Linking Human and Veterinary Health: Trends, Directions and Initiatives

Submitted: July 1, 2002; Accepted: July 1, 2002; Published: October 15, 2002

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ABSTRACT The objective of this brief article is to provide an overview of some of the important harmonization efforts that are currently under way within the animal health community. Topics include: scientific networks and interdisciplinary communication; organizations that address animal-related public health concerns; the role of the veterinary pharmaceutical scientist within human health-oriented professional organizations; recent publications pertaining to veterinary pharmacology, pharmaceuticals and therapeutics; and the role of global networking in veterinary product research and development.

KEYWORDS: communication, globalization, veterinary medicine.

INTRODUCTION Several important harmonization and globalization efforts are currently under way within the veterinary sciences. These are intended to facilitate interactions not only between human and veterinary pharmaceutical experts but also among the diverse areas of specialization within the field of veterinary pharmacology, pharmaceuticals, and therapeutics. Knowledge and communication are 2 of the keys to successful research and development of veterinary pharmaceuticals. In the past, we have witnessed the lack of accessible communication networks, failure to share information perceived as being proprietary, and a lack of outlets for the dissemination of knowledge. However, this view is being superseded by global scientific networks that encourage interdisciplinary communication, organizations that address animal-related public health concerns, the publication of books and Theme Issues of international journals, and the establishment of global networks for the dissemination of veterinary-related information.

This article reviews current efforts in each of these areas, highlighting the advantages such activities have brought to the area of veterinary pharmacology, pharmaceuticals, and therapeutics.

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MEETING THE NEED FOR ESTABLISHING SCIENTIFIC NETWORK AND ENHANCED INTERDISCIPLINARY COMMUNICATION:

Addressing Public Health Concerns

Food and Agriculture Organization¹⁻³

The Food and Agriculture Organization of the United Nations (FAO) was founded in 1945 with a mandate to raise levels of nutrition and standards of living, to improve agricultural productivity, and to better the condition of rural populations. The joint FAO/World Health Organization (WHO) Conference on Food Additives was held in 1955. From this meeting, there evolved the Joint FAO/WHO Expert Committee on Food Additives (JECFA), an international expert scientific committee involved in the safety evaluation of food additives, food contaminants, naturally occurring toxicants, and residues of veterinary drugs in food. To date, JECFA has evaluated more than 1300 food additives, approximately 25 contaminants and naturally occurring toxicants, and the residues of approximately 80 veterinary drugs.

The JECFA is responsible for establishing international standards for an Acceptable Daily Intake (ADI) for various food additives. The ADI is an estimate of the amount of an additive (expressed on a body weight basis) that can be ingested daily over a lifetime without any appreciable detriment to human health. These ADI's are then used by the FAO/WHO Codex Alimentarius Commission (CAC) to establish acceptable maximum residue limits (MRLs) and withdrawal times. A withdrawal time is defined as that time period between the last administration of a drug and the collection of edible tissue or products from a treated animal that ensures that the residue content in the food complies with the MRL for that particular veterinary compound.

Food standards established by the FAO/WHO CAC improve the safety of materials intended for human consumption. It provides an opportunity for member nations to harmonize their various food standards, facilitating the international trade of edible materials. Codex standards and guidelines cover more than 200 food commodities, set safe limits for over 3000 contaminants and residues, and have become the seminal global reference point for consumers, food producers and processors, national food control agencies, and the international food trade.

Pan American Health Organization's Veterinary Public Health Program⁴

The Pan American Health Organization's (PAHO's) Veterinary Public Health Program has been established to support the programs of member countries in several key areas. These include zoonoses (diseases transmitted by animals to humans), food protection, education in veterinary public health, biomedical models for the development of human drugs and vaccines, and the organization of veterinary public health. PAHO member countries have joined forces to eradicate diseases such as foot-and-mouth disease that can cause major economic losses and impede trade among the region's countries. Progress has also been made in preventing animal-to-human transmission of diseases such as rabies. PAHO, which serves as the WHO's Regional Office for the Americas, was officially established in 1902 and currently is the world's oldest international health organization. It works with all of the countries in the Americas to improve health and quality of life.

National Antimicrobial Resistance Monitoring System^{5,6}

The National Antimicrobial Resistance Monitoring System (NARMS) was established in 1996 as a collaborative effort among the Food and Drug Administration's Center for Veterinary Medicine (FDA CVM), the U.S. Department of Agriculture (USDA), and the Centers for Disease Control and Prevention (CDC). The NARMS program monitors changes in susceptibilities of human and animal enteric bacteria to 17 antimicrobial drugs. Bacterial isolates are collected from human and animal clinical specimens, from healthy farm animals, and from animal-derived raw products to provide descriptive data. The ultimate goal of these activities is to prolong the lifespan of approved drugs by promoting the prudent and judicious use of antimicrobial compounds.

Another important outcome of these activities is the identification of research questions needing further investigation. The system is set up as 2 nearly identical parts: a veterinary arm and a human arm. Veterinary testing is conducted at the Agricultural Research Service's (ARS's) Russell Research Center in Athens, Georgia. Human-origin isolates are submitted by 16 State Departments of Health for testing at the National Center for Infectious Disease, CDC, in Atlanta, Georgia. With the additional funding provided by the Food Safety Initiative Surveillance budget, epidemiological research has been initiated. This research is intended to characterize and reduce the incidence of foodborne disease associated with emerging and drug-resistant pathogens. It includes a field study, several farm-based efforts, and molecular genetic research.

Examples of Veterinary Interests Addressed Within Human Health Societies

The following examples are not intended to provide an exhaustive list of harmonization/communication efforts or of the state-of-the-art literature, but rather to represent the depth and breadth of opportunities that are currently available.

The CRS Committee Focusing on Veterinary Products⁷

The Controlled Release Society (CRS) was conceived in 1973 and currently serves 3500 members from 50 different countries. Its mission is to advance the science and technology of chemical and biological delivery systems. It provides a forum for promoting the advancement of controlled release technologies associated with agriculture, veterinary medicine, cosmetics, and human medicine (refer to www.controlledrelease.org).

In 1997, the CRS Committee Focusing on Veterinary Products was established to represent, and work on behalf of members of the CRS who have an interest in or are developing controlled release products for animal health. It currently works under the title The CRS Veterinary Products Subcommittee. Included among its many achievements over the past 5 years are:

- Establishment of a Vet Forum (Web-based discussion forum on the Home Page of the CRS)
- Establishment of a Vet Column in the CRS Newsletter
- Organization of social and scientific activities at Annual CRS Symposium
- Organization of a Veterinary Minisymposium (at the 2001 Annual CRS Symposium in San Diego)
- Organization of a 2-day workshop on Controlled Release Technologies for Veterinary Products (Boston 1998)
- Development of a joint program with the American Association of Pharmaceutical Scientists (AAPS) and the American Academy of Veterinary Pharmacology and Therapeutics (AAVPT) (workshop, Chicago, 2002)
- Establishment of the Animal Health Consortium (AHC)
- Development of the Controlled Release Veterinary Drug Delivery Web site (www.geocities.com/vetcdd/).
- Organization of a Special Issue of the Journal of Controlled Release on veterinary drug delivery, which includes a special section on vaccine delivery

The Animal Health Consortium⁸

Today's rapidly changing environment necessitates the integration of the multifaceted activities associated with animal health. The complexity of issues arising in veterinary medicine, husbandry practices, drug development, drug regulation, and international marketing and trade necessitate improved intercommunication. For this reason, the Animal Health Consortium (AHC), an interna-

tional network of professional organizations, is intended to help overcome many of the obstacles impeding effective inter-disciplinary communication. The mission of the AHC is to provide a forum for communication between member organizations via electronic newsletters and Web-based interactions. This innovative effort is the first international Web-based initiative to unite animal health scientists from all areas of expertise, thereby fostering a better understanding of the challenges encountered within each specialty and providing unique perspectives on issues to assist in creative problem solving.

In addition to bi-annual news reports, the AHC Web site provides several important features:

- A moderated discussion group that allows for scientists and practitioners within the animal health community to post questions, answers, concerns, etc.
- Discussion group archive
- Upcoming meetings at a glance
- Links to announcements about animal health meetings announcements occurring throughout the world
- Hot links to all AHC member organizations
- Information resource
- Hot links to Web-based information sources
- An opportunity to propose collaborative efforts
- A human resource center where people can post resume's for up to 6 months

American Association of Pharmaceutical Scientists Animal Health Focus Group⁹

The AAPS is a professional, scientific society of more than 11000 members who are employed in academia, industry, government, and other research institutes worldwide. Founded in 1986, the mission of AAPS seeks to advance science through the open exchange of scientific knowledge, serve as an information resource, and contribute to human health through pharmaceutical research and development (refer to www.aapspharmaceutica.com).

While the majority of issues discussed within AAPS center on the challenges associated with human drug product development, it was recognized that these same issues and technologies affect the veterinary health industry. In addition, the animal health scientist must also address problems unique to veterinary medicine. For this reason, in January 2000, the AAPS Animal Health Focus Group (AHFG) was formed to provide an opportunity for animal health scientists to explore issues facing the development and regulation of animal health products.

To date, the AHFG has co-sponsored a collaborative workshop (AAPS-AAVPT-CRS), developed a veterinary Theme Issue of *AAPS PharmSci*, and co-sponsored 3 symposia during the AAPS Annual Meetings:

- The Challenges of Veterinary Pharmacology (2000)
- BCS Extensions: Use of In Vitro Dissolution Methods to Support Waiver Requests for BCS Class 1 (Veterinary), and Class 2 And 3 (Veterinary And Human) Compounds (2001)
- Drug Regulation versus Antimicrobial Resistance (2002)

Literature: Recent Trends and Its Role in Veterinary Product Research and Development

The following is intended to serve as an initial listing of scientific publications serving the veterinary community. Readers are encouraged to provide additional suggested references, (along with a brief description of that reference) to Dr. Martinez (MMartin1@cvm.fda.gov) within the United States or Dr. Rathbone (mjr@interag1.co.nz) outside the United States. An updated list will be provided in a subsequent animal health Theme Issue of *AAPS PharmSci*.

Theme Issues of Human Health Publications

A recent and most welcome trend has been the increase in authoritative review articles appearing in professional journals and technical publications. This trend is continuing, with an increasing number of journals providing page space to topics related to veterinary drug delivery. For example, *Advanced Drug Delivery Reviews* continues to support an ever increasing number of Special Issues on veterinary drug delivery. *AAPS PharmSci* has provided an opportunity for Theme Issues devoted specifically to this topic. The *Journal of Controlled Release* has committed a Special Issue to original research publications related to veterinary drug delivery. Several books have also been commissioned and published, adding to the information resources available to formulation scientists.

Advanced Drug Delivery Reviews. *Advanced Drug Delivery Reviews* aims to provide a forum for the critical analysis of advanced drug and gene delivery systems and their applications in human and veterinary medicine. The scope of the journal is broad, covering the key issues for effective drug and gene delivery, from administration to site-specific delivery systems. Each Theme Issue provides a comprehensive yet critical examination of current research and the clinical application of emerging trends in the design and development of advanced drug and gene delivery systems. Articles review state-of-the-art technologies, giving equal emphasis to the identification of major challenges to successful drug and gene delivery, the shortcomings in current conceptual and technical approaches, and a discussion of the possible

solutions to these problems. Over the past 5 years, 5 special Theme Issues of the *Advanced Drug Delivery Reviews* have been published on the topic of veterinary drug delivery. This effort has resulted in a large number of review articles appearing in the scientific literature, covering a diverse range of topics.

Journal of Controlled Release. The *Journal of Controlled Release* is the official journal of the Controlled Release Society and of the Japanese Society of Drug Delivery Systems. The journal deals with the science and technology of the controlled release of active agents. Relevant work dealing with toxicology, pharmacokinetics, and biocompatibility is also included. The journal serves a wide range of specialists and publishes papers on various aspects of controlled release of therapeutic agents for human and animal use. It also includes articles dealing with insect control, post management fertilizers, weed control, and marine antifouling applications. The *Journal of Controlled Release* recently commissioned a Special Issue to be prepared on the topic of veterinary drug delivery. The Special Issue will contain original papers on veterinary drug delivery and will include a section on vaccine delivery.

AAPS PharmSci. *AAPS PharmSci* is an electronic journal dedicated to serve the needs of the pharmaceutical scientist. The audience deals largely with the development and regulation of human health products, although many of the basic science issues are equally pertinent to any target animal species. Published manuscripts are included in Medline, and there is free access to all full-text articles.

Given the state-of-the-art research published within this journal and its access to some of the top scientific talents, *AAPS PharmSci* provides a unique platform for encouraging greater communication between pharmaceutical scientists in animal and human health. For this reason, Theme Issues of *AAPS PharmSci* will be dedicated to important topics in animal pharmacology. The AAPS AHFG and the Regulatory Science Section of AAPS co-sponsor this effort.

Books Examples

The following are examples of recently published books that provide insights into the biological, therapeutic, and pharmaceutical challenges associated with the development and use of veterinary pharmaceutical dosage forms.

- Development and Formulation of Veterinary Dosage Forms (2nd Edition), Hardee GE and JD Baggot JD, eds, New York: Marcel Dekker; 1998.

The second edition of this popular book contains new and updated chapters covering topics such as protein/peptide formulation, specification development, stability assessment, and the evaluation of product bioavailability/bioequivalence of veterinary dosage forms.

- Controlled Release Veterinary Drug Delivery: Biological and Pharmaceutical Considerations, Rathbone MJ, Gurny R, eds, Amsterdam, Netherlands: Elsevier Science BV; 2000.

This book describes both commercially available and emerging veterinary systems for controlled release drug delivery. It highlights the problems facing the formulation scientist and offers solutions to those problems. The book covers the unique opportunities and challenges within the field of controlled release veterinary drug delivery systems. It contains 13 chapters covering the biopharmaceutical, pharmacokinetic, formulation, and regulatory challenges encountered during the veterinary product research and development process.

- Antimicrobial Therapy in Veterinary Medicine (3rd Edition), Prescott JF, Baggot JD, and Walker RD, eds, Ames, IA: Iowa State University Press; 2000.

This publication details the use of antimicrobial therapy in veterinary medicine, describing the basic principles of prudent drug use and the unique issues associated with antimicrobial therapy in veterinary medicine. In addition to chapters on species-specific considerations when prescribing antimicrobial therapy, the book provides detailed overviews of the pharmacology and veterinary uses of the various classes of antimicrobial agents.

CRC Handbooks. The CRC handbooks are probably the only published compilation of a broad range of pharmacokinetic data. They are not a textbook, but rather a compilation of analyses, many of them executed specifically for the books.

- Handbook of Comparative Pharmacokinetics and Residues of Veterinary Antimicrobials, Riviere JE, Craigmill AL, Sundlof SF, eds, Boca Raton, FL: CRC Press, Inc; 1991.
- Handbook of Comparative Pharmacokinetics and Residues of Veterinary Therapeutic Drugs, Craigmill AL, Sundlof SF, Riviere JE, eds, Boca Raton, FL: CRC Press, Inc; 1994.
- Handbook of Comparative Veterinary Pharmacokinetics and Residues of Pesticides and Environmental Contaminants, Sundlof SF, Riviere JE, Craigmill AL, eds, Boca Raton, FL: CRC Press, Inc; 1995.

- Comparative Pharmacokinetics: Principles, Techniques and Applications, Riviere JE, Ames, IA: Iowa State University Press; 1999.

This textbook on pharmacokinetics provides a unique attempt to blend physiology with pharmacokinetics, and it takes a very different slant than other pharmacokinetic texts currently published. It focuses on how pharmacokinetics can be used as a tool to study physiology, providing parameters that can be used as experimental endpoints.

Dedicated Veterinary Science Journals:

The following is intended to serve as an initial listing of scientific publications that are dedicated to veterinary pharmacology and that cover state-of-the-art research efforts pertaining to issues in animal health:

Infectious Diseases

1. *Comparative Immunology, Microbiology and Infectious Diseases*
2. *Fish and Shellfish Immunology*
3. *Veterinary Immunology and Immunopathology*
4. *Veterinary Parasitology*

Basic Science: Veterinary Pharmacology

1. *Research in Veterinary Science*
2. *Journal of Veterinary Pharmacology and Therapeutics*

Comparative Physiology/Therapeutics

1. *Veterinary Clinics of North America*
2. *Compendium of Continuing Education for the Practicing Veterinarian*
3. *Journal of the American Veterinary Association*
4. *Journal of Animal Science*
5. *American Journal of Veterinary Research*
6. *Comparative Biochemistry and Physiology*

Reproduction

1. *Theriogenology*
2. *Veterinary Record*
3. *Journal of Reproduction and Fertility*
4. *Animal Reproduction Science*
5. *Journal of Dairy Science*
6. *Biology of Reproduction*

Ectoparasites

1. *Journal of Economic Entomology*
2. *Journal of Medical Entomology*
3. *Journal of Agricultural Entomology*
4. *Medical Veterinary Entomology*
5. *Veterinary Parasitology*
6. *International Journal of Parasitology*

Infectious Diseases

1. *Avian Diseases*
2. *Avian Pathology*
3. *Veterinary Microbiology*
4. *Vaccine*

Controlled Release Drug Delivery

1. *Journal of Controlled Release*
2. *Pharmaceutical Research*

3. *European Journal of Pharmacy*
4. *International Journal of Pharmaceutics*
5. *Journal of Pharmaceutical Science*
6. *Journal of Microencapsulation*

Examples of Global Networking and its Role in Veterinary Product Research and Development

Food Animal Residue Avoidance Databank¹⁰

The Residue Avoidance Program (RAP) was initially founded by the USDA Food Safety and Inspection Service (FSIS) and focused on reducing the rate of animal residue violations through education rather than enforcement. As part of the RAP, pharmacologists and toxicologists at the University of California, Davis, University of Florida, North Carolina State University, and the University of Illinois developed the Food Animal Residue Avoidance Databank (FARAD).

The FARAD is a computer-based decision support system designed to provide livestock producers, extension specialists, and veterinarians with practical information on how to avoid violative drug, pesticide, and environmental contaminant residues. It provides comprehensive residue avoidance information, and is available both nationwide and internationally.

The FARAD maintains an up-to-date computerized compilation of the following:

- Current label information including withdrawal times on all drugs approved for use in food animals in the United States and on hundreds of products used in Canada, Europe, and Australia
- Official tolerances for drugs and pesticides in tissues, eggs, and milk
- Descriptions and sensitivities of rapid screening tests for detecting residues in tissues, eggs, and milk
- Data on the fate of chemicals in food animals

FARAD Producer's Guide to Residue Avoidance Management (ProGRAM) and the Veterinarian's Guide to Residue Avoidance Management (VetGRAM) are Windows®-based software applications that contain the same information as the FARAD Compendium. The ProGRAM and VetGRAM are searchable, decision-support databases that provide the user with unlimited flexibility in accessing food animal drug information. The FARAD ProGRAM and VetGRAM are available without charge from the Western Regional Access Center at the University of California, Davis. (farad@ucdavis.edu). In addition, the 3 CRC pharmacokinetic handbooks previously described in this article were based upon information contained within the FARAD.

VICH^{11,12}

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for

Human Use (ICH) brings together the regulatory authorities and pharmaceutical industry experts of Europe, Japan, and the United States. These conferences are vehicles for discussing scientific and technical aspects of product registration, for considering recommendations for achieving greater harmonization in the interpretation and application of technical guidelines, and for the harmonization of requirements for product registration. The 6 founding members of the ICH are:

- The European Commission - European Union (EU)
- The European Federation of Pharmaceutical Industries and Associations (EFPIA)
- The Ministry of Health, Labor and Welfare, Japan (MHLW)
- The Japan Pharmaceutical Manufacturers Association (JPMA)
- The US Food and Drug Administration (FDA)
- The Pharmaceutical Research and Manufacturers of America (PhRMA)

Since the ICH was initiated in 1990, there have been observers associated with the process, acting as links with non-ICH countries and regions. The observers to ICH are:

- The WHO
- The European Free Trade Area (EFTA), represented at the ICH by Switzerland
- Canada, represented at the ICH by the Drugs Directorate, Health Canada

In a similar vein, the veterinary ICH (VICH) was created as a trilateral (EU-Japan-United States) program aimed at harmonizing technical requirements for veterinary product registration. The VICH was officially launched in April 1996 ([www. EUDRA.org](http://www.EUDRA.org)).

The objectives of the VICH are:

- To provide a forum for a constructive dialogue between regulatory authorities and the veterinary medicinal products industry on the real and perceived differences in technical requirements for product registration in the EU, Japan, and the United States, with the expectation that such a process may serve as a catalyst for improved international harmonization
- To identify areas where modifications in technical requirements or greater mutual acceptance of research and development procedures could lead to a more economical use of human, animal, and material resources without compromising safety

- To generate recommendations on practical ways to achieve harmonization of technical requirements affecting registration of veterinary products, and to implement these recommendations in the 3 regions. Once adopted, the VICH recommendations are intended to replace corresponding regional requirements. These recommendations focus on the essential scientific requirements needed to address a particular issue
- To be conducted in a transparent and cost-effective manner, the VICH provides an opportunity for public comment on draft recommendation

CONCLUSION With the close interrelationship between humans and animals, many of the health concerns are becoming increasingly similar. This affects not only the safety of drug residues in food and the environment, but also concerns regarding zoonotic pathogens and the selection of drug resistance. In addition, animal models are becoming increasingly important in the development of human medicine. Therefore, when evaluating new pharmaceutical agents and dosage forms, it is important to understand a species' idiosyncrasies in drug absorption and metabolism, as well as its physiological responses to disease. For the animal health scientist, the importance of harmonization is no less important as they are faced with the challenge of applying novel delivery systems and drug substances in the treatment of a host of disease conditions.

The list of information sources, and committees, and activities discussed in this review provide only a small subset of the many valuable resources that are available. Therefore, we welcome input from our colleagues with regard to other information sources that should be mentioned in future veterinary Theme Issues of *AAPS PharmSci*.

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