



1111 North Dunlap Avenue
Savoy, Illinois 61874 USA
phone: 217/356-3182
fax: 217/398-4119
E-mail: fass@assoqh.org
Web Site: http://www.fass.org

EXECUTIVE VP - ADMINISTRATION

Charles L. Sapp
1111 North Dunlap Avenue
Savoy, IL 61874
217/356-3182
FAX 217/398-4119
chucks@assoqh.org

EXECUTIVE VP - SCIENTIFIC LIAISON

Robert G. Zimbelman
9650 Rockville Pike
Bethesda, MD 20814
301/571-1875
FAX 301/571-1837
rzimbelman@compuserve.com

PRESIDENT

Larry D. Satter (ADSA)
USDA, ARS
US Dairy Forage Research Center
608/263-2030
FAX 608/264-5147
office@dfrc.wisc.edu

PRESIDENT-ELECT

Mary Ann Ottinger (PSA)
University of Maryland
301/405-5780
FAX 301/314-9059
mo20@umail.umd.edu

TREASURER

Dennis N. Marple (ASAS)
Iowa State University
515/294-2160
FAX 515/294-6994
dmarple@iastate.edu

DIRECTORS

Elton D. Aberle (ASAS)
University of Nebraska
402/472-3571
FAX 402/472-6362
ansc202@unlvm.unl.edu

Henry M. Engster (PSA)
Perdue Farms, Inc.
410/543-3411
FAX 410/543-3965
hme@shore.intercom.net

Barbara P. Glenn (ASAS)
USDA, ARS
301/504-8315
FAX 301/504-8162
bglen@ggpl.arsusda.gov

Roger P. Natzke (ADSA)
University of Florida
352/392-1981
FAX 352/392-5595
natzke@dps.ufl.edu

Anthony J. Pescatore (PSA)
University of Kentucky
606/257-7529
FAX 606/323-1027
apescato@ca.uky.edu

William E. Sandine (ADSA)
Oregon State University
909/506-9966
FAX 909/506-2800
sandine@pe.net

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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane Rm. 1061
Rockville, MD 20852

To Whom It May Concern:

Enclosed please find a copy of my testimony from the August 19, 1998 Public Meeting Section 406(b) of the FDA Modernization Act of 1997. If you have any questions of require any further information, please let me know.

Thank you for your help.

Sincerely,

Dr. Robert G. Zimbelman
Executive Vice President – Scientific Liaison
Federation of Animal Science Societies

98N-339V

TSI

Stakeholder Comments for FDA/ Center for Veterinary Medicine
August 19, 1998 Public Meeting
Section 406(b) of the FDA Modernization Act of 1997
Docket Number 98N-0339
Robert G. Zimbelman, Ph.D., PAS
Executive Vice President - Scientific Liaison
Federation of Animal Science Societies

I am speaking today on behalf of the Federation of Animal Science Societies. This is a new federation as of January 1, 1998 with three member societies. They are American Dairy Science Association, American Society of Animal Science, and Poultry Science Association. The members of these three professional societies represent the bulk of animal science research, education, and extension activities in academia, industry, and government in the United States. Each society also publishes an internationally recognized journal based on rigorous peer review. Some part of my recommendations to the board of directors for this statement was based on my 27 years of experience in the animal health industry prior to representing the animal science professions in Washington, DC.

We wish to thank the FDA for this opportunity to comment relative to the requirement to develop and publish a plan for achieving compliance with its obligations under section 406 (b) of FDAMA. Rather than comment on all of the questions, we choose to focus on the issue of ensuring an appropriate scientific infrastructure and the ramifications this has for future challenges. Legislators, regulators, and the broader public all support a "science-based decision making process". How to achieve this is however beyond the understanding and clarity which is implied in that statement. The implication is that a single scientific consensus is always evident and can be simply applied to a given situation. In reality, science is a constant process of challenging the current dogma and reevaluation of what is known, what data exist, and what is the individual interpretation of various knowledgeable scientists. It becomes even more of a challenge when non-scientists choose a favored interpretation or select certain data out of context to make a point favorable to their interests. Often, both sides on a contentious issue will claim to have science on their side. It is also possible to find a given scientist who might support a minority, rather than a consensus, interpretation of any given study or set of data. Determining the scientific consensus can sometimes be a challenge. Let us proceed to some specific examples:

1. Toxicology studies:

Toxicology is, after all, biology. Over the years there has been a tendency to require standardized tests. Partially, this is defensible on the idea that various drug sponsors should have similar challenges. In some cases, however, there is adequate biological understanding to modify the protocol to provide a more meaningful set of results. This seems unlikely to happen unless the scientific expertise of FDA reviewers and sound justifications allow more meaningful testing to be conducted. In addition, some persons have concluded that small doses of exposure to large groups of animals or people are uneconomical or infeasible to study. So they propose that large overdoses of drugs to reasonable groups of animals are an appropriate model. This is the so-called maximum tolerated dose (MTD) concept for long-term studies. Biological considerations are not consistent with such a view. One animal with a million times dose is not the same as one million animals at one times the dose. Nor does a 100x or 1000x dose in a thousand animals really reflect an accurate description of expectations. Mechanisms of drug inactivation or excretion are certainly not the same at all doses. This leads to the situation where a compound that is frankly toxic can appear ok at doses below the MTD,

but a non-toxic compound that has physiological effects will look bad at extreme doses in long-term tests.

2. Efficacy studies:

As with toxicology, a standard set of studies for efficacy may fail to be the best course of action for drugs with markedly different purposes and modes of action. We believe the Animal Drug Availability Act (ADAA) intended to provide some flexibility in designing more appropriate studies to evaluate efficacy. It appears that there is difficulty in implementing that standard or perhaps in justifying it to various parties. A strong scientific analysis and understanding by the various constituencies or stakeholder groups could be helpful in permitting and defending a more tailored approach to such studies.

3. Risk assessment:

Risk assessment is a vital first step to risk management and risk communication. This is particularly true for issues such as food safety, residues, antibiotic resistance, and other concerns which the public might have. Risk assessment involves numbers and the desire for the public and other groups to have a definitive figure on which they can rely. This can be misleading. The relative risk depends on the level of exposure to the material or situation as well as the effects of such exposure. As stated above, the toxicology results are always going to have some degree of uncertainty as well as the potential exposure. In this day and age of computer capability for handling large amounts of data, it is tempting to have great confidence in certain numbers that might result from such data processing. Having a relative risk number is progress from the days when compounds were declared good or bad, but mathematics cannot replace biology. The assumptions that go into such models are likely to be very crucial to the final interpretation of such manipulations of data. Most often, the biological understanding of a given drug will likely influence any interpretation of relative risk. For example, with antibiotic resistance, there are at least three biological mechanisms involved in development of resistance. These are: Chromosomal, Plasmid, or Transposon mediated. Also, resistance to certain drugs confers resistance to other drugs. In addition, resistance can be defined in different ways, or concluded to have occurred when the drug is totally ineffective or when its susceptibility has changed by a certain factor. Unless these or other biological considerations are taken into account, relative risks coming from a mathematical approach only could be misleading. An antibiotic with a larger number than another with a smaller number may not be better if the biological considerations are not considered.

FDA/CVM needs to expand its scientific base for making and defending such complicated decisions. Perhaps, it could seek assistance from professional associations for assistance in assessing a scientific consensus on such issues. New drugs are developed by a broad variety of scientists depending on the specific drug discovery program. These include chemists, pharmacologists, physiologists, immunologists, microbiologists, nutritionists, biostatisticians, and others. Animal scientists are often involved in field or other studies which confirm efficacy and target-animal toxicity. If I look at the CVM Advisory Committee, it does not appear that there is an adequate representation of such scientific disciplines if they are expected to assess the scientific consensus. Many decisions in recent times appear to be focused on the clinical application and control of drugs. Clinical judgments and experience are vital factors in proper use of certain drugs, but the scientific underpinning may be most important in certain consideration of public health aspects. Mechanisms to get such scientific input are important as well as mechanisms to update the scientific capabilities of CVM reviewers as the science base changes rapidly with time. Careers of scientists may last longer than their initial scientific training. If adequate representation of a specific discipline is not available on your staff, perhaps you should consider outside contracting for review talent. Staffing at CVM should be balanced regarding appropriate disciplines to the extent possible.

We wish to compliment Dr. Sundlof and his staff for their past level of interaction with the American Society of Animal Science. They have participated at annual meetings of the ASAS Regulatory Agencies Committee (usually early March) and at symposia, which take place at the ASAS Annual meeting (usually in July). This level of interaction is very much appreciated. CVM is making many changes and we offer our assistance where we can be helpful

If you wish to discuss these ideas in more detail, please contact our EVP-SL, Dr. Robert G. Zimbelman at (301) 571-1875 or by E-mail at <RZimbelman@compuserve.com>.

CAN SOCIETY OF ANIMAL SCIENCE

ckville Pike
1, MD 20814-3998



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Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, MD 20852