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FDA Issues Drug "Indexing" Proposal Under MUMS

The Food and Drug Administration (FDA) has proposed a rule for placing drugs for minor species in an "index" that allows companies to legally market new animal drugs without developing a standard new animal drug application.

FDA proposed the rule under the Minor Use and Minor Species Animal Health Act of 2004. In passing the legislation, Congress recognized a need for limited-demand drugs that was not being met because animal drug sponsors could not expect returns from the market sufficient to pay the cost of the application process.

The indexing proposal would permit drug companies to legally market unapproved new animal drugs. The drug requestor and FDA would use a panel of outside experts for advice in determining whether a product is safe and effective for its intended uses.

The indexing rule would apply to drugs for non-food minor species, except in some cases in which a drug could be used for early life stages of food animals (e.g., fish eggs, oyster spat). Drugs for minor uses in major species cannot be included in the index. (Major species are dogs, cats, horses, cattle, pigs, turkeys and chickens.)

The rule will primarily help drug manufacturers legally market drugs sold in pet stores and drugs intended for use in wildlife and zoo animals.

Under the proposed rule, a drug sponsor would ask FDA to determine if a drug is eligible for addition to the index. The drug sponsor (requestor) would provide information about the intended use of the drug, the species to be treated, and conditions of use—dosage, route of administration, warnings, contraindications, or other significant limitations.

The requestor would be required to supply information on the need for the drug, and provide an estimate of expected annual distribution. The statute requires that the labeling of a new animal drug that is the subject of an index listing state: "NOT APPROVED BY FDA – Legally marketed as an FDA indexed product. Extra-label use is prohibited."

FDA will not accept index requests for products contained in, or that are the product of, transgenic animals. And FDA will not accept an index request for the same drug, dosage form, and intended use as a product that is already approved or conditionally approved.

The request for a determination of eligibility for indexing must include information to establish that the intended use of the product will pose no food safety hazard as well as information supporting either an environmental assessment or a categorical exclusion from an assessment.

Under the indexing proposal, FDA would ease the requirements for information about a drug's chemistry and manufacturing processes. With a traditional application, the drug sponsor must provide a "full description" of the production process. Under the indexing proposal, the requestor would submit only a comprehensive summary of the manufacturing process that demonstrates that the requestor understands current Good Manufacturing Practice requirements and has established appropriate manufacturing specifications.

FDA is required to respond to requests for determination of eligibility for indexing within 90 days for drugs for non-food species, and within 180 days for requests for early-life-stage food-producing animals.

Expert panel review

If FDA determines that a product is eligible for indexing, the next step is an evaluation by an external panel of experts of the requestor's target animal safety and effectiveness information to determine if that information is sufficient to permit the product to be added to the index list.

The requestor would propose individuals to serve on the panel, who have appropriate scientific training and experience to review safety and effectiveness information about the drug submitted for inclusion in the index. FDA would review the qualifications of the proposed panel members and could

(Continued, next page)

In This Issue

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Dr. Dunham Is New OMUMS Director at CVM

Dr. Bernadette Dunham is the new Director of the Office of Minor Use and Minor Species Animal Drug Development (OMUMS) at the Center for Veterinary Medicine (CVM). She succeeds Dr. Andrew Beaulieu, who will be retiring in early January 2007.

Dr. Dunham previously served as Deputy Director in CVM's Office of New Animal Drug Evaluation. Immediately before coming to CVM in December 2002, Dr. Dunham was acting director of the American Veterinary Medical Association's Government Relations Division in Washington, DC. In that position, Dr. Dunham represented the Association in a coalition of veterinary and animal drug industry groups that championed the MUMS legislation in Congress. She is a strong supporter of the Minor Use and Minor Species Animal Health Act of 2004 (MUMS Act).

Dr. Bernadette Dunham, D.V.M., Ph.D., the new Director of CVM's Office of Minor Use and Minor Species Animal Drug Development.

Dr. Dunham has an extensive background in both human and animal medicine. She received her Doctor of Veterinary Medicine degree from Ontario Veterinary College, University of Guelph, Ontario, Canada. She has a Ph.D. in cardiovascular physiology from Boston University. She has worked as a practicing veterinarian in Canada. She also has been a research associate at Harvard Medical School, Boston, MA, and research assistant professor at Boston University.

(Continued, next page)

FDA Issues Drug "Indexing" Proposal... *(Continued)*

accept, reject proposed or suggest alternative members.

The panel members must be free of any conflict of interest or even the appearance of one.

The panel will draft a report evaluating the drug's target animal safety and effectiveness, and stating the panel's opinion regarding whether the benefit of allowing the drug on the market outweighs the potential risk to the target animal, taking into account the harm associated with not permitting legal access to the drug.

If the panel supports the drug's inclusion in the index, the panel will either provide draft labeling for the product, including all conditions of use that the experts think are needed to assure that the product's benefit outweighs the risk, or provide narrative information about what the requestor should put on the label.

FDA will decide, after reviewing the report, whether to add the product to the index.

If FDA decides not to index the drug based on deficiencies in the panel report or product labeling, the requestor can submit a second request addressing any shortcomings FDA cited in the initial request, using acceptable information from the first request. Alternatively, the requestor can ask FDA for an informal conference to have the Agency reconsider its denial based on the evidence already available. If FDA's decision is still to deny the request, that denial constitutes the Agency's final action in the matter pending the submission of further information from the requestor.

After indexing

Once a product has been added to the index, the holder of an index listing can modify labeling to add cautionary information. Also, if FDA agrees, the holder can request modification to the Index or the label, to add new intended uses or species, or change the active ingredients or concentration of the active ingredient.

The holder of an index listing must report serious product defects to the Agency within three days, and serious and unexpected adverse drug reactions within 15 days. A holder must also file annual reports that describe the amounts of drug marketed, identify minor changes to the formulation or manufacturing process, and describe adverse drug experiences not already reported.

FDA can suspend an index listing if it identifies a reasonable probability of health risk to humans or animals. FDA also can partially remove a listing if, for instance, the drug creates problems for some of the species originally included on the label.

For more information

Information about the proposed rule is available on the MUMS page of FDA's Center for Veterinary Medicine website, *www.fda.gov/cvm/minortoc.htm*.

FDA VETERINARIAN

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Dr. Dunham is New OMUMS Director at CVM *(Continued)*

Office of Minor Use and Minor Species Animal Drug Development

The Center for Veterinary Medicine's (CVM) Office of Minor Use and Minor Species Animal Drug Development (OMUMS) was authorized under the Minor Use and Minor Species Animal Health Act of 2004 (MUMS Act). The office has the responsibility at CVM for implementing the provisions of the MUMS Act, which are designed to encourage the development and legal marketing of drugs for minor species and minor uses.

Minor species are any species except the major species, which are cattle, swine, chickens, turkeys, horses, dogs, and cats. Minor use drugs are for major species, for infrequent use and use in a limited number of animals. These markets have been underserved because drug sponsors are unwilling or unable to seek approvals for such products due to the limited return on investment.

Congress drafted the MUMS Act to provide incentives for drug companies to develop products for these underserved markets. The three major incentives of the MUMS Act are:

- Designation, which gives new MUMS products extended periods of market exclusivity and makes them eligible for grants and contracts;
- Conditional approval, which allows companies to market products for up to five years, after demonstrating safety and a reasonable expectation of effectiveness, while working to confirm effectiveness and achieve full approval; and
- Indexing, which permits the legal marketing of unapproved new animal drugs for minor species following the Food and Drug Administration's (FDA) acceptance of recommendations from external expert panels.

In addition to implementing the provisions of the MUMS Act, OMUMS is also responsible for liaison work with the U.S. Department of Agriculture's minor species research program, NRSP-7, and serves as FDA's resource for policy questions regarding minor use and minor species.

Additional information about minor use and minor species at FDA/CVM can be found at *www.fda.gov/cvm/minortoc.htm*.

She also served as the Director of Laboratory Animal Medicine and an Adjunct Professor of Pharmacology at the State University of New York Health Science Center, Syracuse, NY. Her research focused on the molecular regulation of cardiac gap junction proteins.

In addition, Dr. Dunham is an Adjunct Professor with the Department of Biomedical Sciences and Pathobiology at the Virginia-Maryland Regional College of Veterinary Medicine in Blacksburg, VA. She lectures on a variety of topics from emerging issues and opportunities in veterinary medicine to the role of consensus building in policy development.

MUMS Act

In an interview with *FDA Veterinarian*, Dr. Dunham said the MUMS Act will help veterinarians as they treat many types of pets, wildlife, and zoo animals, as well as minor species food-producing animals. "Veterinarians want drugs available that they know are safe to use. They want to know the indications and the dosages that are appropriate to use," she said. With so few approved drugs currently available for minor species, or for limited uses in major species, veterinarians often do not have legal access to the drugs they know will work. The MUMS Act and the provisions that CVM is implementing under its authority should go a long way to addressing that problem, she added.

Dr. Beaulieu and Dr. Meg Oeller of OMUMS, along with Dr. Jeff Punderson of CVM's Policy and Regulations Staff, have already done a great deal of work to develop and implement the MUMS Act regulations, Dr. Dunham said. The next phase, which she will be most involved with, will be the finalization of the new regulations and execution of the new programs.

Dr. Dunham stated that Dr. Beaulieu is truly an icon at CVM, and he will be leaving some very large shoes for her to step into. "Having an opportunity to work directly with Dr. Beaulieu during the next few months before he retires will be an incredibly rewarding experience," she said.

She is grateful for the wonderful support she has received from everyone at CVM and she is looking forward to the exciting work that the OMUMS will be embracing.

Veterinary Medicine Advisory Committee Meeting on Antimicrobial Scheduled

The Food and Drug Administration's (FDA) Veterinary Medicine Advisory Committee (VMAC) is scheduled to meet on September 25, 2006, to discuss the microbial food safety of an antimicrobial drug application currently under review for use in food producing animals.

The panel will review the microbial food safety of cefquinome formulations for parenteral injection to treat bovine respiratory disease in cattle. A review by an external panel of the microbial food safety aspects of an antimicrobial under review for potential approval is in accordance with FDA's Center for Veterinary Medicine's (CVM) Guidance for Industry, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern" (Guidance for Industry #152, available electronically at *www.fda.gov/cvm/Guidance/fguide152.pdf*).

Microbial food safety is that part of the human food safety evaluation that looks at the impact of the use an antimicrobial drug on the development of resistance among pathogenic, zoonotic bacteria of human health concern, such as *Salmonella*, *E. coli*, and *Campylobacter*.

The drug sponsor has submitted information to the Agency to address microbial food safety concerns. The Agency has reviewed that information, and now seeks input from the VMAC as to whether the Agency's assessment of the information and strategies for managing any potential microbial food safety risks are appropriate. The Agency will be posing a series of questions to the VMAC to promote discussion and ultimately gain VMAC recommendations with regard to the Agency's assessment.

Details

DATE: September 25, 2006

PLACE: DoubleTree Hotel, Plaza Rooms II-III, 1750 Rockville Pike, Rockville, MD.

TIME: 8:30 a.m. to 5:00 p.m.

Comments

Interested persons may present data, information, or views, orally or in writing, on the issues pending before the committee. Written submissions may be sent to Aleta Sindelar, Center for Veterinary Medicine (HFV-3), Food and Drug Administration, 7519 Standish Place, Rockville, MD, 20855. Written comments must be submitted by September 13, 2006.

Oral presentations from the public will be scheduled between approximately 1:00 p.m. and 2:00 p.m. The time allotted for each presentation may be limited. Individuals wishing to make oral presentations should notify Aleta Sindelar (by telephone, at 240-276-9004, by e-mail, at *aleta.sindelar@fda.hhs.gov*, or by mail, at the address above) before September 13, 2006. They should submit a brief statement of the general nature of the evidence or arguments they wish to

(Continued, next page)

CVM Issues Drug User Fees for FY 2007

The Center for Veterinary Medicine (CVM) has announced animal drug user fee rates and payment procedures for fiscal year (FY) 2007 under the Animal Drug User Fee Act (ADUFA).

ADUFA authorizes FDA to collect user fees for animal drug applications on animal drug products, establishments where such products are made, and sponsors of such animal drug applications and/or investigational animal drug submissions, covered under the Act.

According to a notice in the August 2, 2006, *Federal Register,* for FY 2007, the fees are:

- $168,600 per application for an animal drug application
- $84,300 for a supplemental animal drug application for which safety or effectiveness data are required
- $4,115 for the annual product fee
- $51,350 for the annual establishment fee, and
- $44,850 for the annual sponsor fee

FDA will issue invoices for FY 2007 product, establishment, and sponsor fees by December 30, 2006, and these invoices will be due and payable 30 days after they are issued. FDA will not accept an application for filing unless the sponsor has paid all the fees it owes.

The notice also provides procedures that animal drug sponsors should use to pay the FY 2007 fees. The application fee rates are effective for applications received by FDA's Center for Veterinary Medicine from October 1, 2006, until September 30, 2007, the dates for FY 2007.

The ADUFA legislation permits FDA to collect a total of approximately $43 million plus inflation over the five-year life of the Act. The additional resources from user fees are used to supplement appropriated resources for animal drug review.

For more information about the user fees for FY 2007, contact Robert Miller, Center for Veterinary Medicine (HFV-10), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 240-276-9707. Send general questions to the Center for Veterinary Medicine at *cvmadufa@fda.gov*. More information about ADUFA is available at *www.fda.gov/cvm/adufa.htm*.

Indiana Cattle/Dairy Operation Signs Consent Decree in Drug Residue Case

Two co-owners of a cattle dealership and dairy operation in Indiana that had sold animals containing illegal drug residues signed a consent decree in June that requires the owners to take several steps to prevent residue violations in animals they sell.

The court Consent Decree of Permanent Injunction was filed June 13, 2006, against Chris Parker and Ted Parker, as individuals, and against their company, Jay Parker and Sons, LLC, Silver Lake, IN.

The Food and Drug Administration's (FDA) Detroit District Office, working with FDA's Center for Veterinary Medicine, conducted the investigations that led to the Consent Decree.

The U.S. Department of Agriculture (USDA), Food Safety and Inspection Service (FSIS), which samples animals at slaughter for illegal drug residues, reported 23 illegal drug residues in nine cows and one veal calf sold by the defendants during a period beginning in 1999 and ending in 2005. USDA inspectors reported finding illegal residues of several antibiotics—streptomycin, neomycin, gentamicin, oxytetracycline, flunixin, and sulfadimethoxine—at levels exceeding FDA-permitted tolerances or for which FDA has assigned no tolerance level.

The farm managers had previously received letters from USDA/FSIS advising them of the problem. In 2004, FDA investigators visited the farm and found problems severe enough in the drug administration and recordkeeping system that FDA issued the firm a Warning Letter citing specific violations. A follow-up inspection in 2005 found that the firm had not addressed the problems cited in the Warning Letter.

The Consent Decree places several requirements on the defendants if they are to stay in business.

The defendants must establish and implement a system that identifies by a tag number each animal they control.

The defendants must establish a written recordkeeping system that will help prevent the sale of any animal that contains illegal drug residues.

The firm is prohibited from using drugs in an extralabel manner (in a way not specified on the label) without a written order from a licensed veterinarian who has firsthand knowledge of the animals to be treated—otherwise known as a valid-client-patient relationship. (See article: "FDA Permits Extralabel Drug Use Under Certain Conditions" on page 6.) The defendants must implement a system that will prevent the defendants from using new animal drugs that are not in conformance with FDA approved labeling.

The defendants must establish and implement an inventory system for drugs that prevents them from selling or delivering animals containing violative drug residues and prevents medicated animals from being sold during a drug's withdrawal period.

The Consent Decree requires the defendants to explain in writing how they will comply with these requirements. In addition, the defendants must send a copy of the decree to all of their agents, employees, and other representatives that purchase animals from this firm.

Whenever it deems necessary, FDA can come onto the Jay Parker and Sons dairy farm to inspect the facilities to be sure that animal drugs are being properly used and documented. In accordance to the decree, the defendants "shall reimburse FDA for the costs of conducting and evaluating all inspectional, laboratory, analytical, and other work that FDA deems necessary to evaluate the defendants' compliance…." The fees will be charged at a standard rate.

USDA/FSIS inspectors often found multiple residue violations in one violative animal from Jay Parker and Sons, LLC. For example, a violative animal reported in April 2005 had residues of sulfadimethoxine in the kidney and liver. Because FDA has not established a tolerance for the drug in either organ, each of the two findings is one violation. In some violative cows, USDA/FSIS found illegal residues in three or more tissues, and in some cases found illegal residues of more than one drug.

Besides FDA's Detroit District Office and CVM's Division of Compliance, FDA's Office of the Chief Counsel, the U.S. Department of Justice's Office of Consumer Litigation, and the U.S. Attorney's Office in the Northern District of Indiana worked on the case.

…Meeting on Antimicrobial Scheduled *(Continued)*

present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation. They will be notified of their allotted time prior to the meeting.

Additional information

Information concerning the issues of microbial food safety is available to the VMAC members and the public in advance of the meeting and posted on CVM's website (*www.fda.gov/cvm*). Additional information about the VMAC meeting also will be posted on the CVM website.

Up-to-date information on the VMAC meeting is also available on the FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC, area), code 301-451-2548.

FDA Permits Extralabel Drug Use Under Certain Conditions

Veterinarians have the right to prescribe the "extralabel" use of drugs beyond the approvals indicated on the label, under a rule that went into effect about 10 years ago, but the Food and Drug Administration (FDA) places limits the extralabel use of drugs to protect public health.

The final rule about extralabel use of veterinary drugs, which went into effect in December 1996, was authorized by the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994. Prior to AMDUCA, veterinarians were not legally permitted to use an animal drug in any way except as indicated on the label.

A drug is used extralabelly in an animal if the drug's actual or intended use is in a manner not in accordance with the approved labeling. For instance, a drug is being used extralabelly if it is used or intended to be used:

- To treat a species not listed on the label;
- For an indication, disease or other condition, not on the label;
- At a dosage level or frequency not on the label; or
- With a route of administration not on the label.

The extralabel use rule allows veterinarians to legally go beyond label directions in using animal drugs, and permits them to use legally obtained human drugs in animals. However, the rule does not permit extralabel use of a drug in or on animal feed. Further, drugs cannot legally be used extralabelly except by, or on the order of, a veterinarian.

In addition, the prescribing veterinarian must be operating within a valid veterinarian-client-patient relationship, which means that the veterinarian must have firsthand knowledge of the animal being treated and will advise the owner on steps necessary, in the case of a food animal, to ensure a sufficient withdrawal period (the period after the last time the drug is administered and before any meat, milk, eggs, or other food product is marketed from the treated animal) for the drug.

Veterinarians are limited in using drugs extralabelly to cases in which the health of the animal is threatened, or suffering or death may result from a lack of treatment. Veterinarians cannot legally use drugs extralabelly to enhance production.

A drug is used extralabelly in an animal if the drug's actual or intended use is in a manner not in accordance with the approved labeling.

Also, veterinarians can consider using drugs extralabelly in food-producing animals only when no approved drug is available for use that contains the same active ingredient in the required dosage form and concentration, or that the veterinarian finds that the approved drugs are not clinically effective for their intended use.

In addition, the veterinarian must:

- Make a careful diagnosis or evaluation of the conditions to be treated;
- Establish a substantially extended drug withdrawal period that is supported by scientific evidence;
- Take the steps necessary to be sure the withdrawal period is met and no illegal drug residues occur in food from the treated animals; and
- Institute procedures to make sure the treated animal's identity is known.

The regulation also places requirements on the veterinarian to properly label the drugs used extralabelly to give the livestock owner complete instructions about proper use of the drug and withdrawal times, and to identify the veterinarian who prescribed the drug.

Under no circumstances can a non-veterinarian order the extralabel use of a drug in animals.

Prohibited from extralabel use

AMDUCA also gives FDA the right to prohibit the use of certain drugs from extralabel use.

FDA can prohibit extralabel use of drugs if no acceptable analytical method for determining tissue residues has been established, or the use of the drug or class of drugs presents a risk to public health.

The prohibition can be against all uses of a drug, or against the use in limited species, or for certain indications, dosages, forms, routes of administration, or a combination of factors.

The list currently includes:

- Chloramphenicol
- Clenbuterol
- Diethylstilbestrol
- Dimetridazole
- Furazolidone, nitrofurazone, other nitrofurans
- Fluoroquinolones
- Glycopeptide
- Ipronidazole
- Other nitroimidazoles
- Phenylbutazone animal and human drugs in female dairy cattle 20 months of age or older
- Sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethozine, sulfabromomethazine, and sulfaethoxpyridazine

These drugs, or classes of drugs, are prohibited from use in chickens, turkeys, and ducks:

- Adamantanes
- Neuraminidase inhibitors

The Science and Art of Measurement: The Work of CVM's Division of Residue Chemistry

by David H. Heller, Research Chemist

Science and research depend on measurement. If a thing cannot be measured, it cannot be studied via science. Measurements are an essential part of scientific experiments, which are controlled situations in which the measurements provide evidence of relationships among various forces and parameters. In a well-designed experiment, some aspects are held constant while others are varied in a controlled manner. The data may reveal a cause-and-effect relationship between certain variables.

The Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) relies on measurement science to evaluate animal drugs and ensure the safety of food from animals. But measuring for residues is not simple. Analytical chemists at CVM's Office of Research, Laurel, MD, employ highly sophisticated systems to measure residues.

Here's a tour of the field of residue chemistry and FDA's mission to protect animal and human health.

Measurements are integral to all of FDA's work

The need for measurement is written into all of FDA's laws and regulations; measurements are integral to our work in several fundamental ways.

1. The heart of the FDA's mission is to ensure that products are effective and safe. Effectiveness may be demonstrated with controlled experiments that relate a product's dosage to some beneficial effect, and this relationship is established with measurements.
2. Other experiments evaluate product safety by measuring the dosage at which negative effects may occur. These experiments often show that a product is healthful at a certain level, but not at a higher level.
3. Products are safe and effective only when used in the approved manner, so other measurements are also needed to verify that approved products are used in the approved manner.

For these different cases, CVM's mission requires the development and evaluation of two different kinds of methods: For 1 and 2 above, *Research Methods* to help establish conditions for a compound's proper use, study the compound's distribution in various tissues, or track its depletion rate from those tissues; and for 3, *Regulatory Methods* to provide surveillance data on usage patterns and support legal action against violations, such as excessive or unapproved uses.

These two types of methods can be differentiated in another way, according to who will make use of the results and how they are discussed. The customers for data acquired with Research Methods are typically other CVM scientists, but the customers for data acquired with Regulatory Methods are CVM's compliance officers and legal counsel (lawyers).

Residue chemistry fundamentals

Residue chemistry means both identifying the presence of a compound that has been administered to an animal and measuring its concentration in the animal's tissue.

At CVM, tissues might refer to samples drawn from living animals, such as blood, milk, or eggs. It could also mean food products derived from animals, such as muscle or liver. Or it could be by-products from animals, such as fat or skin.

The residue can be the compound itself, a metabolite (a form of the compound that has been modified by the body), or a contaminant that was inadvertently administered to or consumed by the animal.

In most cases the residues we at CVM's Division of Residue Chemistry deal with are of antimicrobial compounds, such as tetracycline, penicillin, or neomycin, which are administered to keep the animal healthy and to promote growth.

Residue chemists have five major areas of concern:

- **Fitness:** Did we measure the right thing in the right way? Success in the laboratory results from addressing these concerns in order of importance. Before beginning laboratory work, the fitness of a technical solution depends on defining the technical problem jointly between the residue chemist and the customer for the data. It is also important to know if there will be scientific or legal evaluation of the results.
- **Uncertainty:** How sure are we? What is the degree of bias and uncertainty? There will always be some uncertainty associated with the results of a residue

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…The Work of CVM's Division of Residue Chemistry *(Continued)*

analysis. The existence of uncertainty is unavoidable; scientists strive to assess and control uncertainty, not to eliminate it. When non-scientists hear results that are qualified by a discussion of potential error and imprecision, this is a good thing, not a reason to question their validity. There is no such thing as a perfect method that always gives the exact same answer every time. The closest we can come is a measured value obtained with a known degree of confidence. Measurement error, or bias, is the difference between a "true" or known value and the value found by actual analysis. Measurement precision describes how consistent the method is when run repeatedly on the same sample. Uncertainty is controlled by setting limits for accuracy, precision, concentration range, and identification confidence, and by not adopting methods that don't meet the acceptance criteria.

Dr. Mayda Lopez, a chemist with CVM's Office of Research, setting up the operating conditions for a liquid chromatograph and mass spectrometer (the darker component to her right) instruments, which are used to detect minute amounts of residues from tissues. The ability of residue chemists to detect trace amounts of drugs is essential in determining safe levels and in enforcing rules concerning the proper use of drugs.

- **Quality:** Could we have made a mistake? Quality management plays a critical role in establishing the validity of results. Laboratory quality is built from many individual steps that are carried out according to standardized procedures and acceptance criteria. There are procedures to test, control, and double-check critical steps as they are carried out, then to audit the results afterwards. Data must be shown to have been acquired when the method was under control. Only if known samples give proper results when analyzed alongside unknown samples can the values for unknowns be acceptable.
- **Quantitative:** How much is present? Are these results consistent with proper use? Is the level sufficient to call for legal action?
- And **Qualitative:** Is a particular product present in tissue?

Maintaining laboratory quality and assessing method uncertainty are major elements of our day-to-day laboratory work. Methods are tested for ruggedness in a variety of ways after they are developed. No method is used for critical analyses without extensive testing known as a method validation. Nearly every laboratory activity, from weighing chemicals, mixing standard solutions, or calibrating instruments to conducting entire research studies and documenting results are covered by standardized procedures. Once these procedures are in place, laboratory work can begin.

There are two technical disciplines that must be grasped to make sense of modern analytical laboratory practice: separation science, or extraction, and instrumental analysis.

Separations at the molecular level

How do you remove the proverbial needle from a haystack? Residue analysis poses a similar problem. Drug residues occur in complex biological tissues consisting of proteins, fats, fibrous connective tissue, carbohydrates, and an amazing variety of other small molecules. The residues of concern have to be separated from this matrix by any means possible. For an analogy, think of a haystack which is doused with gasoline and set on fire; this is a chemical reaction that converts the hay to gases while leaving minerals behind (such as a metal needle). If the hay is doused with water and allowed to rot, this is a biochemical digestion (carried out by microbes). If the hay is probed with a giant electromagnet, magnetic metal needles may be recovered by a physical process of attraction.

(Continued, next page)

…The Work of CVM's Division of Residue Chemistry *(Continued)*

Other separation steps can be carried out by manipulating solution chemistry. For example, a mixture of salt and pepper can be separated with water, by dissolving the salt to take advantage of its differential solubility. You could use a form of residue chemistry yourself if extra-hot BBQ sauce burns your lips. It is more effective to drink milk than water to ease the burning sensation, because the spicy components are more fat-soluble than water-soluble. Tarnished metal can be treated with acid (a lower pH value) to change the solubility of the oxidized metal surface. Juice is removed from apples by grinding, pressing, and filtering.

Basic techniques such as these are now supplemented by more sophisticated approaches, such as solid phase extraction, or SPE. Think "tea bag" when visualizing the SPE process. A small amount of specially treated particles (tea) is loaded inside a permeable container (the bag) and chemical components (caffeine) are extracted with a solvent (boiling water). SPE particles come in various "flavors" based on their chemical affinity: lipophilic (fat-loving), hydrophilic (water-loving), or ionic (possessing electrostatic attraction).

In summary, the initial step in separation science is a lab-scale extraction based on a combination of chemical, physical, or biochemical processes, where the goal is to recover 100% of the compound of interest in a more purified form.

Chromatography further separates the compounds in a mixture from one another. Chromatography is carried out in a specially lined tube through which liquid or gas flows. Different compounds have different affinities for the stationary lining of the tube compared to the moving liquid or gas, so they move through the tube at different rates. Imagine a large crowd lining a busy street. An agile jogger can maneuver fairly quickly by avoiding contact and "diffusing" quickly to the far side of the crowd. However, a candidate for public office might stop to talk with each person, and thereby take many times longer to emerge from the crowd. If the two had arrived at the edge of the crowd at the same time, the jogger would always emerge first. This "retention time" is a feature that both separates and helps characterize the components of a mixture.

Instrumental analysis

Advances in technology and computers have steadily changed the way residue analyses are conducted. In earlier years, the most common approach to antibiotic detection was to measure their inhibition of bacterial growth in laboratory cultures. Now, instrumental detectors based on chemical and physical principles can provide direct analysis of specific chemical entities with amazing sensitivity.

Physico-chemical detectors provide a response that is proportional to the amount of compound present; the more response, the higher the concentration must be. A calibration curve is prepared from solutions of certified standards at known concentrations. When the response of an unknown sample is compared against the calibration curve, the sample's concentration can be computed.

There are two primary types of instrumental detectors used in today's residue laboratories. Spectroscopic detectors are based on the absorbance of light by the compound. Mass spectrometric detectors respond directly to the molecules themselves, after they have been ionized and separated according to mass in a specialized vacuum chamber. In fact, the development of electrospray ionization mass spectrometry has become so critical in pharmaceutical and other applications that its developer, John Fenn, was a co-recipient of the Nobel Prize in Chemistry in 2002.

These detectors are sophisticated instruments that are heavily dependent on electronics, computer control, and automated digital data processing. You can't see what is happening inside, and the operator doesn't necessarily have to understand every internal process to obtain valid data. Mass spectrometers are normally inside heavy boxes with noisy vacuum pumps. Instrumental laboratories require good ventilation and temperature control, so they tend to be noisy and filled with computers connected to large boxes with flickering lights.

The power of mass spectrometry can be illustrated with an example based on a familiar compound. A typical soda contains about 0.1 mg of caffeine per ml. One quarter of a liter (about 8 ounces) contains about 25 mg caffeine, which corresponds to about 75,000,000,000,000,000,000 molecules. If that 8 ounces is diluted by 100,000 times, say, by pouring it into a tanker truck, electrospray tandem mass spectrometry could still detect the caffeine. Detection limits might be on the order of 10 picograms, or 30,000,000,000,000 molecules. This extreme sensitivity puts pressure on CVM's toxicologists and regulators to determine at what point detectable residues begin to create a health risk to consumers.

Mass spectrometers can also identify a particular compound with a high degree of confidence. These instruments respond directly to signals from the intact molecule and its constituent pieces. The resulting

(Continued, next page)

…The Work of CVM's Division of Residue Chemistry *(Continued)*

A Brief History of CVM'S Division of Residue Residue Chemistry

The components of today's Division of Residue Chemistry (DRC) of the Center for Veterinary Medicine (CVM) have existed for more than four decades.

In 1963 the Food and Drug Administration's (FDA) Veterinary Research facility opened in rented space at the U.S. Department of Agriculture's Beltsville Agricultural Research Center, in Maryland, just outside Washington, DC. This facility was part of the Veterinary Medical Branch in the Bureau of Medicine.

By the late 1970s, residue method development and testing was being performed by chemists in the Bureau of Foods (now FDA's Center for Food Safety and Applied Nutrition) in downtown Washington. This methods group transferred to Bureau of Veterinary Medicine (the forerunner of the Center for Veterinary Medicine [CVM]) in the early 1980s and became part of the Chemistry Division of the Office of Human Food Safety (now CVM's Office of New Animal Drug Evaluation).

Then, in the mid 1980s, the methods group relocated to Beltsville, MD, and later merged with chemists from Veterinary Medical Research to form a new analytical branch. The analytical staff was increased in the early 1990s and the branch achieved division status within CVM.

In 1996, CVM's Office of Research opened at the FDA laboratory and research facilities at "MOD2" at the Muirkirk Road Campus in Laurel, MD. This facility, dedicated in October 1996, was the first new construction of the FDA consolidation.

CVM's MOD2 facilities include more than 165 acres of pastures and other land for animals, and contain large animal research buildings, specialized laboratories, pastures, feed mixing facilities, and quarantine facilities.

"mass spectra" are highly specific, much like fingerprints or bar code tags.

Traceability

Traceability refers to comparing the response of an unknown sample against that of a certified standard.

The calibration process depends on a detector response that is proportional to the amount of compound present. Calibration standards are prepared at a series of concentrations using a standard whose amount is certified by the manufacturer.

Mass spectrometry can be used to confirm the presence of a suspect compound by comparing the specific mass values from a mass spectrometer against the corresponding signals from standards.

Every physical parameter we can measure has some ultimate benchmark to which measured values can be traced back. That benchmark is the basis for the validity of results.

Conclusion: The Critical Eye – What to Look for In Evaluating Measurements

A significant part of a regulatory chemist's time is spent evaluating the work of others, whether internal or submitted by animal drug sponsors or other government laboratories. Over time one develops a process for checking the most critical aspects of measurements and methods. Here are some important questions that can be asked of measurements in any context.

- **Qualitative:** How selective is the separation and detection? Could the signals arise from any other compound?
- **Quantitative:** What are the upper and lower performance limits? How much of the analyte is recovered by the extraction?
- **Quality:** Did the quality assurance samples give the correct result? Have the data been audited by an independent expert?
- **Uncertainty:** What is the method's degree of bias and uncertainty?
- **Fitness:** What is at stake? How sure do you have to be?

In the final analysis (so to speak), regulatory analysts provide a service in support of regulatory decision-makers. We respond to method needs that are determined by toxicology studies and risk assessment. We provide methods and data that can be relied upon by those who determine what action to take on the basis of the numbers.

BSE INSPECTION UPDATE

CVM Reports BSE Inspection Figures as of August 5, 2006

As of August 5, 2006, the Food and Drug Administration (FDA) had received more than 47,000 reports of inspections done under the ruminant feed rule designed to prevent the establishment and spread of bovine spongiform encephalopathy (BSE) in the United States.

Approximately 68 percent of the inspections were conducted by State officials under contract to FDA, with the remainder conducted by FDA officials.

Inspections conducted by State and FDA investigators are classified to reflect the compliance status at the time of the inspection, based upon whether objectionable conditions were documented. Based on the conditions found, inspection results are recorded in one of three classifications:

- **OAI (Official Action Indicated)** when inspectors find significant objectionable conditions or practices and believe that regulatory sanctions are warranted to address the establishment's lack of compliance with the regulation. An example of an OAI classification would be findings of manufacturing procedures insufficient to ensure that ruminant feed is not contaminated with prohibited material. Inspectors will promptly re-inspect facilities classified OAI after regulatory sanctions have been applied to determine whether adequate corrective actions have been implemented.
- **VAI (Voluntary Action Indicated)** when inspectors find objectionable conditions or practices that do not meet the threshold of regulatory significance, but warrant an advisory to inform the establishment that inspectors found conditions or practices that should be voluntarily corrected. VAI violations are typically technical violations of the 1997 BSE Feed Rule. These violations include minor recordkeeping lapses or conditions involving non-ruminant feeds.
- **NAI (No Action Indicated)** when inspectors find no objectionable conditions or practices or, if they find objectionable conditions, those conditions are of a minor nature and do not justify further actions.

(Note: The following figures are as of August 5, 2006.)

Renderers

These firms are the first to handle and process (i.e., render) animal proteins. After they process the material, they send it to feed mills and/or protein blenders for use as a feed ingredient.

- **Number of active firms whose initial inspection has been reported to FDA** – 275
- **Number of active firms handling materials prohibited from use in ruminant feed** – 177 (64 percent of those active firms inspected)

  Of those 177 firms:

  ❖ 2 (1.1 percent) were classified as OAI

  ❖ 1 (0.6 percent) was classified as VAI

Licensed feed mills

In the inspection report database, FDA lists medicated feed licensed feed mills separately from non-licensed feed mills. But the licensing has nothing to do with handling prohibited materials under the feed ban regulation. FDA requires feed mills to have medicated feed licenses to manufacture and distribute feed using certain potent drug products, usually those requiring some pre-slaughter withdrawal time, to produce certain medicated feed products.

- **Number of active firms whose initial inspection has been reported to FDA** – 1,086
- **Number of active firms handling materials prohibited from use in ruminant feed** – 438 (40 percent of those active firms inspected)

  Of those 438 firms:

  ❖ 1 (0.2 percent) was classified as OAI

  ❖ 5 (1.1 percent) were classified as VAI

Feed mills not licensed by FDA

These feed mills are not licensed by the FDA to produce medicated feeds.

- **Number of active firms whose initial inspection has been reported to FDA** – 5,138
- **Number of active firms handling materials prohibited from use in ruminant feed** – 2,270 (44 percent of those active firms inspected)

  Of those 2,270 firms:

  ❖ 2 (0.1 percent) were classified as OAI

  ❖ 49 (2.2 percent) were classified as VAI

Protein blenders

These firms blend rendered animal protein for the purpose of producing feed ingredients used by feed mills.

- **Number of active firms whose initial inspection has been reported to FDA** – 345
- ***Number of active firms handling materials prohibited from use in ruminant feed*** – 176 (51 percent of those active firms inspected)

(Continued, next page)

Comings and Goings

New Hires

OFFICE OF SURVEILLANCE AND COMPLIANCE

- Diana Bargo, Consumer Safety Officer

OFFICE OF NEW ANIMAL DRUG EVALUATION

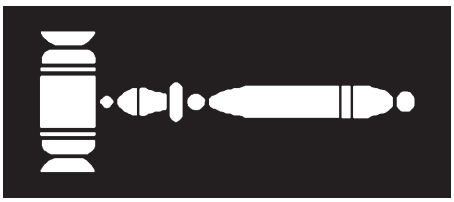
- Trudie Willis, Legal Instruments Examiner

Departures

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Sabine Ladd, Veterinary Medical Officer, Staff Fellow
- Anna Caponiti, Project Management Specialist

Regulatory Activities



A WARNING LETTER was issued to Mark A. Hickman, president, Peco Foods, Inc, Tuscaloosa, AL, because an investigation of the licensed medicated and non-medicated animal feed mill located in Philadelphia, MS, found significant deviations from current Good Manufacturing Practice (cGMP) regulations for medicated feeds set forth in Title 21, *Code of Federal Regulations*, Part 225 (21 CFR 225). Such deviations cause the medicated feeds manufactured at this facility to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FFDCA). The investigation found the firm failed to conduct potency assays on at least three representative samples of each medicated feed at periodic intervals during the calendar years 2004 and 2005. In addition, the firm failed to document investigative and corrective actions when medicated feeds failed assay specifications.

A WARNING LETTER was issued to Chester J. Claudon and Russell E. Weaver, owners, Western Illinois Grain Co., Macomb, IL, because an inspection conducted at the medicated feed mill located in Fairview, IL, found that the feed mill caused the new animal drug chlortetracycline to be unsafe within the meaning of Section 512 of the FFDCA and adulterated within the meaning of Section 502(a)(5) of the FFDCA. In addition, the new animal

(Continued, next page)

CVM Reports BSE Inspection Figures... *(Continued)*

Of those 176 firms:

- ❖ 1 (0.6 percent) was classified as OAI
- ❖ 1 (0.6 percent) was classified as VAI

Renderers, feed mills, protein blenders

This category includes any firm that is represented by any of the above four categories, but includes only those firms that manufacture, process or blend animal feed or feed ingredients using prohibited materials.

- **Number of active renderers, feed mills, and protein blenders whose initial inspection has been reported to FDA** – 6,572
- **Number of active renderers, feed mills, and protein blenders processing with prohibited materials** – 487 (7.4 percent of those active firms inspected)

Of those 487 firms:

- ❖ 4 (0.8 percent) were classified as OAI
- ❖ 15 (3.1 percent) were classified as VAI

Other firms inspected

Examples of such firms include ruminant feeders, on-farm mixers, pet food manufacturers, animal feed salvagers, distributors, retailers and animal feed transporters.

- **Number of active firms whose initial inspection has been reported to FDA** – 15,544
- **Number of active firms handling materials prohibited from use in ruminant feed** – 4,712 (30 percent of those active firms inspected)

Of those 4,712 firms:

- ❖ 5 (0.1 percent) were classified as OAI
- ❖ 127 (2.7 percent) were classified as VAI

Total firms

- **Number of active firms whose initial inspection has been reported to FDA** – 18,231
- **Number of active firms handling materials prohibited from use in ruminant feed** – 5,476 (30 percent of those active firms inspected)

Of those 5,476 firms:

- ❖ 8 (0.1 percent) were classified as OAI
- ❖ 137 (2.5 percent) were classified as VAI

(NOTE: A single firm that has more than one function can be listed in different industry segments, which also means that the total presented here may be less than a combination of all the segments listed above.)

Kansas Feed Mill Cited for GMP Violations

On August 16, 2006, the U.S. Attorney's Office in the District of Kansas filed a Consent Decree of Permanent Injunction in the U.S. District Court for the District of Kansas against the feed manufacturer Cooperative Agricultural Services, Inc. (CO-AG), of Grinnell, KS, and CO-AG's feed department manager, for multiple violations of current Good Manufacturing Practice (cGMP) requirements for medicated feed production.

CO-AG produces medicated and non-medicated feed for consignees in Kansas, Oklahoma, and Colorado.

Inspectors went to the manufacturing facilities as part of an investigation into the death of several livestock that consumed feed from CO-AG. Inspectors at the CO-AG facilities documented many violations of the cGMP requirements for feed manufacturing, found under Title 21 *Code of Federal Regulations*, Part 225.

Inspectors went to the manufacturing facilities as part of an investigation into the death of several livestock that consumed feed from Cooperative Agricultural Services, Inc. (CO-AG). Inspectors at the CO-AG facilities documented many violations of the current Good Manufacturing Practice requirements for feed manufacturing….

Under the terms of the Consent Decree, the defendants have agreed to stop manufacturing and distributing medicated animal feeds until they provide assurance to the satisfaction of Food and Drug Administration (FDA) officials that their medicated feeds are made in compliance with current cGMP requirements, in accordance with label specifications, and in a manner ensuring that all uses of new animal drugs conform to each drug's approved application.

Also under the Decree, the defendants are required to retain an expert consultant to conduct inspections of their manufacturing facility and certify to FDA that corrections have been made. FDA will continue to monitor these activities.

The Decree requires the defendants to have a qualified laboratory conduct analyses on their medicated feeds and they must take corrective action for all medicated feeds that the laboratory determines are outside the assay (potency) limits set by FDA regulation.

The Decree says that FDA can require a recall or shutdown in the event of future cGMP violations.

FDA's Kansas City District Office conducted the investigations that led to this Consent Decree. FDA's Center for Veterinary Medicine, Division of Compliance, and FDA's Office of the Chief Counsel worked with the U.S. Attorney's Office in processing the case.

Regulatory Activities *(Continued)*

drug chlortetracycline was misbranded within the meaning of Section 502(o) of the FFDCA. The inspection also found significant deviations from the cGMP regulations for medicated feeds. Such deviations cause the feeds being manufactured at this facility to be adulterated. The inspection revealed that the firm purchases intact bags of the new animal drug chlortetracycline, a Category I, Type A medicated article, and repackages the contents of the original bags into smaller portions, which are subsequently sold. This repacking operation establishes the firm as a producer of a new animal drug, subject to the requirements of Section 510 of the FFDCA. Establishments manufacturing Type A medicated articles are required to register annually as drug establishments and must submit a list of every drug in commercial distribution. In addition, an approved New Animal Drug Application (NADA) is required for the manufacture of a Type A medicated article containing a new animal drug unless exempted under 21 CFR 558.15. A review of the Food and Drug Administration's (FDA) records shows that this veterinary drug repackaging establishment is not registered and has no drug listed with FDA. In addition, the firm purchased, received, and sold the new animal drug chlortetracycline in a manner that does not conform to an approved NADA in accordance with Section 512. Because the chlortetracycline is not covered by an approved NADA, the drug is unsafe, and thus is adulterated. In addition, all drugs manufactured, propagated, compounded, or processed by the firm are misbranded because the firm is not registered and/or has no drug listed. The cGMP violations included (1) failure to maintain procedures for the identification, storage, and inventory control of all Type A medicated articles and Type B medicated feeds intended for use in the manufacture of medicated feeds to aid in assuring the identity, strength, quality, and purity of these drug sources; and (2) failure to maintain buildings and grounds in a manner that minimizes vermin and pest infestation.

Approvals for July 2006

CVM has published in the *Federal Register* notice of the approval of these Supplemental New Animal Drug Approvals (NADA)

CARBOCAINE-V (mepivacaine hydrochloride) Sterile Aqueous Solution (NADA 100-703), filed by Pharmacia & Upjohn Co., a Division of Pfizer, Inc. The supplemental NADA provides for revised food safety labeling for mepivacaine injectable solution used in horses for local anesthesia. Notice of approval was published July 13, 2006.

SALIX (furosemide) Injection 5% (NADA 034-478), filed by Intervet, Inc. The supplemental NADA provides for the revision of a food safety warning on labeling of furosemide injectable solution for use in horses for the treatment of edema (pulmonary congestion, ascites) associated with cardiac insufficiency and acute non-inflammatory tissue edema. Notice of approval was published July 13, 2006.

EXCEDE (ceftiofur crystalline free acid) Sterile Suspension (NADA 141-209), approved for veterinary prescription use by injection in cattle for respiratory disease, filed by Pharmacia & Upjohn Co., a Division of Pfizer, Inc. The supplemental NADA provides for use of ceftiofur crystalline free acid suspension via a new subcutaneous injection site in beef and nonlactating dairy cattle (subcutaneous injection in the posterior aspect of the ear where it attaches to the head at base of the ear), and for use in lactating dairy cattle by subcutaneous injection in the base of the ear for the treatment of respiratory disease. The supplement also provides for the establishment of a 13-day pre-slaughter withdrawal period in cattle. FDA is amending the regulations to revise the tolerance for residues of ceftiofur in bovine kidney to accommodate these new conditions of use. Notice of approval was published July 13, 2006.

NAXCEL (ceftiofur sodium) Sterile Powder for Injection (NADA 140-338), EXCENEL RTU (ceftiofur hydrochloride) Sterile Suspension (NADA 140-890), SPECTRAMAST LC (ceftiofur hydrochloride) Sterile Suspension (NADA 141-238), and SPECTRAMAST DC (ceftiofur hydrochloride) Sterile Suspension (NADA 141-239), filed by Pharmacia & Upjohn Co., a Division of Pfizer, Inc. NAXCEL and EXCENEL RTU are approved for veterinary prescription use in livestock by injection for the treatment or control of bovine respiratory disease (shipping fever, pneumonia) associated with *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni*; acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.* SPECTRAMAST LC and SPECTRAMAST DC are approved for veterinary prescription use by intramammary infusion in dairy cows for the treatment of bacterial mastitis. The four supplemental NADAs establish or revise preslaughter withdrawal periods in cattle injected with a solution made from ceftiofur sodium powder or with a suspension of ceftiofur hydrochloride, or receiving an intramammary infusion of ceftiofur hydrochloride consistent with the tolerance for residues of ceftiofur in bovine kidney, which was revised for EXCEDE (ceftiofur crystalline free acid) Sterile Suspension (NADA 141-209), which is described above. Notice of approval for these supplemental NADAs was published July 13, 2006.

HYLARTIN (sodium hyaluronate) Injection (NADA 112-048), filed by Pharmacia & Upjohn Co., a Division of Pfizer, Inc. The supplemental NADA provides for a revised food safety warning on the labeling of sodium hyaluronate approved for veterinary prescription use by intra-articular injection for the treatment of joint dysfunction in horses due to noninfectious synovitis associated with equine osteoarthritis. Notice of approval was published July 12, 2006.

(Continued, next page)

Approvals for July 2006 *(Continued)*

Supplemental New Animal Drug Approvals (Continued)

THRUSH-XX (copper naphthenate) (NADA 100-616), filed by Farnam Companies, Inc. The supplemental NADA provides for a revised food safety warning on the labeling of copper naphthenate, a solution approved for topical use on horse and pony hooves as an aid in treating thrush. Notice of approval was published July 5, 2006.

CVM has published in the *Federal Register* notice of the approval of these Abbreviated New Animal Drug Approvals (ANADA)

IVERMECTIN PASTE 1.87% (ANADA 200-390), filed by Med-Pharmex, Inc. The ANADA provides for oral use of ivermectin paste in horses for treatment and control of large strongyles, small strongyles, pinworms, roundworms (ascarids), hairworms, new threadworms, large-mouth stomach worms, and bots. Med-Pharmex's Ivermectin Paste 1.87% is approved as a generic copy of Merial Ltd.'s EQVALAN Paste, approved under NADA 134-314. Notice of approval was published July 14, 2006.

HEIFERMAX 500 (melengestrol acetate) Liquid Premix, BOVATEC (lasalocid), and TYLAN (tylosin phosphate) single-ingredient Type A medicated articles (ANADA 200-430), filed by Ivy Laboratories, Division of Ivy Animal Health, Inc. The ANADA provides for use of single-ingredient Type A medicated articles containing melengestrol, lasalocid, and tylosin to make dry and liquid, three-way combination drug Type C medicated feeds for heifers fed in confinement for slaughter. This ANADA is approved as a generic copy of NADA 138-992, sponsored by Pharmacia and Upjohn Co., a Division of Pfizer, Inc., for combination use of MGA 500 (melengestrol acetate) Liquid Premix, BOVATEC, and TYLAN in cattle feed. Notice of approval was published July 12, 2006.

VETRO-MAX (gentamicin sulfate, USP; betamethasone valerate, USP; and clotrimazole, USP, ointment) (ANADA 200-283), filed by Altana, Inc. The ANADA provides for the veterinary prescription use of gentamicin sulfate, betamethasone valerate, clotrimazole ointment for the treatment of canine acute and chronic otitis externa associated with yeast (*Malassezia pachydermatis*, formerly *Pityrosporum canis*) and/or bacteria susceptible to gentamicin. Altana, Inc.'s VETRO-MAX Otic Ointment is approved as a generic copy of Schering-Plough Animal Health Corp.'s OTOMAX Ointment approved under NADA 140-896. Notice of approval was published July 6, 2006.

GRISEOFULVIN (griseofulvin) Powder Microsize (ANADA 200-391), filed by IVX Animal Health, Inc. The ANADA provides for veterinary prescription use of griseofulvin powder orally as a systemic antifungal agent in horses. IVX Animal Health's Griseofulvin Powder Microsize, is approved as a generic copy of Schering-Plough Animal Health Corp.'s FULVICIN-U/F (griseofulvin) Powder approved under NADA 039-792. Notice of approval was published July 5, 2006.

OXYTETRACYCLINE HCl (oxytetracycline hydrochloride) Soluble Powder (ANADA 200-305), filed by Vétoquinol NA, Inc. The ANADA provides for use of Oxytetracycline HCl Soluble Powder to prepare medicated drinking water for the treatment of various bacterial diseases of livestock. In chickens, it is used for the control of infectious synovitis caused by *Mycoplasma synoviae* susceptible to oxytetracycline; for control of chronic respiratory disease and air sac infections caused by *Mycoplasma gallisepticum* and *Escherichia coli* and fowl cholera caused by *Pasteurella multocida* susceptible to oxytetracycline. In turkeys, it is used for control of hexamitiasis caused by *Hexamita meleagridis*

(Continued, next page)

Approvals for July 2006 *(Continued)*

Abbreviated New Animal Drug Approvals (Continued)

susceptible to oxytetracycline and for control of infectious synovitis caused by *Mycoplasma synoviae* susceptible to oxytetracycline; in growing turkeys, it is used for control of complicating bacterial organisms associated with bluecomb (transmissible enteritis, coronaviral enteritis) susceptible to oxytetracycline; in swine, it is used for control and treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis*, bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline; and in breeding swine, it is used for Leptospirosis (reducing the incidence of abortion) and shedding of leptospira caused by *Leptospira pomona* suspectible to oxytetracycline. Vétoquinol NA, Inc.'s Oxytetracycline HCl Soluble Powder is approved as a generic copy of Alpharma, Inc.'s OXY-TET (oxytetracycline hydrochloride) Soluble approved under NADA 130-435. Notice of approval was published July 5, 2006.

CVM has published in the *Federal Register* notice of the approval of these Supplemental ANADAs

- CLINSOL (clindamycin hydrochloride) Liquid (ANADA 200-291), filed by Virbac AH, Inc. The supplemental ANADA provides for an expanded dose range and revised wording of indications for the oral use of clindamycin hydrochloride liquid in dogs and cats for the treatment of certain bacterial diseases. Notice of approval was published July 13, 2006.
- CLINITABS (clindamycin hydrochloride) tablets (ANADA 200-316), filed by Virbac AH, Inc. The supplemental ANADA provides for an expanded dose range and revised wording of indications for the oral use of clindamycin hydrochloride tablets in dogs for the treatment of certain bacterial diseases. Notice of approval was published July 12, 2006.
- IVERSOL (ivermectin) Liquid for Horses (ANADA 200-292), filed by Med-Pharmex, Inc. The supplemental ANADA provides for revisions to label indications and to the food safety warning for ivermectin liquid administered by mouth or nasogastric tube to horses for treatment and control of various internal parasites or parasitic conditions. Notice of approval was published July 5, 2006.

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