The Use of Drugs in Food Animals

Benefits and Risks

National Research Council

THE USE OF DRUGS IN FOOD ANIMALS

BENEFITS AND RISKS

Committee on Drug Use in Food Animals
Panel on Animal Health, Food Safety, and Public Health

Board on Agriculture
National Research Council

Food and Nutrition Board
Institute of Medicine

CABI *Publishing*
in association with

NATIONAL ACADEMY PRESS
1999

CABI *Publishing* • A Division of CAB INTERNATIONAL
Wallingford • Oxon OX10 8DE • UK
in association with
National Academy Press · 2101 Constitution Avenue, NW · Washington, D.C. 20418

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

This material is based upon work supported by the U.S. Department of Agriculture, Agricultural Research Service, under Agreement No. 59-0700-1-141, the Department of Health and Human Services, Food and Drug Administration under Agreement No. 1-R13-FDO1495-01, and the Pew Charitable Trusts under Agreement No. 90-02372-000. Partial support was provided by the American Veterinary Medical Association and the American Feed Industry Association. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

About the cover: The background of the cover is an electron micrograph of *Staphylococcus aureus* and its secretion of a polysaccharide that increases the virulence of this microbe. When these bacteria secrete this matrix, they can decrease the ability of immune cells like neutrophils to attack and destroy them. Credit for the picture is given to Dr. Albert Guidry, Dr. William Wergin, and Mr. Eric Erbe, all associated with the U.S. Department of Agriculture, Agricultural Research Service at Beltsville, Maryland.

Library of Congress Catalog Card Number 98-58111

ISBN 0-85199-371-0

This edition has been authorized by the National Academy Press for exclusive sale by CABI Publishing in all territories outside of North and Central America.

CABI *Publishing*
CAB INTERNATIONAL
Wallingford
Oxon OX10 8DE, UK

Tel: +44(0)1491 832111
Fax: +44(0)1491 833508
Email: cabi@cabi.org

Printed in the United States of America.

Committee on Drug Use in Food Animals

JAMES R. COFFMAN, *Chair,* Kansas State University
JOHN AUGSBURG, American Cyanamid Company, Princeton, New Jersey[1]
GEORGE W. BERAN, Iowa State University
HARVEY R. COLTEN, Washington University School of Medicine, St. Louis, Missouri
CONNIE GREIG, Little Acorn Ranch, Estherville, Iowa
JEAN HALLORAN, Consumers Union of U.S. Inc., Yonkers, New York
DERMOT HAYES, Iowa State University
JOHN B. KANEENE, Michigan State University
ALEXANDER MACDONALD, Pharma Science, Inc., North Caldwell, New Jersey[2]
KRISTEN MCNUTT, Consumer Choices, Inc., Winfield, Illinois
DAVID L. MEEKER, Ohio State University
STEPHEN C. NICKERSON, Hill Farm Research Station, Louisiana State University
THOMAS SEAY, Atlanta Cancer Care, Atlanta, Georgia
R. GREGORY STEWART, Bayer Animal Health, Inc., Watkinsville, Georgia

Panel on Animal Health, Food Safety, and Public Health

JOHN A. SHADDUCK, *Chair,* Heska Corp., Ft. Collins, Colorado
KENNETH BERNS, University of Florida
MICHAEL P. DOYLE, University of Georgia
HOLLIS N. ERB, Cornell University
JOHN FERRY, Adams, New York
JERE E. GOYAN, Alteon, Inc. Ramsey, New Jersey
WERNER HEUSCHELE, San Diego Zoo
HELEN H. JENSEN, Iowa State University
FRANKLIN M. LOEW, Medical Foods, Inc., Cambridge, Massachusetts
JOY A. MENCH, University of California, Davis
HARLEY MOON, Iowa State University
WILSON G. POND, Cornell University, Ithaca, New York
R. GREGORY STEWART, Bayer Animal Health, Inc., Watkinsville, Georgia

Staff

MICHAEL J. PHILLIPS, *Program Director*
THEODORE H. ELSASSER, *Project Director*
SHIRLEY THATCHER, *Senior Project Assistant*
JULIEMARIE GOUPIL, *Project Assistant*
MARY I. POOS, *Program Director* (through April 30, 1997)
DEBORAH FAISON, *Senior Project Assistant* (through July 30, 1995)
DENNIS BLACKWELL, *Senior Project Assistant* (after July 30, 1995)

[1]Served through August, 1995
[2]Served through May, 1995

BOARD ON AGRICULTURE

Staff

FOOD AND NUTRITION BOARD

CUTHBERTO GARZA, Cornell University
JOHN W. ERDMAN, University of Illinois
LINDSAY H. ALLEN, University of California
BENJAMIN CABALLERO, Johns Hopkins School of Hygiene and Public Health
FERGUS M. CLYDESDALE, University of Massachusetts
ROBERT J. COUSINS, University of Florida
MICHAEL P. DOYLE, University of Georgia
JOHANNA T. DWYER, New England Medical Center
SCOTT M. GRUNDY, University of Texas Southwestern Medical Center
CHARLES H. HENNEKENS, Harvard Medical School
JANET C. KING, University of California
SANFORD A. MILLER, University of Texas Health Science Center
ROSS L. PRENTICE, Fred Hutchinson Cancer Research Center
A. CATHARINE ROSS, Pennsylvania State University
ROBERT E. SMITH, R.E. Smith Consulting, Inc.
VIRGINIA A. STALLINGS, Children's Hospital of Philadelphia
VERNON R. YOUNG, Massachusetts Institute of Technology

Staff

ALLISON YATES, *Director*
BERNADETTE MARRIOTT, *Project Officer*

The National Academy of Sciences is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Bruce Alberts is president of the National Academy of Sciences.

The National Academy of Engineering was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. William A. Wulf is president of the National Academy of Engineering.

The Institute of Medicine was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Kenneth I. Shine is president of the Institute of Medicine.

The National Research Council was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Bruce Alberts and Dr. William A. Wulf are chairman and vice-chairman, respectively, of the National Research Council.

Preface

The raising of livestock for meat, milk, and eggs has been an integral component of the food production system in this country since its first settlement in the 1600s. The U.S. capacity for food production is tremendous and remarkable, considering that now less than 2 percent of the population is genuinely vested in the raising of food for the rest of the country. Pressures for land development and the vast increase in population have commanded a shift in food-raising practices and the efficiency of food-animal production is testimony to the successful implementation of scientific discoveries in breeding, genetics, nutrition, and animal health on the farm.

Veterinary drugs are a critical component of food-animal production. They provide many benefits related to animal health, animal welfare, and economic return for the industry. Since the benefits of subtherapeutic use of antibiotics in enhancing growth and feed efficiency in animals were first observed almost half a century ago, the number and use of these products has increased. In fact, the discovery of the benefits of subtherapeutic use of antibiotics is often credited with the move toward more intensive animal production management systems, thereby allowing fewer people to produce greater quantities of food.

For decades, the quality, efficiency, value, and safety of food production in the United States has been exceptional; it has served as a model for the rest of the world. However, the U.S. food production system must continuously improve if our country expects to be successful in today's highly competitive global market and if producers hope to deliver animal-derived foods that meet the ever-increasing expectations of the consuming public.

A totally risk-free system of food production is an unreasonable and funda-

mentally unattainable goal. Actual human health risks associated with food-producing animals are most immediately brought into focus in reviewing the number of cases of human illness that occur from food contamination with microorganisms of animal origin. The magnitude of this risk is somewhat difficult to assess. In terms of tracing the origin of an illness directly back to the animal, a complicated intertwining of farm, wholesale–retail, and consumer practices exists that create opportunities for disease to emerge. However, because many aspects of the risk are known and acknowledged, it could be thought of as manageable, because logical courses of action can be applied. The potential risk to human health directly associated with the use of antibiotic drugs in food animal production is a more nebulous issue but still of great concern because of what is not known, what *could* occur, and a general attitude that control and management of the situation need to be improved.

The gains that have been made in food production capacity would not have been possible were it not for the ability of reliable agricultural chemicals to contain the threat of disease to crops and animals. The health of food-producing animals is intrinsically linked to human health. That is to say, factors that affect food-animal health will, in turn, affect human health. The logic is, if you improve the health of our animals, the health of the human population should not be compromised. The use of animal drugs, antibiotics in particular, is considered by some to pose an increased health risk to the people who consume the products from those animals. The use of all drugs (in humans as well as animals) creates both benefits and risks. With proper controls, the benefits should exceed the risks, and "new" risks will replace the "old" risks at a lower level of threat. For example, the risk of suffering from an antibiotic-resistant bacterial infection is considered acceptable when compared with the risk of dying from the bacterial infection left untreated.

Public attention today focuses primarily on the favorable and unfavorable effects of animal drug use on human health. For livestock producers and veterinarians, attention also is focused on the favorable and unfavorable effects of animal drug use on animal health and on the consequences of the inadequate numbers of approved drugs available for use. Antibiotic agents are one class of drugs used extensively in food-animal production therapeutically and subtherapeutically. By far the most important concerns among stakeholders today are microbial resistance to these compounds and residues of these compounds in the food supply. In addition, significant concerns have come to the forefront from manufacturers, producers, and veterinarians that the ever-increasing cost and length of time to approve new drugs have produced a crisis in drug availability. These issues have already generated legislative activity on two occasions, in the Animal Medicinal Drug Use Clarification Act, which was passed in 1994, and in the Animal Drug Availability Act, which was signed into law October 9, 1996. There is reason to believe that, in the near future, these issues will be joined by others, particularly those related to genetic engineering technology.

As a result of these concerns and the conflicting interests surrounding them, the Panel on Animal Health, Food Safety, and Public Health, jointly sponsored by the National Research Council's Board on Agriculture and the Institute of Medicine's Food and Nutrition Board, initiated a project to contemporize the understanding of the issues and relevant information concerning use of drugs in food animals and to establish recommendations regarding a new approach to addressing the problems pertaining to availability and the effective and safe use of drugs in food animals. The Panel on Animal Health, Food Safety, and Public Health convened the Committee on Drug Use in Food Animals to address these issues. Specifically, the committee was charged with examining the benefits and risks associated with drug use in food animal production and to prepare a report with recommendations that:

- review the role of drugs in food-animal production, including accessibility and accountability in their use;
- summarize available knowledge on human health effects of drug use in food animals;
- evaluate the approval and regulatory process and delivery systems for animal drugs; and
- assess emerging trends, technologies, and alternatives to drug use in food animal production.

The committee commissioned background papers to provide an historical perspective on the role of drugs in animal production, a status report of the animal health industry, and an historical perspective on the regulatory approval process for animal drugs. The committee met four times and, on two of these occasions, held open sessions and a workshop to gather detailed information from federal regulatory agency personnel concerning the new drug approval process, procedures for setting residue tolerance levels, and drug residue testing. Representatives of the various livestock, poultry, and aquaculture organizations provided information concerning current husbandry and production practices and quality-assurance programs.

During the evaluation process, it became evident that the existing system that encompasses the total spectrum of drug development, regulation, and use is in part paralyzed by politics and perceptions. The need for a more coordinated, flexible system for tactical decision making and for strategic planning related to policies affecting animal drug use is striking. Issues attendant to drug use in food animals will continue to evolve. Thus, there is a need for a process for evaluating needs and risks in the uses for human and animal drugs that continuously updates the issues and restructures decisions rather than one that periodically resolves crises.

As the committee pursued its work, four primary objectives were identified. The unifying theme among these goals is to offer to policy makers, consumers,

the communications industry, food producers, drug manufacturers, and other audiences our recommendations for needed improvements related to:

- drug resistance monitoring;
- drug residue monitoring;
- drug use and alternative strategies; and
- an integrated, continuous, decision-making process with shared responsibilities of all stakeholders to enhance availability of needed drugs and to move toward global harmonization of this process.

In addressing its charge, through these four areas, the committee developed a line of logic, which guides the elaboration of this report, as follows:

- The residue-monitoring process is critical to the protection of the consumer's health—it must be effective and match the patterns of use for *all* classes of drugs in animal production systems.
- The drug approval process is critical to the availability and accountable use of *all* classes of drugs used in animal production systems, and in the future this will include emerging issues such as genetic design strategies.
- If the drug-residue-monitoring system is effective, then the remaining risk–benefit issue of major proportion is microbial resistance to antibiotics. Based on this line of logic, and because of the urgent nature of this matter, it is treated more extensively than any other topic in this report.

Chapter 1 provides an overview of the use of drugs in food animals and some of the controversy that has existed concerning this practice for the past 30 years. It also sets the stage for examining the perceptions of the risks associated with antibiotic use in food animals and the complexity of the intertwining of food production economics, animal health, industry drug development, and consumer preferences. Chapter 2 provides an overview of current production practices in the major food-animal species and describes the industry-initiated quality-assurance programs in place for cattle (beef and dairy), swine, and poultry producers. Chapter 3 discusses the primary benefits and hazards to human health of the use of drugs in food-animal production. Chapter 4 presents issues related to development of new drugs, the current approval process, and issues related to new developments in the approval process that are attempting to relieve some of the time lag and expense of developing new drugs. Antibiotic approval is the most pressing aspect of this process. Recommendations are offered to focus resources on public health risks. Chapter 5 summarizes the pertinent features of the drug-residue-monitoring program in the United States, explaining that an effective system is the critical assumption upon which all other strategies rest. In recent years significant interest has emerged, as has fear, in the development of antibiotic resistance in human and veterinary health arenas. The importance of this

area of concern cannot be understated, and the specifics of this topic are presented in Chapter 6. The effects of therapeutic and subtherapeutic use of antibiotics on resistance in animals are discussed, as are the mechanisms through which resistance can develop. Finally, new data are presented that underscore much of the controversy in views regarding the approval of new antibiotics for general use in food animals with particular reference to the class of antibiotics called fluoroquinolones targeted to the development of resistance in *Salmonella*. Chapter 7 describes the economic implications of eliminating subtherapeutic drug use in food animals, and Chapter 8 discusses alternative strategies to reduce the need for drug use and highlights promising areas for further research.

Successful food-animal production management systems are continuously changing as advances are made in biomedical and agricultural science. Furthermore, consumer trends shift, and multiple factors alter the priorities and practices of the food production and pharmaceutical industries as well as of public health and health care policy makers.

Capitalizing on opportunities and solving problems pertaining to food-animal production systems now and in the future will be best accomplished through an integrated process that continuously assesses the strengths and weaknesses of the total system, rather than the various components separately, and uses the expertise of all stakeholders. This will be successful only if the various stakeholders define the best long-term solutions instead of short-term wins and losses and have access to information that is relevant, comprehensive, and accurate.

Since the committee began its deliberations, movement has indeed begun in this direction, as indicated by the alliance of food-animal producers, veterinarians, the animal pharmaceutical industry, and the Center for Veterinary Medicine of the Food and Drug Administration to work out a solution to accelerate the approval process for needed new animal drugs.

James R. Coffman, *Chair*
Committee on Drug Use in Food Animals

Acknowledgments

The committee would like to acknowledge the generous support for this study provided by the U.S. Department of Agriculture Agricultural Research Service, the Department of Health and Human Services Food and Drug Administration, and the Pew Charitable Trusts. In addition, the committee appreciates the support provided by the American Veterinary Medical Association and the American Feed Industry Association.

The committee wishes to thank Theodore H. Elsasser and Michael J. Phillips for their dedication and untiring efforts in seeing this project through to completion. In addition, the committee thanks Lester Crawford, Harold Hafs, and John Welser for the preparation of commissioned papers important to the committee's deliberations. Appreciation is also given to Juliemarie Goupil, Shirley Thatcher, Lucyna Kurtyka, Melinda Simons, Charlotte Kirk Baer, Suzanne Patrick, and Anne Kelly for their assistance with the report preparation, and to Mary Poos for her work in the early stages of the project.

This report has been reviewed by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council (NRC) Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the authors and NRC in making the published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The content of the review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their participation in the review of this report: Dale Bauman, Cornell University; Charles Carpenter, Brown

University; H. Russell Cross, IDEXX; John Dowling, Harvard University; Johanna Dwyer, New England Medical Center; D. Mark Hegsted, Southborough, MA; Larry Katzenstein, Bronx, NY; Kirk Klasing, University of California; James Peters, Alpharma, Inc.; Eileen van Ravenswaay, Michigan State University; H.E. Umbarger, West Lafayette, IN; and Judi Weissinger, Weissinger Solutions Inc. While these individuals listed above provided many constructive comments and suggestions, responsibility for the final content of this report rests solely with authoring committee and with NRC.

During the course of the study, committee member R. Gregory Stewart changed employment to became affiliated with a pharmaceutical firm that has a drug approval application pending before the Food and Drug Administration for a fluoroquinolone antibiotic. As a result, Dr. Stewart has excused himself from the committee discussion and deliberations pertaining to this class of antibiotics.

Contents