

July 9, 1995

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DRUGS

AND

THERAPEUTICS

FOR

POULTRY

1995 AAAP SYMPOSIUM - DRUGS AND THERAPEUTICS FOR POULTRY

Sunday, July 9, 1995

First Morning Session Moderator: Dr. Dennis Wages

- 8:00 Introduction of Symposium and Organizing Committee - Dr. Dennis Wages
- 8:05 Welcome - Dr. Oscar Fletcher
- 8:15 Current Activities of the Center for Veterinary Medicine - Dr. Steven Sundlof
- 9:15 The Animal Health Industry and the Center for Veterinary Medicine - Dr. Martin Terry
- 9:45 The Center for Veterinary Medicine: Outside Looking In - Dr. Dick McCapes
- 10:05 Break

Second Morning Session Moderator: Dr. Donna Hill

- 10:20 Antibiotic Use in the Turkey Industry - Dr. Peter Poss
- 10:40 Antibiotic Use in the Laying Hen Industry - Dr. Kenton Kreager
- 11:00 Antibiotic Use in the Broiler Industry - Dr. Tom Holder
- 11:20 Pharmacology of Drug Compounding - Dr. Jim Riviere
- 12:05 Lunch

Afternoon Session Moderator: Dr. Don Waldrip

- 1:30 Antibiotic Susceptibility Patterns - Dr. Doug Waltman
- 2:10 Pharmacokinetics of the Tetracyclines - Dr. TerHune
- 2:30 Pharmacokinetics of the Fluoroquinolones - Dr. John Glisson
- 2:50 Pharmacokinetics of Macrolides and Aminoglycosides - Dr. Gordon Brumbaugh
- 3:10 Pharmacokinetics of the Sulfonamides - Dr. Messersmith
- 3:30 Antibiotic Sensitivity Theory and Interpretation - Dr. Doug Waltman
- 3:50 The Future of Antibiotic Use in Poultry - Dr. Greg Stewart
- 4:30 Adjournment - Dr. Wages

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Dr. Donna Hill
Dr. Birch McMurray
Dr. Nick Primm

Dr. William Swafford
Dr. Greg Stewart
Dr. Don Waldrip

Current Activities of the Center for Veterinary Medicine

Martin K. T. PhD
Stephen F. Sundlof

The Presentation will focus on the current work at CVM which is of most interest to members of the American Association of Avian Pathologists (AAAP).

Congress revised the Federal Food, Drug, and Cosmetic Act in October 1994 and provided two years for finalization of the new regulations. The revision is called the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) and it incorporates the principles of the extra-label drug use compliance policy guide (CPG) which remains in effect during the period in which AMDUCA regulations are being finalized. AMDUCA contains more legislation than the extra-label drug use CPG, for example, it introduces the concept of safe level. The presentation will outline the chief principles of AMDUCA and include comments from a discussion of it at the May meeting of the Veterinary Medicine Advisory Committee meeting.

The CVM has determined that some of the new antimicrobial drugs can only be approved as prescription drugs. This applies to the products that can be administered in the feed as well as other routes of administration. A coalition of professional organizations, including AAAP, industry, and producer representatives have proposed that CVM utilize a procedure called a Veterinary Feed Order (VFO) as the means to permit these drugs to be used in feed. The presentation will include a detailed discussion of the principles and status of the VFO.

The CVM has undertaken a review of all its activities under a strategic planning initiative. There will be discussion of the status of this work and forecasts of next steps.

The formal presentation is expected to take about 40 minutes and to be followed by 20 minutes for questions and answers.

In recent years, industry has seen a slowdown in the animal drug approval process. The poultry industry has experienced first-hand the effects of this slowdown. In the last ten years, only five new chemical entities have been approved for use in poultry -- halofuginone, narasin, ceftiofur, maduramicin and semduramicin. Note that only one of these compounds is approved for therapeutic purposes. At the same time, the poultry industry has seen a number of useful products taken off the market, including the nitroimidazoles, the triple sulfas, the nitrofurans, maduramicin combinations and neomycin. Note that all but one of these extinct product groups were approved for therapeutic purposes. That is, over the past decade there has been a significant loss of valuable therapeutic antimicrobials which have not been replaced by new products.

Thus, the declining number of drug approvals, combined with the increasing number of product withdrawals -- in most cases not due to any human or animal health concerns -- have left

The Animal Health Industry and Center for Veterinary Medicine: The Team Approach

Martin K. Terry, DVM, PhD

The ultimate goals of both the animal health industry and the Food and Drug Administration's Center for Veterinary Medicine are closely aligned. Manufacturers of animal health products, such as vaccines, antibiotics and diagnostics test kits, are primarily concerned with the business of developing medicines to protect the health and well-being of animals. At the same time, they are ever mindful of their responsibility to ensure that the products they manufacture are safe for humans and the environments, as well.

The Center for Veterinary Medicine's (CVM) primary mission is to protect and promote the public health by assuring the safety and effectiveness of animal drugs. Secondly, they are concerned with the health and safety of animals.

This slight difference in focus between the industry and its regulators -- with industry's **primary** interest leaning toward animal health and CVM's primary interest on human health -- can at times result in different approaches between the two groups. When this happens, industry and government strive to work together to arrive at a solution that gives consideration to all relevant sides of the issue.

Examples of this process at work abound, but for purposes of this presentation, I will concentrate on three major projects of interest to the poultry industry. One -- improving the product review and approval process to yield more drug approvals, more quickly. Two -- flexible labeling efforts designed to give producers and veterinarians greater latitude in determining appropriate treatments. And three -- the "veterinary feed order" (VFO) initiative which aims to keep many drugs from prescription-only status while ensuring a higher level of veterinarian involvement in the treatment of animals than currently exists with traditional over-the-counter medications.

Fixing what's broken with the animal drug approval process

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Thus, the declining number of drug approvals, combined with the increasing number of product withdrawals -- in most cases not due to any human or animal health concerns -- have left

gaping holes in the drug armamentarium. There currently exists a number of animal diseases for which there are no approved drugs to provide adequate treatment.

Two factors internal to CVM have impacted the product availability situation. They can be characterized as cultural and statutory. The cultural aspects boils down to the question of how individual employees within the agency view their role in the larger society. A number of CVM employees see their primary role as pharmaceutical police whose job it is to keep "bad drugs" off the market. Clearly, that mindset does not lend itself to approving safe, effective new products. While screening out unsafe products in the NADA evaluation process is certainly an important function of CVM, it should not be the central focus of the agency -- animal health and food safety should be most important.

Others at CVM believe they can best serve society by ensuring that additional safe and effective products are made available to animal agriculture and veterinary medicine -- that the contribution they make by approving safe new products and keeping animals healthy, yields a healthier supply of meat, milk and eggs.

The question becomes, which of these groups will become the dominant force within CVM? Under the new leadership of Dr. Stephen Sundlof, there is hope that the latter will prevail.

But institutional cultural change does not come about overnight. Dr. Sundlof and his staff at CVM need all the support that we -- their constituents -- can give to move things in a positive direction.

The animal health industry, through its trade association the Animal Health Institute (AHI), is working in partnership with its customer groups, as well as with CVM, to remove some of the statutory roadblocks to an improved animal health product review process.

AHI has joined with a number of its principal allies to form the Coalition for Animal Health -- a group effort to push product availability legislation on Capitol Hill. Carefully crafted, the coalition's bill -- the Animal Drug Availability Act of 1995, or S. 773, which was introduced in the Senate in May of this year -- aims to remove some of the extraneous, burdensome, and costly statutory roadblocks dealing with effectiveness testing, exports, minor species and combination drug applications.

The Coalition for Animal Health has shared its legislation and suggestions with officials at the CVM. And while CVM can not endorse this (or any other) legislation, a number of constructive conversations have taken place as a result, and progress is beginning to be realized.

Forums for information and technology exchange aid drug availability

Another crucial piece of product availability puzzle is the exchange of scientific information between industry and government. With cuts in funding for many federal agencies, it has been difficult for government scientists to keep up with innovations in science. Most new scientific discoveries and new scientific methods are developed by industry. A problem arises when existing regulatory policies

fail to keep pace with modern science -- an all too familiar occurrence these days.

Through numerous workshops and seminars sponsored jointly by AHI and CVM, a dialogue has been created to allow a flow of information on pressing topics. During these workshops, industry scientists have been able to share new technologies and scientific methods with CVM reviewers and regulators. Government scientists, in turn, have been able to explain some of the reasoning behind their decisions. This two-way communication greatly helps in shaping policies that are realistic, fair, enforceable and consistent with current good scientific practices.

Industry groups work with CVM on flexible labeling proposal

A recent example of such a workshop was one which reopened the debate on the flexible labeling initiative -- an ongoing attempt by industry, government and veterinarians to agree on the parameters for creating an animal drug product label that would be more useful to practicing veterinarians.

Flexible labeling would allow for the establishment of a **dosage range**, and also for the inclusion of **more information** in a product's labeling -- information which **may** include toxicity, pharmacokinetic data and/or MIC data for various bacteria if appropriate. The idea is that, armed with this added information, veterinarians can better use their professional judgement in prescribing drugs for a flexible range of safe and effective uses. Thus, by facilitating the approval of drugs with multiple doses, species, routes of administration and disease indications, flexible labeling will enhance drug availability. Basically, it's a "win-win" situation for everyone involved.

The birth of the Veterinary Feed Order

A little more than a year ago, the Food and Drug Administration proposed a rule that would have taken new therapeutic drugs out of the hands of feed manufacturers and put them under veterinary prescription. Under the plan envisaged, food animal producers would have been required to obtain a prescription from their veterinarian if they needed a medicated feed containing a prescription-only antibiotic.

This plan posed a number of problems for industry and its customers, placing an undue burden on feed companies and would most likely drive up the cost of the drug and possibly reduce product availability. It also did not give credit to the feed industry's well-established record of properly handling new animal drugs.

A coalition of industry groups, including the AHI, and the American Feed Industry Association teamed up with FDA's CVM to come up with an alternative plan that would take all sides of the situation into consideration. Thus the Veterinary Feed Order (VFO) was born.

In a nutshell, the VFO satisfies CVM's need for the involvement of a veterinarian in diagnosis, drug and dose selection for certain antimicrobials used in medicated feeds, satisfies the need of feed companies to operate within their current structure, and satisfies the need of animal drug

manufacturers to get new animal drugs approved by CVM.

Cooperation may not yield quick results, but it does yield positive results

In talking about a number of joint government/industry/ally initiatives, it may appear that reaching compromise is an easy task. Anyone who has gone through the legislative, regulatory and scientific process knows that isn't true. Real cooperation and compromise take a great deal of effort on the part of everyone involved. What's more, it takes genuine commitment on the part of all parties to generate constructive, positive solutions to tough problems.

At a time when FDA bashing is *de rigueur*, the animal drug industry knows that such behavior is not the solution. We in the animal drug industry have a long history of partnership with FDA. That is something we have nurtured and something we are proud of, and so we have no interest in taking jabs at the FDA just because it's become politically popular.

The Animal Health Institute and its member companies strongly urge all involved in veterinary medicine and the animal production industries to resist the urge to join the "FDA-bashing bandwagon". This is not to say that honest and fair criticism has no place in the drug availability dialectic -- obviously it does. But the primary focus should be to roll our sleeves up and participate in the plain hard work -- much of which takes place in the dust and heat of Washington politics -- to solve the multiple and complex problems involved in mending the drug approval process.

The Center for Veterinary Medicine: Outside Looking In

R. H. McCapes

I. RACING TO RESPOND TO THE PUBLIC'S VIEW OF GOVERNMENT

In the February issue of "The Atlantic Monthly", Peter. F. Drucker pointed out in his article on "Really Reinventing Government" that less than a fifth of American public trust government to do anything right. He also stated the public would vote against continuing two fifths, if not half, of all civilian agencies and programs and almost none of them would win a vote - that is, be deemed to be properly organized and operating well - by a large margin.

On February 12, 1995, the "Sacramento Bee" newspaper, the most liberal California newspaper with which I am familiar, headlined its editorial "Crossing Delaney." It stated the 1958 law, known as the Delaney clause, which sets a "zero risk" standard and tolerates no traces of a carcinogenic pesticide in processed food is unwarranted today because its assumptions are outdated. It spoke of expert findings that traces of certain pesticides in processed foods present no more than a negligible risk of cancer and recommend revision of the law to accommodate this new information. The editorial suggested that if the Environmental Protection Agency cannot lead on the issue, Congress should and chances are good that it will. Furthermore, it stated that Delaney should reflect what is scientifically known about human tolerance of trace amounts of pesticides, not the fears of the past.

On the very same day, February 12, 1995 and 3,000 miles to the east, the "New York Times" ran a story by Philip Hilts which was titled "F.D.A. Becomes Target of Empowered Groups." It stated the Food and Drug Administration (FDA) has become the first and biggest target in the push for deregulation and that conservatives seek to show that the agency is a prime example of what is wrong with federal regulation. Proposals to overhaul the agency vary, but all make a similar point "Delay in approving drugs is harmful, not only to patients, but to America's competitive edge." Reshaping the way government works, rather than making the agency more efficient is the motivation for change. Interestingly, it observed that traditional opponents of FDA, including representatives of the pharmaceutical industry, are uneasy about their new conservative bedfellows and concerned that their solutions could "create chaos" and end up "throwing the baby out with the bath water."

On March 4, 1995, President Clinton directed a memorandum entitled "Regulatory Reinvention Initiative" to heads of departments and agencies and directed them to focus on four steps: 1) Cut obsolete regulations - He ordered a page-by-page review of all agency regulations now in force and to eliminate or revise those that are outdated; 2) Reward results, not red tape - He directed heads to change the way they measure performance so as to focus on results, not process and punishment; 3) Get out of Washington and create grass roots partnerships - Heads were directed to immediately convene groups of front line regulators and the people affected by

their regulations in locations around the U.S.; 4) Negotiate, don't dictate - He stated it was time to move to a process where people work in partnership to issue sensible regulations and directed heads to expand efforts to promote consensual rule making.

On April 6, 1995, Drucker's perception of the public's generally low esteem for government effectiveness was evident during a C-Span televised hearing of the Senate Labor and Human Resources Committee in which FDA Commissioner Donald Kessler announced additional regulatory changes at the agency to speed up the approval of low-risk human medical devices and to allow the export of unapproved human drugs and devices to foreign countries. In response, observed the April 7 edition of the "Wall Street Journal", several senators scolded FDA and urged even more sweeping changes. Senator Nancy Kassabaum, Chair of the Committee, indicated although the changes were common sense and long overdue, more changes were needed. She also asked whether the agency was looking into change in the animal drug approval process. Senator Judd Gregg (R. NH) said he hears frequent complaints from constituencies about a "culture of confrontation rather than cooperation" at the agency. Senator Barbara Mikulski (D. Md) warned Kessler that the agency needs to adopt a "culture of change" and "if you don't change, Congress will run right over you."

It seemed to me, as I watched C-Span, that Commissioner Kessler had hoped the changes he had proposed would be favorably received as evidence of FDA's willingness to accommodate new ideas and to go the extra mile. Instead, the senators seemed to brush these aside as needed change, but peripheral to a more basic concern, and demanded sweeping change in the way FDA does business.

There seems to be an air in the country, as reflected by the President's memorandum, the Senate hearing and the quoted articles that there is at least a four-way race between the Administration, Congress, liberals and conservatives to respond to the public's disdain for our "old" federal government operations. One also senses that each of the four has differing idea or vision for "new government" and what change is needed (Figure 1).

Speaker of the House Newt Gingrich addressed this issue directly in his national television address to the nation on April 8, 1995, by stating that the purpose of government is to improve the life of its citizens. But, he went on to say, something is not quite right today with regard to our federal government, that it is out of touch and in need of deliberate, deep change.

Drucker pointed out that taxpayers, that's all of us here, are becoming more contemptuous of government and its promises and that neither maintaining nor curtailing it in its current state is acceptable. He further observed that as the deficit explodes by 1997, the demand for cutting government may become irresistible, overwhelming congress, the bureaucracy and the lobbyists.

He goes on to state that the Vice President's plan to reinvent government is of little interest as these are the types of things we are all expected to do without fanfare or praise and that patching here, there and yonder never accomplishes anything. Instead, Drucker calls for a

restructuring and rethinking of government, including the concept of continuous improvement and bench marking all processes. This, he says, will require a definition of performance objectives, quality objectives and cost objectives and a definition of the results an agency is supposed to attain. A clear mission is required as well as the agreement that it useful and worth carrying out.

II. CLEAR VIEW OF CENTER FOR VETERINARY MEDICINE OBSCURED BY ISSUES, PERCEPTIONS AND EXPERIENCES

The veterinary profession must be actively involved in any process of deliberate and deep change involving the CVM from the onset. And to do so, we must have a clear vision of what the results of such change should be. To start this process, it is perhaps instructive to examine the mission and function of the CVM today.

For many, a clear view of the CVM's mission and operations is obscured by an opaque cloud of immediate issues, conflicting perceptions and experiences and which belies the agency's actual structure, function and interaction with constituencies (Figure 2). It is, for example, likely that our view of the CVM is influenced by the widespread public disdain about federal government effectiveness in general, as well as by personal experience. How can this not be the case?

In 1995, a critical issue clearly visible in the cloud (Figure 2) is the lack of legal therapeutic options for use in animals. For the individual, it is a time consuming and often baffling exercise to grope through this opaque cloud in an attempt to arrive at a complete understanding why this is so. And yet, the understanding of such issues is the prerequisite for effective involvement and leadership in this accelerating era of change, which will inevitably involve the CVM and, ultimately, the practice of veterinary medicine.

Over the years as a poultry clinician, I have attempted to work my way through the cloud and have come to view the CVM as an agency made up of three basic components: 1) the Federal Food Drug & Cosmetic Act (FFDCA); 2) the FFDCA regulations pertaining to animals and; 3) a structured, mission-oriented bureaucracy. These components, in turn, define and shepherd three activities: 1) new animal drug evaluation; 2) surveillance & compliance and; 3) research (Figure 3).

The CVM, in relation to poultry, interacts, to one degree or another, with at least six primary external constituencies (Congress, Administration, veterinary profession, pharmaceutical industries, poultry industries, consumer groups and public opinion) who, in turn, interact with each other (Figure 3). The din of diverging views emanating from these first and second tier external interactions contributes to the opaqueness of the cloud surrounding the CVM. It is this din of interactions, however, that brings about change to both the components and the activities of the CVM. For this reason, it is important that these interactions be effective as well as appropriate.

III. SOME OF THE REASONS CONTRIBUTING TO A LACK OF LEGAL THERAPEUTIC OPTIONS AND OTHER ISSUES

A. CVM's Mission -

The CVM was renamed in 1984, superseding the Bureau of Veterinary Medicine, and is one of six centers within the FDA, which in turn, is a part of the U.S. Public Health Service. It has a staff of approximately 270 and an annual budget in the neighborhood of \$40 million.

The FDA is a principal consumer protection and regulatory agency charged with enforcing federal laws involving food, drugs, medical devices and cosmetics as set forth in the FFDCA. Within this framework of consumer protection and regulation, the CVM operates with a new mission statement as follows:

CVM Mission Statement - "The CVM is a public health organization that enables the marketing of effective animal drugs, feed additives, feed ingredients, and animal devices that are safe to animals, humans and the environment. We, in partnership with federal and state agencies and other center customers, ensure animal health and the safety of food derived from animals. We make timely, quality decisions and take regulatory actions to ensure that these products provide for quality health care of animals, minimize the transmission of zoonotic diseases, and increase efficiency of production of animal-derived food and fiber. To support our decisions, we perform research, monitor product safety and efficacy, and continually strive to improve the quality of our processes."

It is important for all of us to recognize that the safety aspects of CVM's mission has three objectives, the protection of human health, the environment and animal health. And the mission clearly states that first and foremost, the CVM is a public health organization. This triple-objective safety mission and legislated tilt towards public health adds complexity to consideration of new animal drug proposals and is a factor in the lack of legal therapeutic options. As we consider ways to address this issue, it is important to recognize that the CVM will always first consider any new animal drug approval in light of its potential impact on public health.

As veterinarians, we understand a mission balanced between animal and public health as it is clearly a part of our veterinary oath (see below). On the other hand, many are probably not as focused or conversant on the environmental safety objective. I'm certainly not. And the environmental safety issues may very well be a growing factor in the lack of therapeutic options.

The Veterinary Oath - "Being admitted to the profession of veterinary medicine, I solemnly swear to use my scientific knowledge and skills for the benefit of society through the protection of animal health, the relief of animal suffering, the conservation of livestock resources, the promotion of public health, and the advancement of medical knowledge. I will practice my profession conscientiously, with dignity, and in keeping with the principles of veterinary medical ethics. I accept as a lifelong obligation the continual improvement of my professional knowledge and competence."

B. Federal Food Drug and Cosmetic Act (FFDCA)

The current FFDCA was enacted in 1938 and, for the first time, manufacturers were required to provide evidence of product safety before distributing new drugs. The Durham-Humphrey Amendment of 1951 required the use of physician prescriptions for certain types of drugs and led to the veterinary prescription regulations. The Food Additive Amendments of 1959 expanded authority over animal food additives and drug residues in animal-derived food. The Kefauver-Harris Amendments of 1962 authorized FDA to monitor clinical trials and, for the first time, manufacturers were required to test new drugs for effectiveness as well as safety before they could be cleared for marketing. It also required retroactive efficacy testing for drugs previously tested for safety alone and reporting adverse effects of drugs on the market. In 1968, the FFDCA was amended to include a new "Section 512 - New Animal Drugs" which consolidated and revised the law to ensure that animal drugs were safe and effective for their intended uses and that they do not result in unsafe residues in foods from treated animals. In 1994, the Animal Medicinal Drug Use Clarification Act (PL 103-396) amended the FFDCA to provide veterinarians the ability to utilize, under certain conditions, drug treatment regimes for which no approved drug label exists (extra-label use).

The 1938 FFDCA and the 1951, 1959 and 1962 amendments placed increasing restrictions on the approval of drugs to be marketed. Of particular interest to us today is the 1962 legislation which required prospective and retrospective efficacy testing for new drug approval and provided for monitoring of clinical field trials. The effects of the retroactive efficacy testing requirement of 1962 is being felt in 1995 by the removal from market of drugs, such as penicillin and streptomycin or dihydrostreptomycin combinations in 1993. In the case of these drugs, my understanding is that the manufacturers voluntarily chose to withdraw these drugs from the market and not to submit the necessary retroactive efficacy information.

The 1962 requirement for prospective efficacy testing as part of the New Animal Drug Approval process, and in particular, the requirement for clinical field trials is a major issue of debate in 1995 in relation to lack of legal therapeutic options. Legislation is being proposed to eliminate clinical field trials as a required part of efficacy testing.

The 1968 amendment to the FFDCA ushered in the issue of extra-label use of animal drugs by making it illegal for anyone, including veterinarians, to utilize new animal drugs for any use other than explicitly permitted on the label. The 1994 Animal Medicinal Drug Use Clarification Act amendment was passed to repeal the 1968 extra-label use restrictions on veterinarians and to allow such use.

The 1994 Animal Medicinal Drug Use Clarification Act is a landmark amendment of the FFDCA as it is a roll-back of a previous law, not unlike the call for a roll-back of outdated law by the "Sacramento Bee" regarding the Delaney clause. Prior to 1994, amendments to the FFDCA, in relation to animals, had generally been to add additional restriction, requirements and regulations. The 1994 legislation is a shift to repeal prior restriction on the use of animal drugs is quite extraordinary and perhaps the beginning of a trend.

C. Interaction with and among constituencies-

As pointed out above, constituencies views and understanding of the CVM can be clouded and incomplete (Figure 2) and the two tiered interaction of constituencies with the CVM and among themselves creates a din of often divergent views difficult for any one person to fully comprehend (Figure 3). Both of these situations can result in ignorance of and slower progress toward solutions of issues of common concern, such as lack of legal therapeutic options for animal treatment. The complexity of the interactive system, which inevitably brings change to CVM, dictates that an enormous effort must be expended by the CVM and all its constituencies to develop and maintain effective, appropriate relationships.

Einstein, as I recall, pointed out something to the effect that the appearance of things is relative to the location of the observer. Stretching this metaphor, it is likely that the CVM itself has a "clouded" view of some of its constituencies similar to that seen in Figure 2. How clear CVM views and understands the poultry industries, for example, is quite important in its assessment of needs, priorities, etc.. Likewise, how Congress views the poultry industries and the veterinary profession is similarly important in regard to issues, such as lack of legal therapeutic options for the treatment of animals.

D. Performance of federal agencies in general

In 1991, Congress held hearings on legislation that would require all federal agencies to develop standards and goals and to measure and report progress towards them. In response, the General Accounting Office issued a 1992 report entitled "Program Performance Measure: Federal Agency Collection and Use of Performance Data, 1992" which was a survey of 103 federal agencies to determine to what extent they had developed performance standards and goals and had created at least some measure of progress towards these goals.

The report stated that traditional management practices involve creation of long term strategic plans and regular assessments of progress towards stated goals. Strategic planning is an effort to establish long term goals and objectives that will shape and guide activities and programs to fulfill an organizations mission. Performance measures are a key tool to help managers assess progress towards goals or objectives stated in their plans. They are also an important accountability tool to communicate agency progress to Congress and the public. Performance measures include such things as: inputs, outputs, outcomes, efficiency, workload, customer satisfaction, timeliness and service quality.

GAO concluded that although many agencies had a range of program performance measurements, relatively few reported having the organizational characteristics that would make it more likely for them to use their performance measures to assess progress towards the goals in their strategic plans. GAO stated that not only could such a link provide managers information about accountability, efficiency and effectiveness, but also can provide Congress and the public with information on how public resources are being used.

Of interest to me were the findings that although over 50% of the agencies report some measurement of external customer satisfaction, most retain such information for internal use and only 28% report these finding to Congress and only 20% to the Office of Management and Budget. Also of interest was the finding that only 38% of the agencies reported that they asked customer/clients to assist them in developing the agency's performance measurements.

The overall feeling I had as I read this report is that there are likely areas where the CVM can embrace the traditional management practices, cited by GAO, of strategic planning coupled directly to performance measurement and including significant input from their constituencies in both planning and performance measurement. Performance management of this type could be of critical importance to their constituencies and, at the same time, clarify their mission, strategic plan and progress towards its goals and improve essential interactions (Figure 3).

IV. PATHS OF ACTION ADDRESSING LACK OF LEGAL THERAPEUTIC OPTIONS AND OTHER ISSUES

The real and perceived lack of legal therapeutic options for the treatment of animals has, over the years, triggered into motion a cascade of actions, all aimed at relieving the situation. This paper examines nine specific actions recently completed or under consideration and three proposals for action brought forward by the author. This cascade of 12 specific actions are categorized under five Action Paths as follows (Figure 4):

A. Action Path #1 - Agency performance

1. Government Performance Act and Results Act of 1993

Following the 1992 GAO report on program performance measure, Congress enacted the "Government Performance Act and Results Act of 1993" for the purpose of improving the efficiency and effectiveness of federal programs by establishing a system to set goals for program performance and to measure results. In writing this legislation, Congress found that "waste and inefficiency in federal programs undermine the confidence of the American people in the government and reduces the government's ability to address vital public needs." It also stated a purpose of this legislation is to "improve the confidence of the American people in the capability of the government by systematically holding agencies accountable for achieving results;" There is no question that the driving force behind this legislation was anything other than public opinion.

This legislation contains some of the ideas expressed by Drucker and can, I feel, have a significant and positive impact on federal agency job effectiveness by requiring the implementation of performance measurement system. In other words, each agency, and in this context I am thinking of CVM, will identify its mission and specific goals in a strategic plan and then develop a performance plan to measure annual performance in attaining those goals and then will report them ultimately to the Congress. This will be a results oriented management system and will measure outcomes as well as output. At present, congressional policy making, spending

decisions, and oversight are all seriously handicapped by lack of both sufficiently precise program goals and of adequate program performance information. It seems incredible that such a plan has not been in effect. It seems so simple an idea.

The law identifies the following elements as parts of the performance measurement system are: 1) strategic plan; 2) performance plan; 3) performance reports; 4) management flexibility waivers and; 5) performance budgeting. These elements will be phased into operation over a period of several years. All agencies are required to submit a five year strategic plan and an annual performance plan to the Office of Management and Budget (OMB) on or before September, 1997. In January, 1998 OMB will submit to Congress performance plans with the FY 99 budget. In March, 2000 each agency will submit a performance report for FY 1999 and annually thereafter. Pilot projects will be completed for performance plans, managerial flexibility and performance budgeting. The implementation of performance budgeting will require additional legislation.

Of interest is the specific statement that while developing a strategic plan, the agency should solicit and consider views of interested members of the public in the process of preparing the plan. The strategic plan will be a public document. The veterinary profession, indeed all CVM constituencies, should take as active a role as possible in this performance measurement system in relationship to the CVM as a part of FDA. This will be an opportunity to improve the effectiveness and clarity of interaction with CVM, to play a useful public service role in assisting improvement of performance of government and, ultimately, improvement in animal and public health and the practice of veterinary medicine.

2. End-user involvement in New Animal Drug Approval Process: A Proposal

The new animal drug approval process involves, as has been pointed out by others, a bipolar working relationship between the drug manufacturer and the CVM in relation to the evaluation of the product. The added participation of the end user of the proposed drug, the turkey industry for example, in the new animal drug approval process from start to finish would, I feel, bring useful insight and additional resources to the drug's evaluation.

Drucker might categorize this proposal as "paste here, there and yonder," but implementation of this proposal could assist, in the short run, the timeliness of the new animal drug approval process and in the awareness of both CVM and the manufacturer to special needs of the drug-users and opportunities to serve those needs. In the case of the turkey, broiler and commercial egg industries, these end-users have the practical and technical capacity to effectively represent and participate in this type of scientific issue.

B. Action Path #2 - Legislation

1. Animal Medicinal Drug Use Clarification Act of 1994 (PL 103-396)

The Animal Medicinal Drug Use Clarification Act of 1994, became law in October, 1993 and amends the FFDCA by amending several sections of the Act, including the addition of two

new paragraphs (4) and (5) to Section 512. The legislation was sponsored by the American Veterinary Medical Association and widely supported by agribusiness and producer organizations.

Paragraph (4) states that, except as limited by the Secretary for public health and other defined considerations, an approved new animal drug shall not be deemed unsafe in terms of misbranding with respect to a different use or intended use in animals, other than use on or in animal feed, if such use: 1) is on or by the lawful order of a licensed veterinarian within a valid veterinary/client/patient relationship as defined by the Secretary; and 2) is in compliance with FDA regulations defining the conditions of such use.

Thus, veterinarians would be permitted extra-label use of approved new animal drugs in food and non-food animals, except in or on animal feeds, in accordance to FDA regulations to be written after passage of the bills and subject to certain findings of the Secretary. Access to veterinarians' medical records is provided to the Secretary under certain conditions where public health is deemed to be at risk.

Paragraph (5) states that an approved human drug shall not be deemed unsafe in terms of misbranding with respect to use or intended use in animals if such use: 1) is on or by the lawful order of a licensed veterinarian within a valid veterinary/client/patient relationship as defined by the Secretary; and 2) is in compliance with FDA regulations defining the conditions of such use.

Strangely, this new paragraph (5) does not contain language prohibiting use of approved human drugs in or on animal feed, nor does it contain language providing the Secretary the ability to limit use of approved human drugs in animals subject to public health and other considerations. In other words, the new law seems to put more restrictions on the extra-label use of approved new animal drugs in animals than it does the use of approved human drugs in animals.

This disparity demonstrates that even with a huge effort to maintain clear and effective interactions between Congress and the various effected constituencies, that glaring discrepancies can make their way into law. This difference in the law between extra-label new animal and human drug use in animals will most likely be addressed by implementing regulations.

The Secretary has two years to promulgate the necessary regulations pertaining to this new law and the conditions of the extra-label use of both approved new animal and human drugs in animals.

2. Animal Drug Availability Act of 1995

The Animal Health Institute (AHI) and the National Turkey Federation are proposing similar, but not identical, legislation named the "Animal Drug Availability Act of 1995" for consideration by Congress. The proponents state this bill would amend the FFDCA to provide for improvements in the process of approving and using animal drugs and for other purposes. The primary purpose of this bill, in my interpretation, is the pharmaceutical industries desire to eliminate the need for field investigation as a required part of the new animal drug approval

process as is now the case.

The AHI proposed legislation finds that: the drug approval process is too slow; useful drugs are being kept from the market; the health and well being of animals are at risk; the expense and delay of effectiveness testing outweigh the benefits of such testing; over-reliance on field investigations is the primary problem; that it is a benefit to public health and safety to have as many animal drugs as economically feasible reviewed and approved by the FDA; and economic and regulatory incentives are necessary to convey unlabeled use to approved, labeled uses.

The bill is composed of several sections dealing with change of the Act. The following is a discussion of some of them contained in the AHI version:

a. Evidence of effectiveness - Original applications - This section amends Section 512 (d)(3) and completely redefines the term "substantial evidence" in relation to efficacy testing of proposed new animal drugs. Perhaps most significantly, this redefinition eliminates the current requirement for "well-controlled ... field investigation." It does provide that the Secretary can require field investigation under certain conditions. The redefinition also provides for recognition of "any studies voluntarily undertaken by or for the applicant," which would seem to open the door, for example, for other interested parties to participate in the new drug approval process of a particular product.

Supplemental Applications - This would delete the requirement for "new clinical studies or field investigations ..." in relation to supplemental applications for an approved new animal drug and substitute the above new definition of "substantial evidence."

Minor Species and Uses - The current Act does not address minor species or minor use. The proposed change states that lack of "substantial evidence" would not be a reason to disapprove a previously approved product for a subsequent proposed claim for use in a minor species or for a minor use.

Combination Drugs - The current Act does not address combination drugs. This section addresses situations where a drug contains more than one active ingredient or its labeling prescribes, recommends or suggests its use in combination. In such cases, the Secretary would consider when evaluating safety and efficacy the following:

- Whether the combination alters the safety of any of the active ingredients or drugs or interferes with methods of their analysis.
- Whether each of the active ingredients or drugs in the combination claiming the same effect actually contribute to that effect or whether a particular drug in the combination, not claiming the same effect, represents appropriate concurrent therapy for a targeted population (microorganisms, etc.).

Implementation - This legislation directs the Secretary to take into account several items during deliberation in the implementation of the Act within 24 months. These include the

encouragement of submission of applications, flexible labeling and consensus with industry on appropriate evidence for efficacy of combination drugs.

b. Dispute Resolution - This legislation adds a new process of dispute resolution between an applicant and FDA in addition to the hearing process in the current law. Under the proposed legislation, the applicant can declare that an "impasse" exists in the review of the application for a specific issue. Whereas the current hearing process comes at the very end of the review process, the impasse declaration can come anytime before that. The impasse declaration sets into motion a third party review involving either an existing advisory committee, a special advisory committee or an individual acceptable to the Secretary and the applicant. A report is submitted to the Secretary within 60-90 days and the Secretary, in turn, responds within 30 days.

My first reaction to the impasse declaration is that it will likely slow down the process of approval, rather than speed it up. On the other hand, others have pointed out that the inclusion of outside experts into dispute resolution will provide much needed intellectual competition within CVM.

c. Limitations on Residues - This legislation changes the wording of the Act in regards to residues, by stating that approval will be denied if the recommended or suggested labeling use of a drug will result in residues in excess of the tolerance found by the Secretary to be safe.

The current law can result in denial if tolerance limitation proposed exceeds that reasonably required to accomplish the effect for which the drug is intended, meaning one should not use more of a drug than is necessary to accomplish the intended purpose.

d. Export of New Animal Drugs - Would allow a new animal drug not approved in the U.S. to be manufactured in the U.S. for export to a country where the drug is lawful. The current law generally prohibits this, but FDA has a case by case discretion under certain investigational conditions.

3. Eliminate CVM efficacy testing for new poultry drugs: A Proposal - There is something that bothers me, a poultry clinician, and others about the proposed Animal Drug Availability Act of 1995 sponsored by AHI. On the one hand, the pharmaceutical industry wants to do away with field investigation as a required part of the efficacy testing in the new animal drug process. On the other hand, as a poultry clinician, I'm not going to recommend the use of a new therapy without the knowledge and confidence regarding efficacy that can only be gained through well controlled clinical investigations under field conditions of the proposed use the treatment in question.

Regardless, then, of whether or not the FFDCA requires it, clinical field investigations will be carried out, one way or another, in relation to new drugs proposed for the broiler, turkey and commercial egg industries. If the law is changed as proposed by AHI, these poultry industries are still going to demand clinical field investigations as part of their assessment of a proposed new drug's efficacy.

The elimination of field investigation from the FFDCA as proposed by the AHI initiative, seems to me to fit squarely into Drucker's "patch here, there and yonder" category, with the result enabling the pharmaceutical industries to eliminate clinical field investigations, yet retain the same FDA sanctioned credibility for efficacy as they now enjoy. In other words, get the cake and eat it too.

As an alternative to this "patch here, there and yonder scheme", we should be "rethinking" (as Drucker recommends) the entire issue of government efficacy testing in relation to new poultry drugs and to ask question "Is it necessary for FDA to include efficacy testing for approval of new animal drugs for use in poultry?" In my and others' opinion, the answer is "No." CVM need only to evaluate new poultry drugs for safety to the target animal, the environment and humans, from the point of view of residues in foods of poultry origin. Such a change would, in my and others' opinion, significantly speed up the CVM new drug approval process for poultry drugs. The elimination the efficacy testing requirement for new poultry drugs would require an amendment to the FFDCA.

The pharmaceutical industries in collaboration with the broiler, turkey and commercial egg industries have the management and science-based resources to determine, by themselves, the efficacy of new animal drugs utilized in poultry. Perhaps a third party efficacy testing process, such as the Underwriters Laboratory (UL) for electrical appliances, could be an effective way to go. Restriction of the use of such products to the order of a licensed veterinarian operating within a valid veterinarian/client/patient relationship might also be considered for professional oversight for the first year of sales.

CVM expressed, in a September 1994 letter to National Turkey Federation, that lack of drug effectiveness represents both a human food and target animal safety issue and, therefore, efficacy testing is required for human health as well as animal health reasons. Failure of an anti-infective drug, for example, might result in prolonged suffering in the animal and the spread of pathogens to both animals and humans. If a sponsor of a new animal drug cannot establish effectiveness for an intended use, in CVM's view, there is no rationale for exposing animals or the consuming public to the drug.

My response to this CVM position is that they are operating on too general a level and are viewing all of their animal owning constituencies as a homogeneous lot. This is a very clouded view of their constituencies (Figure 2) and, as a result, I feel the Center is overlooking important differences among the animal owning publics and their capabilities to assess and control drug use in animals. In my and other's opinion, the poultry industries represent an opportunity for CVM to break out of the mold of status quo or traditional mindset and to lead the FDA in rethinking its mission and how to reach its objectives.

The economics of the poultry industries' market place demands the industries avoid use of ineffective drugs because they will not alleviate real problems. If a drug is ineffective, illness is not alleviated, productivity decreases and production costs increase. The poultry industries, and

especially the meat industries, are highly vertically integrated and have the management controls and the science-based capability to determine whether or not a drug is working. The competition between companies and with other competing livestock industries for market share is intense and fractions of cents per pound in production costs influence drug use decisions. There is no economic incentive to incur increased costs in order to utilize ineffective drugs and nor is there an incentive to purposely expose its customers to unsafe drug residues both of which can result in loss of market share. The incentives are all in the opposite direction. The poultry industry is now and will be looking after the best interests of itself and its customers.

For the above reason, in my opinion, eliminating efficacy testing by CVM for poultry industry drugs would not lead to increased illness in animals nor associated increased risk to human health from residues or spread of pathogens. Quite the contrary, the resulting speed up of new poultry drug approvals would decrease illness and reduce the risk to human health. It should also be pointed out that extra-label use of human drugs in animals by definition is the use of drugs in which no efficacy testing has been accomplished and, which according to the Animal Medicinal Drug Use Clarification Act of 1994, is now permitted by law.

C. Action Path #3 - Rethink existing FFDCA law

1. Professional/Flexible labeling - CVM is considering guidelines on flexible, prescription labeling of anti-microbials which would enable veterinarians, operating within a veterinary/client/patient relationship, to select appropriate therapy from an approved dose range within given restrictions. A 1991 AVMA/AHI citizens petition proposed professional/flexible drug labeling for use by veterinarians. In 1993, CVM published the document "Points to Consider: Preliminary considerations for development of a guideline enabling flexible labeling of antimicrobials for therapeutic use" and is now considering responses to that document in relation to developing the above guidelines.

In its Points to Consider document, CVM perceives flexible labeling to be prescription labeling which bears: suggested doses for each claim within an acceptable dose range and; in vitro microbial sensitivity information and pharmacokinetic information about the drug (including information correlating dose and residue depletion) useful to the attending veterinarian.

The proposed "Animal Drug Availability Act of 1995" requests the Secretary to consider the AVMA/AHI petition pertaining to flexible labeling in the implementation of the proposed legislation.

2. Veterinary Feed Order - A March 17, 1995 draft of a concept paper "Coalition to Develop a Veterinary Feed Order" (VFO) Drug Alternative" states that FDA has expressed the need for greater control over certain new therapeutic antimicrobial drugs in the pipeline, such as the fluoroquinolones, when administered in the feed. The development of a VFO would provide a mechanism that can be used by new animal drug sponsors when faced by this need for greater control over a drug. It further states that the VFO is an alternative to prescription status for these

medicated feeds and thus avoids triggering state pharmacy laws and regulations which would be disruptive to the marketplace.

The basic idea of the VFO is to provide control over these drugs in a manner compatible with current feed manufacturing and use practices by enlisting the oversight and professional judgment of licensed veterinarian operating under a valid veterinarian/ client/ patient relationship.

Scenario for use of VFO Drugs - This concept paper calls for the licensed veterinarian, working within a valid veterinary/client/patient relationship to initiate the control procedures required by FDA for use of certain new therapeutic antimicrobial drugs in medicated feed.

After being called in by the producer, the veterinarian determines use of the VFO drug is necessary and issues a pre-printed VFO form provided by the drug manufacturer for Type B or C medicated feed. This form includes instructions for the producer and the producer's feed manufacturer in regard to use and manufacture of the medicated feed, specifics about the location of the farm and animals it is to be used in, the name and addresses of all concerned, the veterinarian's signature and its expiration date. Copies maintained by all concerned.

All drugs used with a VFO are considered Category II drugs. Feed manufacturers have to meet certain requirements depending on their role in the manufacture of the VFO drug and whether Type A, B or C medicated feeds are involved. Inventory stocking of Type A, B or C VFO drugs is allowed under certain restrictions by feed manufacturers. Type B and C VFO medicated feeds can be inventoried by producers under certain restrictions. Type B and C VFO medicated feeds cannot be fed to animals without a VFO.

D. Action Path #4 - Regulatory discretion

1. Compliance policy guides - The Compliance Policy Guide is CVM's primary action path to identify and verbalize its policies and priorities for enforcement of the various sections of the FFDCA. That is, the identification of those infractions of the law that are considered most serious and should result in enforcement action and those infractions which, under normal circumstances, will not be subject to regulatory enforcement. This is accomplished by issuing Compliance Policy Guides (CPGs) which, in turn, guide the field enforcement arm of FDA on where to focus its attention and resources for attaining compliance with the most important aspects of the law. The CPG also serves to instruct the public, such as users of new animal drugs, for example, on CVM's enforcement priorities.

In terms of enforcement priorities pertaining to Section 512's current prohibition of extra-label use of new animal and human drugs and related issues (until implementation of the Animal Medicinal Drug Use Clarification Act of 1994), CVM has issued CPG #7125.06 - Extra-label use of new animal drugs in food-producing animals (7/20/92); CPG #7125.35 - Human-labeled drugs distributed and used in animal medicine (7/20/92); CPG #7125.37 - Proper drug use and residue avoidance by non-veterinarians (7/9/93). It is also developing a compliance policy guide for

veterinary pharmaceutical compounding.

During the two year period, beginning in October 1993, CVM will develop regulations for implementation of the Animal Medicinal Drug Use Clarification Act of 1994. As part of this regulation development, CVM will consider the above compliance policy guides and will likely, I would think, include much of their content in the new regulations and/or refer to them in the new regulations. This is particularly true of CPGs #7125.06 and #7125.37 and the CPG being developed for veterinary pharmaceutical compounding.

Special mention should be made of "CPG 7125.37 - Proper drug use and residue avoidance by non-veterinarians" as, among other things, it sets down CVM's findings that live food animals are considered to be unprocessed food, just as unroasted coffee beans are and, for that reason, the live food animal is subject to all the provisions of the FFDCA pertaining to unprocessed food. This has far reaching ramifications as the presence of certain residues and microorganisms in unprocessed food (live food animals) can result in that food (live food animal) being considered adulterated. Also, CVM considers the lack of drug-use controls and records on the farm to fit within the meaning of "unsanitary conditions", and thus a potential reason for declaring the food (live food animals) to be adulterated under Section 402 (a) (4) of the Act.

E. Action Path #5 - Professionalism

1. Professional Standards for Proper Drug Use by Veterinarians: A Proposal

Background - The Animal Medicinal Drug Use Clarification Act of 1994, the professional/flexible labeling proposal, the Veterinary Feed Order proposal, and the five compliance policy guides, including the proposed compliance guide on veterinary pharmaceutical compounding have three themes in common as follows:

a) Food safety - All place their highest priority on preventing illegal drug residues in raw foods of animal origin.

b) Professional judgment and responsibility - All delegate to the licensed veterinarian, through enforcement discretion or legislation, the ability and responsibility for the use of certain new animal or human drugs in an extra-label or controlled manner in specified circumstances and ways in animals.

c) Societal controls for safe drug use - All identify and require a valid veterinarian/client/patient relationship between producer and veterinary practitioner and specified drug use record systems as the primary societal control measures to ensure safe drug use in animals.

These common themes and cascading actions are placing more and more responsibility on the veterinary profession to assure society that not only is animal well being be cared for by sound drug use in animals, but that human health and the environment are also being safeguarded at the same time. It occurs to me that, as a profession, we are not fully prepared to accept this responsibility or to demonstrate to society, over time, that we are up to human health and environmental responsibilities as well as the animal health responsibility. Others have expressed

similar views.

Professional Standards for Proper Drug Use by Veterinarians: A Proposal - I believe the veterinary medical profession must demonstrate to itself, FDA, Congress and the public that it can effectively carry out the societal responsibilities delegated to it by law and regulation for control of the use of drugs in animals. The profession must clearly assure society that effective prevention of illegal drug residues in foods of animal origin and the controlled use of drug therapy in food and non-food animals are compatible goals and that oversight by the veterinary profession can assure this compatibility.

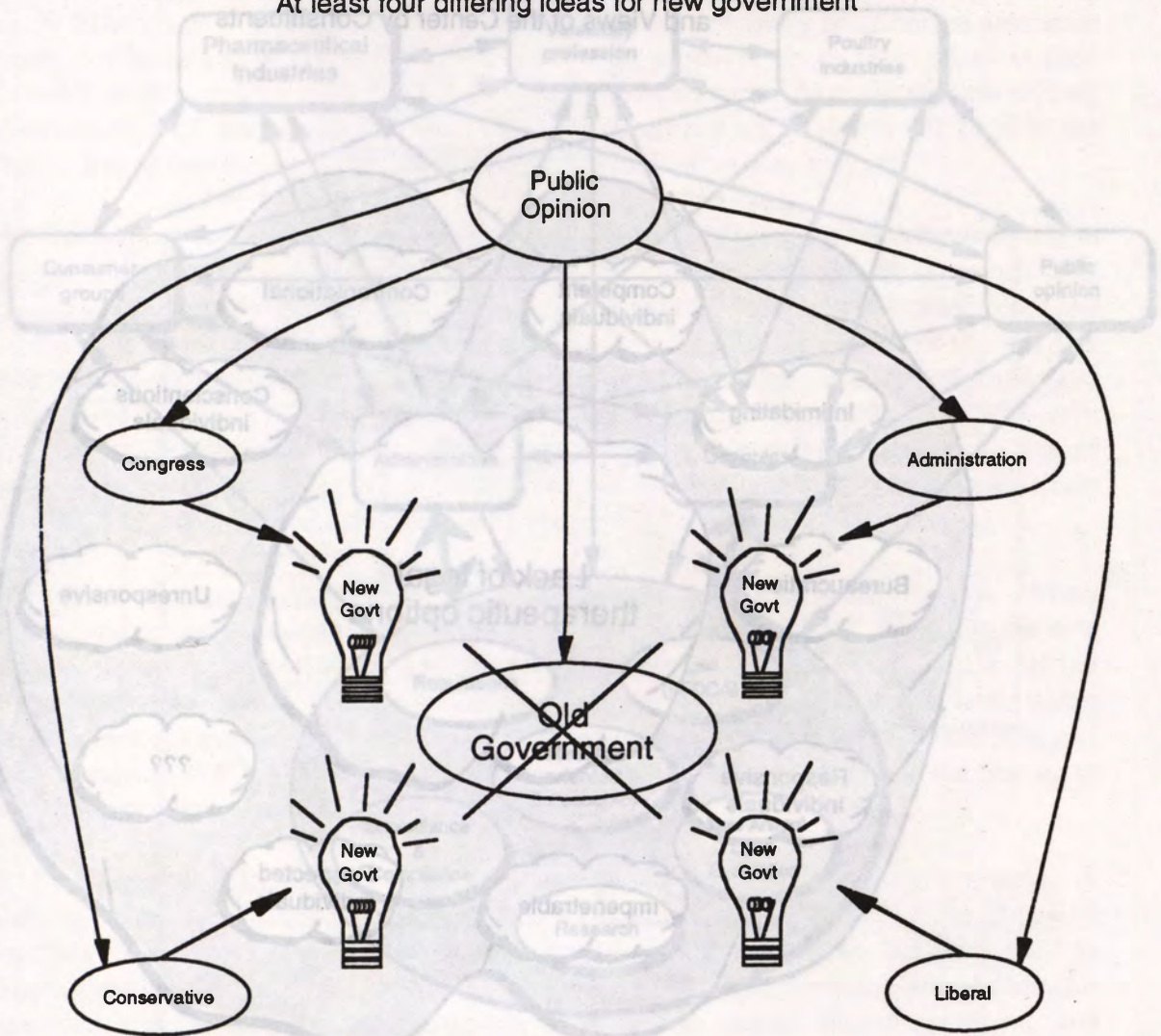
Providing assurance to society can be best accomplished by initiating a fifth action path to establish and recognize professional standards for proper drug use by veterinarians. Such a program would be a profession-wide quality assurance or accreditation program spelling out standards of practice pertaining to use of drugs in food and non-food animals by veterinarians. I feel the veterinary profession itself should implement and administer such a program, perhaps through the American Veterinary Medical Association, the United States Animal Health Association, and/or state veterinary associations in cooperation with animal owners and regulatory agencies. Others have suggested the state licensing boards as possible vehicles for such a program.

D: Action Path #4 - Regulatory Discretion

(a) Food safety - All place their highest priority on preventing illegal drug residues in raw foods of animal origin. (b) Professional judgment and responsibility - All place the highest priority on the use of drugs in animals. (c) Societal controls for drug use - All recognize and support a valid veterinarian-client-patient relationship between producer and veterinarian, pharmacist and veterinarian, and veterinarian and animal. (d) Compliance policy guides - The Compliance Policy Guide is CVM's primary action path to assure society that the veterinary profession is committed to the highest standards of practice and responsibility. All place the highest priority on the use of drugs in animals. (e) Compliance policy guides - The Compliance Policy Guide is CVM's primary action path to assure society that the veterinary profession is committed to the highest standards of practice and responsibility. All place the highest priority on the use of drugs in animals. 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Figure 3
Center for Veterinary Medicine: Components, Activities
and Interactions With and Among Constituencies

Figure 1
Response To Public Disdain for Old Government:
At least four differing ideas for new government



similar views.

Professional Standards for Proper Drug Use by Veterinarians: A Proposal - I believe the veterinary medical profession must demonstrate to the FDA, Congress and the public that it can effectively carry out its responsibility for the regulation for control of the use of drugs in animals. In addition, the profession must demonstrate that effective prevention of illegal drug residues in foods of animal origin and the controlled use of drug therapy in food and non-food animals are compatible goals and that oversight by the veterinary profession can assure this compatibility.

Figure 2
Center for Veterinary Medicine: Some Issues
and Views of the Center by Constituents

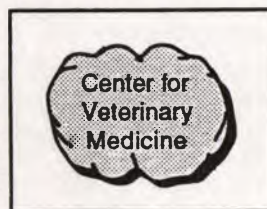
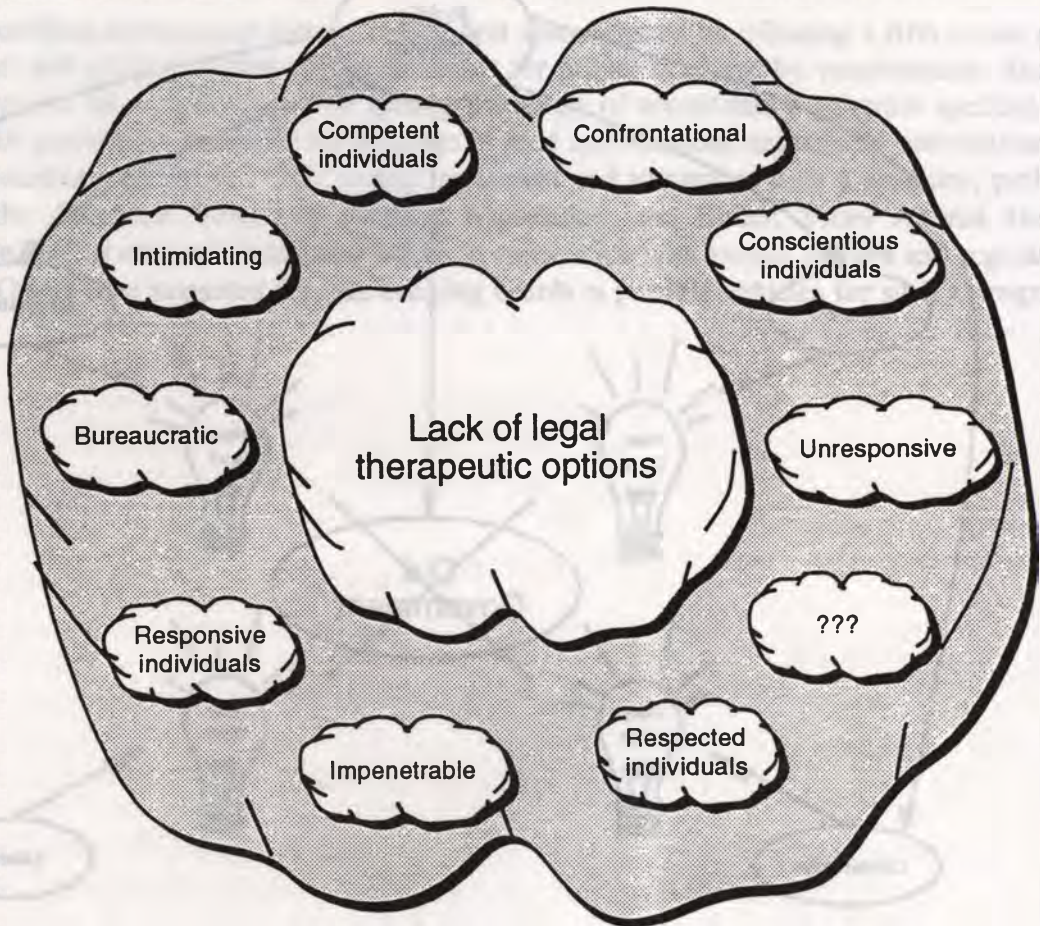


Figure 3
Center for Veterinary Medicine: Components, Activities
and Interactions With and Among Constituencies

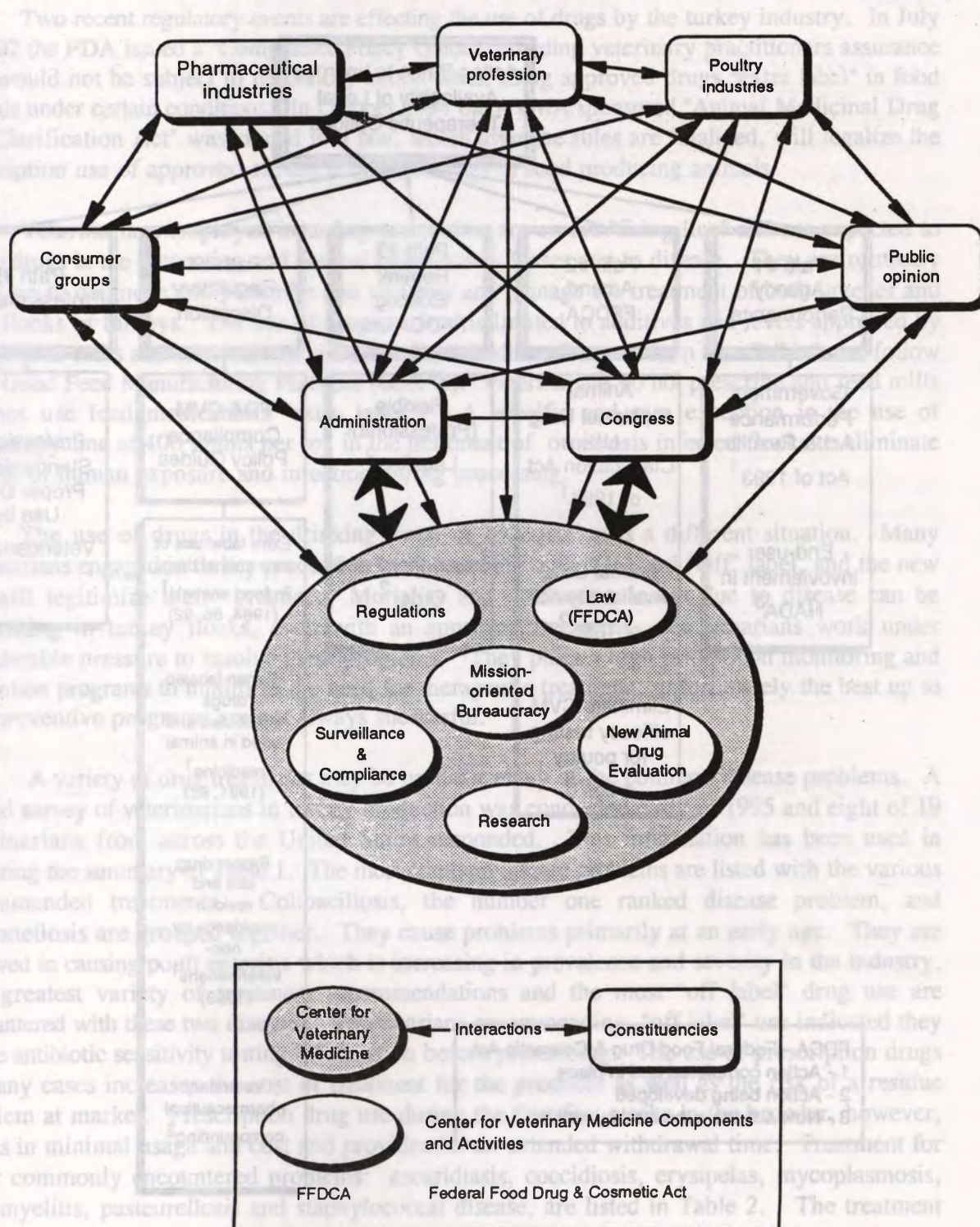
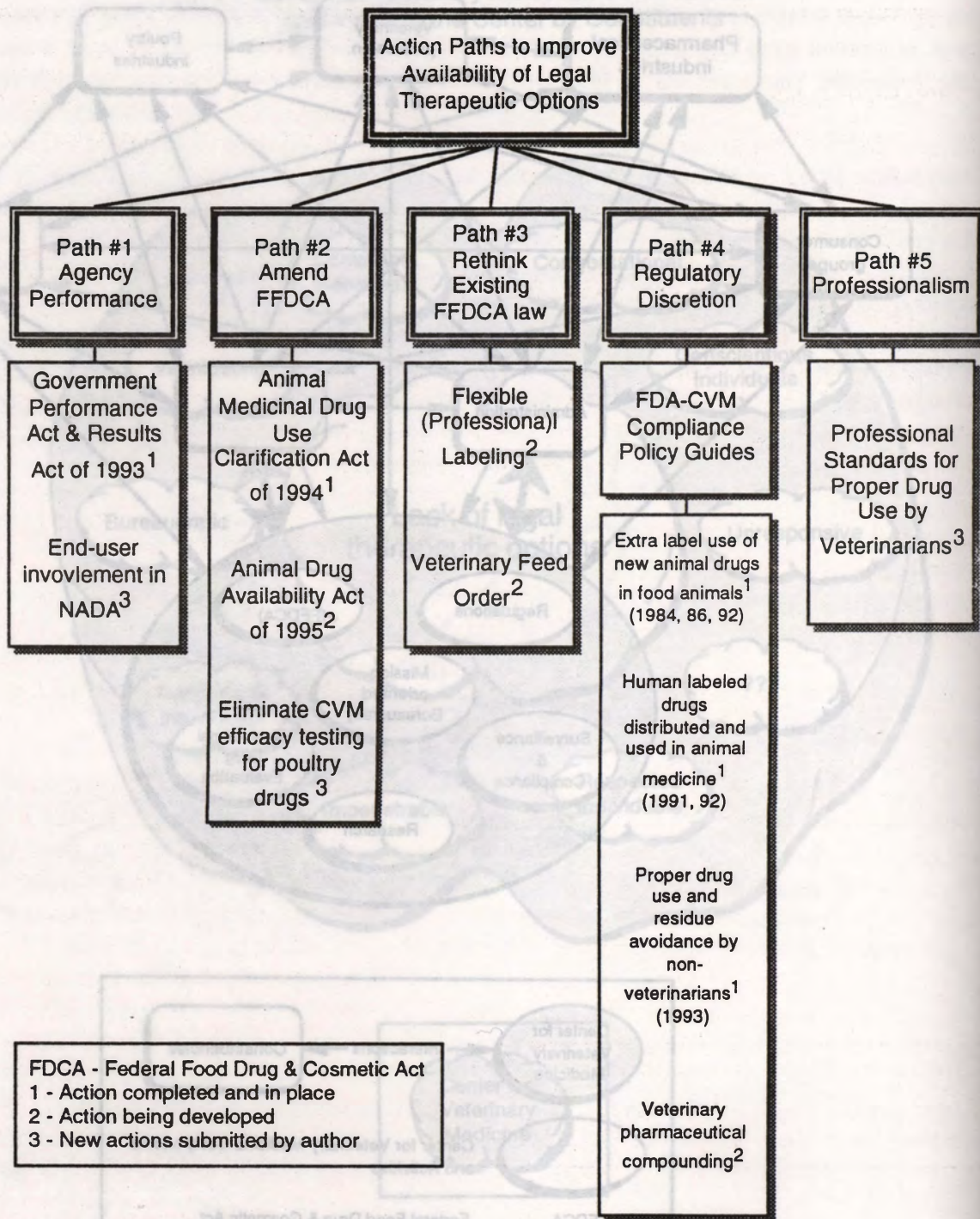


Figure 4
Action Paths to Improve Availability of Legal
Therapeutic Options



Drugs and Therapeutics in the Turkey Industry

Peter E. Poss

Two recent regulatory events are effecting the use of drugs by the turkey industry. In July of 1992 the FDA issued a "Compliance Policy Guide" providing veterinary practitioners assurance they would not be subject to regulatory action when using approved drugs "extra label" in food animals under certain conditions. In October 1994 the AVMA sponsored "Animal Medicinal Drug Use Clarification Act" was signed into law, which after the rules are finalized, will legalize the prescription use of approved animal or human drugs in food producing animals.

Veterinarians employed in turkey production are on the "firing line" and are expected to utilize drugs in the prevention and control of economic losses due to disease. They are routinely called on to diagnose and prescribe and to direct and manage the treatment of both breeder and meat flocks of turkeys. The use of drugs in feed is limited to additives and levels approved by FDA. Feed mills and veterinarians utilize the Feed Additive Compendium as a "bible" and follow FDA Good Feed Manufacturing Practices (GMP'S). Veterinarians do not prescribe and feed mills can not use feed medications "extra label." A specific and rare exception is the use of chlortetracycline at 400 grams per ton in the treatment of ornithosis infected flocks to eliminate the risk of human exposure and infection during processing.

The use of drugs in the drinking water or by injection is a different situation. Many veterinarians engaged in turkey production work prescribe both "On" and "Off" label, and the new law will legitimize their practice. Mortality and production losses due to disease can be devastating in turkey flocks, even with an approved treatment. Veterinarians work under considerable pressure to resolve these problems. They place a high priority on monitoring and prevention programs to minimize the need for therapeutic treatment, unfortunately the best up to date preventive programs are not always successful.

A variety of drug treatments may be used for many of the common disease problems. A limited survey of veterinarians in turkey production was conducted early in 1995 and eight of 19 veterinarians from across the United States responded. This information has been used in preparing the summary in Table 1. The most common disease problems are listed with the various recommended treatments. Colibacillosis, the number one ranked disease problem, and salmonellosis are grouped together. They cause problems primarily at an early age. They are involved in causing poult enteritis which is increasing in prevalence and severity in the industry. The greatest variety of treatment recommendations and the most "off label" drug use are encountered with these two diseases. Veterinarians recommending "off label" use indicated they utilize antibiotic sensitivity testing information before prescribing. The use of prescription drugs in many cases increases the cost of treatment for the producer as well as the risk of a residue problem at market. Prescription drug use during the first few weeks in the brooder, however, results in minimal usage and cost and provides for an extended withdrawal time. Treatment for other commonly encountered problems: ascaridiasis, coccidiosis, erysipelas, mycoplasmosis, osteomyelitis, pasteurellosis and staphylococcal disease, are listed in Table 2. The treatment

recommendations were provided to the author on a confidential basis to be included in this summarized report. The drugs and dosages listed in the tables should not be taken as labeled use or dosage. They reflect differences in company operations and geographical locations and should not be taken as specific recommendations nor with any guarantee as to efficacy or untoward reactions.

Feed medication usage information was not included in the survey. Growth promotant feed additives are widely used to take advantage of the improvement they provide in weight gain and feed efficiency. Coccidiostats are widely used to prevent mortality and morbidity and are rotated by many operators to minimize resistance problems. Feed medication can be cost effective but is not a major therapeutic treatment practice in most operations because of the difficulty in establishing timely treatment and in controlling withdrawal time.

Drug combinations are generally not utilized except in cases of concurrent coccidiosis and/or crop mycosis with poult enteritis. Adverse reactions are seldom observed or reported since the industry has discontinued the use of nitrofurans. An exception is the "knock down" problem associated with the coccidiostat monensin, which occurs in some operations and in some areas of the country.

Other treatments mentioned in the survey and not reported in the summary include the use of acidified copper sulfate, citric acid, electrolytes, kaolin and pectin, potassium chloride, probiotics, sodium hypochlorite, disinfectants and vitamins.

A large number of economically important health problems are not listed in the report because no treatment is available or treatment is ineffective or too expensive. Examples of these conditions are aspergillosis, BART, blackhead, shaky leg, tibial dyschondroplasia, poult growth depression (PGD), and a host of viral diseases and the secondary problems they cause (avian influenza, Blue Comb, rotavirus and other enteric viruses, Viral Hepatitis, etc.).

The onerous and costly procedure for new drug approval has all but stopped the availability of new drugs for the turkey industry. The National Turkey Federation is currently working on FDA to streamline the process both by citizen petition and legislative effort. FDA should not be concerned with efficacy since a drug sponsor will not expend the resources to clear a useless compound and the industry will know if it works very quickly, once it is on the market.

Note: I would like to thank the veterinarians who participated and provided information for this report.

COLIBACILLOSIS and SALMONELLOSIS

Generic Name	Brand Name *	Sponsor *	Age Range	Route of Admin.	Dose Range	Treat Period	Withdrawal Time
ampicillin	-	-	0-4 wk	water	0.25-0.5 gm/gal.	3-5 day	> 8 wk
apramycin	Apralan	SmithKline	1-4 wk	water	0.375 gm/gal	5-7 day	> 8 wk
ceftioflur	Naxel	Upjohn	1 day	SQ.	0.5-0.8 mg/poult	one dose	> 12 wk
gentamicin	Garasol	Schering-Plough	1 day	SQ.	1-2 mg/poult	one dose	NA
lincomycin	Lincomix	Upjohn	1-6 wk	water	.25 gm/gal	3-7 day	> 6 wk
neomycin	-	-	1-8 wk	water	0.15-0.5 gm/gal	3-6 day	14 day
3 nitro-phenylarsonic acid	3-Nitro	CEVA	2-12 wk	water	28.4 gm/256 gal	2-3 day	5 day
spectinomycin	Spectam	CEVA	1 day	SQ.	5-10 mg/poult	1 day	NA
sulfachlorpyridiazine	Vetsulid	Solvay	1-4 wk	water	20-25 mg/Lb.	2-5 day	> 8 wk
sulfadiazine + trimethoprim	Tribressen	Coopers	1-4 wk	water	10 mg/Lb. SDZ	3-7 day	> 8 wk
sulfadimethoxine	Albon	Roche	1-12 wk	water	32 oz/128 gal	3-6 day	5 day
sulfaethoxypyridizine	S.E.Z. 6.25%	Cyanamid	1-4 wk	water	1 oz/ gal	3-6 day	> 8 wk
sulfamethazine	Sulmet	Cyanamid	1-12 wk	water	1 oz/gal	2-6 day	10 day
sulfaquinoxaline	-	-	1-12 wk	water	20 oz/128 gal	3-4 day	10 day
tetracyclines**	-	-	0-12 wk	water	0.4 gm/gal. to 25 mg/Lb.	7-14 day	5 day

* Many drugs have multiple sponsorship/brand name. Specific examples are not meant to be exclusionary.

** Tetracyclines includes chlortetracycline, oxytetracycline and tetracycline.

Citric acid is used with oxytetracycline to increase solubility, absorption and effective blood levels

Table 1.

Other Significant Disease Problems

Disease/Generic Drug	Brand Name Examples	Sponsor Examples	Age Range	Route of Admin.	Dose Range	Treat Period	Withdrawal
Ascarids							
levamisol	Levisol	Pitman-Moore	6 wk - ?	water	3.63-5 mg/Lb.	4-6 hour	6 day
piperazine	-	-	6 wk - ?	water	25 oz/50 gal or 30-50 mg base/Lb.	4-6 hour	2-5 day
Coccidiosis							
amprolium 9.6 %	Amprol	Merk	1-6 wk	water	4 - 16 oz./50 gal.	3-5 day	5 day
sulfaquinoxaline 20 %	-	-		water	20 oz./128 gal	3-4 day	10 day
Erysipelas							
erythromycin	Gallimycin	Abbott	8 wk - ?	water	0.25-0.5 gm/gal	3-7 day	7 day
penicillin potassium	-	-	8 wk - ?	water	1-1.5 gm/gal	3-7 day	5 day
Mycoplasmosis							
gentamicin	Garasol	Schering-Plough		egg dip	500-1,000 PPM		NA
tylosin	Tylan	Elanco		egg dip	1,000-2,000 PPM		NA
tetracyclines	-	-	6 wk - ?	water	1 gm/ gal to 25 mg/Lb.	7-14 day	5 day
Osteomyelitis							
penicillin potassium	-	-		water	1-1.5 gm/gal	3-7 day	5 day
tetracyclines	-	-		water	25 gm/Lb.	7-14 day	5 day
Pasteurellosis							
penicillin G procaine	-	-	4 wk - ?	SQ.	8-12,000 IU/Lb.	1-3 day	10 day
tetracyclines	-	-	4 wk - ?	water	1 gm/gal - 25 mg/Lb.	7-14 day	5 day
sulfadimethoxine	Albon	Roche		water			
sulfaquinoxaline 20 %	-	-		water	20 oz/128 gal	3-4 days	10 day
Staphylococcosis							
erythromycin	Gallimycin	Abbott	1 wk - ?	water	0.5 gm/gal	3-7 day	7 day
penicillin potassium	-	-	1 wk - ?	water	0.5-1.5 gm/gal	3-7 day	5 day
tetracyclines	-	-	1 wk - ?	water	0.4 gm/gal to 25 mg/Lb.	7-14 day	5 day

Note: Tetracyclines includes chlortetracycline(CTC), oxytetracycline (OTC) and tetracycline which are similarly dosed. CTC has labeled 24 hour withdrawal.

Table 2.

Antibiotic Use in the Laying Hen Industry

Kenton Kreager

Antibiotics are used in the layer industry for a variety of purposes. Most often they prevent or treat secondary bacterial infections during viral disease or other stressful periods. Less commonly they are used to treat primary bacterial diseases. The legal choices of antibiotics approved for pullets and layers are quite limited and for the most part, are not used excessively by the industry.

The antibiotics approved as feed additives for pullets and layers and their respective levels are as follows:

	<u>Pullets (grams/ton)</u>	<u>Layers (grams/ton)</u>
bacitracin Zn, MD	4 - 50	10 - 25
chlortetracycline	10 - 200	10 - 100
erythromycin	185	92.5
neomycin (with oxytetracycline)	35 - 140	35 - 140
novobiocin	200 - 350	none
oxytetracycline	50 - 200	10 - 200
penicillin	2.4 - 100	2.4 - 100
tylosin	4 - 50	20 - 50

In addition, various combinations of these antibiotics with anticoccidials, growth promotants, and de-wormers are allowed as feed additives.

The following information was obtained in a survey of 53 large layer companies in the US, of which 30 responded. This represented approximately 90,000,000 layers, or about 1/3 of the industry. It was designed to determine the conditions being treated with antibiotics in the layer industry, the antibiotics used for each condition, and whether the administration was by feed or water.

In the 30 questionnaires returned, there were 84 uses reported for antibiotics. Of those, 66 (79%) were feed treatments and only 18 (21%) were water treatments. Feed treatment is considered more economical, but sometimes cannot be started as rapidly as desired because of existing feed inventory in the bin. Water treatment is usually reserved for situations needing more immediate treatment or where the feed product is unavailable for some reason.

The following table summarizes the uses of antibiotics as reported by the layer company managers. These are divided into three general areas: primary bacterial diseases, non-specific and/or secondary infections, and stress-related conditions.

Primary Bacterial Diseases

There are relatively few primary bacterial diseases in the US layer industry that require treatment with antibiotics. Those that are present, such as Mycoplasma gallisepticum (MG) and coryza, are often adequately controlled by vaccination. Antibiotics may be used for a short period during the acute stage of the disease, or in the case of complicated infections when they occur with other viral diseases or secondary bacterial infections.

MG was the most common such disease treated with antibiotics. It is still quite common in older multi-age commercial layer complexes. Some recommend treating infected flocks with a low level of antibiotics for their entire life. However, the need may be questionable after the acute stage of the infection when all birds have turned serologically positive. Antibiotics will not eliminate the mycoplasma, but simply reduces the clinical effects during the active infection. A good vaccination program should eliminate the need for any antibiotic treatment and may be a more economical means of control.

Mycoplasma synoviae (MS) is usually not considered a primary pathogen in pullets and layers. However, some strains have been reported to be relatively pathogenic, much like MG. It is often identified as a co-infection along with bronchitis in young layers in a multi-age complex. As such, it can lead to mild respiratory disease and secondary respiratory infections. A bacterin is available for MS, but is usually considered prohibitively expensive. Where MS is considered significant, it is treated with a tetracycline, erythromycin, or tylosin.

Coryza (Hemophilus paragallinarum) is endemic in only a few states. Like MG, it is often controlled primarily by vaccination. However, co-infections with MG or viral agents more likely lead to complications that require antibiotic treatment. The few respondents who reported treating coryza all used oxytetracycline.

Although salmonella, especially S. enteritidis (SE), is a large concern in the layer industry, only one reported using an antibiotic specifically for that purpose. If this is an accurate reflection of the industry, it is reassuring to see that antibiotics are not being viewed as a cure for SE. Most professionals probably agree that antibiotics should play little or no role in salmonella control.

Non-specific and/or Secondary Infections

Although pure primary bacterial diseases are relatively uncommon in layers, secondary-type infections are frequently encountered for a variety of reasons. These often result from a combination of primary viral diseases, mycoplasma infection, and environmental stresses, such as dust and ammonia. The result is often a mixed infection of E. coli and other coliform bacteria, causing lesions such as airsacculitis or peritonitis. These were the type of conditions most commonly reported to be treated with antibiotics.

Peritonitis is often identified as a leading cause of mortality in layers. It appears as a yolk-like fluid or more caseated accumulations of yellow material in the abdominal cavity. E. coli is normally isolated, but other coliforms may be as well. The bacterial invasion is generally secondary to either

respiratory tract damage or vent/cloacal trauma. Cases appearing early in production are more often associated with respiratory tract damage from virus (bronchitis or LT), mycoplasma (MG or MS), and environmental stresses (dust and ammonia). More than one of these factors is probably required acting together to cause peritonitis. Cases appearing later in production are more often related to ascending infections from traumatized tissue in the vent area. This may be from cannibalism, partial prolapse, retained eggs, etc. Because the infections associated with peritonitis are secondary, they can be quite difficult to treat with antibiotics unless the inciting causes are also remedied. Oxytetracycline is used most often as it is broad spectrum and relatively economical. Erythromycin is generally the second choice if the first is ineffective.

Enteritis is a diagnosis that seems to be frequently made by company field personnel. It was by far the most frequently reported condition treated with antibiotics in the survey. Much of this may be misinterpretation of intestinal appearance, but nonetheless is treated with antibiotics. A number of antibiotics are used for this purpose, but bacitracin is the most common. Ulcerative enteritis is sometimes seen in floor-grown pullets that have experienced some recent coccidiosis intestinal damage. It does respond well to bacitracin.

Most flocks of newly hatched chicks contain some degree of omphalitis, acquired from eggshell contamination in the hatchery. The incidence depends on environmental conditions in the breeder house, eggshell sanitation practices, and hatching egg handling and storage. Antibiotics, either in the Marek's vaccine diluent or in the first feed or water, are commonly used to counter these infections and do seem to reduce early mortality. Those applied with the Marek's vaccine must be compatible with the live vaccine cells. Garasol (gentamicin) and Naxcel (ceftiofur) are generally felt to be safe and effective for this purpose. A variety of products are used in the feed or water for the first week.

Severe respiratory vaccine reactions should be avoided with proper scheduling and application of vaccinations. However, when they do occur, they frequently result in secondary airsacculitis. Those may be prevented by medicating in anticipation or treated after they occur with either tetracycline or erythromycin.

Stress Treatment

Probably the least justified use of antibiotics is that reported to be administered during "stress". The definition of "stress" probably varies by producer. It apparently includes such things as molting, production drops for unknown reasons, Marek's disease, etc. Some report treating with antibiotics just as a matter of routine. Fortunately, it does not appear there is a lot of misuse of antibiotics in the layer industry. Indeed, seven of the 30 respondents specifically mentioned that they strictly limit their antibiotic usage. I believe most take a very responsible approach to antibiotics.

Economic Considerations

Antibiotics can be easily administered to any flock that demonstrates a disease condition. Health professionals may feel they are not doing their job if they leave a flock without making a treatment recommendation, which could easily include an antibiotic. How often do we consider the

economic benefit to the producer and carefully analyze the cost/benefit ratio of our recommendations? Antibiotics are a significant expense item and the degree of the problem we identify may not always justify an antibiotic treatment.

Oxytetracycline is one of the less expensive feed grade antibiotics at \$4.00/100 g or \$8.00 g/ton of feed treated at the maximum 200 g/t. Layers typically consume 22 lb./100/day, so the treatment cost for a typical 100,000 size flock would be \$616/week. Normal mortality should be 0.10% per week or less. If peritonitis were causing doubled mortality to 0.20% per week, at best we could only expect to save that extra 0.10% per week, or 100 birds. The maximum value of pullets at the start of lay is around \$2/bird, so the very most we could save with treatment would be \$200/week, which is considerably less than the cost of the treatment. As the flock ages, bird value approaches zero, which makes treatment even less rewarding.

Erythromycin is approximately twice as expensive as oxytetracycline. Using similar figures, it would require a mortality rate of 0.72% per week (assuming all the excess could be prevented with the antibiotic) just to justify the cost of treatment. This calculation assumes no continuing of treatment from permanently "knocking-out" the infection, but in the case of the secondary infections like peritonitis, that is seldom the case.

Summary

Antibiotics are used for a variety of conditions in the pullet and layer industry, mostly for complicated secondary-type infections. Most producers voluntarily limit their antibiotic usage for well justified causes. Besides considering the medical rationale, we must also keep the economic justification in mind.

Antibiotic Use in the Broiler Industry

Tom Holder

Antibiotic Uses Reported in Pullets and Layers

	<u>bacitracin</u>		<u>chlortetracycline</u>		<u>erythromycin</u>		<u>neomycin/oxytet</u>		<u>oxytetracycline</u>		<u>penicillin</u>		<u>tylosin</u>	
Primary Bacterial Diseases	F	W	F	W	F	W	F	W	F	W	F	W	F	W
MG					2	1			1				1	
MS			1		1								1	
Coryza									2	1				
Salmonella									1					
Staph											1		1	
Pasteurella					1									
Secondary Infections														
Peritonitis					1		3		8	1	1			
Airsacculitis					1	2			3	1	1			
Enteritis	7	1	2	1			3	3	2	1	1			
Omphalitis	1		1						1		1			
Vaccine Reaction					1				2					
Stress Conditions														
Molt									1					
Production Drops		1	1				1	3	1					
Marek's			1											
Stresses	1		1						5	1				
Routine									1	1				

1. Cost - twice as expensive as feed medication

2. Inconsistency of administration

a. Equipment - medications

b. Grower - unreliable

c. Water quality - drinker problems

Antibiotic Use in the Broiler Industry

Tom Holder

Antibiotics have been available for use in broilers for many years and have played a major role in the growth of our industry. However, during recent years, antibiotics, especially therapeutic, have not been a major player in most broiler company programs, because the emphasis is on management and preventative disease programs beginning with the breeder hen. The comments in this paper will be limited to meat type birds only (cornish, broiler and roaster) and not breeders.

Antibiotic usage will be discussed by categories.

I. Therapeutic

A. Feed (seldom used because)

1. Timing in a feeding program is critical
2. Mixing of feeds in the bin lowers efficacy
3. Most diseases are viral precipitated
4. Nipple drinkers - less bird to bird transmission of disease
5. Genetics - much of the mortality is physiologically caused rather disease related
6. Lack of response to available antibiotics
7. Lack of combination clearances
8. Removal of drugs from the market
9. Impaired immune system
10. Withdrawal times
11. Cost benefit
 - a. To medicate a 4 week old broiler for 6 days with a therapeutic level of an antibiotic will cost \$11 per thousand birds
 - b. To break even, an improvement of 3 points of feed conversion, 15 points of body weight or 3% mortality or any combination of the above must be realized
 - c. To therapeutically medicate all broilers in the United States from November thru March would cost \$32 million or 2.2 cents per pound

B. Water - seldom used because:

1. Cost - twice as expensive as feed medication
2. Inconsistency of administration
 - a. Equipment - medicators
 - b. Grower - unreliable
 - c. Water quality - drinker problems

II. Injectables - used frequently

- A. Used in day old chicks or 18 day old embryos
- B. Prevent low grade bacterial infections from hatchery and breeder flock to chick
- C. Interference with Marek's vaccination
- D. Cost effective
- E. Healthy chick - healthy end product

III. Sub-therapeutics - growth promotants - commonly used

- A. Improved efficiency-growth, feed conversion or combination of both
- B. Combination available - with coccidiostats
- C. Time of year
- D. Intestinal integrity
- E. Cost

Another area that needs discussion is the lack of understanding between the broiler industry, drug industry and the Center for Veterinary Medicine (CVM). We, as an industry, have not been aggressive in communicating to either of the other parties, our problems and what is needed to solve them. Likewise, the drug companies have not sought advice from the industry in setting priorities for clearances. We have been at the mercy of the drug companies to use what is developed. Too many "me to" products. And lastly, the CVM's slow response to drug applications rather than responding in a timely manner as the law requires.

Since Dr. Stephen Sundlof has been director of CVM, this attitude is slowly being replaced with one of cooperation and helpfulness. The one area that needs rethinking is that of efficacy. A few hundred or thousand birds in test pens under ideal conditions can not determine the efficacy of a drug or combination of a coccidiostat and drug. Be practical in efficacy testing. A drug company is not going to spend several million dollars on a drug what will fail after 6 months of use. The industry will determine the efficacy and/or the feeding program best suited for a product.

Antibiotics are an essential part of a broiler growing program. The drug companies and CVM are encouraged to work together and with broiler industry to meet our present and future needs. Regular dialogue between the three groups is needed for progress to continue with drug clearances.

PHARMACOLOGY OF DRUG COMPOUNDING IN POULTRY

Jim E. Riviere
Tomas Martin-Jimenez

1. - Introduction

Much too often a common pattern of civilized human thinking regarding almost any issue is "the more, the better". Concerning therapeutics, we may sometimes have the idea that if one antimicrobial drug is good, two should be better, and three should cure almost any pathological condition. While this notion of common sense has proved to be valid in a number of instances, there is also good evidence that many times the exception turns to be the rule.

The issue of pharmaceutical compounding by veterinary practitioners has recently achieved a great deal of attention because of the new Compliance Policy Guide established by the Food and Drug Administration (FDA) in order to regulate this practice. Combining medications which are not approved for compounding has a considerable risk because a new drug is obtained in which there are no studies on bioavailability, safety and residues approved by the FDA. Before two or more medications can be combined, we have to be sure that the drugs themselves and the conditions are appropriate. It is not as simple as combining products just because they go into solution together. Safety of consumers should be the first concern of all the professionals involved in the food production chain.

One of the problems to face when dealing with a topic such as compounding is the lack of agreement as to what the definition of compounding is, and whether the benefits warrant the potential risks. The AVMA² has defined pharmaceutical compounding as "the preparation of a medicament that combines **legally obtained ingredients** and/or appropriate vehicles that have not been specifically excluded from administration to animals by regulatory action of the FDA, United States Department of Agriculture (USDA) or Environmental Protection Agency (EPA)". This definition is neutral as to the nature of the active ingredient, but from a pharmacologic and pharmacokinetic perspective, the nature of the active ingredient is the critical factor in addressing this topic.

2.- Pharmaceutical and Pharmacological considerations

Either the route of administration is extravascular or oral, pharmaceutical factors are critical in determining the extent and rate of subsequent absorption.

When more than one drug are combined, there is the potential for pharmacologic/pharmacokinetic changes, affecting the entire fate of the drug into the target individual or population.

Several issues are inextricably bound to the issue of compounding:

Several issues are inextricably bound to the issue of compounding:

Extra-label drug use.- Many times, the practicing veterinarian has to treat pathological conditions against which there are not specifically approved drugs by the FDA. Assuming that compounding is necessary, we must learn how this can best be accomplished to ensure a safe and effective dosage form. The key question becomes whether a veterinary practitioner compounding a drug formulation (another form of extra-label use) can be assured of its bioavailability and, thus, therapeutic efficacy and safety.

Tissue residues and food safety.- Through the act of compounding, we may change the residue depletion pattern of the individual ingredients. The interaction between drugs, modified kinetics or pH variations when mixed could potentially lead to the generation of violative tissue residues.

Pharmaceutical interactions. Chemical compatibility.- It is the potential for physical or chemical interactions among the drugs that are being combined, or between drugs and other components, that is the primary concern in assessing the effects of compounding. As an approximate measure of compatibility, two drugs may be considered compatible if, when mixed, do not precipitate, form a hazy solution, or have a color change, and there is less than 10% decomposition of one or more of the components in the mixture within 24 hours.¹⁰ Nevertheless, we have to take into consideration that the changes that drugs experience when compounded are often more subtle, developing over time, and may not be noticed by visual inspection (physical changes such as degree and type of crystallinity, particle size, etc)^{1,8}. Minimal changes in the physical or chemical nature of the drug may alter its diffusibility, degree of ionization and so its dissolution rate, and particle size, thus preventing effective absorption and distribution. Frequently one or more drugs are simply inactivated⁷. Interactions in preparations can occur between drugs, between drugs and additives (eg, base or salt form, solubilizers, stabilizers) and between the drugs and the container where the mixture takes place. These interactions may even lead to the development of toxic breakdown products.

Pharmaceutical interactions. Bioequivalence.- Compounding and bioequivalence are closely intertwined since the goal of compounding is to formulate a drug with specific therapeutic efficacy and by extension, bioavailability. Bioequivalence is the comparison of the bioavailabilities of two formulations of the same active pharmaceutical ingredient. The same drugs produced by different pharmaceutical companies may have different effectiveness at the same dosage even though the amount of active ingredient is the same. This can be due to different particle size, vehicles, stabilizers, etc. Two bioequivalent products should be viewed as being interchangeable by the practicing veterinarian.⁹

Pharmacodynamic interactions.- When antibacterial medications are combined, one drug may directly alter the physiological response to another drug. There are four classifications for such interactions:

- **Antagonist:** Reduction on the efficacy, either due to competitive antagonism at the same receptor site or at different sites but through the same physiological pathway.
- **Synergistic:** Enhance of the response due to synergistic effects either at the same receptor site or at different sites but through the same physiological pathway.
- **Additive:** Resembles the administration of a higher dose. Both drugs act through the same mechanisms referred above.
- **Independent:** Each drug works independently.

Pharmacokinetic Interactions.- In many instances the aforementioned drug interactions have a pharmacokinetic rather than a pharmacodynamic basis. The rates of absorption, distribution, excretion or metabolism of one drug may be affected by the concomitant administration of a second drug, leading to changes in its clinical effects.

The absorption and hence the bioavailability of a drug may be modified or impaired if a concurrently administered drug lead to variations in the drug's passage through biological structures or to changes in local pH, integrity of biological membranes, regional blood flow or gastrointestinal motility. Since the compounded drug hasn't been tested following a scientific protocol previously to its use, the potential to negatively affect the tissues from which combination will be absorbed, modifying in such case the rate of disintegration, dissolution, barrier diffusion and consequently bioavailability.

The distribution of drugs can also be altered by competition for protein binding sites between two drugs with high protein binding affinity.⁷ Since protein binding is a reversible phenomenon, the drug with the highest affinity for protein displace the drug with less affinity. The free form of the displaced drug is pharmacologically active and as such the potential for adverse reactions or tissue residues accumulation is increased. Drug distribution also may be altered by drug-induced variations in regional organ blood input or changes in the affinity of a drug for certain tissue proteins.

Concurrently administered drugs may also interact through mechanisms involving their metabolism. Some drugs are known to induce microsomal enzyme activity. This usually leads to an increased clearance and loss of activity, but if the metabolites are toxic or more active than the parent drug, then the efficacy and/or safety of the combined preparation may be changed. Similarly, certain drugs may inhibit drug metabolism, increasing the potential for toxicity or exaggerated pharmacological response of concurrently administered drugs.

Finally, the excretion patterns of the drugs can also be altered as a consequence of compounding. Pharmacokinetic drug interactions may alter urinary excretion due to changes in glomerular filtration, competition between the drug for active tubular secretion, or both. Renal excretion may be affected by drugs that alter urinary pH and tubular resorption. For example, changes in the urinary pH may lead to an increase in the unionized fraction of a drug, thus to an increased tubular reabsorption and a prolonged clearance.⁷

A final consideration related to the fate of compounded drugs in animals is what can be referred as *pharmacokinetic compatibility*. The pharmacokinetic parameters of two or more drugs may prevent compounding of a rational mixture even if there is not any particular interaction between them. Let's say we have two drugs we can mix such as the effect of one of them lasts 24 hours and the effect of the other only 4-6 hours. How often should the combination be administered if one wishes to maintain a therapeutic and reasonably safe blood level?.

Stability.- When we mix different products there is the potential for changes in the pH, solvents, adjuvants, etc. of the mixture and for changes in the way drugs react with the container. As a result of all of this the rate of breakdown of the different ingredients with time may vary affecting the shelf life and quality of the drug. The stability of certain compounds, for example the combinations trimethoprim-sulfonamide, may be decreased when exposed to sunlight, thus it is necessary to keep them in proper containers.¹⁰

Sterility.- It's obvious that the conditions in which compounding is accomplished in the field are quite different than those governing the industrial production of drugs. These may lead in many cases to undesired contaminations of the mixed product.

Effects on production.- There is a lack of scientific data as to whether the different variables governing animal production are affected when compounding, and in which ways.

3.- Bioavailability plays a central role in drug compounding

Compounding of drugs not approved for combination may affect bioavailability, that is the rate and extent of drug absorption. For most pharmacologically active agents, the shape of the serum concentration-time profile is related to the drug's pharmacodynamic profile, thus making bioavailability a useful indicator of drug efficacy. To illustrate how slight changes in formulation impacts on the resulting bioavailability of a compound drug we will summarize a pharmacokinetic simulation recently published. (JAVMA, Vol 205, No. 2, 226-231. 1994).

In this study a simple pharmacokinetic model was constructed assuming that the hypothetical drug in question is distributed to

two compartments (central, peripheral) and is eliminated from the central compartment. The drug is given orally. The clearance of the drug is 1 ml/min/kg and the volume of distribution ($V_{d_{ss}}$) is 0.7 L/kg with a resulting half-life of approximately 8 hours.

The effect of changing these basic absorption parameters were then simulated by use of a computer program.

Two other important assumptions were made in this study.¹¹ First, interindividual variability was not simulated so that the effects of parameter changes could more easily be examined. This, then assumes the unrealistic position that every animal dosed with a drug is identical, but it allows for only the effects of compounding errors to be studied. Should this data be extrapolated to field situations where variability exists, the predicted effects on bioavailability will be further exaggerated. Second, the absorption parameters were usually varied only by $\pm 15\%$. Because of the nonlinear relationship of pharmacokinetic rate constants, this results in larger and smaller changes in the primary parameters assessing bioavailability. For bioequivalence studies, resulting parameters must be within $\pm 20\%$ of the reference product. This tolerance should be kept in mind when examining the effects of only a 15% change in the underlying absorption parameters that result secondary to compounding.

Four metrics were calculated for every simulation profile, namely area under the curve (AUC), the peak or maximal plasma concentration (C_{max}), the time of maximal concentration (T_{max}) that provides information on time to potential therapeutic effect, and finally the serum concentration at 24 hours (C_{24}), a number which would reflect accumulation and potential residue concerns in food-producing animals.

Figure 1 assesses the effect of changing only the actual administered dose from the control dosage (a; 50 mg/kg) to 42.5 mg/kg (b) or 57.5 mg/kg (c). This scenario would occur if the active ingredients were not stable, were inaccurately weighed or dispensed, did not completely disintegrate, or formed an insoluble complex (eg Ca^{2+} /tetracycline; aminoglycoside/penicillin). When the dose is changed, the extent metrics of AUC and C_{max} are linearly affected, both changing by 15%. The serum concentration at 24 hours is likewise directly affected, whereas T_{max} is not changed because the absorption rate constants are fixed.

The next simulation (Fig. 2) illustrates the dosage being held constant at 50 mg/kg, but the absorption rate (K_{13}) being changed to 0.17 (left) or 0.23 (right). This would result if there were interactions between the reference drug and formulation components or other active ingredients (eg, complexations, chemical inactivations) that altered the rate of product disintegration, dissolution, or absorption. Changes in product particle size, nature of excipients and buffers, or vehicles would be expected to change these factors. In this case, AUC and C_{max} are minimally

affected, whereas $T_{\max}$ and C_{24} are dramatically changed. This is an excellent illustration in which a proportional change in a rate constant yields disproportionate changes in rate-dependent metrics. Notice that increasing K_{13} to 0.23 (right) has less effect than decreasing it (left), which prolongs C_{24} by 18%.

The simulation depicted in figure 3 combines both conditions by decreasing the dosage and K_{13} by 15% (left) or by increasing them (right). In this scenario, concentration-time profiles with various shapes are produced. The AUC is changed by approximately 17%, yet still falls within the established threshold. In contrast, $C_{\max}$ for both scenarios is outside of the 20% confidence interval, whereas C_{24} is minimally affected. These profiles may be expected to be therapeutically inequivalent.

Figure 4 is the converse of figure 3 in which K_{13} and dosage are inversely changed. In one simulation (left), K_{13} is decreased, whereas dosage is increased by 15%. In the other simulation (right), the K_{13} is increased, whereas dosage is decreased. In this scenario, $C_{\max}$ is minimally affected, whereas AUC and, especially, C_{24} are changed. Notice that C_{24} is increased by 39% (left) and reduced by 27% (right); well outside of the 15% error in compounding that was initially made. The consequences of these alterations may be substantial from the perspective of tissue residues in food-producing animals.

As can be appreciated from these theoretical simulations, in most cases, errors of 15% in compounding will have tolerable effects on drug bioavailability if the rate of absorption of the compound is not affected. However, many of the potential pharmaceutical interactions involving binding, complexation, dissolution, or solubility interactions may affect absorption rate.

Plausible errors in preparation of dosing materials can affect accepted metrics of bioavailability. In the real world, it is unlikely that any single factor would be present. With normal biological variability, compounding errors much less than the 15% used in these simulations would have dramatic effects.

It must be stressed that these factors are controlled in the professional drug manufacturing process by rigid quality control at critical points in the process. The lack of this level of quality control by a veterinary practitioner who compounds drugs could result in unacceptable variability in the behavior of the final product.

These factors are of even more concern in food-animal medicine, because violative tissue residues may result. Even if products have equivalent bioavailabilities, there is no guarantee that tissue residue depletion profiles and, hence, withdrawal times will also be equivalent.⁹ Compounding problems that result in slower absorption may become the primary determinant of the withdrawal time for a food-producing animal.

The activities of drugs usually are dependent on the formulations in which they are dosed, so the conclusion from this analysis must be that small errors in compounding may result in unpredictable effects on a drug's bioavailability, which may adversely affect efficacy, safety or tissue residue depletion.

4.- Some hints about compounding

Despite these reservations and complexities, it is often necessary for the veterinarian to compound drugs in certain situations.

In poultry, as in other intensive animal production environments, clinical disease rarely is a simple etiologic event. Many of the diseases the practitioner fights are multifactorial, so a broad spectrum therapeutic scope is needed in order to attain therapeutic success in groups of treated animals. Given the fact that decreasing number of FDA-approved medications have a broad-spectrum activity, veterinary pharmaceutical compounding represents an important component in protecting animal welfare and achieving successful yet economic therapy.

There are some simple situations where compounding would be predicted to cause problems.

Combining antibiotics in feed or water

Feed medication is particularly effective for the long-term prophylactic administration of antimicrobials. For therapeutic purposes, incorporation of antimicrobials into feed is less effective because of the time necessary to manufacture a suitable medicated feed and because one of the first symptoms of disease is anorexia as a consequence of developing fever. High ambient temperature may also reduce feed intake.

Water medication is most effective for the treatment of clinical disease outbreaks but can equally well be used for short-term prophylaxis. Medication in water has the advantage of rapid response, with medication reaching the birds within a relatively short time, and convenience of administration. One problem is that water consumption may vary considerably, and so it is important to avoid misdosing. Many of the specific drug interactions presented are especially relevant in water medication.

Traditionally a volumetric dosing approach has been used in water medication in poultry. Feed ingredients, water quality, body weight, temperature and average flock health affect water consumption. Should the water consumption be lower than expected this can lead to under dosing with a lack of treatment efficacy. Obviously, over-consumption of drinking water can lead to overdosing, which may cause residue and toxicity problems. An attempt must be made to monitor water consumption to prevent this scenario from occurring.

When dosing on a per pound basis instead of using the volumetric approach (parts per million or milligrams per gallon) we account for the milligrams of antibacterial per volume of body weight, and this is more accurate than the dosage based on a specific concentration of antibacterial in the drinking water to be consumed by the birds. When dosing on a per pound basis, water pH, drug half-life, drug excretion and water consumption are taken into consideration for a proper dosing.

The modification of pH not only may have a deleterious effect on drug absorption but also in water intake, because when drinking water pH is less than 6, overall performance and water consumption are decreased.

When combining medication in water and feed problems may arise because there is an increase in the number of components that can elicit interaction. There are more possibilities of undesired physico-chemical and pharmacological interactions. Compounds in the feed may cause interactions with drugs in the water and viceversa. The possibility of increased interactions can lead to additional variation in absorption, tissue depletion and required WDT.

pH and mechanistic effects

Most of the drugs are administered in a reduced form, so they may also undergo oxidation when improperly managed.¹⁰

Some vitamins or electrolytes can modify the pH of water when added to the mixture, potentially modifying the absorption patterns and effectiveness of antibiotics. The reason is that drug absorption in the gut depends upon the extent to which the drug exists in the non-ionized lipid-soluble form which in its turn depends on its pKa and pH of the environment.

Erythromycin, tetracycline, aminoglycosides and lincomycin (weak bases) are more active in acidic solutions (pH 6 to 7), while sulfonamides, penicillins and cephalosporins (weak acids) are more effective in basic or "hard" water (pH > 7). Due to the variations in activity of the different antibiotics depending on the pH of the solutions, is it advised to check the pH of the drinking water where the antibiotic is going to be dissolved, and ascertain that the compounding of certain drugs do not modify the initial pH of the water.

In urine, passive reabsorption depends upon the same factors just referred to when talking about oral absorption. Only the unionized form of a drug is able to diffuse back through the lipid membranes of the tubule cells. At high pH values, weakly acid drugs (sulfonamides, penicillins and cephalosporins) largely exists as ionized lipid-insoluble molecules which are unable to diffuse into the tubule cells and will therefore be lost in the urine. The converse will be true for weak organic bases. Therefore pH changes which increase the amount in the un-ionized form (alkaline urine

for acidic drugs, acid urine for bases) increase the loss of the drug, whereas moving the pH in the opposite direction will increase their retention. Ascorbic acid (vitamin C) is an urinary acidifier, and thus may favor the excretion of concurrently administered weak bases that are excreted unchanged. Conversely, sodium bicarbonate (sometimes indicated together with mineral complexes to prevent egg shell weakness) may favor the excretion of weak acids or retention of weak bases, a potential residue problem.

When administered together, certain antibiotics will compete for tubular secretion. These include the weak acids (anions) penicillins, cephalosporins and sulfonamides. When mixed, some of them will retard the clearance of the others, leading to a longer half-life of the "less competitive" drug which results in an enhanced effect and longer tissue residue depletion.

Antibacterials with different mechanism of action should generally not be combined. An antibacterial with bactericidal action, together with one of bacteriostatic action, may be antagonists. The accepted reason for this is that bacteriocidal drugs such as penicillin, which inhibits bacterial cell synthesis, require cells to be actively growing and dividing to be maximally effective. In presence of bacteriostatic antibiotics such as the tetracyclines, there is not bacterial growing so the activity of penicillin is impaired. However, if these drugs are targeted to different pathogens, the antagonism may not be relevant. Bactericidal antibiotics include: penicillins, bacitracin, gentamicin and cephalosporins, while therapeutically used. Bacteriostatic antibiotics include: tetracyclines, lincomycin, tylosin, erythromycin and sulfonamides.

Appendix I: Specific Interactions

There are some additional reported interactions which may be relevant in poultry:

Gentamicin and cephalosporins in some species interact in vivo synergistically increasing the nephrotoxic effects of the aminoglycoside.

Erythromycin and lincomycin have been reported to show antagonism in vivo, probably secondary to ribosomal interaction. In vitro antagonism has been seen when a strain of staphylococci⁵ (resistant to erythromycin but sensitive to lincomycin) was exposed to both antibiotics together.

Erythromycin is physicochemically incompatible in vitro with vitamin B complex with vitamin C.

Penicillins are physicochemically incompatible in vitro with many drugs, among them aminoglycosides, lincomycin, tetracyclines, vitamin B complex with vitamin C, sulfonamides.

Penicillin and erythromycin have a similar range of antibacterial activity, thus they should not be used together. Very little is known (even in humans) about the effectiveness of concurrent use, although certain studies have shown an **antagonism**.

Tylosin and oxytetracycline show synergistic effect in vivo and in vitro against *Pasteurella multocida*.

Lincomycin has been reported in humans to be poorly absorbed when administered in the presence of food, even though the mechanism is not well understood.

Aminoglycoside antibiotics are inactivated by β -lactam antibiotics, so they are not recommended for combination, although when administered separately to the same animal inactivation is eliminated and they may even have synergistic effects.

Tetracycline and vitamin A quickly lose potency in water mixtures.

Spectinomycin has been reported to antagonize tetracycline absorption.

It also has been reported the fluoroquinolones are inactivated by the chlorine that the producer add to the water to increase its microbiological quality.

Excessive levels of iron, magnesium and calcium will reduce the absorption of all tetracyclines. High levels of these cations can be found in some drug premixes, and concurrent use is a potential source of tetracycline malabsorption. Conversely, long term feeding of low calcium or magnesium diets to facilitate medication with tetracyclines may result in nutritional disorders.

Concurrent administration of citric acid (1:1 ratio) can enhance tetracycline absorption from medicated water.

Copper sulphate has been reported to impair the action of nitarsone.

Some antimicrobials will undergo inactivation when they are in contact with metal containers. Chlortetracycline is recommended to be prepared fresh every 12 hours where galvanized water troughs are used, while is advised every 24 hours with plastic watering system. Therefore, different drug compounding may give rise to similar chemical interactions that may impair partial or totally the activity of the drug.

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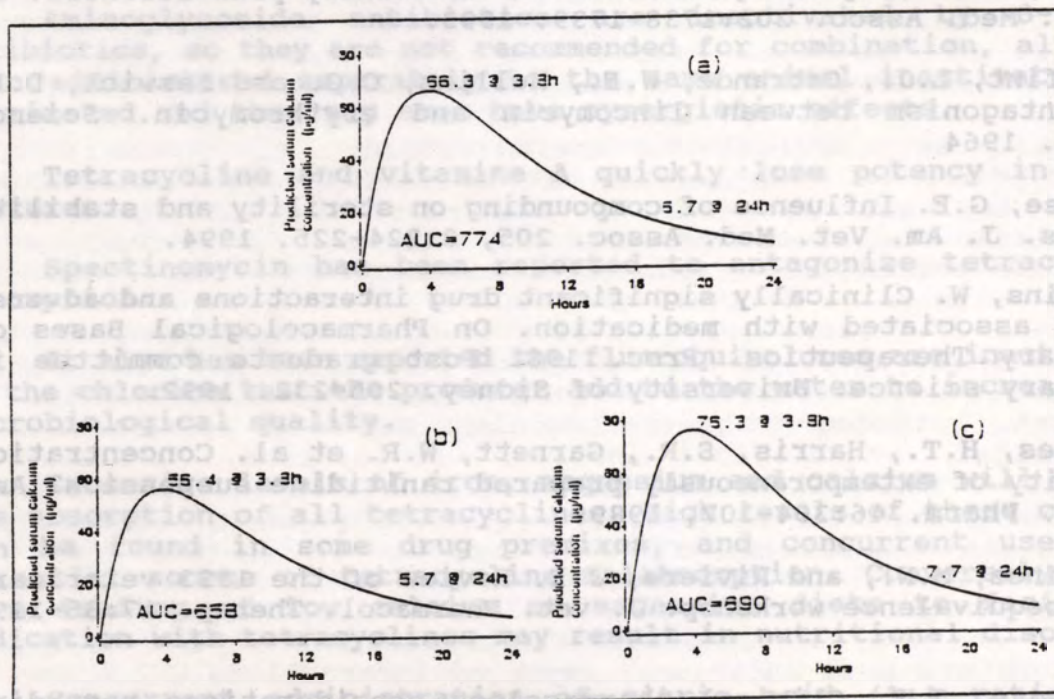


Figure 1.- Effect on bioavailability of changing dosage from 50 mg/kg (a) to 42.5 mg/kg (b) or 57.5 mg/kg (c); AUC = area under the curve.

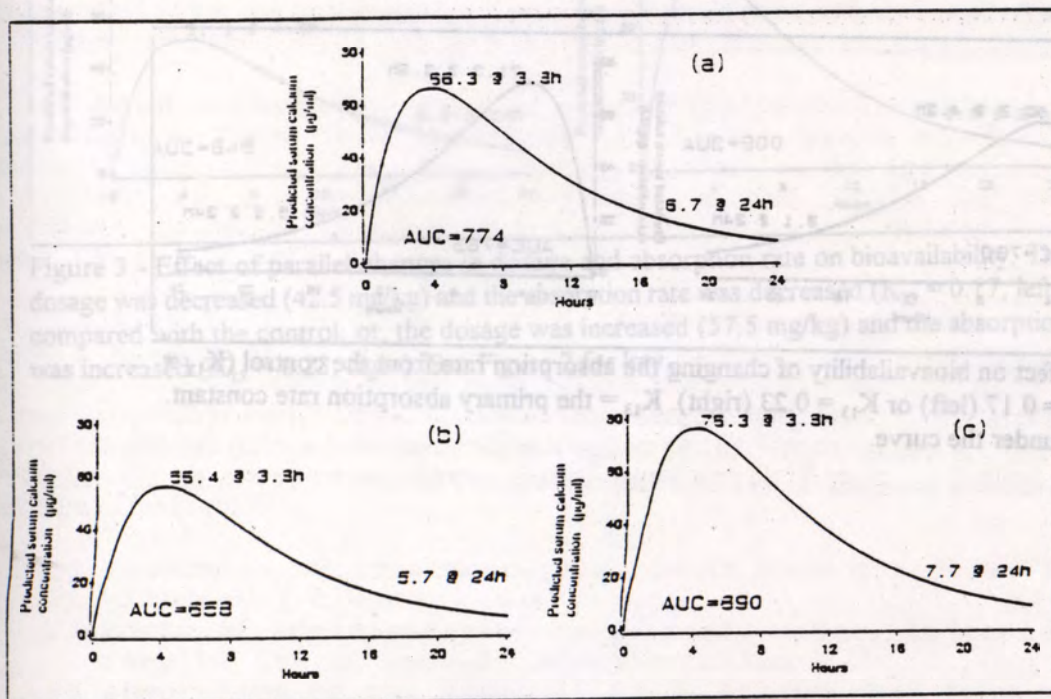


Figure 1.- Effect on bioavailability of changing dosage from 50 mg/kg (a) to 42.5 mg/kg (b) or 57.5 mg/kg (c); AUC = area under the curve.

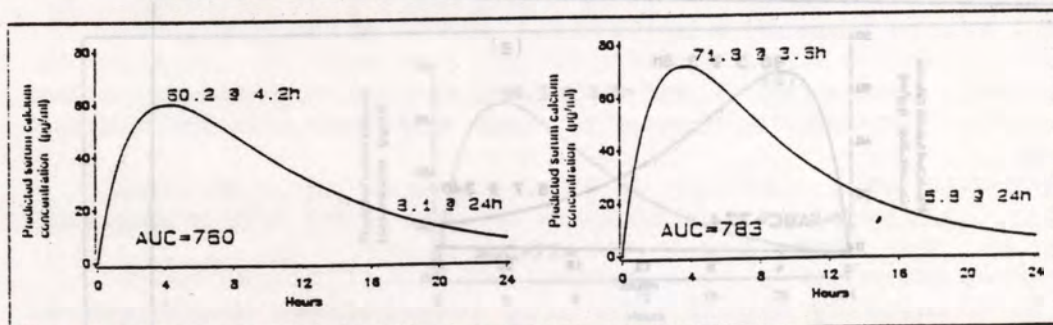


Figure 2.- Effect on bioavailability of changing the absorption rate from the control ($K_{13} = 0.20$) to $K_{13} = 0.17$ (left) or $K_{13} = 0.23$ (right). K_{13} = the primary absorption rate constant. AUC = area under the curve.

Antibiotic Susceptibility Patterns

W. Douglas Salzman

Antimicrobial susceptibility testing has become an integral part of the therapeutic process. In general, the days of assuming a bacteria is susceptible to a given antimicrobial agent are gone. The development of resistance to antimicrobial agents has made it necessary to test the susceptibility of most bacterial pathogens to a variety of antimicrobials. Another reason for conducting antimicrobial susceptibility tests is to monitor the developing resistance of bacteria to antimicrobials as a means of individual companies.

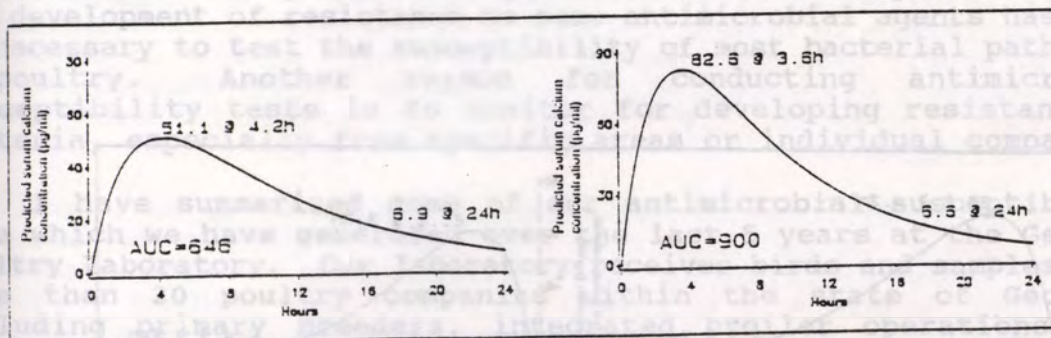


Figure 3.- Effect of parallel changes in dosage and absorption rate on bioavailability. The dosage was decreased (42.5 mg/kg) and the absorption rate was decreased ($K_{13} = 0.17$; left), compared with the control; or, the dosage was increased (57.5 mg/kg) and the absorption rate was increased ($K_{13} = 0.23$; right). See Figure 2 for key.

- 1) Economics of treatment (i.e. is it cost effective?)
- 2) Withdrawal times
- 3) Route of administration (e.g. feed, water, injection) and feasibility of such an administration
- 4) Absorption of the agent (i.e. is it absorbed from the intestinal tract?)
- 5) Distribution of the agent (i.e. does it get to the site of infection at therapeutic levels?)
- 6) Pharmacological effects
 - a) is its activity effected by pH changes?
 - b) is there interference with other chemical substances (e.g. calcium)?
 - c) is there antagonism with other agents?
- 7) Activity of agent (is it bacteriostatic or bactericidal?)
- 8) Host factors
 - a) age or weight of birds
 - b) immunological status of the flock
 - c) will they consume sufficient amounts of the agent?

Antimicrobial Susceptibility Data

The antimicrobial susceptibility of the 4 primary pathogens of poultry, *Escherichia coli*, *Salmonella*, *Pasteurella multocida*, and *Staphylococcus aureus*, are listed in Tables 1-4. The data covers clinical isolates over the last 5 years. The list of antimicrobial

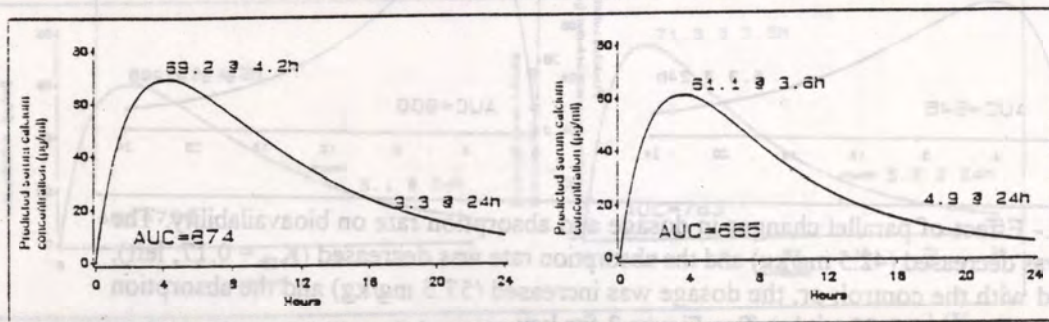


Figure 4.- Effect of inverse changes in dose and absorption rate on bioavailability. The dosage was increased (57.5 mg/kg) and the absorption rate was decreased ($K_{13} = 0.17$; left), compared with the control (Fig 1a); or, the dosage was decreased (42.5 mg/kg) and the absorption rate was increased ($K_{13} = 0.23$; right). See Figure 2 for key.

Antibiotic Susceptibility Patterns

W. Douglas Waltman

Antimicrobial susceptibility testing has become an integral part of the therapeutic process. In general, the days of assuming a bacteria is susceptible to a given antimicrobial agent are gone. The development of resistance to some antimicrobial agents has made it necessary to test the susceptibility of most bacterial pathogens of poultry. Another reason for conducting antimicrobial susceptibility tests is to monitor for developing resistance of bacteria, especially from specific areas or individual companies.

I have summarized some of our antimicrobial susceptibility data which we have generated over the last 5 years at the Georgia Poultry Laboratory. Our laboratory receives birds and samples from more than 20 poultry companies within the state of Georgia, including primary breeders, integrated broiler operations, and layer farms.

Caution must be taken when interpreting susceptibility data, since a number of factors must be considered before in vitro data can be translated into in vivo effectiveness. In fact, susceptibility testing would better be termed resistance testing, since usually the determination of resistance correlates better with in vivo response than does susceptibility. Some of the factors include:

- 1) Economics of treatment (i.e. is it cost effective?)
- 2) Withdrawal times
- 3) Route of administration (e.g. feed, water, injection) and feasibility of such an administration
- 4) Absorption of the agent (i.e. is it absorbed from the intestinal tract?)
- 5) Distribution of the agent (i.e. does it get to the site of infection at therapeutic levels?)
- 6) Pharmacological effects
 - a) is its activity effected by pH changes?
 - b) is there interference with other chemical substances (e.g. calcium)?
 - c) is there antagonism with other agents?
- 7) Activity of agent (is it bacteriostatic or bactericidal?)
- 8) Host factors
 - a) age or weight of birds
 - b) immunological status of the flock
 - c) will they consume sufficient amounts of the agent?

Antimicrobial Susceptibility Data

The antimicrobial susceptibility of the 4 primary pathogens of poultry, Escherichia coli, Salmonella, Pasteurella multocida, and Staphylococcus aureus, are listed in Tables 1-4. The data covers clinical isolates over the last 5 years. The list of antimicrobial

agents at the top of each table are those which may be used in poultry. However, it must be emphasized that individual agents are approved for specific diseases, for certain types and ages of birds, for specific routes, and for specific withdrawal times.

The antimicrobial susceptibility of clinical isolates of E. coli is given in Table 1. Less than 20% of E. coli isolates were susceptible to chlortetracycline or oxytetracycline (probably the most widely used therapeutic antimicrobial agents in poultry). The resistance of E. coli to tetracyclines is probably due to its widespread use in poultry, since, in many cases, it is the only agent available.

Sulfamethoxazole-trimethoprim (SXT) closely approximates the poultry agent sulfadimethoxine-ormetoprim, and may be used to predict susceptibility to the latter agent. This agent is relatively effective, however, its use in poultry is very restricted. The approved sulfonamides have similar restrictions, but there in vitro effectiveness is more like that of the tetracyclines. Gentamicin may only be injected at day of age. Erythromycin and penicillin G are classically gram positive bacterial agents, which E. coli are inherently resistant to. Notice the 5 agents listed, which are unapproved for use in poultry, and their relatively high degree of effectiveness.

I have recently heard the statement, that the poultry industry really does not need any additional antimicrobial agents. I hope from this data and the data to follow that I will shatter that misconception. Furthermore I believe much of our resistance problems that we have today is due to the fact that we do not have other available agents that can be used on a rotational basis.

The antimicrobial susceptibility of clinical isolates of Salmonella are listed in Table 2. The susceptibility profiles are better than for E. coli, but still are lacking in many cases. Sulfadimethoxine-ormetoprim is very effective if it can be used. Tetracyclines may be effective if the particular salmonellae is susceptible.

The antimicrobial susceptibility of clinical isolates of P. multocida is given in Table 3. P. multocida is somewhat of an enigma, in that it acts like a gram positive bacteria, yet it is gram negative. In the laboratory, P. multocida is highly susceptible to a wide range of antimicrobial agents. Unlike E. coli and Salmonella, P. multocida has shown very little, if any, trend toward developing resistance.

The antimicrobial susceptibility of clinical isolates of S. aureus is given in Table 4. The susceptibility to tetracyclines is marginal, however, erythromycin and penicillin G are still fairly effective.

The antimicrobial susceptibilities of these bacteria to

additional agents is given in Table 5. As expected the use of the sulfadimethozine-ormetoprim disk paralleled the results with SXT. Ceftiofur is very effective with all bacteria tested, however, this agent currently is only injected at day of age. Novobiocin, clindamycin, and bacitracin are classically gram positive agents, however, they have some activity with P. multocida. Sarafloxacin, a fluoroquinolone not currently approved, was uniformly effective for all bacteria tested.

The antimicrobial susceptibility of E. coli from all sources is given in Table 6. There are few differences, with the possible exception that environmental isolates may be more susceptible.

Over the last 5 years, the data shows little if any trend toward increasing resistance. There are a few situations where there appears to be minor increases, but there are an equal number of situations where the resistance appears to be decreasing.

Another often spoken concern with antimicrobial resistance is the potential for it to transfer to the human clinical area. We have compared our susceptibility data with that of some local hospitals (Tables 7 and 8). It is important to note that we used disk diffusion and they were using broth dilution procedures. From these comparisons, it can be seen that the poultry isolates are often more resistant than their human counterparts to poultry agents. However, the human isolates still show high levels of susceptibility to these same agents. Moreover, for S. aureus, the poultry isolates are significantly more susceptible than those from clinical areas. Certainly the transfer of resistance from veterinary to human populations have been documented, and certainly the potential exists, however, I personally do not see evidence of a lot of this occurring. I believe most of the resistance problems encountered in the clinical area are derived from human sources.

Furthermore, if we look at the antimicrobial agents approved for use in poultry and the situations in which those agents are the drugs of choice for human diseases, we see very few instances where poultry pathogens would have the opportunity to pass this resistance to the respective human pathogens (Table 9).

Conclusion

There is a vital need for additional effective antimicrobial agents to be approved for use in poultry. The addition of new agents may actually reduce the overall incidence of resistance by allowing for alternative agents to be used or rotated.

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Table 1. Antimicrobial susceptibility of clinical isolates of *E. coli*.

Antimicrobial*	% Susceptible				
	1990 (376)**	1991 (402)**	1992 (543)**	1993 (335)**	1994 (439)**
Chlortetracycline	17.3	16.2	10.5	13.4	16.4
Oxytetracycline	18.1	15.9	11.4	12.8	17.1
SXT	82.4	86.1	89.9	86.5	89.5
Sulfonamide	38.0	42.5	35.9	38.5	35.5
Gentamicin	74.5	65.4	63.5	63.9	57.4
Erythromycin	1.3	1.0	0.0	0.6	1.0
Penicillin G	1.1	1.0	0.0	0.0	0.4
Neomycin	70.7	74.6	81.0	78.5	82.2
Nalidixic acid	97.3	98.0	99.4	99.1	99.3
Nitrofurantoin	94.4	94.8	98.2	97.0	97.0
Chloramphenicol	99.5	99.2	99.8	99.4	98.9
Ampicillin	84.3	80.3	77.0	72.8	69.9

* Chlortetracycline, oxytetracycline, SXT (actually ormetoprim-sulfadimethoxine), triple sulfonamides, gentamicin, erythromycin, and penicillin G are approved for use in poultry. The other antimicrobial agents are not approved for use.

** Number of isolates tested.

Table 2. Antimicrobial susceptibility of clinical isolates of Salmonella.

		% Susceptible			
Antimicrobial*	1990 (191)**	1991 (304)**	1992 (412)**	1993 (169)**	1994 (150)**
Chlortetracycline	74.3	71.0	70.1	74.6	71.3
Oxytetracycline	73.3	62.5	70.6	74.0	67.3
SXT	99.5	96.4	96.4	96.4	99.3
Sulfonamide	81.2	69.7	76.4	65.1	74.0
Gentamicin	87.4	81.6	88.8	80.5	86.7
Erythromycin	2.6	0.2	0.0	0.6	2.0
Penicillin G	3.1	0.2	0.0	0.6	2.0
Neomycin	89.5	92.8	96.1	91.7	90.7
Nalidixic acid	98.4	99.7	99.5	99.4	98.0
Nitrofurantoin	99.0	98.7	97.8	97.6	98.7
Chloramphenicol	100.0	99.7	98.5	99.4	100.0
Ampicillin	82.7	91.8	92.0	88.2	81.3

* Chlortetracycline, oxytetracycline, SXT (actually ormetoprim-sulfadimethoxine), triple sulfonamide, gentamicin, erythromycin, and penicillin G are approved for use in poultry. The other antimicrobial agents are not approved for use.

** Number of isolates tested.

Table 3. Antimicrobial susceptibility of clinical isolates of *P. multocida*.

Antimicrobial*	% Susceptible				
	1990 (87)**	1991 (110)**	1992 (116)**	1993 (87)**	1994 (139)**
Chlortetracycline	93.1	95.4	93.1	98.8	95.0
Oxytetracycline	92.0	98.2	97.4	98.8	99.3
SXT	100.0	99.1	99.1	100.0	100.0
Sulfonamide	73.6	82.7	85.3	82.8	89.2
Gentamicin	100.0	100.0	100.0	100.0	99.3
Erythromycin	92.0	98.2	99.1	98.8	98.6
Penicillin G	98.8	100.0	100.0	100.0	99.3
Neomycin	100.0	100.0	100.0	98.8	95.7
Nalidixic acid	97.7	99.1	100.0	100.0	100.0
Nitrofurantoin	100.0	100.0	100.0	100.0	100.0
Chloramphenicol	100.0	100.0	100.0	100.0	100.0
Ampicillin	100.0	100.0	100.0	100.0	100.0

* Chlortetracycline, oxytetracycline, SXT (actually ormetoprim-sulfadimethoxine), triple sulfonamide, gentamicin, erythromycin, and penicillin G are approved for use in poultry. The other antimicrobial agents are not approved for use.

** Number of isolates tested.

Table 4. Antimicrobial susceptibility of clinical isolates of *S. aureus*.

Antimicrobial*	% Susceptible				
	1990 (101)**	1991 (126)**	1992 (149)**	1993 (104)**	1994 (79)**
Chlortetracycline	45.5	35.7	33.6	28.8	25.3
Oxytetracycline	45.5	37.3	36.9	28.8	30.4
SXT	100.0	96.8	100.0	99.0	98.7
Sulfonamide	90.1	96.0	87.9	96.2	93.7
Gentamicin	100.0	95.2	96.6	96.2	97.5
Erythromycin	87.1	77.8	71.1	80.8	82.3
Penicillin G	62.4	73.0	74.5	84.6	88.6
Neomycin	98.0	96.0	98.0	97.1	98.7
Nalidixic acid	57.4	57.9	47.0	41.3	36.7
Nitrofurantoin	98.0	99.2	100.0	100.0	100.0
Chloramphenicol	100.0	100.0	100.0	100.0	100.0
Ampicillin	64.4	79.4	74.5	85.6	92.4

* Chlortetracycline, oxytetracycline, SXT (actually ormetoprim-sulfadimethoxine), triple sulfonamide, gentamicin, erythromycin, and penicillin G are approved for use in poultry. The other antimicrobial agents are not approved for use.

** Number of isolates tested.

Table 5. Antimicrobial susceptibility of E. coli, Salmonella, P. multocida, and S. aureus to additional agents.

Antimicrobial*	<u>E. coli</u>		<u>Salmonella</u>		<u>P. multocida</u>		<u>S. aureus</u>	
	No.**	%Susc	No.**	%Susc	No.**	%Susc	No.**	%Susc
Ormet/sulfa	995	81.4	302	93.7	131	92.8	103	100.0
Ceftiofur	999	99.9	324	100.0	134	100.0	115	100.0
Novobiocin	744	15.2	336	0.0	109	95.4	115	93.9
Clindamycin	1086	0.0	336	0.0	134	31.3	115	94.8
Bacitracin	1086	0.0	336	0.0	109	38.5	115	96.5
Sarafloxacin	940	100.0	276	100.0	102	100.0	97	100.0
Cephalothin	1075	96.6	336	95.8	134	100.0	115	100.0

* Ormetoprim-sulfadimethoxine, ceftiofur, novobiocin, clindamycin (lincomycin), and bacitracin are approved for use in poultry. The other antimicrobial agents listed are not approved.

** Number of isolates tested from all sources.

Chlortetracycline, oxytetracycline, EXT (actually ormetoprim-sulfadimethoxine), triple sulfamonomethoxine, trimethoprim, ampicillin, ampicillin G, and penicillin G are approved for use in poultry. The other antimicrobial agents are not approved for use.

(101)** (136)** (143)** (104)** (116)**
 ** Number of isolates tested

Table 6. Antimicrobial susceptibility of *E. coli* isolated at the Georgia Poultry Laboratory 1990 - 1994 from clinical, day-old chick monitor, and environmental sources.

Antimicrobial*	% Susceptible		
	Clinical (2,095)**	Day-old chicks (1,802)**	Environmental (684)**
Chlortetracycline	14.6	16.5	21.2
Oxytetracycline	14.9	16.8	21.3
SXT	87.1	87.8	91.7
Sulfonamide	37.9	50.1	69.3
Gentamicin	64.7	73.0	87.6
Erythromycin	0.5	0.4	1.0
Penicillin G	0.3	0.3	0.6
Neomycin	77.8	76.4	75.3
Nalidixic acid	98.7	99.2	98.4
Nitrofurantoin	96.4	97.5	96.2
Chloramphenicol	99.4	99.3	99.3
Ampicillin	76.8	75.6	78.2

* Chlortetracycline, oxytetracycline, SXT (actually ormetoprim-sulfadimethoxine), triple sulfonamide, gentamicin, erythromycin, and penicillin G are approved for use in poultry. The other antimicrobial agents are not approved for use.

** Number of isolates tested.

Table 7. Comparison of antimicrobial susceptibility between poultry and human isolates of *E. coli*.

Antimicrobial	% Susceptibility		
	GPL (2938)*	Hosp A (2773)*	Hosp B (724)*
Tetracycline	15.3	83.3	84.1
SXT	88.2	93.9	91.3
Sulfonamide	46.9	-	71.7
Gentamicin	70.3	97.4	97.5
Nalidixic acid	98.9	96.6	-
Nitrofurantoin	97.2	98.4	98.1
Chloramphenicol	99.3	-	95.0
Ampicillin	75.8	66.8	71.7

* Number of isolates tested.

Table 8. Comparison of antimicrobial susceptibility between poultry and human isolates of S. aureus.

Antimicrobial	% Susceptibility		
	GPL (525)*	Hosp A (1003)*	Hosp B (400)*
Tetracycline	37.0	92.7	93.0
SXT	99.0	91.4	94.8
Sulfonamide	93.3	-	40.0
Gentamicin	97.1	-	93.5
Nitrofurantoin	99.2	-	98.5
Chloramphenicol	100.0	-	91.2
Ampicillin	80.2	-	6.5

* Number of isolates tested.

Table 9. Antimicrobial agents used in the poultry industry and their use in human medicine.

Antimicrobial	Drug of choice*
Tetracycline	<u>Calymmatobacterium granulomatis</u> <u>V. cholerae</u> Chlamydia Mycoplasma Rickettsia Borrelia
Gentamicin	<u>Francisella tularensis</u>
Erythromycin	<u>Corynebacterium diphtheriae</u> <u>Bordetella pertussis</u> <u>Haemophilus ducreyi</u> Mycoplasma
Sulfa/Trimeth	Moraxella <u>Yersinia enterocolitica</u> <u>Aeromonas</u> spp. <u>Haemophilus influenzae</u> <u>Pseudomonas cepacia</u>
Penicillin G	Non-penicillinase staphylococci <u>Streptococcus pyogenes</u> Group B streptococci Viridans streptococci <u>Streptococcus pneumoniae</u> <u>Neisseria meningitidis</u> <u>Bacillus anthracis</u> Leptospira Treponema Actinomyces

* According to the Medical Letter, 1992.

Pharmacokinetics of the Tetracyclines in Poultry: A Review

Terry N. TerHune

Introduction

The tetracycline antibiotics have long provided broad spectrum poultry disease control since their discovery and development in the 1940s and 1950s. Among the antibacterials employed in poultry medicine, the tetracycline class of antibiotics has enjoyed the longest track record of broad application dating back to the infancy of commercial bird production.¹

Upon identification of tetracycline as the class of choice for therapy, selection must then be made from class members approved for avian medicine. Tetracycline, chlortetracycline, and oxytetracycline are available in water soluble; feedgrade and water soluble; and injection, feedgrade, and water soluble forms, respectively. These distinctions, in themselves imply individual differences of use flexibility between the compounds and a "best-fit" approach to treatment of a specific disease entity. For example, only one formulation is licensed for the injectable route: oxytetracycline, up to a maximum of 25 mg activity per pound of body weight. All three tetracycline versions are applicable through water medication with nearly identical disease claim labeling.

Parenteral mass medication has fallen into disfavor because of the obvious problem of increasing labor intensity with the increasing of live production volume experienced particularly in the United States. Nevertheless, injection continues to be indicated among outbreaks of valued genetic stock, especially when the birds are being handled individually as a routine (e.g. AI in turkey breeders).

As parenteral treatment lost popularity, treatment-level water supplementation became a more favorable method of medicating. Recognizing this popularity and the need to bring water usage in line with desired injectable dosage rates, regulatory guidance has taken the form of NAS/NRC (National Academy of Sciences, National Research Council) proposals to standardize labeling among all commercial water solubles (tetracycline: 25 mg/lb, all claims; oxytetracycline and chlortetracycline: 25 mg/lb for organisms secondary to bluecomb enteritis, 400-800 mg/gal for other claims).

Feed medication continues to be applied in great volume, though greatly reduced from years past. Clearances range from growth promotion programs to high-level disease claims (oxytetracycline: 5-500 g/ton; chlortetracycline: 10-500 g/ton).³ In step with water medicants, feed preferences have shifted from low-level continuous towards aggressive treatment-level therapy, many times in adjunct to water treatment.

Discussion

McMillan et al.⁴ described serum profiles of commercial turkeys following intravenous injection or oral gavage of equivalent doses of tetracycline hydrochloride. Though on a much lesser scale than

Table 9. Antimicrobial agents used in the poultry industry and their use in human medicine.

the injectable route, oral dosage showed appreciable peak activity within a comparable time frame of 2 hours and apparent half-life of 2.44 hours. More importantly, this comparison confirmed water as a "next best" dosing approach pharmacologically, reflecting the NAS/NRC basis for milligrams per pound accuracy conventionally associated with injectables.

Water is used routinely to monitor flock health status and is by far the most dynamic drug medium in that one can start, stop, or change quickly. Usually consumed better than dry feed by diseased birds, water treatment may be most appropriate for birds not seriously ill. As opposed to injectables, however, relative intake must be reckoned with in attempts to dose according to weight of bird. Daily water consumption falls predictably within a normal ambient temperature range for chickens and turkeys as the bird ages. This, in turn, necessitates higher and higher antibiotic concentrations at the drinker and stock solution levels to maintain the same relative dose over the course of the flock growout cycle. Fortunately, dosing charts and slide rules analogous to a calibrated syringe can aid in calculating the amounts of water and powder required to assure accurate dispensation.

Short, intensive water medication (given over a period of 6 hours), based on body weight and average daily water consumption, is being proposed as a better strategy for the treatment of systemic bacterial infections in poultry when compared to traditional 24 hour continuous water medication administered at the recommended levels for a given number of days.⁵ This proposed treatment alternative uses the same amount of product required for 24 hour water medication but under a short, intensive regimen during peak water consumption.

Higher serum and tissue levels were obtained with short, intensive water medication (given over a period of 6 hours) when compared with traditional 24 hour continuous water medication. This type of medication would be very useful in acute systemic bacterial infections that require prompt and effective levels in affected organs, such as those of the respiratory system, and constitutes another treatment alternative for the field veterinarian. This proposed alternative is no more expensive than the traditional 24 hour water medication program, since the same amount of product is used but under a shorter, more intensive regimen during peak water consumption hours.

Compared to water solubles, feed medication is more economical especially for prolonged therapy as less labor is demanded and it may better match a heterogenic health status within the flock. Pharmacologically, feed mimics a slow-release system resulting in less fluctuation in vivo. Of particular advantage is the storage of medicated feed in the crop from which there is a delivery of drug. Significant dose-responsive serum levels have been observed in commercial turkeys by Kula.¹ However, being even more restricted by intake relative to bird size than water, inclusion rates in feed would have to be greatly enhanced (600-2000 grams per ton) well beyond currently approved maximums in order to match the allowances through water. During the course of disease outbreak, inappetence of moribund birds exacerbates this inadequacy.

There are inherent differences that exist between the individual tetracyclines, regardless of formulation or trademark. To understand the qualities unique to each member of the tetracyclines, the basic differences in their chemical structure must be appreciated. As the name implies, a four benzene ring arrangement forms the molecular skeleton common to all tetracyclines. All of the major

differences between chlortetracycline and oxytetracycline result from the chlorine atom (Cl⁻) on the last ring of chlortetracycline and the presence of a hydroxyl group (OH⁻) on the second ring of oxytetracycline. By its nature, chlorine is very reactive, particularly with multivalent ions. This tends to create chemical instability of the chlortetracycline molecule and accounts for its relatively high degree of tissue irritation, precluding an injectable form. In contrast, the extra hydroxyl group found on oxytetracycline stabilizes the compound, making tissue tolerance quite good and solubility excellent for water medication or injection.

Reference made to stability must be defined to the two types involved, physical and chemical, which occur under a closed environment such as medicated drinking water, feed, or the bird itself. Physical stability refers to a change in form (gas, liquid, or solid) without change in composition, while chemical stability involves the ability of a compound to remain chemically intact. If the molecule disintegrates and becomes fragmented or changes one ion for another, it is no longer the original substance but a new product or products.

In order to discuss differences in the physical and chemical stability of chlortetracycline and oxytetracycline, it is necessary to consider pH. In the acid range, chlortetracycline and oxytetracycline share essentially equal stability up to a pH of approximately 4.5. Beyond this point, as neutrality is approached the stability of chlortetracycline rapidly deteriorates.

Oxytetracycline, however, maintains its integrity well into the alkaline range. Both types of stability operate under these conditions. Chemical breakdown of the chlortetracycline molecule due to an exchange of the chlorine ion with, primarily, an OH⁻ group produces a compound with no known antimicrobial activity. In addition, chlortetracycline and oxytetracycline undergo a physical instability in the presence of divalent ions. Alkaline waters are rich in these ions and the end result is polymerization to an insoluble antibiotic precipitate. These same losses could quite conceivably occur in the semi-aqueous environment of ingested feed usually formulated with divalent ions such as calcium.

In vivo pH also poses a threat to the chlortetracycline molecule. With the exception of the proventriculus and ventriculus (pH 2.5), avian body fluids (including blood) remain on the slightly alkaline side. Again, chlortetracycline is unstable in this range. Conversely, the relative stability of oxytetracycline in serum has long been recognized.

Waldroup et al.⁶ observed this drug behavior in the plasma level response of broilers to chlortetracycline and oxytetracycline when included at various levels in the ration. A significant interaction between antibiotic concentration and resulting antibiotic blood level was found (Table 1).

Beyond the expected dose-related response noted for both drugs, oxytetracycline appeared in the blood-stream at consistently higher concentrations at all feed medication levels. Apparently, the assimilation of a significant percentage of chlortetracycline was disrupted by some mechanism that simply did not affect oxytetracycline and, therefore, must be accounted for in some manner other than divalent ion interference (i.e., pH).

Sixty-Five to 75% of circulating chlortetracycline binds to plasma proteins⁷ compared to only 25-30%

of the absorbed oxytetracycline.⁸ Therefore, in terms of drug freely diffusible to the tissues, a limited 25-35% of chlortetracycline versus 70-75% of oxytetracycline would be available to diffuse at any given point in time.

The relationship of plasma drug levels to lung concentrations for oxytetracycline and chlortetracycline were examined.¹ Ninety 12-week-old commercial white poultts were assigned to one of nine separate rations and were divided into nine floor pens according to treatment. Chlortetracycline and oxytetracycline rations were fed *ad libitum* at 100, 200, 400, or 800 grams per ton for a period of 96 hours. At the end of the medication period, individual sera and lungs were collected from each group for bioassay (Table 2). Oxytetracycline produced higher concentrations in both tissue and serum at all rates of medication, the overall concentration being approximately double that of chlortetracycline.

In conclusion, the objective of antibiotic therapy is to deliver drug to the site of infection at effective levels in order that clinical cure may be possible. Pharmacokinetics and drug behavior even within a drug family are important factors to be considered in establishing sound medication rationale.

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FLUOROQUINOLONE USE IN THE POULTRY INDUSTRY

Table 1. Plasma antibiotic concentrations ($\mu\text{g/mL}$).

Antibiotic Inclusion Rate	Chlortetracycline	Oxytetracycline (g/ton)
100	0.150	0.162
200	0.242	0.317
400	0.370	0.653

Mechanism of Action

Table 2 Average Lung and Serum Values ($\mu\text{g/g}$ or mL).

Antibiotic Inclusion Rate (g/ton)	Chlortetracycline		Oxytetracycline	
	Lung	Serum	Lung	Serum
100	0.13	0.08	0.14	0.14
200	0.13	0.12	0.27	0.20
400	0.23	0.20	0.40	0.36
800	0.31	0.29	0.93	0.68

Since resistance is not plasmid mediated, clinical problems resulting from resistance have been much less common than with other classes of antimicrobials. There is evidence however, that resistance may be quite stable once it develops.

FLUOROQUINOLONE USE IN THE POULTRY INDUSTRY

John R. Glisson

Introduction:

The quinolones are a group of synthetic antimicrobial compounds initially developed about thirty years ago. The first quinolone reported was nalidixic acid, in 1962. Nalidixic acid has bactericidal activity against Gram-negative organisms, but is not distributed well in the tissues. It has been used primarily to treat urinary tract infections in humans. During recent years, a great deal of effort has been directed toward the development of quinolone compounds with greater potency and improved pharmacokinetic properties. This effort led to the synthesis of a group of compounds, called fluoro-quinolones (6-fluoro-7-piperazino-4-quinolones) which, when compared to nalidixic acid, have greatly increased antimicrobial activity and more favorable tissue distribution characteristics.

Mechanism of Action:

The primary mechanism of action of the fluoroquinolones appears to be mediated through their interaction with the bacterial enzyme, DNA gyrase. DNA gyrase is responsible for the supercoiling of the bacteria's circular DNA. This supercoiling is necessary for the bacterial chromosome to be packaged into the bacterial cell. DNA gyrase is composed of two subunits, gyr A and gyr B. Fluoroquinolones exert their influence on gyr A, whereas another group of antibiotics, represented by novobiocin, inhibit the function of gyr B. Essentially, the fluoroquinolones inhibit bacterial DNA synthesis during replication by the inhibition of DNA gyrase, but recent evidence indicates that fluoroquinolones may have additional bactericidal activities as well. These additional bactericidal activities may represent multiple mechanisms by which the compounds can inhibit DNA gyrase.

Resistance to Fluoroquinolones:

Unlike most antimicrobial compounds, resistance to fluoroquinolones is not mediated by plasmids. A chromosomal mutation is required for resistance to develop. These mutations are typically in the DNA gyrase genes or in genes which control membrane integrity and function and influence the permeability of the membrane to fluoroquinolones. The newer fluoroquinolones are 100-to 1,000-fold less prone to the selection of single-step spontaneous resistant organisms than is nalidixic acid. Mutations which result in resistance to one fluoroquinolone generally confer resistance to the other fluoroquinolones, but not to unrelated antibiotics.

Since resistance is not plasmid mediated, clinical problems resulting from resistance have been much less common than with other classes of antimicrobials. There is evidence however, that resistance may be quite stable once it develops.

Fluoroquinolone Use in Human Medicine:

Several fluoroquinolones have been developed for use in people. These include Ciprofloxacin (Bayer), Norfloxacin (Merck), Ofloxacin (Hoechst), and Enoxacin (Warner-Lambert). These products and others have been used extensively to treat urinary tract infections, skin infections, osteomyelitis, joint infections, sexually transmitted diseases, and respiratory tract infections.

Many of the fluoroquinolones have several outstanding characteristics which have made them the drug of choice for treating many bacterial diseases. They generally have a long half life, are distributed well in tissues, are absorbed well orally, and are very potent against most Gram-negative pathogens and many Gram-positive pathogens.

Fluoroquinolone Use in Poultry:

Many of the older quinolones, such as nalidixic acid have been used in poultry in some countries for many years. Their use has been somewhat limited because of lack of efficacy. In recent years, the more highly efficacious fluoroquinolones have been used in poultry. The two compounds which have been used most widely are enrofloxacin (Baytril-Bayer) and danofloxacin (Advocin-Pfizer). No fluoroquinolone has yet been approved for use in poultry in the United States and many European countries.

The fluoroquinolones have an antimicrobial activity which is ideally suited for treatment of bacterial diseases of poultry. Most fluoroquinolones are very potent against E. coli, Salmonella sp., Pasteurella multocida, Hemophilus sp., and Bordetella sp. In addition, many fluoroquinolones have high antibacterial activity against many Mycoplasma sp. Both enrofloxacin and danofloxacin are highly efficacious against avian mycoplasmas.

The fluoroquinolones represent the first available compounds which are highly effective against both E. coli and Mycoplasma gallisepticum (MG). This unique characteristic has led to their widespread use in many countries to treat MG-induced chronic respiratory disease in broilers. They are typically used in the drinking water for the first three days of life and again for 3 days at the time broilers are reacting to Newcastle disease vaccination. Because fluoroquinolones are the most expensive antibiotics available, their use is often restricted to the first 3 days of life. Fluoroquinolone use does not eliminate MG infection from treated birds but greatly reduces the number of organisms in the birds, increases the difficulty of reisolation of MG from the birds, and delays or prevents seroconversion. Unpublished data indicate that fluoroquinolone use in MG-infected breeders may dramatically decrease transovarian transmission of MG.

In countries where fowl typhoid and pullorum disease are endemic, fluoroquinolones have been used quite successfully to treat these Salmonella diseases. Neither of these diseases have been eliminated through fluoroquinolone use. However, morbidity and mortality can be greatly reduced.

Fowl coryza, caused by Hemophilus paragallinarum, is another disease which can be treated quite successfully with fluoroquinolones. In fact, fluoroquinolones have such a dramatically positive effect on birds suffering from fowl coryza, that response to fluoroquinolone therapy can be used to help diagnose the disease. Fluoroquinolones, like with MG, do not eliminate Hemophilus paragallinarum from an infected flock. Therefore, a few days after medication is withdrawn the disease often reappears and treatment must be repeated. Poultry disease specialists in many countries have found that it is important to allow 30-40% of the birds in a flock to begin to show signs of coryza before treatment with a fluoroquinolone is initiated.

Because of their broad range of potential applications in the poultry industry, fluoroquinolones have been used very extensively in many developing nations in which MG, Pullorum, and Typhoid infection of breeders and progeny is common. This has led to the attitude that only fluoroquinolones can be used to treat these diseases. The result has been the emergence of resistant organisms. Reports of resistant poultry pathogens have come from the Middle East and Latin America. Since the compounds are expensive, many farmers and companies decrease the dosage used. The use of sub-optimal doses of fluoroquinolones has been shown to be another way to potentially enhance resistance development. Although, resistance to fluoroquinolones is usually slow to develop, the overuse and abuse of fluoroquinolones will result in resistance development.

Another troubling source of pressure for development of resistance to fluoroquinolones is through the continued use of early generation quinolones such as oxolinic acid. These compounds induce resistance development much more readily than do the newer fluoroquinolones and resistance development to these older drugs often provides at least partial resistance to the newer compounds.

The fluoroquinolones are the most effective antimicrobial compounds ever developed for use in poultry. They represent a totally new class of drugs for the poultry industry in many countries. They will likely be the only new class of antimicrobial compounds available to the poultry industry for many years. It is extremely important that the poultry industry use these compounds so that their effective lifetime can be extended as many years as possible. Fluoroquinolones should not be used routinely to treat any sick flock but should be used to treat diseases for which no other efficacious drug is available. Full dosages and full treatment regimes should be followed to minimize resistance development. Companies should cease usage of the older, less effective quinolones to prevent development of cross-resistance to the fluoroquinolones. These steps should help extend the useful life of these compounds.

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Pharmacokinetics of Aminoglycosides and Macrolides

Gordon W. Brumbaugh

Specific studies of pharmacokinetics of drugs with poultry are rare. Most variables that affect pharmacokinetics are qualitatively, but not necessarily quantitatively, similar in birds and mammals.^{1,2} Some clinically relevant generalizations can, therefore, be made from results of studies with other birds or with mammals.

Aminoglycosides are polar, water-soluble drugs that are poorly absorbed following oral administration.³ This attribute makes them useful for treating luminal enteric conditions, but for systemic conditions aminoglycosides must be injected. Rate and extent of absorption of gentamicin are similar if it is injected subcutaneously or intramuscularly.⁴ Distribution of aminoglycosides by passive diffusion across biological membranes is poor. They readily distribute in extracellular fluid (V_d , 0.20 to 0.25 L/kg).^{2,5,6,7} Concentrations of > 10 mcg gentamicin/ml of plasma are considered adequate for most gram-negative, aerobic bacterial infections and require doses of at least 5 mg/kg. Aminoglycosides do not undergo biotransformation and are eliminated relatively rapidly ($t_{1/2}$, 1.4 to 2.5 h; Cl , 0.06 to 0.13 L/kg/h), as parent drug, by renal filtration. Renal accumulation of aminoglycosides (gentamicin or neomycin) is an important consideration because accumulated drug is eliminated very slowly and violative residues may occur.

Macrolides are administered orally or parenterally to birds. Whether administered orally in feed or water, systemic absorption can be expected to be erratic, and generally inadequate (concentrations of < 0.5 mcg erythromycin/ml of plasma) for birds that are ill.^{8,9} This is partly due to anatomy and physiology of the avian intestinal tract. Retention times, microflorae, and pH of different parts of the tract; type of feed; dissolution of medication; and intake are all critical to adequate absorption of active medication.^{8,9,10,11} Macrolides are widely distributed into extravascular tissues and intracellularly because of their relatively high lipid-solubility. Concentrations of erythromycin and of tylosin in lung and trachea, liver, and kidney were higher than were concurrent concentrations in plasma.^{9,10,11} Macrolides are rapidly eliminated in urine and bile as active drugs. Biliary elimination exposes intestinal flora and biliary tract to high concentrations of the drugs.

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Sulfonamides for Poultry

R. E. Messersmith

The earliest report of therapeutic administration of sulfonamides (S) to poultry was by Levine in 1939 (sulfanilamide for cocci). S and potentiated S are broad spectrum antibacterial/antecoccidial drugs useful for poultry and animals. The activity toward pathogens involves interference with folic acid metabolism in the pathogen. This activity is generally "static" with S and "cidal" with potentiated S.

Sulfonamides - Mode of Action

S are structural analogues of paba, and structural derivatives of sulfanilamide. All have the same nucleus, to which groups have been added. These changes produce compounds with varying physical, chemical, pharmacological and/or antibacterial properties. The S are mistaken for paba, but cannot be used for making dihydrofolic acid by bacteria or protozoa. The result is inhibition of growth/multiplication of susceptible organisms, those that cannot use preformed folate. The effect is bacteriostatic: it is diminished in chronic infections (pathogens not growing), or in areas with poor circulation such as abscesses, bone or tendons. Body immune/defense mechanisms must be functional.

S- Absorption/Distribution

S are administered via drinking water (DW) or feed in poultry. They are generally added to DW as alkaline Na salt, although some sulfonamides are amphoteric. S are absorbed from small intestine into blood, circulated to all organs. In blood, S are present as free drug, reversibly bound to protein, or as acetylated S. Free S migrates into/from tissue by passive diffusion. They are excreted from body via kidneys. The acetylated salts of sulfamethazine, sulfamerazine, sulfadimethoxine and sulfadiazine are very soluble, precluding problems with crystaluria.

S- Antimicrobial Activity/ Spectrum

S are broad spectrum drugs. The claims for poultry include treatment of fowl cholera, fowl typhoid and coccidiosis. The types of pathogens susceptible and not susceptible to S include:

Susceptible *

gram +
gram -
streptococci
staphylococci
salmonella
escherichia
anthracas
coccidia
toxoplasma

Not Susceptible

clostridia
proteus
pseudomonas
klebsiella
leptospira
mycoplasma
viruses
rickettsiae

* inhibited by 30 mcg/ml or less in vitro

Because of differences in dosage/withdrawal recommendations for different S products, the dosage recommendations on the label should be followed.

Some sensitivity discs used for in vitro testing contain much greater S than can be achieved in plasma or tissues. These are intended to be used to test pathogens isolated from urinary infections, where the S will be concentrated by the kidneys. Such discs might give a false positive result for respiratory pathogens. Resistance to S occurs by mutant selection, or r-factor (plasmid) mediation, and it is thought to develop fairly rapidly. Cross-resistance to other sulfonamides is the rule. Some clinicians report good clinical response to S therapy despite isolation of resistant strains from the flock. There is discussion about the value of in vitro tests for S.

S are used for treatment of infections in other species such as:

Cattle- respiratory infections, foot rot, coccidiosis.

Swine- respiratory infections, enteritis.

Horses- Respiratory infections

Small animals- respiratory infections, soft tissue infections, coccidiosis.

S Safety

S are safe to use in growing poultry. They may cause lowered egg production in layers and breeders. Some of the eggs may have soft shells during this time. The production may return to normal after the S is withdrawn. Administration of radiolabeled sulfadimethoxine resulted in deposition of radioactivity into the yolk, to a lesser extent into the albumen, and to a still lesser extent into the shell. Because of the time involved in formation of yolk, activity took longer to build up and longer to clear. Activity in albumin and the shell cleared rapidly. S are not permitted in laying chickens or turkeys because S egg residues are prohibited.

Before availability of modern feed supplements of vit k, S therapy often resulted in "hemorrhagic disease". This was a hemorrhagic condition associated with hemopoetic aberrations and high mortality. This condition is rare today. Modern S products do not seem to result in crystaluria problems.

S- Special Considerations: Solubility in drinking water.

The typical ph of S solutions:

Market product (Na salt)	10
Proportioner stock solution	8.5
Unmedicated drinking water at ES	6.5
Medicated drinking water	6.7

Direct addition of S to water lines with highly acidic water or containing acidic additives (tetracyclines, citric acid, etc) may cause a precipitate to form. Before using S in dw, water lines should be flushed first. Suppliers have directions for handling.

S- Special Considerations: Palatability.

Turkeys (and sometimes chickens) have been reported to "back off" water consumption with some S, for example, with sulfamethazine.

Poultry have been found to readily accept sulfadimethoxine and sulfaquinoxaline, which is probably why they are the predominant S products used in poultry.

S- Special Considerations: Withdrawal.

Residue problems with S in poultry are easily preventable. The withdrawal period for S administered in dw is 5 days (Albon, SKB) to 10 days (sulfaquinoxaline, Salsbury, Russell, others). In event of accidental or deliberate overdose of S, the withdrawal period will be extended, but not much (doubling the dose would probably extend the withdrawal period by only a day or two).

The tolerance for S in edible tissues is 0.1 ppm, except in eggs, where it is zero (exception with Rofenaïd in turkeys- see PS section). While being medicated, S residues are highest in kidney > liver > muscle. During withdrawal, S disappears first from muscle, then liver, and finally blood and kidney. Thus, removal of liver and kidneys could be a useful factor in trouble-shooting a potential residue situation. Residues of S cannot be cooked out of contaminated carcasses. Analytical techniques have been refined by USDA to cope with S residue problems. The first step identifies presence of S, the second step identifies the specific S involved. Most analytical labs use the USDA technique. Careful use of S will not cause residue problems. Such problems result from S intake during the last few days prior to processing.

S- Special Conditions: Current regulatory status

In 1989, FDA terminated interim marketing rights for some S manufacturers who chose not to compile and submit data to support their products as requested by the agency. Companies who complied with their request, or whose NADA's already met current standards continue to market their products. In chronic toxicity tests sponsored by FDA, at elevated doses sulfamethazine (the only S tested) feeding was found to result in thyroid tumors. A consortium of S manufacturers sponsored extensive studies with sulfamethazine and demonstrated that pathology attributed to sulfamethazine was the result of a secondary mechanism. Thyroid hypertrophy and tumors do not appear to be a problem in primates. Interaction with FDA continues. The outcome of the sulfamethazine case may spill over to other S products.

Potentiated Sulfonamides

S Potentiators (P) - Mode of action.

Trimethoprim, pyrimethamine, methoprim, aditoprim and ormetoprim are diaminopyrimidines which were found to have antifolate activity- they block dihydrofolic acid reductase. This action happens in the pathway for use of folic acid in the manufacture of DNA and RNA, but at a different location than S. In the pathway paba---(a)---dihydrofolic acid---(b)---tetrahydrofolic acid, S blocks (a) and P blocks (b). P have antibacterial/anticoccidial activity. These P have a much higher binding effect on bacterial than mammalian dihydrofolate reductases, by a factor of 50,000 to 100,000. The action of P is more rapid than S because the effect occurs at a point closer to actual utilization of folic acid. In vitro resistance to P alone can occur rapidly.

The action of P and S in combination is synergistic and bactericidal. Development of resistance to PS is much less rapid than to P or S alone.

PS- Types of products.

In the US, there is only one PS product marketed for poultry, Rofenaïd 40 (HLR), a feed premix. There are injectable and tablet PS products available for mammals, both animals and human.

Rofenaïd 40 for poultry contains sulfadimethoxine, 25%, and ormetoprim, 15% (5:3 ratio). Romet 30 for fish is a companion product which contains sulfadimethoxine, 25%, and ormetoprim, 5% (5:1 ratio). Other PS products for mammals contain 5:1 ratios of S:P, and are intended primarily for bacterial infections. The 5:3 ratio in Rofenaïd was chosen specifically to provide better efficacy against cecal coccidiosis in chickens.

PS Spectrum.

In vitro tests utilize a 20:1 ratio of S:P. This has been shown to be a ratio achieved in plasma and tissues when the 5:1 product is administered to humans or laboratory animals. In a residue study in turkeys fed Rofenaïd 40 continuously, on 0-day (while still receiving medicated feed), ratio of sulfadimethoxine: ormetoprim was also approximately 20:1. Sensitivity discs for potentiated sulfonamides contain 20:1 ratios of S:P. Discs containing any PS combination will probably give similar results in vitro. HLR makes 20:1 sulfadimethoxine-ormetoprim discs available to diagnostic laboratories.

PS are active against the same types of bacteria affected by S. In addition, clostridia, klebsiella and proteus are inhibited in vitro. Because of the synergistic effect of PS in combination, the same effect can be achieved with less drug.

PS uses in Poultry.

Rofenaid is approved only for addition to feed for:

Turkeys: Prevention of coccidiosis and fowl cholera

Chickens: Prevention of coccidiosis and fowl cholera, coryza, and E. coli infections.

Ducks: Control of fowl cholera, E. coli and P. anatipestifer infections.

PS vs various bacteria in vitro.

Results of sensitivity testing in vitro against isolates of avian origin suggest potential advantages of PS over S.

antibacterial	Study		
	1	2	3
	% resistant strains		

(# isolates)	(335)	(42-196)	(60)
erythromycin	8	82(183)	
tetracycline	13	82(196)	93
sulfonamide	51	42(36)	82
Rofenaid	1	3	38

Study 1: Siegel, 1979, P. multocida isolates

Study 2: Rosenberger, 1984, E. coli isolates

Study 3: Rosenstein, 1983, E. coli isolates (personal comm.)

PS Safety and Residue Considerations.

Rofenaid is safe for growing turkeys and chickens. Rofenaid is also safe for laying and breeding chickens and turkeys, but is prohibited for laying/breeding chickens because of egg residues. Sulfadimethoxine and ormetoprim are deposited into eggs of turkey breeders. FDA permits use of Rofenaid in turkey breeders because they do not perceive turkey breeder eggs as entering the food chain.

The tolerance for ormetoprim in edible tissues is 0.1 ppm. Residues of ormetoprim cannot be cooked out. Ormetoprim residues always are lower than sulfadimethoxine (SDM) residues in poultry fed Rofenaid. Therefore Rofenaid residues may be monitored by monitoring SDM concentrations. At 0 day withdrawal, 15 week turkeys that had recieved 0.01% Rofenaid continuously had the following SDM tissue concentrations;

Muscle	0.57 ppm
Liver	1.31 ppm
Kidney	5.72 ppm

The approved dose level in turkeys is 0.01% in feed (1/2 lb Rofenaid/ton). Feeding 10% of that level (0.001%) during the withdrawal period was found to result in SDM residues at the tolerance level. There are specific tests for SDM in feed.

Antimicrobial Susceptibility Theory and Interpretation

W. Douglas Waltman

The susceptibility of a microorganism to a particular antimicrobial agent or agents has become a vital part of treating diseases in any host. With rare exceptions, gone are the days, where the susceptibility of an individual bacteria can be predicted to a given antimicrobial agent. The development of antimicrobial resistance makes susceptibility testing as important, or more so, as identifying the organism. Since the susceptibility determination has become so critical in defining the treatment regimen, it is paramount that the information provided by the susceptibility test be accurate, reliable, and as close as possible predict the in vivo response.

There are essentially two methods of determining antimicrobial susceptibility: disk diffusion and dilution testing. The disk diffusion test is probably the most widely used procedure in veterinary laboratories. The dilution test procedure may be conducted in broth or in agar. When performed in broth it may be in a macro- or micro- format. With the dilution test procedure, the antimicrobial concentration may be serially diluted to provide Minimal Inhibitory Concentrations (MIC's) for individual organisms.

Theory

Antimicrobial susceptibility testing is an in vitro procedure whereby the inhibitory effects of various antimicrobial agents may be tested against the etiological agent of some disease. When various host, pharmacological, and practical aspects are taken into consideration the clinician should be able to use this information to predict the in vivo response and to choose the best agent for the particular disease situation.

The disk diffusion procedure is commonly employed in most veterinary diagnostic laboratories, however, with the development of commercially available systems, the microtiter broth procedure is becoming more widespread. The disk diffusion procedure uses antimicrobial impregnated disks that are standardized by FDA as to antimicrobial concentration and disk characteristics. The principle of the test involves the radial diffusion of the antimicrobial agent out of the paper disk into the agar medium. As the agent diffuses from the disk a concentration gradient is produced that decreases as it moves away from the disk. Simultaneously, with the diffusion of the agent into the media, the inoculated test organism is growing over the entire surface of the plate. The bacteria is able to grow everywhere, except areas where the antimicrobial agent concentration is sufficient to inhibit the bacteria. Since the agent diffuses radially, this results in circular zones of inhibition around the disks. The size of the

zone diameter, or the distance the agent has traveled away from the disk, represents the concentration of the agent that is inhibitory to the respective bacteria. The concentration of the agent may be determined by correlation with the broth dilution test (ie. MIC value).

In theory, the results of the two test methods, disk-diffusion and broth dilution, are inversely correlated (5). Generally, larger zone diameters correspond to higher MIC values. Figure 1 illustrates the relationship between zone diameters and MIC values. This relationship is established by testing more than 100 isolates and plotting them as a scattergram. The regression line is then calculated to express the relationship (1). The regression line will usually be different for each agent tested.

Standardized Procedures

In order to insure accuracy and reproducibility, the test procedures have been standardized and must be followed.

1. Media

a. Mueller-Hinton:

The recommended medium for both the disk diffusion and broth dilution procedures is Mueller-Hinton (MH) agar or broth, respectively. This media has been formulated to allow good growth of most of the Enterobacteriaceae, staphylococci, and enterococci. It contains little or no thymidine or thymine which inhibits the activity of sulfonamides. Figure 2 illustrates the importance of using MH. Tryptose (TRYP), brain heart infusion (BHIA), and nutrient (NA) agars all contain substances that alter the activity of antimicrobial agents, especially the sulfonamides.

b. pH of media:

The pH of the test media must be controlled, because the activities of many antimicrobial agents are effected by changes in pH. The standard pH should be 7.2 - 7.4. Figure 3 illustrates the effect of changing the pH of the media. Aminoglycosides, macrolides, and clindamycin/lincomycin are more active at basic pH's; tetracyclines, methicillin, novobiocin, and nitrofurantoin are more active at acidic pH's; and penicillin and chloramphenicol are not effected significantly by pH changes (6).

c. Agar depth:

The depth of the agar is critical in order to standardize the diffusion properties of the individual antimicrobial agents. Agar that is too thin will produce larger zones and conversely, agar that is too thick results in smaller zones of inhibition. The agar should be approximately 4 mm thick. This corresponds to 25 - 30 ml of agar for 100 mm petri dishes and 60 - 70 ml for 150 mm petri dishes.

d. Divalent cations:

The concentrations of divalent cations, in particular, calcium and magnesium, are important for testing P. aeruginosa. Reactivity to tetracyclines and aminoglycosides may vary with different concentrations. Generally, the magnesium concentration should be 20-35 mg/l and for calcium should be 50-200 mg/l (6). Usually, the media manufacturers are listing the concentrations of these cations on their products.

e. Growth of fastidious strains:

To test strains that fail to grow satisfactorily on standard MH agar, 5% defibrinated sheep blood may be added to the medium. Certain agents, especially nafcillin and novobiocin should not be tested when blood is added to the medium.

2. Antimicrobial disks

a. Selection of agents to test:

The antimicrobial agents to be tested should correspond to the agents approved for use in the animal species of concern. In some cases families of agents may be tested by a single member, for instance, the tetracycline family may be represented by using tetracycline alone. Lincomycin is more accurately tested using the clindamycin disk. Although in poultry, ormetoprim-sulfadimethoxine is the approved agent, it is routinely tested for with the trimethoprim-sulfamethoxazole (human agent) disk.

Agents other than those approved for use may be tested to provide taxonomic or epidemiological information. However, the results of these tests should not be reported to the clinician to avoid confusion.

b. Potency of the disks:

A commonly asked question is why are some disks 10 ug, 30 ug or 300 ug. The potency of the disks are selected for each agent based on the reactivity to a panel of more than 100 strains of bacteria with differing MICs. Three or four disks containing different concentrations of the agent are tested with the panel. The resulting zone diameters for each disk are plotted against the MIC, and from that data a decision is made concerning the best disk potency (1). Generally, a 2-fold increase in disk potency only increases the zone diameter 3 or 4 mm (2). Typically, a disk concentration is selected that provides zone diameters between 20 and 30 mm for susceptible strains.

c. Storage of antimicrobial disks:

With the exception of beta-lactam agents, which should be stored frozen, disks should be stored desiccated under refrigeration. The working disks should be refrigerated until use. They should be allowed to warm to room temperature before using.

3. Inoculum preparation

Susceptibility tests should only be conducted on pure cultures. They should not be conducted directly from clinical material.

a. Broth method:

Select a well isolated colony or colonies from agar media and transfer into 5 ml of tryptic soy broth. Incubate the broth until turbid. Adjust the turbidity using sterile saline to approximate a McFarland 0.5 turbidity standard. This adjustment may be visually or with the help of a spectrophotometer.

The adjusted broth culture is inoculated onto the surface of the MH agar plate using a sterile swab. The swab is dipped into the broth, the excess liquid is expressed out, and the entire agar surface is streaked. The agar surface is streaked 3 times, rotating the plate 60 degrees each time. It is recommended that the MH plate be warmed to room temperature and that there is no visible moisture on the surface of the agar.

b. Plate method:

Instead of growing the bacteria in broth, sufficient bacterial growth may be removed from a non-selective plating media to make a solution corresponding to a McFarland 0.5 turbidity. Sometimes sufficient thymidine or thymine may be carried over by this method, which may effect the testing of sulfonamides.

c. Turbidity adjustment:

It is important to standardize the inoculum density before testing. Figure 4 illustrates the effects of changing the density of the inoculum. Generally, as the density is increased the zone diameters will be smaller, conversely if the density is not enough the zone diameters will be too large. A McFarland 0.5 turbidity corresponds to about 3×10^8 bacteria/ml.

4. Placement of disks

a. Number of disks:

The number of disks tested on each plate should be limited to the number which allows the measurement of individual zones of inhibition. Typically, this is 12 or fewer disks for a 150 mm plate and 6 or less for a 100 mm plate. Individual disks should be at least 15 mm from the edge of the plate and at least 15-20 mm from another disk (1).

b. Time of placement:

The disks should be added to the plate from 5 - 15 minutes after inoculating the plate. Once the disks are added to the plate they should not be moved, because the antimicrobial agent begins diffusing immediately. Each disk should be lightly touched with a sterile instrument to insure contact with the agar surface.

5. Incubation of plates

a. Temperature:

Within 15 minutes of adding the disks, the plates should be inverted and placed in the incubator at 35 C. The temperature is important since it can effect the growth rate of the bacteria. Figure 5 illustrates the effect temperature may have on the test results. In this example, using S. aureus, the bacteria did not grow at 25 C.

A temperature of 35 C has been shown to be critical when determining methicillin resistance of S. aureus.

b. Atmosphere:

The plates should be incubated aerobically. Incubation under increased carbon dioxide levels or anaerobically may effect the activity of some of the antimicrobial agents. Figure 6 illustrates the effect of incubation under increased carbon dioxide concentration. There is an initial decrease in pH, which will alter the effect of some antimicrobial agents.

6. Reading and recording

The plates are incubated for 16-18 hours before reading the results. The diameters of the zones of inhibition are measured to the nearest mm with the unaided eye. The zone diameter is measured to the outermost rim of the area which exhibits a homogenous and complete zone of growth. There are some exceptions, which are outlined by Acar (1) and Barry and Thornsberry (2).

For broth dilution tests, the MIC is the lowest concentration that completely inhibits the growth of the organism as detected by the unaided eye.

Interpretation

The NCCLS has established guidelines for interpreting the results of the disk diffusion and broth dilution tests (5). These guidelines are valid when the tests have been conducted under the standard procedures outlined above. Based on the magnitude of the zone diameters or the MICs, an individual bacteria may be categorized as susceptible, intermediate, or resistant to a particular antimicrobial agent. The three categories have been selected based on achievable blood or tissue levels of each agent in the human. The following definitions apply:

Susceptible: "an infection due to the strain of bacterium can be inhibited by achievable serum or tissue levels to the dosage of antimicrobial agent recommended for that type of infection and infecting species, unless otherwise contraindicated (5)"

Intermediate: "strains with MICs that approach or can exceed usually attainable blood or tissue levels and for which response rates can be lower than for strains in the susceptible category (5)". Under certain circumstances bacteria may be inhibited that fall into this category.

Resistant: "strains that are not inhibited by the usually achievable systemic concentrations of the agent with normal dosage schedules and/or fall in the ranges where specific microbial resistance mechanisms are likely, and where clinical efficacy has not been reliable in treatment studies (5)".

Interpretation of disk diffusion tests based only on the presence or absence of a zone of inhibition without regard to the magnitude of the zone as an indicator of susceptibility is not acceptable (5).

The broth dilution test may generate MIC values which provide quantitative data as to the amount of the antimicrobial agent that is required to inhibit the particular bacteria. More commonly the broth dilution test is not formatted to provide MIC values, but to provide "breakpoints". These are designed to approximate the 3 categories listed above, susceptible, intermediate, and resistant.

The interpretative guidelines that have been established are for the treatment of systemic diseases and are not to be used for interpreting susceptibility results for agents used for non-therapeutic purposes (ie. prophylaxis or growth promotants) (5).

Limitations

The limitations of the disk diffusion test include:

- a) can only test rapidly growing microorganisms, such as members of the Enterobacteriaceae, staphylococci, and enterococci,
- b) test must be conducted aerobically,
- c) there may be diffusion problems with some agents (e.g. polymyxins),
- d) varying concentrations of combinations of agents can not be tested.
- e) not quantitative

An important consideration for the testing and interpretation of antimicrobial susceptibility results of bacteria from veterinary sources is the fact that the NCCLS guidelines are based on human blood or tissue levels. There is presently an effort through NCCLS and AAVLD (possibly others) to provide guidelines for veterinary testing and interpretation. The NCCLS has recently produced a proposed standard, M31-P (5), that is undergoing review. This standard is based on NCCLS documents M2-A5 (3) and M7-A3 (4), the "human" clinical counterparts.

Quality Control

An important, often overlooked, part of antimicrobial susceptibility testing is the existence of a routine quality control program. This insures that the standard procedures being used are in fact producing accurate, reproducible results. The common method of quality control consists of running control strains along with the test isolates. Commonly used control strains include E. coli ATCC 25922 and ATCC 35218, S. aureus ATCC 25923 and ATCC 29213, and P. aeruginosa ATCC 27853. The results obtained for these strains should be compared to the expected results found in published tables (NCCLS M31-P). Generally, if the results of more than 1 out of 20 consecutive tests for each agent/organism are outside the control limits, then corrective action should be taken to determine where the problem lies.

The testing of control organisms should be daily for a period of one month. If after that period there has been little or no evidence of problems the testing frequency may be cut back to weekly.

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The Future of Antibiotic Use in Poultry

R. Greg Stewart

Introduction and History

Perhaps the title of this presentation should be "Is there a future for antibiotic use in poultry?" The most recent drug development information collected by the Animal Health Institute suggests that the future is not bright. We remain hopeful and optimistic that a kinder, gentler Center for Veterinary Medicine (CVM) is in the making under the leadership of Dr. Steve Sundlof. Even if the throughput time can be reduced it is doubtful that cost of the regulatory component of drug development will ever decrease. The average cost spent by the pharmaceutical industry to develop a new chemical entity for food animals is now 22 million US\$. A supplemental approval for an animal drug averages 5 million US\$ (Anonymous 1995). It averages 11 years to bring an animal drug to market and only one drug in 7,500 screened ever makes it through the approval process. More than 3 years of this eleven is spent by the government regulators in reviewing the product (Anonymous 1993).

During the last ten years, the poultry industry has seen the introduction of a short list of new chemical entities, ceftiofur sodium (Naxcel™), semduramycin (Aviax™), narasin (Monteban™), halofuginone (Stenorol™) and Maxiban™ (combination of narasin and nicarbazine). Note: Cygro™ (maduramycin) was introduced into the market and then withdrawn. We still do not have appropriate combination clearances for Aviax™ which makes it nearly unusable. The industry still awaits combination clearances on Monteban™ and Maxiban™. Though not limited to just the last ten years, our armamentarium is shrinking. The industry has lost triple sulfas, sulfathiazole, neomycin-terramycin™ soluble, ipronidazole, dimetridazole, neomycin, gentian violet, coumaphos, nystatin, phenothiazine, butynorate (dibutyltin dilaurate), Wormal™ (combination of piperazine, phenothiazine, and butynorate) and the nitrofurans family, i.e. nitrofurazone and furazolidone. The nitrofurans family was removed because of their potential carcinogenicity. The histomonad treatment drugs ipronidazole (Ipropan™) and dimetridazole (Emtrymix™) were removed from the market not because they created significant risk to human health when used in a label manner or because they were unsafe in the target species but because another animal industry was using the drugs in an "extralabel" manner and that this misuse created an unsafe situation whereby the drug could be removed from the market by CVM. Instead of enforcing the regulatory guidelines on the offending groups, the Food and Drug Administration's

Center for Veterinary Medicine (FDA/CVM) removed the drug from the market leaving the turkey industry with no effective therapy for "blackhead" or histomoniasis. Paradoxically, the removal of these two treatment drugs that were used in a limited fashion when histomoniasis appeared has resulted in increased drug usage in turkeys. This has caused the industry to use preventatives, histomonostats, routinely and it is known that these drugs create hazardous waste during their manufacturing process. For every salable pound of 4-nitrophenylarsonic acid there is over two pounds of hazardous waste produced (Roney, personal communication). The FDA/CVM recently took steps aimed at the removal of piperazine, an anthelmintic, recently have stalled the action but will ultimately remove the drug. The turkey industry has estimated that this removal would cost them 375,000,000 US\$ annually (Deterling 1995). It also would have left the industry with another disease for which we had no label claim treatment. To examine what effect the "gridlock" in the regulatory process has had on the poultry industries, focus on the number of diseases for which we have no current label treatment or for which the price of the existing treatment has risen sharply because the regulatory process, in effect, created monopoly or oligopoly sources of supply.

Table 1.

Disease Conditions in Poultry without Label Treatments

<u>Disease</u>	<u>Species</u>	<u>Drug(s) Withdrawn</u>	<u>Current Therapy Effective</u>
<i>Salmonella arizona</i> (<i>Arizona paracolon</i>)	turkey	nitrofurans neomycin neo-terramycin™(^)	no current over 3 days of age.
<i>Salmonella sp.</i> (paratyphoids)	turkey	nitrofurans neomycin neo-terramycin™(^)	no current
<i>Salmonella sp.</i> (paratyphoids)	chickens	nitrofurans neomycin neo-terramycin™(^)	no current

<u>Disease</u>	<u>Species</u>	<u>Drug(s) Withdrawn</u>	<u>Current Therapy Effective</u>
<i>Escherichia coli</i>	chicken	nitrofurans triple sulfa neo-terramycin™(^)	no ■
<i>Escherichia coli</i>	turkey	nitrofurans neomycin triple sulfa neo-terramycin™(^)	no ■
Tapeworms	chicken	butynorate Wormal™	no current
	turkey	butynorate Wormal™	no current
<i>Histomonas meleagrid.</i>	turkey	dimetridazole ipronidazole	no current
	chicken	dimetridazole ipronidazole	no current
<i>Heterakis gallinarum</i>	turkey	phenothiazine	no current
	chicken	phenothiazine	no current
<i>Capillaria sp.</i>	chicken	coumaphos	no current
	turkey	coumaphos	no current
<i>Mycoplasma meleagrid.</i> (air sacculitis in young turkeys)	turkey	no	no current
<i>Eimeria sp.</i>	chickens	triple sulfa	no ■
	turkeys	triple sulfa	no ■

<u>Disease</u>	<u>Species</u>	<u>Drug(s) Withdrawn</u>	<u>Current Therapy Effective</u>
<i>Clostridium perfringens</i> (necrotic enteritis)	chickens	no	(+/-) □
<i>Clostridium perfringens</i> (necrotic enteritis)	turkeys	no	no current
<i>Candidiasis</i> (crop mycosis)	chickens	nystatin gentian violet	no current
	turkeys	nystatin gentian violet	no current
<i>Staphylococcus aureus</i> (arthritis)	turkeys	no	□ (\$)
	chickens	no	□ (\$)
<i>Bordetella avium</i>	turkeys	no	no current
	chickens	no	no current
<i>Hemophilus paragallin.</i> (coryza in laying birds)	chickens	sulfathiazole	no current
<i>Clostridium sp.</i> (gangrenous dermatitis)	chickens	no	no current
<i>Clostridium sp.</i> (ulcerative enteritis)	quail	no	no current
<i>Aspergillosis</i>	turkeys	no	no current
	chickens	no	no current

<u>Disease</u>	<u>Species</u>	<u>Drug(s) Withdrawn</u>	<u>Current Therapy Effective</u>
Chlamydiosis (<i>Chlamydia psittaci</i>)	turkeys	no	no current
<i>Pasteurella anatipestifer</i>	turkeys	no	no current
Broodiness in hens	turkeys	no	no current
	chickens	no	no current
<i>Mycoplasma iowae</i>	turkeys	special	no current
Non-specific diarrhea	chickens	no	no current
	turkeys	no	no current
Hysteria in hens	chickens	no	no current
	turkeys	no	no current
<i>Campylobacter jejuni</i>	chickens	no	no current
	turkeys	no	no current
Osteomyelitis (bacterial)	turkeys	no	no current

Character footnotes:

special- a special temporary approval for eradication use in primary breeders was withdrawn

(^) - water soluble form

(\$)- current cost of medication makes it unusable in birds over 10 days of age.

▣ - label claims do exist for the indication yet are considered ineffective or less than optimal in effectiveness.

Table 2.

Drugs whose Prices have risen sharply due to Limited Sources

<u>Compound</u>	<u>Market Status</u>
Sulfaquinoxaline	current
Sulfamethazine	current
Sulfadimethoxine	current
Nystatin	withdrawn
Erthyromycin	current
Novobiocin	current
Potassium Penicillin	current

Current Situation

Realistic choices and flexibility among therapeutics in poultry are diminishing with each passing year. Many drugs needed by the turkey industry are not available. Because of the smaller market size when compared to broilers drug sponsors almost always forego turkey new animal drug applications (NADAs) in favor of other projects. To license a product for leghorn breeders (less than 4 million birds per year) or turkey breeders (less than 5 million birds per year) would guarantee that the market would not cover the development and regulatory costs. The same is probably true for broiler breeders (approximately 66 million birds per year). The CVM Director has publicly discussed "life stages" as an alternative to granting turkeys or breeders a minor species exemption (IR-4). Drug sponsors and the Director should continue these discussions for the sake of the animal industries and ultimately for the sake of animals. In a time of increased pressure from consumer groups about "things in our stuff", i.e. chemical and pesticide residues, the industry currently holds the best record in the residue category (Anonymous 1993). This consumer group pressure coupled with some previous regulatory activities has also molded decisions made by poultry companies on their choice of therapeutics. In the meat and egg market, the protection of one's brand is of paramount importance. Therefore, many poultry companies have chosen to use only species specific label claim compounds. On one hand this appears to be an appropriate

decision yet when animal suffering, mortality, sources of infection, disposal of carcasses, and food safety are all properly evaluated together, there is reason to question the decision.

The regulatory process is more time consuming and more difficult in the USA than in other developed countries (Augsburg, personal communication). Combination clearances for coccidiostats, growth promotants, and organic arsenicals must be evaluated at each specific level rather than for a maximum of all three. If a maximum level of all three is cleared and there are no human risks, why must we wait for years for each three way claim to satisfy efficacy? All one has to do is examine the regulations in Switzerland, Japan, and the European Union as they pertain to combination clearances to see how well grounded in common sense they are. International harmonization discussions and negotiations between the EU and the USA are currently in process. In the opinion of the author, the harmonization will cause the CVM to give ground on some of these issues. Ultimately, harmonization will be a good thing for the poultry industry.

If a product is without efficacy in this the most analyzed animal industry of all, the producer and the integrator will know in short order and market factors will control the situation. Therefore, the CVM should relax the efficacy sections of NADAs or at the very least relax them on minor species, life stages or for three way combinations where the efficacy of the maximum level is known. To remain only at label levels for some coccidiostats may be overkill in certain climates or at certain times of the year. In very arid regions or when the relative humidity and/or litter moisture are low, the author has seen long term efficacy of coccidiostats used well below the label level. The excess usage in this type setting may cause the birds to become anorexic and increase cost in two ways. First by the excess cost per ton of feed and second by decreased weight gain both which raise live cost.

The industry wants the CVM and its Director to be successful in their current quest and stated goals. We need to fill in some holes and help with some of the CVM's opportunities. First, it is apparent that the regulatory reviewers do not have a depth of knowledge in the species that they review. If depth were developed, the CVM would come to learn that we slaughter chickens at weights that vary from 490 grams all the way up to nearly 4000 grams and that the density, nutrition, vaccination program, and drug program is very different at each weight. When that is understood, the industry will help the CVM to understand that another permutation can be superimposed on nearly all the above weight ranges for yellow versus white skinned birds. Can we call this "affirmative action in chickens"? In the 1970's the CVM was made up of

veterinarians many of whom had been in practice and who knew agriculture first hand. A lot of those folks are no longer on the roster. Has the CVM ventured too far away from first hand knowledge about how animal agriculture works?

The CVM must admit the obvious. The industry shuttles coccidiostats and growth promotants on the same chickens. One broiler chicken may see two or three shuttle programs in its life not just one. The industry must also rotate programs very frequently to ensure that we are not contributing to the development of resistant strains of coccidia. This is the result of many thousands of man-hours and necropsy evaluations each year. The author knows of no other industry where this level of attention to detail is paid. The CVM should work with the industry in developing the best regulatory pathway for ensuring success in this area. The industry is currently using a paucity of drugs. In broilers, less than 2.0 % of the live cost of the animal is spent on total medication. In turkeys, less than 2.2 % of the live cost of the animal is spent on total medication (Brown 1995). When the industry has a legitimate need for the use of a therapeutic, it expects that the drug will be available. The industry is growing at twice the rate of other animal industries (Anonymous, 1995). The regulatory quagmire and the resulting failure to fund research and development that it has precipitated is now compromising the industry's vibrant growth and future. We have no effective treatments for our most devastating disease conditions. How are we to treat respiratory conditions in chickens and turkeys?

There has been much discussion about the impending licensure of the fluoroquinolone family of antimicrobials. Some of this discussion has included how veterinarians have not been responsible in their use of antimicrobials or that the CVM would be irresponsible in granting such licenses. Let us examine who is preaching doom. Infectious disease "specialists" in human medicine appear to be concerned about antimicrobial resistance occurring in farm animals. They also embellish the theoretical hazard that these bugs once resistant will automatically become zoonotic and create treatment problems for human patients. No valid scientific evidence exists to support such a theory. This theory overlooks history, host adaptation in the microbes in question, and appears to neglect an old adage about getting your own house in order before you attempt to transform other households. There is widespread antimicrobial resistance to quinolones in human pathogens. This problem occurred without the help of the veterinary community. Examine how frequently the veterinary community makes use of culture and sensitivity testing of our animal pathogens. The data gleaned in this pursuit are then used to make informed choices about antimicrobials.

Has anyone ever compared the use of these tests in human medicine? When my children go to the pediatrician with bacterial sinusitis, otitis, or tonsillitis they have never been cultured for correct identification and characterization of the offending organism. Empirically, if the chosen therapy does not work and the patient is still alive the medication is changed to another drug again without culture and sensitivity testing. Perhaps the efforts of these same infectious disease "specialists" should be redirected towards helping their own colleagues make informed choices. Will there be a danger to approving quinolones for animals if all the human pathogens are already resistant to them ? Longer delay will ensure this.

Population Medicine and Preventive Medicine

Heretofore, the industry has relied upon rapid response time from the research community and biologics manufacturers to provide it with efficacious products that prevent clinical disease outbreaks. The population and preventative medicine approaches to avian medicine make optimal use of this fact. In the last two years, the cost of licensing of avian biologicals and the time required for same have risen substantially. The industry can no longer rely on this rapid response time to solve its problems. Delays in registration may ultimately lead to increased drug use in poultry. A recent analysis of drug use in a north Georgia broiler company found that in the absence of licensed biological annual drug (antimicrobial) use was nearly seven times higher than when the biological became available. After the biological was made available both drug use and condemnations were greatly decreased (Stewart, unpublished data). The United States Department of Agriculture's (USDA) Animal Plant Health Inspection Service (APHIS) division of Biotechnology, Biologicals, and Environmental Protection (BBEP) has recently suffered losses in manpower, a move to a new location with the loss of a mailbox for a month, and are rapidly training new personnel. All the while costs are escalating. The current cost of development for a food animal biological is now 2,000,000 US\$, more than double the cost of a companion animal product, and the registration period is four and one half years. Over one year is spent by regulators in reviewing the product (Anonymous 1995). This is however highly species variable. The largest variable in the cost of development relates to the cost of test subjects or target animals. For example, poultry species are less expensive than equidae. A general survey of poultry biological development and licensing firms suggests that for poultry clearances the following costs would be reasonable. A innovative non-biotechnology product would likely cost between 500,000 and 800,000 US\$ and take three plus years to register and license. A "me too" product would likely cost less than 500,000 US\$ and take approximately

1.5 years to register. Biotechnology products, of which there has been, at this writing, one licensed for poultry, cost considerably more to license because of the increased governmental requirements. It has been said that 59 billion doses of animal vaccine are produced in the USA and that over 50 billion doses are used in feathered species. The industry should expect that the BBEP should have experts in the field on staff that can quickly review biologicals destined for use in poultry. Deep concern has been expressed by the industry through the United States Animal Health Association to the BBEP. This slow down and sharp rise in cost may precipitate several scenarios, 1)that integrators will ultimately develop biological expertise to solve the problem on their own outside the formal review process or that they will use autogenous vaccines produced by licensed facilities, or 2)that because biologics are no longer rapidly available, actual drug use will increase due to a failure in the prevention of disease syndromes.

Summary

This presentation is near or at the end of an all day symposium on drug use in poultry species. We have heard from nearly all stakeholders and we have heard a plethora of information about pharmacokinetics, antibiotic sensitivity theory and interpretation, and even compounding. All of this is purely academic if we don't roll up our sleeves and get the pipeline fixed. A successful part of American agriculture that is rapidly growing and increasing exports every year is what can be compromised. The industry will continue to search for alternatives to drug use, preventive methods, and improvement in genetic stocks but all these doctrines cannot obviate the legitimate need for therapeutic agents. What the CVM and the industry must foster is a cooperative effort. The industry has extended its hand many times in sincere efforts to help the agency become more knowledgeable on the feathered species. Before this cooperative effort can be successful, the agency could take a lesson for its counterparts in Australia and New Zealand. The main difference is that their agencies want their animal industries and their allied industries**to succeed.**

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