements, (3) data collection capabilities available at the leader laboratory and at other laboratories in the region, (4) level of funding required, (5) whether a proper field research program is underway that will provide samples for analysis, and (6) initiate negotiations for such financial support as may be needed for performance of necessary work at other universities, federal agencies, or private concerns.

Where possible and appropriate Regional Coordinators will work closely with the National Coordinator in establishing proposed priority lists for projects, in negotiating for laboratory and field work that may be performed in their regions, and in delegating authority to them for conducting sub-projects funded in their regions. The Regional Coordinator may award "grants-in-aid" or contracts for field and laboratory work necessary to obtain the required data for registration petitions. Decisions to conduct specific projects are based on unanimous approval by the Technical Committee of the Animal Drug Program. Other experts will be consulted as deemed necessary to help with prioritizing projects.

Finally, in order to ensure that the program is responding to developing needs of minor species, research priorities are continually updated through review of producer group workshops and meetings. Weighting algorithms have been used to provide a general

ranking or prioritization of requests. It has been found, however, that weights may change from year to year and the best process is continued, annual evaluation of stakeholder priorities.

Objective 2 - Generate and disseminate data for the safe, effective, and legal use of drugs used primarily in therapy or reproductive management of minor animal species.

The following outlines the steps undertaken to initiate the generation and dissemination of data:

2.1 All projects are initiated by the submission of an Animal Drug Request (ADR) form to the National or a Regional Animal Drug Coordinator. The ADR's are forwarded to the FDA/CVM to request comments regarding the extent of the data package that would be required for drug/compound approval (e.g. target animal safety, efficacy, residue depletion, and/or environmental assessment studies-see below). The appropriate pharmaceutical sponsor in cooperation with the efforts of NRSP-7 will seek to gain FDA/CVM approval of the drug formulation. Pending favorable initial review by both the sponsor and FDA/CVM, the ADR is ranked according to priority for the funding by the program. Upon receipt of the reviews from FDA/CVM and the pharmaceutical sponsor, a decision can be made to fund the project. The project objectives may be directed toward generating sufficient data to seek FDA/CVM approval of the drug (Objective #3), or when that is not practicable, toward generating data sufficient to support safe, effective and legal use under the AMDUCA legislation through publication in peer reviewed journals. Research not conducted in the laboratories of the Regional Animal Drug Coordinators is conducted under subcontracts, managed by the Coordinators, to scientists in qualified laboratories at other institutions.

2.2 A product development meeting will be held for the participating Regional Animal Drug Coordinator(s) and FDA/CVM to identify specific data requirements needed to seek approvals. Investigators under subcontract with approved projects must prepare detailed research protocols that fulfill these requirements under the guidance of the Regional Animal Drug Coordinators, pharmaceutical sponsor and FDA/CVM.

2.3 Following research protocol review and refinement with FDA/CVM and the pharmaceutical sponsor, the research may begin. Studies typically required in this phase include efficacy (is the drug effective and at what dose), target animal safety (toxicity), human food safety (drug residues in edible products), and environmental assessment (as required).

2.4 Upon completion of the required studies, formal reports of the required studies are submitted to FDA/CVM for evaluation. Upon completion of an approved study, these data are published at the FDA/CVM site in either phase review form or completed data package. Once publically available, the manufacture may use this information to reference a new label claim (NADA or ANADA). Another form of dissemination of data occurs when the researcher published the results of the research in a peer-reviewed article.

Objective 3 - Facilitate FDA/CVM approvals of drugs for minor species and minor uses.
Upon completion of each required study, reports of results and all raw data are submitted to the Regional Animal Drug Coordinator for review prior to submission to FDA/CVM. Following acceptance of the data by FDA/CVM, a Public Master File is established that is placed in the public domain (e.g. published in the *Federal Register*). The pharmaceutical sponsor may refer to the Public Master File in support of a New Animal Drug Application (NADA), and ultimately the labeling of the drug for the use in the minor species, or for the minor use in a major species.

Moreover, 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 though out the country. The steps involved in this coordination of efforts are presented schematically in Figure 1.

Expected Outcomes - Data generated through this project will lead to improved animal health and welfare (reduction of pain and suffering) as new applications of drugs for minor species are made available. Many drugs are currently used without appropriate labeling or without an environmental impact assessment of the drug (i.e. aquaculture uses of drugs). In addition, the availability of scientific data supporting proper dose and duration of treatment will reduce the likelihood of antimicrobial resistance developing with implications for human health. The availability of additional approved drugs will also result in reduced economic losses for minor species producers.

Methods for communicating results will include public master files, approved product labeling, peer-reviewed publications in journals, abstracts presented at meetings, publications in producer/trade journals, presentations at workshops, symposia, producer group meetings, and continuing education programs. The beneficiaries of this project include the animals (health and welfare), animal producers (economic), and consumers (economic and safety) of the animal products through the promotion of human health, food safety and environmental protection.

Outcome of Objective 1 - Identify the critical needs of the various producers of minor livestock species

To date 354 drug requests have been submitted by stakeholders to the Minor Use Animal Drug Program for the development of data in support of the submission of a New Animal Drug Allowance (NADA). Through a prioritization process that has included (i) constraints imposed by concerns of antimicrobial resistance, (ii) limitations of availability of certain expensive or rare animal species, (iii) appropriate efficacy models, and (iv) high risk/benefit liabilities and lack of economic incentive for certain pharmaceutical manufacturers, the number of highest priority projects has been estimated at 40. Added to our current active projects, the backlog of projects represents a research commitment stretching over several decades.

The Southern Region has taken responsibility for the NRSP-7 Home-Page [www.nrsp-7.org]. This resulted in reworking the public sector and, the IP limited access site ["Ringer Site"] that continues to allow members of the committee access to archival data, relevant media material, and information on on-going projects. The latter includes an ASP interactive database ["MUMS Rx"] that will complete development in the current year and be available for public access.

Over the last six years, drug coordinators and the FDA/CVM liaison group attend regular monthly teleconferences. These have been coordinated by the PI of the Southern Region and have proved very successful in facilitating communication and coordination among the parties participating. These teleconferences usually take place at noon EST on the first Tuesday of each month. Additionally, twice each year, the Program conducts an annual teleconference meeting as travel costs have prohibited meetings in Washington, D.C.

Outcomes of Objectives 2 and 3 - Generate and disseminate data for the safe, effective, and legal use of drugs used primarily in therapy or reproductive management of minor animal species. Facilitate FDA/CVM approvals of drugs for minor species and minor uses.

Currently there are nine active research projects involving five animal species and seven different drugs (Table 2). Ruminant species remain the predominant group with a majority of Public Master Files (53%) as well. In the 31 years of the Program, data supplied by the Program provided for the modification of 52 label claims to include minor species, an overall average of 1.6 per year. Included in these approvals were one for rabbits, nine for game birds,

16 for fish, lobster and shrimp, 15 for meat and dairy goats, eight for bison and reindeer, one for foxes and two for honey bees (Table 2).

Table 2.
Animal Drug Approvals And Current NRSP-7 Activity By Species

Industry	Activity	
	Approvals (PMF#)	Active Projects (INAD#)
Game Bird	**Chukar partridges** Sulfadimethoxine/Ormetoprim (005-157) Lasalocid (005-429) **Pheasants** Amprolium (003-887) Thiabendazole (003-857) **Quail** Salinomycin (005-020) 2 NADA Bacitracin (005-178) Monensin (005-014) 2 NADA	**Pheasants** Lasalocid (I-009096) Fenbendazole (I-010062)
Rabbits	Lasalocid (005-042)	
Foxes	Ivermectin (005-307)	
Honey Bees	Tylosin (005-783) 3 NADA Lincomycin (005-988)	
Cervid	**Bison** Ivermectin (005-059) 4 ANADA **Reindeer** Ivermectin (003-895) 4 NADA	
Beef Cattle		Ivermectin (I-012056)
Meat Goats	Ivermectin (003-883) Levamisole HCl (005-117) Albendazole (005-582) Ceftiofur sodium (005-671) Fenbendazole (005-118) Monensin (005-055) Decoquinate (005-012) Morantel tartrate (005-366)	CIDR (progesterone) (I-011389) Tulathromycin (I-011512)
Dairy Goats	Ivermectin (003-883) Levamisole HCl (005-117) Ceftiofur sodium (005-671) Fenbendazole (005-118) Monensin (005-055) Decoquinate 005-012) Morantel tartrate (005-366)	CIDR (progesterone) (I-011389) Tulathromycin (I-011512)
Sheep	**Bighorn Sheep** Fenbendazole (005-071) **Sheep** Decoquinate (005-258) Ceftiofur (005-544) Tilmicosin phosphate (005-673) CIDR (progesterone) ()	**Sheep** Florfenicol (I-011836) Tulathromycin (I-011513)
Catfish/Aquaculture†	**Catfish** Sulfadimethoxine/Ormetoprim (005-056) **Finfish** Formalin (005-228) 9 NADA Oxytetracycline (005-667) 4 NADA Hydrogen peroxide (005-639) Florfenicol (005-932) **Lobster** Oxytetracycline (005-028) **Shrimp** Formalin (005-228)	**Fish** Erythromycin (I-006013) Strontium chloride (I-010536)

†Approvals resulted in an additional 16 label claims for these aquatic species.

http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/ucm279396.htm

Additionally, NRSP-7 has published 206 articles in peer-reviewed journals, averaging 6.6 per year over the term of the program. For the last five years, however, publications have nearly doubled to 10.6 per year. Thus, although FDA/CVM drug approvals have waned due to increasing costs, the Program has increased its efforts to supply critical data needs to minor species producers. The data generated by the Program is also shared with the Food Animal Residue Avoidance Database (FARADprogram to further increase visibility. For a detailed description of NRSP-7 dissemination of data and information, see Outreach and Communication.

Management, Budget, and Business Plan

1. Organizational structure - NRSP-7 is composed of a Technical Committee and four Administrative Advisors representing state experiment station directors. These Administrative Advisors provide liaison among the directors of the state experiment stations, USDA/CSREES, FDA/CVM, various animal organizations, and others coordinating the efforts of this program.

The organizational structure of the Minor Use Animal Drug program follows:

Administrative Advisory Committee

The Administrative Advisory Committee is composed of one appointee by Experiment Station Directors from each of the four regions (North Central, Northeast, Southern, and Western). The chair of the committee is selected internally. The role of the Administrative Advisory Committee is to provide liaison among the directors of the agricultural experiment stations in the four regions, colleges of veterinary medicine, the USDA/CSREES, the FDA/CVM, various animal organizations, and with those coordinating the efforts of this program. This committee will establish and set policy consistent with the mission of this project. This committee will also advise on budget and administrative matters relating to this program.

Technical Committee

The Technical Committee is composed of the following representatives:

- National Animal Drug Coordinator (Chair)
- Regional Animal Drug Coordinators representing each of the four regions (North Central, Northeast, Southern, and Western)
- Administrative Advisory Committee Chair (non-voting)
- USDA/CSREES Representative (non-voting)
- FDA/CVM liaison to NRSP-7 (non-voting)

In addition to the above committee, the FDA/CVM has a Minor Use Animal Drug Committee that meets with the Technical Committee generally once a year at the semi-annual meetings of the Technical Committee. This FDA/CVM committee consists of representatives from the Division of Therapeutic Drugs for Food Animals, Antimicrobial Drugs Branch, Methods Validation and Analytical Branch, Companion 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 services.

Cooperating Agencies and Principal Leaders:

US Department of Agriculture/CRESS

Dr. Gary Sherman	USDA/CRESS Representative
Dr. Gary Jensen	USDA/CRESS Representative

US Food and Drug Administration/Center for Veterinary Medicine

Dr. Meg R. Oeller	FDA/CVM Liaison
Dr. Amy Omer	FDA/CVM Liaison
Dr. Dorothy Bailey	FDA/CVM Liaison

Administrative Advisors	
Dr. John Baker (Chair)	Michigan AES
Dr. Margaret E. Smith	New York AES
Dr. Frances D. Galey	Wyoming AES
Dr. Philip H. Elzer	Louisiana AES
National Coordinator	
Dr. John G. Babish	New York AES
Regional Coordinators	
Dr. Lisa Tell	California AES
Dr. Paul R. Bowser	New York AES
Dr. Rodman G. Getchell (elect)	New York AES
Dr. Thomas Vickroy	Florida AES
Dr. Ronald W. Griffith	Iowa AES

2. Funding activities

In the past, Research for the Minor Use Animal Drug Program was funded through a USDA special research grant administered by CSREES in cooperation with the NRSP-7 Technical Committee. Currently, however, NRSP-7 has been dependent on "off-the-top" Regional Research funds allocated to the Minor Use Program. Support for NRSP-7 also comes from pharmaceutical companies, and universities in the form of "in kind" contributions for Regional Coordinators. The program also receives significant "in-kind support from several other sources including the institutions conducting the research (state agriculture experiment stations, colleges of veterinary medicine, federal laboratories), animal producer groups through contributions of animals for research, and pharmaceutical companies. Perhaps the most significant of this "in-kind" support comes through the cooperation of the pharmaceutical companies that provide access to their proprietary data package prepared for the drug approval in a major species, estimated at $20 - $100 million (http://www.ahi.org/about-animal-medicines/industry-statistics/). In addition, the pharmaceutical sponsors complete the approval package by adding the new use of the drug to their current label, and often contribute to the program in the form for drug research, as well as direct financial aid. Without the generous support of the pharmaceutical manufactures, this program would not be possible.

The Regional Animal Coordinators are not compensated by salary for time contributed to the Minor Use Animal Drug Program. In two cases, secretarial and/or technical support services are budgeted from the Program. Funding of $20,000 is provided for the National Drug Coordinator's part-time salary (30%) and the maintenance of an office.

From 1982 through 2009, government funding was awarded from appropriated, line item USDA funds averaging $423,121 per year. Hatch funding, provided in four of the last five years, has averaged $336 K or a 21% decrease in funding that represents approximately 40% of the total cost of the funding the Program and represents amounts used for direct funding of required research. Congressional sequestration budget have further reduced these amounts over the last two years. The non-federal funds and sources provided for NRSP-7 since 1982 have totaled over $9.4 million.

A total of $13.5 million has been granted through Federal funding and an additional 60 percent, on average, has been obtained through nonfederal funds during the 31-year term of the NRSP-7 program. Average federal expenditures per completed research for a drug approval or publication of the 33 Public Master Files was $410 K. The total expenditure (federal plus non-federal) per completed research for a drug approval or publication of a Public Master File was $696K. This figure represents a 75% increase in the average cost per Public Master File of $398,000 computed for the last five-year renewal. Reasons for the increased approval costs for all include the higher standard of reporting expected by FDA/CVM, increased cost of improved

analytical methods and the associated equipment, and the cost of performing bridging assays for validating new analytical techniques. With these increased cost over the last five years, the projected cost per Public Master File is approximately $3.5 million.

Even with the estimated 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 $10 to $25 million for adding a label claim to an existing veterinary drug, information generated for additional label claims by the NRPS-7 program costs only approximately 15 to 35% of pharmaceutical industry costs (http://www.ahi.org/about-animal-medicines/industry-statistics/).

3. Research

Research projects are initiated by requests, usually from researchers or animal producers, to the program's regional coordinators to address a particular minor use animal drug need. These requests, known as ADRs (Animal Drug Requests), are prioritized according (i) to financial and regulatory feasibility, (ii) to importance to the animal industry, and the pharmaceutical manufacturer's commitment to the minor use animal drug approval. Once a request is accepted as a research project, study protocols are developed and reviewed by FDA/CVM. All research projects are conducted in accordance with FDA's Good Laboratory Practices regulations. This process is outlined schematically in Figure 1.

Research Planned for Upcoming Year - To date 354 drug requests have been submitted to the Minor Use Animal Drug Program for the development of data in support of the submission of a New Animal Drug Approval. Through a prioritization process that has included (1) constraints imposed by concerns of antimicrobial resistance, (2) limitations of availability of certain expensive or rare animal species, (3) appropriate efficacy models, and (4) high risk/benefit liabilities and lack of economic incentive for certain pharmaceutical manufacturers, the number of highest priority projects has been estimated at approximately 40. Of these, the Program has been actively working on nine projects.

Over the last five years the total Federal plus non-Federal cost for NRSP-7 to provide the data necessary to support a single label claim has risen to approximately $3.5 million. This increase is due to (1) more sophisticated analytical procedures for residue analysis, (2) the need to conduct all studies under Good Laboratory Practices and auditing of projects, and (3) more expensive environmental assessments. Federal costs per Public Master File are estimated at roughly half this amount or $1.75 million. With NRSP-7 total level of funding of approximately $300,00 per year and cost per drug approval of $1.75 million, the expected time for achieving a drug approval is 5.6 years. Thus, it is anticipated that NRSP-7 will achieve one approval over the next five years.

This level of progress falls critically below the needs and expectations of our stakeholders and it is the objective of the Program to use the next year to evaluate the continued viability of the program in the face of continuing escalating costs and dwindling funding.

Over the next year, the Program will work to organize on several fronts to establish the potential for increased funding. First, the Program will work to obtain more grants from the FDA/CVM Minor Use grant program. Since the inception of the MUMS program at the FDA/CVM, NRSP-7 has taken advantage of this funding for several projects, but can increase this number in the upcoming year. This year I-010536 Strontium Chloride for otolith marking study has applied for MUMS funding to supplement the Program's Hatch Funding.

Second, NRSP-7 will critically review the current nine active projects with the goal of completing two or three of the most visible. Projects likely to be completed in the coming year include I-

006013 Erythromycin in Salmonids, I-011389 CIDR implants for goats, I-010062 Fenbendazole in pheasants, and I-012056 Ivermectin block for Cattle Tick Fever.

Third, USDA/NIFA has been exploring ways to consolidate related programs. This has been successfully implemented for a subset of programs related to plant protection, and task forces are currently working toward consolidation of selected water programs. Early-phase discussions concerning possible consolidation of animal protection and production programs, including NRSP-7, are now underway.

Fourth, the Program will continue communications with the IR-4 Pesticide program liaison Dr. Malamud-Roam to further assess critical pesticide approvals for animals. Finally, the Program will solicit funding from companies interested in developing markets for natural alternatives to antibiotic growth promoters. For example, Dr. John P. Maye of S. S. Steiner, New York, NY, has developed data on the growth promoting and antibacterial properties of hops alpha acids. In US patent 7,090,873 he has demonstrated the growth promoting properties of these alpha acids on cattle. Dr. Maye has contacted the Program for interest in developing these applications for both major and minor species.

4. FDA/CVM approval

A successful research project is submitted to FDA's Center for Veterinary Medicine for review and inclusion in a Public Master File. The availability of the data for use on a label claim is announced through publication of the Public Master File in the *Federal Register*. A pharmaceutical sponsor may then reference, at no cost, the data in the Public Master File to support a new animal drug application for the minor use. The final step in the process is FDA/CVM approval of this application for the pharmaceutical sponsor, so that the product may be labeled and sold for minor use.

5. Assessment of outcomes

Productivity - In the 31 years of the Program, data supplied by the Program provided for the modification of 52 label claims to include minor species, an overall average of 1.6 per year. Included in these approvals were one for rabbits, nine for game birds, 16 for fish, lobster and shrimp, 15 for meat and dairy goats, eight for bison and reindeer, one for foxes and two for honey bees.

Additionally, NRSP-7 has published 206 articles in peer-reviewed journals, averaging 6.6 per year over the term of the program. For the last five years, however, publications have nearly doubled to 10.6 per year. Thus, although FDA/CVM drug approvals have waned due to increasing costs, the Program has increased its efforts to supply critical data needs to minor species producers. The data generated by the Program is also shared with the Food Animal Residue Avoidance Database (http://www.farad.org) program to further increase visibility.

Currently there are nine active research projects involving five animal species and seven different drugs (Table 2). Ruminant species remain the predominant group with a majority of Public Master Files (53%).

NRSP-7 has also provided information on therapeutics in minor species use through peer-reviewed publications, workshops and presentations to stakeholders and at professional meetings. Use of the Internet to optimize communications with stakeholders and program participants continues to improve in this rapidly changing medium. Moreover, NRSP-7 is the only initiative that generates information on the safe and effective use of therapeutics in minor species. Through NRSP-7, producers and veterinarians have the necessary information to reduce pain and suffering in commercially important minor species.

Completion of original objectives – A primary objective of NRSP-7 was to identify the animal drug needs for minor species and minor uses in major species. The Minor Use Animal Drug

Program has received over 354 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. Of these drug requests, the NRSP-7 Technical Committee has identified 40 of high priority. While in one sense NRSP-7 has completed one of our original objectives, withdrawal of available products, antimicrobial resistance, disease prevalence, husbandry practices, and the changing business relationships in the veterinary pharmaceutical industry preclude considering our current list of projects and potential projects as final.

Integration

Program facilitation and coordination exists among animal producers, pharmaceutical manufacturers, FDA/CVM, USDA/CSREES, other government agencies, state agricultural experiment stations, and schools of veterinary medicine. Animal producers have provided the majority of drug requests and they frequently supply animals and facilities for target animal safety and residue depletion studies. Pharmaceutical companies participate through the sharing of analytical methodology and providing commercial drug product for testing. The major contribution of the pharmaceutical manufacturer is, however, is the cost borne for the approval of drugs for a major species, estimated at approximately $20 - $100 million and the cost of adding a label claim at $10 to $25 million (http://www.ahi.org/about-animal-medicines/industry-statistics/).

Since the beginning of the Minor Use Animal Drug Program, The FDA/CVM has supplied a full-time liaison to coordinate the drug approval process. In the last four years, they have added two additional staff positions to support the Program. The four regional coordinators are associated with colleges of veterinary medicine or experiment stations. These coordinators have full responsibility for supervising the development of all data entering the Public Master Files. Regional Coordinators also present and publish results of their studies. USDA/CSREES provides two full time liaison who, along with the Administrative Advisors and Technical Committee, oversee the prioritization of drug requests as well as project planning and implementation. Persons serving as Administrative Advisors are provided by the agricultural experiment stations from the four regions of the United States. The fundamental need for NRSP-7 to operate as a functionally integrated program has existed since its inception and NRSP-7 has spent 31 years cultivating the relationships necessary for optimal efficiency.

Outreach, Communications and Assessment

Public Master Files and New Animal Drug Allowances (NADAs) - The goal of the outreach and communication plan of NRSP-7 is to provide stakeholder access to information regarding program goals, accomplishments and impacts through a variety of channels. One form of outreach consists of the publication of the efficacy, target animal safety and drug residue depletion data generated as a Public Master File in the *Federal Register* and as a New Animal Drug Allowance (NADA) or Abbreviated New Animal Drug Allowance (ANADA). Publication in the *Federal Register* places the required studies in the public domain and a New Animal Drug Allowance provides the producer stakeholder the availability of the drug for the claimed minor use. Table 2 lists the 33 Public Master Files and 52 New Animal Drug Allowances developed from data generated by NRSP-7.

Approvals and projects that have changed the outlook of two industries include the approvals of lincomycin hydrochloride water-soluble powder and tylosin tartrate powder for control of American Foulbrood in honey bees. These approvals represent a significant therapeutic addition to an industry working to reverse the declining honey bee population. Although the use of these products will not substantially increase sales of these drugs, due to the small quantities required. The potential effect on the industry is important. Secondly, the ivermectin/molasses block

formulation study currently being conducted in Texas for the control of Cattle Tick Fever, has the potential of averting a major threat to the U.S. cattle population. Several efficacy studies have supported the use of this novel formulation in cattle tick control. NRSP-7 labs in the Southern Region have worked with producers to assure a uniform distribution of ivermectin in the molasses blocks, insuring that cattle will receive uniform dosing.

Presentations and publications - Presentations, abstracts, publications and doctoral dissertations represent yet another form of communication to the stakeholders. Over the last 32 years, NRSP-7 has produced 206 peer-reviewed publications. Notably, while drug approvals have become more costly and time consuming to obtain over the last five years, NRSP-7 has nearly doubled its publication rate from 6.4 per year to 10.6 per year for the last five years. A liting of these publications follows this report.

Website - The Technical Committee has worked to develop the NRSP-7 website (www.NRSP7.org) 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. Since inception in 1999, the NRSP-7 website has been visited 11,950 times for an average of 4.1 hits per day, an increase of 30% over the last review period. NRSP-7 believes that this represents a significant degree of interaction with stakeholders as well as the public at large.

Sharing NRSP-7 information with FARAD – Another form of dissemination of NRSP-7 data is the publication of drug pharmacokinetic and residue depletion studies through FARAD (Food Animal Residue Avoidance Database). FARAD is a computer-based decision support system designed to provide livestock producers, extension specialists, and veterinarians with practical information on how to avoid drug, pesticide and environmental contaminant residue problems.

The FARAD website (www.FARAD.org) provides:

- Current label information including withdrawal times of all drugs approved for use in food-producing animals in the United States.
- Official tolerances for drug and pesticides in tissues, eggs and milk.
- Database with approximately 43,000 scientific articles and entries with data on residues, pharmacokinetics and the fate of chemicals in food animals.

By supplying FARAD with information developed on minor use animal drug residue depletion and pharmacokinetics, NRSP-7 affords the stakeholder yet another conduit for obtaining critical information to avoid illegal and potentially hazardous drug residues in food animals.

Steps to improve communications – Several changes have been incorporated in an effort to enhance communication both within the program and with stakeholders. First, monthly teleconferences are held by the Technical Committee to discuss potential projects, interactions with stakeholders and progress in studies. Second, stakeholders have been invited to be active non-voting participants in the annual spring teleconferences. The nature of the participation is *ad hoc* and representatives from different stakeholder groups are invited on a rotating basis, without representation from a single or specific group "assigned" to the committee.

Informatics will be better utilized to increase/improve communication with NRSP-7 participants and stakeholders. Improvements to web usage include posting pdf versions of publications and or dissertations that have been supported through NRSP7 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. Stakeholders can be “surveyed” using the web site monitoring capabilities.

Projected Participation

NRSP-7 functions through the coordination of efforts among animal producers, pharmaceutical manufacturers, Food and Drug Administration/Center for Veterinary Medicine, United States Department of Agriculture/Cooperative State Research, Education, and Extension Service, universities, State Agricultural Experiment Stations and veterinary medical colleges throughout the country. Working relationships between the Program and both the FDA/CVM and NIFA/CSRESS have been and should continue to be excellent. Also, USDA/ARS has been participating with NRSP-7 in the Cattle Fever Tick studies in Texas. Participation has also been forthcoming from game bird growers that have donated birds for safety and efficacy studies. Pharmaceutical companies have also provided analysis of feeds and tissues samples in selected studies. When the pharmaceutical companies could not provide analysis, they have provided expertise in the development of analytical methods for the tissue residue studies in minor species.

Peer-reviewed publications:

1. Wu, H., Baynes, R. E., Leavens, T., Tell, L. A., and Riviere, J. E. (2013) Use of population pharmacokinetic modeling and Monte Carlo simulation to capture individual animal variability in the prediction of flunixin withdrawal times in cattle, J Vet Pharmacol Ther 36, 248-257.

2. Washburn, K. E., Fajt, V. R., Lawhon, S. D., Adams, L. G., Tell, L. A., and Bissett, W. T. (2013) Caprine abscess model of tulathromycin concentrations in interstitial fluid from tissue chambers inoculated with Corynebacterium pseudotuberculosis following subcutaneous or intrachamber administration, Antimicrobial agents and chemotherapy 57, 6295-6304.

3. Spitsbergen, J. M., Frattini, S. A., Bowser, P. R., Getchell, R. G., Coffee, L. L., Wolfe, M. J., Fisher, J. P., Marinovic, S. J., and Harr, K. E. (2013) Epizootic neoplasia of the lateral line system of lake trout (Salvelinus namaycush) in New York's Finger Lakes, Vet Pathol 50, 418-433.

4. Snook, T. S., White, S. D., Hawkins, M. G., Tell, L. A., Wilson, L. S., Outerbridge, C. A., and Ihrke, P. J. (2013) Skin diseases in pet rabbits: a retrospective study of 334 cases seen at the University of California at Davis, USA (1984-2004), Veterinary dermatology.

5. Shelver, W. L., Tell, L. A., Wagner, S., Wetzlich, S. E., Baynes, R. E., Riviere, J. E., and Smith, D. J. (2013) Comparison of ELISA and LC-MS/MS for the Measurement of Flunixin Plasma Concentrations in Beef Cattle after Intravenous and Subcutaneous Administration, J Agric Food Chem 61, 2679-2686.

6. McDonnel, S. J., Tell, L. A., and Murphy, B. G. (2013) Pharmacokinetics and pharmacodynamics of suberoylanilide hydroxamic acid in cats, J Vet Pharmacol Ther.

7. Macpherson, M. L., Giguere, S., Hatzel, J. N., Pozor, M., Benson, S., Diaw, M., Sanchez, L. C., Vickroy, T. W., Tell, L., Wetzlich, S., and Sims, J. (2013) Disposition of desfuroylceftiofur acetamide in serum, placental tissue, fetal fluids, and fetal tissues after administration of ceftiofur crystalline free acid (CCFA) to pony mares with placentitis, J Vet Pharmacol Ther 36, 59-67.

8. Grismer, B., Rowe, J. D., Carlson, J., Wetzlich, S. E., and Tell, L. A. (2013) Pharmacokinetics of tulathromycin in plasma and milk samples after a single subcutaneous injection in lactating goats (Capra hircus), J Vet Pharmacol Ther.

9. Goetting, V., Lee, K. A., Woods, L., Clemons, K. V., Stevens, D. A., and Tell, L. A. (2013) Inflammatory marker profiles in an avian experimental model of aspergillosis, Medical mycology 51, 696-703.

10. DeDonder, K. D., Gehring, R., Baynes, R. E., Tell, L. A., Vickroy, T. W., Apley, M. D., and Riviere, J. E. (2013) Effects of new sampling protocols on procaine penicillin G withdrawal intervals for cattle, J Am Vet Med Assoc 243, 1408-1412.

11. Dechant, J. E., Rowe, J. D., Byrne, B. A., Wetzlich, S. E., Kieu, H. T., and Tell, L. A. (2013) Pharmacokinetics of ceftiofur crystalline free acid after single and multiple subcutaneous administrations in healthy alpacas (Vicugna pacos), J Vet Pharmacol Ther 36, 122-129.

12. Cornwell, E. R., Labuda, S. L., Groocock, G. H., Getchell, R. G., and Bowser, P. R. (2013) Experimental Infection of Koi Carp with viral hemorrhagic septicemia virus type IVb, J Aquat Anim Health 25, 36-41.

13. Cornwell, E. R., Bellmund, C. A., Groocock, G. H., Wong, P. T., Hambury, K. L., Getchell, R. G., and Bowser, P. R. (2013) Fin and gill biopsies are effective nonlethal samples for detection of viral hemorrhagic septicemia virus genotype IVb, J Vet Diagn Invest 25, 203-209.

14. Coffee, L. L., Casey, J. W., and Bowser, P. R. (2013) Pathology of tumors in fish associated with retroviruses: a review, Vet Pathol 50, 390-403.

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External Links

NRSP-7: http://www.nrsp-7.org

FARAD: http://www.farad.org

Public Master Files supporting approved New Animal Drug Applications for Minor Uses
http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/ucm279396.htm

Public Master Files (PMFs) in development
http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/ucm287667.htm

Animal Health Institute Statistics:
http://www.ahi.org/about-animal-medicines/industry-statistics/

Cattle Fever Tick Information
http://www.ars.usda.gov/is/AR/archive/nov10/ticks1110.htm

https://www.federalregister.gov/articles/2013/07/24/2013-17804/environmental-impact-statement-proposed-cattle-fever-tick-control-barrier-in-south-texas

Honey Bees
http://www.nrdc.org/wildlife/animals/bees.asp?gclid=CIy_ieDX-7sCFeg-MgodpTAAYw

Global Veterinary Health Products Market to Spike to Over $28 Billion by 2017
http://finance.yahoo.com/news/global-veterinary-health-products-market-193000008.html

Appendix E: Format for Reporting Projected Participation

Part 1: Participant List

Station/Institution and Department	Participant	Objective No.	Research						Extension	
			KA	SOI	FOS	SY	PY	TY	FTE	Program
California –Davis : University of California, Davis	Lisa A Tell	1,2,3	308	3099	1180	0.10	0.00	1.00	0.00	
California –Davis : University of California, Davis	Lisa A Tell	1,2,3	711	3899	1180	0.10	0.00	1.00	0.00	
			711	3820	1180					
			711	3799	1180					
			711	3699	1180					
			711	3299	1180					
			711	3099	1180					
Florida – University of Florida	Thomas W Vickroy, Ph.D. *****	1,2,3	711	3820	1180	0.15	0.15	0.15	0.05	• not specified
			711	3699	1180					
			311	3910	1180					
			308	3099	1180					
			711	3899	1180					
Iowa – Iowa State University	R.W. Griffith **	1,2,3	311	3910	1180	0.30	0.50	0.00	0.00	
			301	3820	1100					
New York –Ithaca : Cornell University	Paul R. Bowser	1,2,3	311	3910	1060	0.10	0.00	0.00	0.00	

Part 2: Research Summary

Combination of KA, SOI, and FOS	Total SY	Total PY	Total TY
301–3820–1100	0.150	0.250	0.000
308–3099–1180	0.130	0.030	1.030
311–3910–1060	0.100	0.000	0.000
311–3910–1180	0.180	0.280	0.030
711–3099–1180	0.017	0.000	0.167
711–3299–1180	0.017	0.000	0.167
711–3699–1180	0.047	0.030	0.197
711–3799–1180	0.017	0.000	0.167
711–3820–1180	0.047	0.030	0.197
711–3899–1180	0.047	0.030	0.197
Grand Total:	0.750	0.650	2.150

Part 3: Extension Summary

Program	Total FTE
Grand FTE Total:	0.05

Appendix F: NRSP-7/MINOR USE ANIMAL DRUG PROGRAM BUDGET REQUESTS SUMMARY

(01 October 1, 2014 – September 30, 2015)
NRSP – 7 Minor Use Animal Drugs
A National Agricultural Program for Minor Use Animal Drugs

MRF FUNDING										
DESCRIPTION	**Proposed FY 1 FY 2014-2015**									
	Dollars	**FTE**								
SALARIES[a]	76,900	2.5								
FRINGE BENEFITS	24,768									
WAGES										
TRAVEL[b]	5,000									
RESEARCH SUPPLIES[c]	213,841									
MAINTENANCE[d]	3,096									
EQUIPMENT/ CAPITAL IMPROVEMENT[e]	1,395									
TOTAL	325,000	2.5								

[a]Includes part-time salaries for National Coordinator, and support staff in Northeast, Southern and Western Regions.
[b]Travel for GLP monitoring of studies and final reports.
[c]Funding of Target Animal Safety, Human Food Safety and Residue Depletion studies.
[d]Maintenance contracts for analytical equipment.
[e]Leasing of analytical equipment.

Appendix F

OTHER SOURCES OF FUNDING

Please check one of the following: ☐ Industry ■ Federal Agencies FDA/CVM ☐ Grants/Contracts ☐ SAESs
US Food and Drug Administration/Center for Veterinary Medicine
☐ Other (please list):_____

DESCRIPTION	Proposed FY 1 FY 2014-2015									
	Dollars	FTE[(a)]								
SALARIES AND WAGES	204,330	1.5								
FRINGE BENEFITS	81,366									
TRAVEL	4,123									
MATERIALS AND SUPPLIES	8,740									
PUBLICATIONS										
CAPITAL EQUIPMENT										
OTHER DIRECT COSTS										
RESEARCH										
GOV'T HOLD BACK										
TOTAL	298,558	1.5								

(a) Salary, benefits, materials and supplies for full-time FDA/CVM liaison and assistant to the NRSP-7 program provided by FDA/CVM.

Appendix F

OTHER SOURCES OF FUNDING

Please check one of the following: ☐ Industry ☐ Federal Agencies ☐ Grants/Contracts ☐ SAESs

■ Other (please list):___College and State Funding_____

DESCRIPTION	Proposed FY 1 FY 2014-2015									
	Dollars	FTE[(a)]								
SALARIES AND WAGES	51,769	0.4								
FRINGE BENEFITS	34,495									
TRAVEL										
MATERIALS AND SUPPLIES										
PUBLICATIONS										
CAPITAL EQUIPMENT										
OTHER DIRECT COSTS										
RESEARCH										
GOV'T HOLD BACK										
TOTAL	86,264	0.4								

(a) Salary and benefits for four regional coordinators to the NRSP-7 program provided by individual college and state funding.

OTHER SOURCES OF FUNDING

Please check one of the following: ■ **Industry**[(a)] ☐ **Federal Agencies** ☐ **Grants/Contracts** ☐ **SAESs**

☐ **Other (please list):**_____

DESCRIPTION	**Proposed FY 1 FY 2014-2015**									
	Dollars	**FTE**								
SALARIES AND WAGES[(a)]	102,990	0.5								
FRINGE BENEFITS	29,867									
TRAVEL										
RESEARH MATERIALS AND SUPPLIES	38,985[(b)]									
PUBLICATIONS										
CAPITAL EQUIPMENT										
OTHER DIRECT COSTS										
SUPPORT R&D[(c)]	(c)									
TOTAL	171,842	0.5								

(a) Includes personnel from the veterinary pharmaceutical and animal production industries needed to review protocols, data submissions, change label claims and file amended anima drug applications. Companies specifically involved with NRSP-7 include Pfizer, Biomedia, Intervet, Schering and Alpharma.

(b) For the years 1999 to 2011, the average **MATERIALS AND SUPPLIES** contribution from industry has increased to $38,985. **MATERIALS AND SUPPLIES** included total costs directly attributable to carrying out the grant including storage and office space rental, supplying drugs, analytical support or animals for efficacy, safety or residue depletion studies.

(c) Cooperation with pharmaceutical companies to sponsor animal drug research projects is vital to the NRSP-7 program. The major contribution to the program is the cost borne by the pharmaceutical industry for the approval of drugs for a major species, estimated at approximately $100 million or more per approved drug.