1 very good data on which to specify limits for critical
2 control points, and I think a lot of folks would look to
3 risk assessment as a way of modeling the process and
4 quantitating the process, if possible, as a way of
5 specifying those types of criteria for a HACCP or quality
6 assurance program.
7 Of course, hazard assessment is an important part
8 of it, quantifying the probability that hazard will exist,
9 in this case drug-resistant pathogens. The third point is
10 the one that most people sort of refer to a lot, and that is
11 getting the estimate of risk from a given scenario. I think
12 a lot of people in the literature say we put too much
13 emphasis on getting the estimate and not enough emphasis on
14 understanding the process, setting out the process and
15 finding out where the data gaps are.
16 Mention has already been made about the trade
17 implications. I won't go into that. I think the bottom
18 line is important in this context, and that is that risk
19 assessment's greatest value in a regulatory scene is to try
20 to assist decision-making, no more than that.
21 [Slide]
22 We need to identify the outcomes of interest, and
23 in general terms the risk to human health of antibiotic use
24 in animals is well described in the framework document, but
25 I think that most people, when they start putting together

1 the specifics, need a lot more specification. There may be
2 subgroups of the population that need to be especially
3 looked at.
4 There needs to be discussion about whether it is
5 possible to do quantitative risk assessment or we may just
6 have to do a qualitative one. It is useful perhaps to think
7 about what are bounds of acceptable risk, and this has been
8 talked about today. So, the risk assessors can give the
9 estimates in those sorts of terms -- is it risk per million
10 of population? Is it risk of too many drug-resistant
11 bacteria in carcasses? What are the bounds of acceptable
12 risk?
13 [Slide]
14 Hazard identification or first stage of risk
15 assessment I won't go into anymore at this point because it
16 has been well laid out in the framework document and we have
17 talked about it already. There is sort of some fine-tuning
18 that we could talk about at some point.
19 [Slide]
20 This is sort of the heart and, again, I apologize
21 for it not showing up too well. There is too much
22 information on one slide. The heart of the risk assessment,
23 the way it is sort of evolving in the microbial food safety
24 area, in my opinion lies within the exposure assessment
25 phase and the dose response modeling phase of the process.

1 Now, the main goal of the exposure assessment phase is to be
2 able to estimate the prevalence of contamination, microbial
3 contamination of the product at the time of consumption.
4 That would be the ideal. And, the concentration of
5 bacteria, or genetic determinants or whatever it happens to
6 be, in the food. So, what total dose is a person getting at
7 the point of consumption? Because microbial agents tend not
8 to be cumulative, we usually don't think in terms of
9 prolonged exposure over a period of time. So, in a one-time
10 setting what is the exposure?
11 The dose-response aspect of it is a very hot topic
12 of research in the food and microbiology area. These are
13 the efforts, a set of efforts that are going into trying to
14 determine what are the expected efforts from a given
15 exposure. That is the prevalence of the organism and, if it
16 is there, what is the concentration. It is a very difficult
17 area to work towards but it is a very important one, and it
18 has implications to this situation as well on the drug
19 resistance side.
20 [Slide]
21 This is a very rough outline of a quantitative
22 microbial risk assessment, 0157 in hamburger, that was done
23 by some colleagues at Guelph, Mike Cassin et al., in the
24 International Journal of Food Micro. This year, I know that
25 USDA is working on this in a modular sort of approach in a

1 very big way, and I know there are other researchers working
2 on it as well.
3 Again, it is not showing up, unfortunately, and
4 the reason I am showing you this is just to give you a rough
5 outline of the types of exercises that other people are
6 working towards and maybe we can learn some lessons on the
7 drug resistance side. On the upper left of the screen,
8 basically this could be a set of equations or a single
9 figure on estimates of prevalence and concentration of 0157
10 in feces of cattle. I had a Ph.D. student who did his
11 thesis on trying to model that component of the process
12 itself. So, it can be simple or it can be complex depending
13 on how you do it.
14 These data from the prevalence and concentration
15 phase feed into processing and grinding module within this
16 risk assessment model, basically looking at the slaughter
17 and processing and handling of ground beef, and trying to
18 determine the various effects of parameters within that
19 system. So, within that little box I have incorporated many
20 different parameters and haven't broken it down for the sake
21 of simplicity.
22 That provides input for another model on the
23 prevalence and concentration in ground beef. So we go
24 successively down the road to the point of consumption. We
25 try to estimate again prevalence and concentration, feed

1 that into a dose-response model and get estimates of
2 mortality as a desired outcome. That is the general outline
3 of the quantitative risk assessment model.
4 [Slide]
5 We could apply the same kind of ideas to the
6 antimicrobial resistance area. On this slide, which is a
7 bit complex, I have partitioned out the different animal
8 species and just given examples of subtherapeutic and
9 therapeutic use. You can look at those differently for a
10 drug or a family of drugs, or what-have-you.
11 We have events that feed from the farm, as we
12 know, to slaughter animals, then through processing, and
13 dose response assessments. We also know that there is added
14 complexity. Reference has been made to birds and transport
15 and rodent vectors, and other things, and we all appreciate
16 that added complexity to the model. But I think it is
17 possible to do these things in a modular sort of format. I
18 don 't know if it is realistic to think about doing food
19 processing modeling for any microbial-resistant pathogens
20 alone. Hopefully, we could borrow a lot of the work that
21 has been done for Salmonella enteritides for poultry drug-
22 related resistance problems, 0157 models in beef perhaps.
23 So we could focus on the on-farm aspects which are most
24 germane to the issue of drug use.
25 In the swine area, just for the sake of argument I

1 have sort of boxed out a little bit the subtherapeutic side,
2 and we could look at that in more detail if the issue
3 happened to be approval of a new drug for subtherapeutic use
4 in swine. If you did that, you might want to structure the
5 model the way the industry works or could work. So, we
6 could try to conceptually lay out the process from birth
7 through transportation to slaughter for swine, and identify
8 the various segments in that life of a fat pig, where drugs
9 enter the system; what drugs are used; what is the duration
10 of treatment; what mixing of animals in shipping phenomena
11 do we have; what is the pathogen infection rate at different
12 stages of the industry. All of these things, and there are
13 many different parameters of each of those, might help us if
14 we better understood them or laid them out at least for how
15 the process works.
16 [Slide]
17 There is a great deal of interest in the whole
18 area of quantitative risk assessment of using tools,
19 information that is much more complete than we have in the
20 past in the sense that we have in the past too often, I
21 think, used point estimates of various parameters when that
22 loses a lot of information. As new techniques become
23 available and computing becomes much more amenable to doing
24 these sorts of things -- there are a lot of people engaging
25 more in Monte Carlo type processes which can handle the very

1 variability that we see in these sorts of parameters.

2 This is an example of one parameter from the 0157

3 risk model that looks at within-herd prevalence of the

4 organism in the literature. Based on information from the

5 literature we know that there is a range of prevalences that

6 have been detected, but there is a lot of uncertainty in

7 that prevalence because of the test methods that were used,

8 or the variation that we know exists in the cattle

9 population, and the actual biological variability that

10 exists. We have to capture that variability in some way and

11 that is what the statistical distributions do to assist us.

12 So, to the extent possible, we try to apply this to other

13 parameters that vary in the model, and try to develop the

14 approach that will best use that information in a full and

15 complete way.

16 [Slide]

17 There are other issues around risk assessment that

18 I think are appropriate for today's discussion. The issue

19 of making default assumptions in the process has been made,

20 and I think in general for most public health agencies they

21 would favor public health, whereas many people have

22 commented in the literature and elsewhere in the past that

23 when you do that successively you end up with risk estimates

24 that are very conservative, and perhaps overly conservative,

25 which may be justifiable on public health grounds but do

1 pose some difficulties.

2 We have considerable problems with uncertainty and
3 variability. One of the great things that impedes movement
4 of quantitative risk assessment into this particular issue
5 is the lack of knowledge of how the biological mechanisms
6 really do work in the field at the microbiological level, at
7 the animal production level, and at the slaughter and
8 consumption level. So, we don't even know perhaps how to
9 correct the structure of the model, let alone the problems
10 that we have with respect to not knowing much about how to
11 specify the parameters. We don't have very good data so
12 that creates lots of difficulties.

13 Validation is always an issue, and when people
14 talk about modeling we always want to know about validation.
15 One of the reasons for doing risk assessment in the first
16 place is because we can't really conduct experiments to look
17 at the whole process. We can't conduct an observational
18 study that would give us all the answers that we are looking
19 for. So, validating with an independent type of experiment
20 is problematic. One way that does come to mind to sort of
21 validate this is to use the idea of alternate models which
22 are themselves based on assumptions and distributions, but
23 if you get similar answers that gives you some confidence
24 that you may have the right approach.

25 [Slide]

1 The yellow light is on so I will skip the links.
2 What I think the FDA should consider embracing in its vision
3 of how to deal with this problem is the idea of a tiered
4 approach to risk assessment, that is, that we acknowledge
5 that we have to take action. We can't, as Dr. Bell says,
6 just delay things in order to get the last word on risk
7 assessment. We have to move ahead to protect public health.
8 But we also should recognize, I think, that the techniques
9 that we have are not perfect; we don't have all the
10 information and so we have to go with the best that is
11 available. That would probably be a qualitative approach
12 that is suggested in the framework document.
13 But, I think down the road, as techniques evolve,
14 as understanding of the way that antibiotic resistance
15 improves, as we get more information, as the techniques for
16 quantitative microbial risk assessment evolve in other
17 fields, and as researchers try to improve things in this
18 field we can see, firstly, a better way where there could be
19 a higher sort of level of tiers of risk assessment modeling
20 which could be more expensive -- well, undoubtedly would be
21 more expensive, more demanding of resources but might give
22 more precise estimates. We might have to rely less on these
23 conservative defaults.
24 [Slide]
25 I think an important message that I would like to

1 give as an international sort of visitor and as a scientist
2 working in the area is that the very fact that FDA would use
3 this type of approach would encourage others to do it as
4 well. People in the industry and people in academia, and
5 students will start to learn about it and would approve the
6 process. Thank you, Mr. Chairman.
7 DR. STERNER: Thank you, Dr. McEwen. We will keep
8 on task and finish one more talk. We will hold questions
9 until later this afternoon for our panel and invited
10 speakers. So if you will write them down so you remember
11 them correctly.
12 Next, we have Dr. Pattie Lieberman, from the
13 Center for Science in the Public Interest, giving their
14 overview of their report on recommendations relevant to the
15 use of antimicrobials in food animals. Dr. Lieberman?
16 **Overview of CSPI Report on Recommendations Relevant**
17 **to Use of Antimicrobials in Food Animals**
18 DR. LIEBERMAN: Thank you very much.
19 [Slide]
20 CSPI has been working since 1971 on nutrition and
21 food safety issues. We are the largest consumer
22 organization which focuses primarily on food issues,
23 reaching more than a million North Americans with our
24 publication, Nutrition Action Healthletter. While we are
25 best known for our nutrition work, recently we have

1 represented consumer interests in efforts to bring about
2 changes in policy concerning the use of antibiotics in
3 doctors' offices, hospitals, and on the farm. We released a
4 report in May, 1998, that is part of the packet today,
5 Protecting the Crown Jewels of Medicine. And, we work with
6 a coalition of other health groups and scientific experts in
7 antibiotic resistance. We appreciate the opportunity to
8 speak at this important meeting.
9 [Slide]
10 In the past few years, many leading experts have
11 urged reductions in agricultural uses of antibiotics. As
12 you know, in the fall of 1997 a World Health Organization
13 commission stated that any antimicrobial agent for growth
14 promotion in animals should be terminated if it is used in
15 human therapeutics, or if it is known to select for cross-
16 resistance to antimicrobials used in human medicine.
17 In February, 1998, Wolfgang Witte, of the Robert
18 Koch Institute in Germany, stated in a commentary in Science
19 magazine, "In the future, it seems desirable to refrain from
20 using any antimicrobials for the promotion of animal
21 growth. As exemplified by the use of virginiamycin in
22 animal feed and the subsequent emergence of enterococci
23 resistant to antibiotics, the use of any antimicrobial can
24 lead to unexpected consequences that limit medical choices."
25 In May, 1998, Stuart Levy , of Tufts University,

1 wrote in the New England Journal of Medicine an editorial
2 that recent findings have "made it even clearer that the use
3 of growth promoters affects the drug resistance of
4 environmental reservoirs, with direct consequences for the
5 treatment of disease in humans" and that "such findings led
6 to a ban on avoparcin in the European Union countries and,
7 recently , on virginiamycin in Denmark."
8 In December, 1998, the European Union voted to ban
9 the use of tylosin, spiramycin, virginiamycin and bacitracin
10 for growth promotion in livestock to come into line with the
11 WHO recommendation.
12 But in the U.S., instead of reducing uses of
13 antibiotics in livestock, we are still expanding into new
14 uses that have the potential to endanger human health.
15 Therefore, we applaud the FDA for at least attempting to
16 slow this trend by including in the new animal drug
17 approvals process new criteria that will consider antibiotic
18 resistance. We strongly agree with the statement in the
19 framework document that "FDA's primary public health goal
20 must be to protect the public health by preserving the long-
21 term effectiveness of antimicrobial drugs for treating
22 diseases of humans." That is a standard that must not be
23 undermined by economic concerns.
24 The FDA framework document has several strengths.
25 The first is that the proposal would require that detailed

1 drug sales information be submitted as part of drug
2 experience reports. In addition to sales data, it is
3 imperative to know how the antibiotics are being, in what
4 species, in what dosage, for what purpose, and for how long.
5 Currently, drug usage information is sorely lacking.
6 Instead, the FDA must rely on rough estimates of how much
7 antibiotics are used. Without detailed information it is
8 difficult to correlate antibiotic use with the emergence of
9 resistance. In order for any post-approval monitoring
10 system to be effective, the FDA needs that piece of the
11 puzzle. Furthermore, that usage information should not only
12 be available to FDA but should be made publicly available to
13 consumers and researchers.
14 In general, CSPI is supportive of a tiered
15 approach to new animal antibiotic approvals, but we disagree
16 on which categories are appropriate for us in food animals.
17 We agree that the categorization should be based on several
18 criteria.
19 First, it should be based on how important the
20 antibiotic is in treating human infections.
21 Second, it should be based on how likely that its
22 use in animals will cause resistance.
23 Third, it should take into account the level of
24 exposure to humans that the use in animals will cause.
25 Certainly a fluoroquinolone, because of its

1 extreme importance in human medicine, should be subjected to
2 a higher level of scrutiny than would an ionophore. And,
3 antibiotics that are given for a long duration or to an
4 entire flock should receive more scrutiny than a short-term
5 use injectable product.
6 [Slide]
7 It is clear that the use of antibiotics in
8 livestock leads to resistance among commensal bacteria in
9 animals that can make people sick, for example enterococci,
10 or can horizontally transfer their resistance factors to
11 human pathogens.
12 A striking example of horizontal transfer of
13 resistance genes to a human pathogen due to agricultural
14 uses of an antibiotic comes from Germany. In 1983, German
15 farmers introduced a new antibiotic, nourseothricin, for
16 growth promotion n swine. Before nourseothricin was used,
17 nourseothricin resistance had never been observed to
18 nourseothricin in bacteria from animals or humans. In 1985,
19 nourseothricin-resistance genes were found in E. coli in
20 swine and pork products. By 1990, E. coli containing the
21 resistance genes were found in farm workers, farmers'
22 families, citizens in the community in which nourseothricin
23 was used, and patients suffering from urinary tract
24 infections caused by E. coli. No nourseothricin-resistant
25 bacteria were isolated from people or animals in other parts

1 of Germany where the antibiotic was not being used. A few
2 years later, the resistance gene was found in Shigella, a
3 bacterium found in primates but not in swine. The
4 appearance of nourseothricin-resistant Shigella suggested
5 that resistance emerged due to the transfer of a resistance
6 gene from bacteria exposed to antibiotics on the farm to a
7 human pathogen. Therefore, the potential horizontal
8 transfer of antibiotic resistance from commensal bacteria to
9 pathogenic bacteria must be considered in ranking the
10 antibiotic's importance. Similar considerations should be
11 paid to antibiotics that select for multi-drug resistance.
12 [Slide]
13 While we agree with the FDA on the basic
14 principles of how antibiotics should be categorized, we
15 disagree on what would be the appropriate way to handle
16 approvals of antibiotics in certain categories. The biggest
17 problem is that Category I drugs should not be approved at
18 all for use in livestock. Drugs that are essential for
19 treating serious or life-threatening diseases in humans, for
20 which there is no satisfactory alternative, or antibiotics
21 that are important for treating foodborne diseases where
22 there are limited therapeutic options, and drugs that are
23 members of classes of drugs that have a unique mechanism of
24 action or a unique resistance mechanism should be preserved
25 to protect human health. As previously stated, the FDA's

1 primary responsibility is to protect the public health by
2 preserving the long-term effectiveness of antimicrobials for
3 treating diseases of humans. Approving any Category I drug
4 for livestock endangers the public health and should only be
5 considered if there are no other effective means, either
6 other available antimicrobials or changes in management
7 practices, to reduce a particular livestock disease.
8 Category II drugs delineated in the framework
9 document should be held to the standards that FDA put forth
10 for Category I drugs. Even though satisfactory alternatives
11 currently exist, we must not allow their use in livestock to
12 compromise their effectiveness in treating human disease.
13 Drugs deemed Category III in the existing
14 framework document should be subdivided into two categories.
15 Antibiotics that are little used in human medicine should be
16 subjected to pre- and post-approval monitoring, detailed
17 drug sales information should be kept, and resistance should
18 trigger withdrawal of approval, as described in the
19 framework document for Category II drugs.
20 Drugs that are not used in human medicine, such as
21 ionophores or polymixins, should be held to the pre- and
22 post-approval studies and monitoring laid out for Category
23 III drugs, unless there is new evidence to suggest that
24 their use in animals endangers human health, for example by
25 causing cross-resistance to antibiotics important in human

1 medicine or selecting for multi-drug resistance.

2 To adequately protect public health, FDA's

3 framework must prevent agricultural drug use from causing

4 human illness. It is not enough to just set guidelines for

5 revoking a drug approval once people get sick. For any

6 antibiotic that is the drug of choice or important in

7 treating potentially serious human disease, decreased in

8 vitro susceptibility in animal isolates may be the

9 appropriate threshold instead of waiting to see decreased

10 susceptibility develop in human isolates, or complete

11 clinical resistance.

12 If after an approval is granted a resistance

13 threshold is reached, the drug should immediately be

14 withdrawn. Our concern is that if the drug is not withdrawn

15 immediately, and a protracted regulatory process is

16 necessary to stop the drug's sale, the public health may be

17 put in danger. For example, if the FDA must rely on section

18 512(e) that allows for industry to request a hearing if FDA

19 wants to revoke an approval, it may be years before an

20 antibiotic that is causing resistance to develop is removed

21 from the market. We also are concerned that the industry

22 will endlessly stall the FDA by arguing that no action

23 should be taken because the threshold set was inappropriate

24 or that it was not based on sound science.

25 After the product is off the market, the drug

1 sponsor could propose mitigation strategies, such as changes
2 in dosage or duration of treatment, education of
3 veterinarians and farmers about proper use, and restrictions
4 on how the drug is marketed, that might decrease the
5 development of resistance and increase safety. If the
6 proposed mitigation strategy is acceptable to the FDA then
7 approval could be reinstated.
8 In the current framework document there is no
9 proposal on how thresholds will be set. In general, and
10 perhaps as expected, we are concerned that they will be too
11 high. For antibiotics used in human medicine, thresholds
12 should be set extremely conservatively to adequately protect
13 the public health. Additionally, any post-approval
14 monitoring system must be sensitive enough to detect even
15 small changes in resistance, and include non-foodborne as
16 well as foodborne pathogens.
17 A major weakness in the framework document is
18 that, as written, it does not address already approved
19 antimicrobials. Since almost half of all antibiotics used
20 in the U.S. are used in agriculture, and those drugs already
21 are approved by the FDA, the framework must be applied to
22 drugs already on the market in order to protect the
23 effectiveness of the antibiotics for human, as well as
24 veterinary, medicine.
25 We are particularly concerned about the

1 antibiotics approved for subtherapeutic use in livestock.
2 In FDA's own words, prudent use of antimicrobials is use
3 that maximizes therapeutic effect while minimizing the
4 development of resistance. CSPI believes that under that
5 definition of prudent use the subtherapeutic, or non-
6 therapeutic use of antibiotics would not be allowed.
7 Subtherapeutic use for growth promotion is not prudent
8 because it increases the likelihood of antimicrobial
9 resistance and jeopardizes the continued efficacy and
10 availability of antimicrobials for use in livestock and
11 people while providing no therapeutic effect. We urge the
12 FDA to take steps similar to what the World Health
13 Organization has proposed and the European Union has
14 implemented to stop wasting these vital drugs on growth
15 promotion. The minor and often unnecessary benefits of
16 improved feed efficiency are not worth the threat that such
17 uses pose to the continued effectiveness of antimicrobials
18 and to the public health.
19 We also are concerned about certain therapeutic
20 uses of antibiotics already on the market. For instance, the
21 1995 fluoroquinolone approval for poultry in the drinking
22 water. Already fluoroquinolone resistance is emerging in
23 poultry in the U.S. Michael Osterholm from the Minnesota
24 Department of Health has reported preliminary findings from
25 a study of poultry. He found that as many as 79 percent of

1 supermarket chickens are contaminated with Campylobacter, 20
2 percent of which were resistant to fluoroquinolones. Among
3 turkeys, 60 percent were contaminated with Campylobacter, 84
4 percent of which were resistant to fluoroquinolones.
5 Campylobacter causes 2 million to 8 million illnesses and
6 200 to 800 deaths per year, and is linked to Guillain-Barre
7 syndrome.
8 We also think that the FDA should not have
9 approved Baytril, the injectable fluoroquinolone product for
10 cattle, in 1998. Previously approved antibiotics are just
11 as effective in treating bovine respiratory infections. At
12 a minimum, the FDA should have required automatic withdrawal
13 of Baytril if harmful fluoroquinolone-resistant bacteria
14 reached predetermined levels set by the FDA and CDC. Bayer
15 agreed to voluntarily withdraw the product from the market
16 if the FDA finds significant increases in fluoroquinolone
17 resistance in post-approval monitoring. But that agreement
18 lacks teeth. And, if resistance develops due to Baytril's
19 use it is likely to result in endless stalling and
20 negotiations.
21 I am encouraged by Dr. Sundlof's recent comments
22 at the FDLI meeting, stating that review of already approved
23 antimicrobials would be possible within the new framework
24 contingent upon available funds. However, the language of
25 the framework document should explicitly state that it will

1 be applied to previously approved antimicrobials. Also, a
2 review of the fluoroquinolone approvals, especially in
3 poultry, should be among CVM's highest priorities.
4 [Slide]
5 We applaud the FDA for considering adding criteria
6 on antibiotic resistance of the animal drug approval
7 process. let me summarize that if the FDA really wanted to
8 protect the public health and preserve the effectiveness of
9 these miracle drugs, then it would need to fine-tune and
10 strengthen the framework document by applying it to drugs
11 that are already on the market, such as antibiotics for
12 growth promotion and fluoroquinolones for disease treatment
13 in poultry and cattle; by more clearly laying out the
14 process that would occur if thresholds are reached to
15 withdraw a drug from the market; and by not allowing
16 Category I drugs to be approved for livestock other than in
17 the most extreme cases to alleviate animal suffering when no
18 other options exist.
19 We urge the members of VMAC to take into account
20 these comments in their deliberations of the framework
21 document. Thank you very much.
22 DR. STERNER: Any questions from the panel members
23 for Dr. Lieberman?
24 [No response]
25 That will conclude our morning commentary. Dr.

1 Geyer has some housekeeping announcements to make.

2 DR. GEYER: I have just two announcements. The

3 first one is crucial because it has to do with lunch. All

4 of you who are seated at the tables and wearing one of these

5 name badges, the area behind the salad bar in the restaurant

6 is reserved for you. The restaurant is on your left as you

7 go out of the doors here.

8 The other announcement is that I would like to

9 remind the guest speakers if you have hard copy of your

10 slides and overheads, we would like to have copies. You

11 should give them to either me or to John Sheid.

12 What time are we going to resume?

13 DR. STERNER: We will start promptly here at one

14 o'clock. The gauntlet has been laid by this morning's

15 speakers. Thank you, one and all, for your timely

16 presentations.

17 [Whereupon, at 11:45 a.m. the proceedings were

18 recessed, to be resumed at 1:00 p.m.]

1 A F T E R N O O N P R O C E E D I N G S

2 [1:00 p.m.]

3 DR. STERNER: We will proceed with this

4 afternoon's deliberations. Since it has been pointed out to

5 me that the ability of the mind to absorb is directly

6 limited by the ability of the rear end to sustain, and

7 recognizing that we have a very long program to get through

8 this afternoon, we will begin this afternoon's deliberations

9 with our representative from the American Veterinary Medical

10 Association, Dr. Lyle Vogel and the need for safe and

11 effective antimicrobials for food animals and the AVMA's

12 efforts regarding prudent use of antimicrobial drugs.

13 Dr. Vogel.

14 **Need for Safe and Effective Antimicrobials for Food Animals**

15 **and AVMA Efforts on Prudent Use**

16 DR. VOGEL: Thank you, Mr. Chairman.

17 [Slide.]

18 The American Veterinary Medical Association is a

19 professional association with over 62,000 members, which

20 includes 85 percent of the veterinarians in the United

21 States. The objective of the association is to advance the

22 science and art of veterinary medicine including its

23 relationship to public hearth, biological science, and

24 agriculture.

25 Since its inception in 1863, the AVMA has

1 continuously integrated the objectives of public and animal
2 health. A portion of the veterinarian's oath that is
3 administered to every United States graduate veterinarian
4 reads: "I solemnly swear to use my scientific knowledge and
5 skills for the benefit of society through the protection of
6 animal health, the relief of animal suffering, the
7 conservation of life cycle resources, the promotion of
8 public health, and the advancement of veterinary ethics."
9 Let me assure that the AVMA takes its
10 responsibility for the protection of public health very
11 seriously.
12 [Slide.]
13 The American Veterinary Medical Association shares
14 the concerns of the public, governmental agencies, and
15 public health community regarding the broad issue of
16 antimicrobial resistance and specifically the potential risk
17 of resistance developing in animals with subsequent transfer
18 to humans.
19 We acknowledge that a significant proportion, but
20 not all cases of human Salmonella and Campylobacter
21 infections originate in foods of animal origin. We also
22 acknowledge that the use of antibiotics by veterinarians
23 could possible contribute to antibiotic resistant bacteria
24 developing in animals which can then be transferred to
25 humans.

1 Because of that concern, the veterinarian
2 profession has invested considerable resources of personnel
3 and money into what we believe will be an effective response
4 to the potential problem.
5 However, we are also concerned that increased
6 regulation of animal drugs that is not commensurate with the
7 actual public health risk may adversely affect animal health
8 and welfare and may have unexpected adverse human health
9 consequences.
10 The magnitude of the human health impact of the
11 use of antimicrobials for animals is unknown, and inordinate
12 and unmeasured regulatory actions may unduly contribute to
13 the existing animal drug availability problem. This will
14 have consequences that negatively affect animal health and
15 welfare and ultimately could create other public health
16 risks, such as an increase in the transmission of zoonotic
17 pathogens to humans.
18 Increased regulation of animal drugs may have
19 significant known and unknown impacts on human and animal
20 health that need to be evaluated.
21 The issue of antimicrobial resistance has already
22 impeded the approval process for, and usage of, animal drugs
23 especially for food animal drugs. Actual label use of
24 fluoroquinolones in food animals has been banned. Drug
25 approvals of antibiotics, particularly the fluoroquinolones,

1 have been slowed. The number of fluoroquinolones approved
2 for food animals is extremely limited.
3 In at least one case, a drug sponsor has halted
4 further development of a good animal antibiotic. Who knows
5 how many other promising antibiotics are not being developed
6 because of the increased regulatory requirements?
7 [Slide.]
8 The use of drugs in animals is fundamental to
9 animal health and well-being. Antibiotics are needed for
10 the relief of pain and suffering in animals. For food
11 animals, drugs additionally contribute to the economics of
12 the industry. The gains that have been made in food
13 production capacity will not have been possible were it not
14 for the ability for reliable drugs to contain the threat of
15 disease to animals.
16 The increased capacity of the American livestock
17 producer has kept high-quality protein available for the
18 majority of U.S. consumers and consumers in many other
19 countries.
20 Other groups also recognize the need for
21 antimicrobials for animals. For example, the report of the
22 1997 WHO meeting states, "Antimicrobials are vital medicines
23 for the treatment of bacterial infections in both humans and
24 animals. Antimicrobials have also proved to be important
25 for sustainable livestock production and for the control of

1 animal infections that could be passed on to humans.

2 The recent report of the National Research Council

3 and Institute of Medicine's Committee states, "The benefit

4 to human health and the proper use of antibiotics in food

5 animals is related to the ability for those drugs to combat

6 infectious bacteria that can be transferred to humans by

7 either direct contact with the sick animal, consumption of

8 food contaminated with pathogens from animals, or

9 proliferation into the environment.

10 [Slide.]

11 We are concerned about the potential human health

12 impact, and we want to maintain the long-term effectiveness

13 of antimicrobials for animal and human use. We seek to

14 increase drug approvals for the treatment of animals.

15 Therefore, the AVMA is committed to ensuring judicious use

16 of antimicrobials by veterinarians for the prevention,

17 control, and treatment of animal diseases.

18 The AVMA has started a profession-wide initiative,

19 and we have included companion and food animal practitioner

20 groups and public health representatives to develop and

21 implement judicious use principles.

22 The approved document which contains the

23 principles is published in the January 15th, 1999 issue of

24 the Journal of the AVMA, and is being distributed in many

25 other ways. I have provided a copy for all of the committee

1 members.

2 [Slide.]

3 The document states the position of the AVMA as
4 when the decision is reached to use antimicrobials for
5 therapy, veterinarians should strive to optimize therapeutic
6 efficacy and minimize resistance to antimicrobials to
7 protect public and animal health.

8 The position statement recognizes that
9 veterinarians consider other therapeutic options before
10 using antimicrobial therapy. The statement encourages
11 veterinarians to balance public and animal health in their
12 considerations.

13 [Slide.]

14 Related to this concept, the objectives of the
15 AVMA are to support development of a scientific knowledge
16 base, support educational efforts, preserve therapeutic
17 efficacy of antimicrobials, and ensure current and future
18 availability of veterinary antimicrobials.

19 Let me share with you a few of the general
20 principles that will serve as a template from which species
21 guidelines will be customized.

22 [Slide.]

23 The first principle states that preventive
24 strategies, such as appropriate husbandry and hygiene,
25 routine health monitoring, and immunization should be

1 emphasized.

2 The second strategy says that other therapeutic

3 options should be considered prior to antimicrobial therapy.

4 [Slide.]

5 The third point is that antimicrobials considered

6 important in treating refractory infections in human or

7 veterinary medicine should be used in animals only after

8 careful review and reasonable justification. Consider using

9 other antimicrobials for initial therapy.

10 In this context, the principle takes into account

11 development of resistance or cross-resistance to important

12 antimicrobials. Taken together, these three principles

13 state that encourage preventive actions to avoid disease, if

14 disease occurs, consider using other options before using

15 antibiotics, and if antimicrobial therapy is needed, don't

16 use the important ones first.

17 [Slide.]

18 The next step is to work with species practitioner

19 groups to develop more detailed guidelines appropriate to

20 each species disease and type of client. This will be

21 addressed at the next meeting of the Steering Committee in

22 March.

23 The AVMA will also work with these groups to

24 develop and deliver a continuing education program to raise

25 the awareness of the profession to the issue and to

1 encourage utilization of the principles.

2 The profession intends to reach the practitioners

3 with this message at state and national meetings, as well as

4 through publications.

5 Additionally, the American Academy of Veterinary

6 Pharmacology and Therapeutics has developed an educational

7 proposal for veterinarians and producers. The proposal

8 includes the development of a coalition of veterinary and

9 producer organizations to implement the program.

10 Educational programs will be presented at national,

11 regional, state, and smaller continuing education

12 conferences.

13 A series of articles will be developed for

14 publication in the Journal of the AVMA. Veterinary schools

15 will be encouraged to incorporate the program into the

16 veterinary school curriculum. This proposal will also be

17 considered further by the AVMA Steering Committee at its

18 next meeting.

19 We also want to maximize the use of good

20 scientific information as veterinarians use their

21 professional judgment in the drug selection process. The

22 AVMA and the American Association of Bovine Practitioners,

23 the American Association of Swine Practitioners, the Academy

24 of Veterinary consultants, and the National Cattlemen's Beef

25 Association are partnering to fund a project to develop a

1 therapeutically-based antimicrobial use informational
2 database. The project's objective is to provide
3 veterinarians with a source of easily assessable information
4 on the therapy of specific diseases to help veterinarians
5 make wise therapeutic decisions.
6 In the past, therapeutic antimicrobial use has
7 focused on clinical efficacy, but now judicious therapeutic
8 use is being redefined to include the optimization of
9 efficacy and the minimization of resistance.
10 The database will allow veterinary practitioners
11 to utilize current peer-reviewed information when they
12 select treatment regimens. The information will include a
13 full range of therapeutic options including alternatives to
14 antimicrobial therapy.
15 The pathogen data will included susceptibility
16 profile information. We anticipate that the informational
17 database will be available in book form, but will also be
18 web-based and possibly distributed on CD-ROM.
19 We believe that these efforts by the veterinary
20 profession will reduce the development of resistant zoonotic
21 pathogens and commensals in animals, and will lessen the
22 apparently already small risk of a human health impact
23 related to the therapeutic use of antimicrobials in animals.
24 [Slide.]
25 Are judicious use principles and education enough?

1 Possibly so. We find it curious that the introduction to
2 the FDA framework document states, "FDA, along with other
3 agencies and groups, is actively working to find ways to
4 encourage the prudent use of antimicrobials in human
5 medicine to help address the significant contribution of
6 human use to antimicrobial resistance."
7 What is curious is that nowhere in the framework
8 document is it mentioned that the FDA, along with the CDC,
9 is working with the AVMA and other groups to encourage the
10 judicious use of antimicrobials in veterinary medicine.
11 The omission gives the impression that the FDA
12 assigns value to the human prudent use campaign, but has
13 judged the veterinary judicious use efforts to be worthless.
14 The impression is further strengthened by FDA's decision to
15 move forward with a complex and expensive new regulatory
16 initiative without taking the time to evaluate the
17 effectiveness of the veterinary profession's initiative.
18 [Slide.]
19 The real answer to the question of whether
20 judicious use principles are enough or whether there is a
21 real need for increased regulation depends upon determining
22 the true risk to human health from the use of antimicrobials
23 in animals.
24 Risk depends not only on the nature and severity
25 of the hazard, but also on the probability of its

1 occurrence, and the probability of the occurrence of an
2 adverse human health effect depends on more than just the
3 prevalence of resistant zoonotic pathogens or commensals in
4 food animals.
5 Risk is also dependent upon the degree of exposure
6 of people to the resistant organism, the likelihood of
7 causing a disease, the probability of the disease requiring
8 antimicrobial therapy. Remember most cases of food-borne
9 diseases do not require antimicrobial therapy, and finally,
10 whether the preferred drug is a specific one for which the
11 pathogen is resistant.
12 What is the risk of a human health impact of the
13 transfer of antibiotic resistant pathogens from animals to
14 humans? My generation calls that the $64,000 question.
15 However, it will cost more than that now to get the answer,
16 but it would be advantageous if we did know the magnitude of
17 the problem. Then, we would know whether we needed to
18 attack the problem with a bee-bee gun, a rifle, a cannon, a
19 cruise missile, or whether an atomic bomb is needed.
20 What constitutes responsible action? Are
21 judicious use principles enough? Judicious use principles
22 combined with an educational program? Judicious use
23 principles plus an educational program that is supported by
24 an easy-to-use informational database to support clinical
25 decisions by veterinarians?

1 We won't know the answers to those questions
2 without a thorough risk assessment. This is a formidable
3 task requiring a significant financial input, as well as
4 scientific manpower, but to proceed forward with increased
5 regulation without an assessment of the beneficial and
6 detrimental effects of that action is unacceptable. Without
7 that information, we are only acting with the hope of
8 favorable results, and we cannot predict the magnitude of
9 the improvement if it does occur.
10 There are many challenges to conducting microbial
11 risk assessments as was explained to us this morning by Dr.
12 McEwen, but people and organizations are learning how to do
13 microbial risk assessments.
14 The USDA has recently completed a risk assessment
15 on Salmonella enteritidis. They are starting another on E.
16 coli 0157:H7 in beef. Georgetown University is performing a
17 risk assessment on antimicrobial resistance associated with
18 animal use of antimicrobials.
19 We are aware that the FDA attempted to perform a
20 risk assessment on fluoroquinolones, which apparently was
21 not completed. At least it has not been shared with the
22 public.
23 It is interesting to note that the USDA has
24 published their preliminary E. coli document and actively
25 sought public comment and input. Additionally, a draft risk

1 assessment report is expected to be released by USDA for
2 external review in June of 1999. FDA should follow a
3 similar public process.
4 [Slide.]
5 There are a number of indications that the risk to
6 humans from animal origin resistance organisms does not
7 constitute an imminent public health crisis and that we can
8 take a reasonable amount of time to properly evaluate the
9 risk, the proposed actions, the expected results of those
10 projected actions, and the potential for unexpected adverse
11 events.
12 For example, Dr. Angulo recently said, "If the
13 same resistance development on food animals should continue
14 in the next 20 years, we would be faced with a major public
15 health problem." This statement implies that we have some
16 time to take responsible action. We do not need to rush
17 forward with experimental regulations.
18 Let's do a proper analysis to determine the most
19 effective and efficient intervention method or methods,
20 whether it be judicious use principles, alterations in the
21 drug approval process, changed in animal husbandry
22 practices, pathogen reduction activities in slaughter and
23 processing plants, improved transportation and storage of
24 food, and/or improved food handling by food service workers
25 and consumers, or a combination of the above.

1 The press release resulting from the 1998 WHO
2 meeting states, "To date there has been little documented
3 impact on human health of fluoroquinolones use in livestock,
4 but there is concern over the potential human health
5 consequences if resistance were to increase and spread.
6 Further research and data gathering are thus essential.
7 [Slide.]
8 The major food-borne pathogens of concern for the
9 development of antimicrobial resistance are Salmonella
10 species and Campylobacter jejuni. The incidence of food-
11 borne disease caused by those pathogens may actually be
12 decreasing.
13 As reported by the U.S. Department of Health and
14 Human Services in the Healthy People 2010 draft document,
15 the incidence of disease caused by these pathogens has
16 already decreased to levels below the year 2000 targets
17 established by the Department.
18 For Salmonella species, the year 2000 target was
19 16 cases per 100,000 people. The preliminary 1997 data
20 demonstrated 13.8 cases per 100,000. For Campylobacter
21 jejuni, the year 2000 target was 25 cases per 100,000, and
22 the 1997 preliminary data demonstrate 23 cases per 100,000,
23 which is more than a 50 percent reduction from the 1987
24 baseline figures.
25 The point is that as the number of human cases of

1 Salmonella and Campylobacter decrease, so do the number of
2 potential cases with decreased susceptibility to
3 antimicrobials.
4 [Slide.]
5 In addition to a reduction in the number of human
6 cases of salmonellosis, a reduction of Salmonella on animal
7 carcasses has been measured. A preliminary report from the
8 first nine months of Salmonella sampling performed by USDA
9 FSIS on animal carcasses as part of its 1998 pathogen
10 reduction program demonstrates significant reductions in the
11 prevalence of Salmonella on chicken and swine carcasses and
12 in ground beef. There was nearly a 50 percent decline in
13 the prevalence on chicken carcasses, a 40 percent decline in
14 ground beef, and a 25 percent decline on swine carcasses.
15 These figures indicate that the exposure potential
16 to Salmonella through the food supply is decreasing along
17 with the potential subset of resistant organisms.
18 [Slide.]
19 Let's turn briefly to addressing the questions
20 posed to the committee. The challenge to VMAC today is to
21 advise on a solution that balances a real drug availability
22 problem with an unquantified potential public health risk.
23 FDA's stated goal is to protect the public health
24 by ensuring that the efficacy of human antimicrobial
25 therapies is not compromised due to the use of

1 antimicrobials in food animals while providing for the safe
2 use of antimicrobials in food animals.
3 The first question that the VMAC is asked to
4 consider is whether the framework document provides a sound
5 scientific basis for achieving FDA's goal of protecting the
6 public health while providing for the safe use of
7 antimicrobials in food animals.
8 The scientific premise of the framework document
9 is that the use of antimicrobials in food animals causes the
10 development of resistance, a hazard, that is or will be a
11 risk to human health; further, that the risk is of the
12 magnitude that justifies the implementation of a complex and
13 expensive drug evaluation and monitoring progress that may
14 have negative animal and human health consequences.
15 We believe that the agency has demonstrated that a
16 hazard exists, however, the agency has not adequately
17 characterized the risk to humans. We accept the premise
18 that use of antimicrobials, whether in animals or humans,
19 will allow resistance to develop, however, the science has
20 not been presented by the agency that demonstrates the
21 probability of human disease occurrence resulting from that
22 resistance.
23 Without the necessary science and risk assessment
24 to evaluate the management efforts, the agency's framework
25 document can impede the development and approval of

1 antimicrobials for animals and remove previously approved
2 antibiotics without knowing whether the effects will have a
3 positive effect on human health.
4 [Slide.]
5 The second question to the committee addresses the
6 categorization of antimicrobial drugs for human medicine.
7 We are concerned because the categories are not well
8 defined. The classification is very subjective which will
9 create uncertainty and will allow controversy for each drug
10 that is being classified.
11 We also propose for the consideration of FDA that
12 another factor should be included in the categorization
13 scheme, and that is the importance of the drug to animal
14 health and welfare.
15 Category I contains some eclectic criteria. For
16 example, the first criterion is that the drug is essential
17 for treatment of a serious or life-threatening disease in
18 human, but then the second criterion included drugs that are
19 important for treatment of food-borne diseases.
20 The first criterion addresses essential drugs, but
21 the second concerns a lesser group of important drugs.
22 Also, in the vast majority of cases, food-borne diseases are
23 not life-threatening nor serious, and for some of the few
24 that are, such as E. coli 0157:H7, antimicrobial therapy is
25 contraindicated or at least the need for antimicrobial

1 therapy is controversial.

2 [Slide.]

3 The third and fourth questions address threshold

4 levels. For both monitoring and resistant threshold levels,

5 a more basic question that needs to be answered first is how

6 do we measure the impact on human health of various

7 threshold levels. The answer can only be determined by

8 risky and costly trial and error or by developing a risk

9 assessment.

10 [Slide.]

11 The fifth question concerns on-farm monitoring.

12 Again, we need to answer the question what is the degree of

13 relationship between resistant levels measured on the farm

14 and the human health impact, what are the outcome

15 measurements.

16 Until those questions are answered, resources

17 would be more appropriately applied to improvement of the

18 National Antimicrobial Resistance Monitoring System.

19 Questions identified by NARMS could then be investigated

20 with specific research projects.

21 This can be likened to Food Net, which, based on

22 the results of active surveillance for food-borne disease,

23 institutes case control studies to answer questions raised

24 by the surveillance program, but the difference is that Food

25 Nets uses the case control studies for the purpose of

1 research, not regulation.

2 To summarize, the AVMA is dedicated to the

3 protection of public and animal health. We are very

4 concerned that the use of antimicrobials to treat food

5 animals may cause a public health risk.

6 Because of that concern, the veterinary profession

7 has invested considerable resources of personnel and money

8 into what we believe will be effective responses to the

9 potential risk, but we are also very concerned that because

10 the human health risk has not been characterized, increased

11 regulation of animal drugs that is not commensurate with the

12 actual public health risk will adversely affect animal

13 health and welfare, and may have unexpected adverse human

14 health consequences.

15 We recommend that the agency work with other

16 governmental agencies and the public to perform a risk

17 assessment. We believe that the framework document is too

18 complex, uncertain, and possibly too restrictive in

19 comparison to the actual public health risk.

20 It appears that much of the framework document is

21 designed to gather the scientific information that is needed

22 to measure the risk. Is it appropriate for a governmental

23 regulatory requirement to be used to gather data that

24 rightfully should be obtained through research? We don't

25 think so.

1 One final thought. Part of the problem may be
2 that the agency is attempting to regulate microbial safety
3 under the rules for food additives instead of as food
4 contaminants.
5 Food additives are those substances deliberately
6 incorporated into foods which includes, for legal purposes,
7 animal drugs.
8 The second group, food contaminants, includes
9 anything not specifically approved for food use. Food
10 contaminants are those substances which are unavoidably
11 present and whose presence is tolerated.
12 According to the Food, Drug, and Cosmetic Act, in
13 general, FDA may not consider values other than safety in
14 approving additives. If a substance is judged reasonably
15 certain to produce no harm when used as intended, FDA is
16 supposed to approve its use.
17 Conversely, for contaminants, FDA must balance
18 several often competing objectives including safety, food
19 costs, and practicality of the regulatory action. These
20 legal requirements imply very different risk assessment
21 needs. For additives, FDA reaches a judgment on an intake
22 level that will be without effect. For contaminants, FDA
23 needs to know of the likelihood of harm.
24 We suggest that the agency reevaluate its
25 regulatory approach to consider if microbial safety is more

1 appropriately regulated as a food contaminant.

2 Thank you.

3 DR. STERNER: Do any of the Veterinary Medicine

4 Advisory Committee have questions for Dr. Vogel? Dr.

5 Angulo.

6 DR. ANGULO: Dr. Vogel, I have heard a couple

7 comments about impressions that this new framework might

8 impede new approvals. It is obviously an essential issue,

9 but it might be peripheral to the questions that are asked,

10 but you raised that under the questions about does this

11 framework based upon a sound scientific basis.

12 So, I am just wrestling with -- I mean I actually

13 have a converse perspective, that I actually think this

14 framework facilitates new approvals. We don't know exactly

15 how it would move forward, the details we don't know

16 essentially, but I see it a way to facilitate new approvals,

17 not to impede new approvals.

18 How does it impede new approvals if we lay a

19 framework out that shows how to move forward with approvals?

20 The current system obviously isn't working.

21 DR. VOGEL: I think the answer to that gets back

22 into the drug approval process and the long time it takes a

23 company to develop a new antibiotic and get it through the

24 system. Which company is going to invest 10 years of time,

25 money, and effort in developing an antibiotic for a food

1 animal when it cannot predict when it's done with its work
2 whether that will be approved by FDA or not?
3 It just does not make sense for a drug company to
4 invest millions and millions of dollars into an
5 unpredictable system.
6 DR. STERNER: Further questions or comments? Dr.
7 Angulo.
8 DR. ANGULO: The second point then on your
9 discussion about the sound scientific basis of achieving of
10 this framework, you mentioned that we haven't quantified the
11 risk, and although you did acknowledge that there is a risk,
12 that it hasn't been fully quantified, which I fully
13 appreciate that it has not been precisely quantified, but
14 the point that should be understood, that the reason why the
15 risk has not been fully quantified is because we have not
16 yet reached antimicrobial resistance that causes treatment
17 failures.
18 The only way we will fully quantify the risk is if
19 we have treatment failures, and it would reckless for public
20 health to await that point in time. In other words, we
21 should not wait until we have fluoroquinolone resistant
22 Salmonella in this country before we revise the drug
23 approval process in the FDA.
24 We want to move towards quantified risk
25 assessments, I agree, but we cannot wait until we get those

1 endpoints of clinical treatment failures to answer that
2 question that you are asking.
3 DR. NORDEN: Dr. Vogel, you raised a lot of
4 points, and your concern about the lack of a quantitative
5 risk assessment, it is correct that it is not there, but
6 what I think is clear, and although I commend your group for
7 judicious use principles and education programs, I think it
8 is very clear from medicine at least, "human medicine,"
9 quote, unquote, that that doesn't work, and it hasn't
10 worked, and we have major problems in medicine with
11 prescription of antibiotics and all of the education
12 programs, and the data is very clear on this, really don't
13 make any great difference.
14 So, I think that it's fine to do it, and I think
15 it's a necessary part of any practice of animal or human
16 medicine, but I think to think that it will make a major
17 difference in the way antibiotics are used is unlikely.
18 DR. VOGEL: Well, I hope veterinary medicine can
19 prove something to the human medical field, that we can make
20 it work.
21 DR. STERNER: Thank you, Dr. Vogel.
22 As has been alluded to earlier, we live in an ever
23 shrinking world, and are more and more influenced by our
24 global economy. To that end, we have an invited speaker
25 from over the Atlantic, from the UK, Dr. Rutter, who is Dr.

1 Steve Sundlof's counterpart in England.

2 **The Authorization of Antimicrobial Products**

3 **in the European Union**

4 DR. RUTTER: Thank you very much, Chairman, and

5 thank you also for inviting me to attend this meeting.

6 [Slide.]

7 It has been a very interesting morning. I am not

8 sure that I am going to introduce any major new insights

9 into the debate. I suspect I may just be repeating what is

10 happening over the water.

11 I usually slip over this first slide pretty

12 quickly, but I did want to emphasize that the Veterinary

13 Medicine's Directorate is the UK regulatory authority, and I

14 am the head of the VMD. We are responsible for authorizing

15 veterinary medicines in the UK for residue surveillance in

16 the UK, and for advising ministers on Veterinary Medicine's

17 policy.

18 I would emphasize that I am not a member of the

19 staff of the European Medicine's Evaluation Agency, which

20 also happens to be based in the UK, in London, although I do

21 sit on the Committee for Veterinary Medicinal Products,

22 which advises the EMEA on the scientific opinions.

23 Neither am I a member of the EU Commission as I

24 noted in one of the draft programs that I was. The EU

25 Commission, of course, is based in Brussels and is the

1 executive arm of the European parliament responsible for
2 legislation.
3 So, having got that clear, I hope, if I could have
4 the next acetate.
5 [Slide.]
6 I am going to cover three broad areas, first of
7 all, say something about the background to this issue as it
8 occurs in the EU, because I think there are some important
9 differences that are worth mentioning; secondly, to talk
10 about the requirements for authorization in the EU; and
11 then, thirdly, to talk about some of the issues which, as I
12 say, are going to be very similar to the issues that you are
13 facing over here.
14 [Slide.]
15 As far as the background is concerned, I wanted to
16 emphasize two points. First of all, that we have harmonized
17 procedures in Europe in the 15 member states, and secondly,
18 we have, and have had for some time, separate procedures for
19 antimicrobials that are used as therapeutic products or as
20 growth promoters.
21 [Slide.]
22 As far as growth promoters are concerned, they are
23 regulated under Council Directive 70/524, and these are the
24 substances that are currently authorized as antibiotic
25 growth promoters in the EU. I will return to this because,

1 as has already been mentioned, the first four of those will
2 be disappearing later this year.
3 [Slide.]
4 Just to emphasize that growth promoters are
5 authorized in the EU at sub-therapeutic levels. They are
6 authorized for extended periods mainly in pigs and poultry
7 throughout the growing period, and they are available
8 without veterinary prescription.
9 [Slide.]
10 In contrast, the veterinary medicinal products
11 authorized for therapy -- and I have listed the major groups
12 that we have products, these I am sure are very similar, I
13 haven't listed the individual products, but these are the
14 major groups that we have. I am sure it is very similar
15 here in the USA.
16 [Slide.]
17 There therapeutic products are authorized at
18 therapeutic doses for defined, generally short periods, and
19 on veterinary prescription. The requirements for
20 authorization, if I can move on to that, and on to the next
21 slide --
22 [Slide.]
23 The requirements for the additives or for the
24 growth promoters include these sort of areas, and these have
25 been set out for new products in Council Directive 87/153.

1 This requires the applicant to provide data of MICs in
2 various pathogenic and nonpathogenic gram-negative and gram-
3 positive species of bacteria, studies on cross-resistance to
4 therapeutic antibiotics by determination of MICs in mutants
5 produced in vitro which exhibit chromosomal resistance and
6 may be needed, and in the case of microorganisms which are
7 resistant to therapeutic antibiotics, the genetic basis of
8 the resistance should be shown.
9 Tests to find out whether the additive is capable
10 of selecting resistance factors are required, which may be
11 performed under field conditions in the animal species for
12 which the additive is primarily intended, whether all
13 factors may have been found, tests required to determine the
14 effect of the antibiotic on the microflora of the digestive
15 tract, colonization, and shedded or excretion of pathogenic
16 microorganisms, and field studies to monitor the percentage
17 of bacteria resistant to the additive should be provided
18 before, during, and one month after use.
19 So, these are the kind of studies that are
20 currently required. Council Directive 96/51 extends these
21 to run specific approval, and there will be new guidelines,
22 and particularly the review of products which have
23 previously been authorized.
24 [Slide.]
25 In contrast, the therapeutic antimicrobials are

1 authorized through a separate procedure. We have
2 essentially three procedures - a centralized procedure which
3 is used for biotech products and is obligatory, but is
4 optional for innovative products, so if there was a new
5 antibiotic coming forward, say, which had a biotech element
6 in it during its manufacture, it will be obliged to go
7 through the centralized procedure.
8 If it were an innovative product, then, the
9 company could choose whether or not to go through that
10 procedure. The centralized procedure essentially involves a
11 single application to the European agency in London,
12 assessment of the dossier against the requirements, and a
13 scientific opinion by the Committee for Veterinary Medicinal
14 Products, leading to if it's a positive opinion,
15 authorization in all 15 member states.
16 The decentralized procedure is a mutual
17 recognition procedure. This would be available for a
18 product that was not innovative, and the company would come
19 say to a member state, say the UK, as the reference member
20 state with its dossier, get an authorization in accordance
21 with the procedure, and then apply for mutual recognition of
22 that authorization in as many other member states that it
23 wanted.
24 [Slide.]
25 The criteria for authorization for therapeutic

1 medicinal products is very much the same as over here.
2 Safety, quality, and efficacy are the three criteria that
3 are required, and on to the next slide.
4 [Slide.]
5 The safety of the product involves the target
6 animal, the operator, the consumer, and the environment.
7 [Slide.]
8 As far as consumer safety is concerned, we have
9 the MRL procedure, the maximum residue limit procedure,
10 which has been obligatory in the EU since 1990. All new
11 actives have to have an MRL before they can be authorized,
12 and we are also reviewing all old actives, so that by the
13 31st of December 1999, an MRL has been set for them, or any
14 substances which don't have an MRL by then will be removed
15 from the market.
16 We also use microbiological MRLs. This is based
17 on the fact that the toxicological MRL for a substance may,
18 for an antibiotic, for example, which may be relatively non-
19 toxic, give a pretty high MRL and a short withdrawal period
20 which could lead to significant residues passing into the
21 human food chain, and therefore, we have a microbiological
22 MRL procedure where the microbiological activity is assessed
23 mainly in vitro, and if this leads to an MRL which is lower
24 than the toxicological MRL, then, that will be the MRL that
25 will operate and give a longer withdrawal period, which will

1 obviously protect the human consumer.

2 We also have residue surveillance much as you have

3 over here, of course, and I think that it is generally

4 recognized that the residues of antibiotics that appear in

5 the food chain don't pose a significant risk to consumers in

6 terms of antibiotic resistance.

7 [Slide.]

8 The next acetate shows the regulatory requirement

9 in 81/851 for the authorization of medicinal products, and

10 again this just summarizes some of the major areas that have

11 to be addressed by the applicant.

12 This would include data on resistance and the

13 likelihood of resistance emerging, data where strains are

14 passaged serially in subinhibitory concentrations of

15 antibiotic and MIC values evaluated at various stages, MIC

16 values for bacterial strains isolated under field

17 conditions, information about resistance to related

18 bacteria.

19 Data from clinical trials before and after

20 treatment may be required, and data from different EC

21 countries. There is also new information that is required,

22 such as the degree to which resistance is developed, and the

23 mechanisms by which it is developed, a commentary on the

24 speed of its development and its geographical distribution

25 and analysis, the likely effects of such factors on the

1 efficacy of the product.

2 There is also a requirement for pharmacokinetic

3 data to ensure that the dosage regime is appropriate, and

4 for pharmacovigilance, although I will come back to

5 pharmacovigilance in a moment. This is suspected adverse

6 reaction reporting because this is an area where there is

7 going to be quite a lot of development over the next year or

8 so.

9 [Slide.]

10 Moving on finally to some of the issues, we have

11 had a number of inquiries and advice given in the UK and in

12 Europe. These are some of the UK committees that have been

13 sitting. I suppose the most significant of those is the

14 House of Lords Committee, which reported last April, and

15 which recognized that the major problems relating to

16 antibiotic resistance in terms of human infections was

17 related to human use and medical use of antibiotics, but

18 clearly, that there was an important issue as far as

19 veterinary use is concerned, and they recommended the

20 phasing out of feed growth promoters which were related to

21 products which were important in human medicine.

22 It also commented on the need for prudent use of

23 fluoroquinolones. The government has responded to that

24 issue, to that report, and is taking it forward. I think

25 one of the important things here is that it has emphasized

1 to the government the multidisciplinary nature of this
2 issue, and the Department of Health and the Department of
3 Agriculture are taking this forward jointly.
4 The Advisory Committee on Microbiological Safety
5 of Food has still to report, and the Veterinary Products
6 Committee, which is an expert advisory committee that
7 advised the licensing authority, is also due to report
8 shortly on some of these issues. It held an open meeting
9 last June, and its report will be published very shortly.
10 [Slide.]
11 This acetate shows the committees operating on a
12 European and international level, and some of these have
13 been mentioned earlier. The WHO meetings on growth
14 promoters and fluoroquinolones at the bottom, the European
15 CMO's meeting which led to the so-called Copenhagen
16 recommendations, but I wanted to mention the two others, the
17 Scientific Steering Committee, which is a committee set up
18 by Directorate General 24 in Brussels, a wide-ranging
19 committee which is look at all aspects of antimicrobial
20 resistance, and is due to report very shortly, and then just
21 say a few words about the CVMP working group.
22 As I have mentioned, the Committee for Veterinary
23 Medicinal Products advises the European agency on scientific
24 matters and on opinion for applications, and the CVMP set up
25 this working group in 1997 to carry out a risk assessment of

1 antibiotic resistance, potential effect on treatment in
2 animals, and the risks of transfer to man.
3 It would then advise the CVMP, who would consider
4 what risk management procedures it should put in place. The
5 group has been working for some considerable time now. Its
6 initial challenge was to collect and review data across the
7 15-member states, and it has collected a great deal of data
8 about products that are authorized, which is the easiest
9 part of it, although even that caused some problems in some
10 cases, the usage of products, and again this is where we
11 started getting into real difficulties because there is very
12 poor information available about usage, and then resistance,
13 again, a lot of information available about resistance, but
14 very, very difficult to analyze because of huge differences
15 between laboratories in how the data had been collected.
16 The group then started looking at risk assessment
17 and rapidly came to the conclusion that a quantitative risk
18 assessment was going to be very difficult, and so it's
19 currently looking to see, to make its best study of a
20 qualitative risk assessment.
21 Also, I think the other important message that has
22 come out from that is that you need to identify the question
23 very precisely if you are trying to carry out a risk
24 assessment. It is not possible to carry out a risk
25 assessment, of the risk of antibiotics in animals to humans,

1 you have got to identify it much more precisely than that to
2 come up with any meaningful data, but the group is still
3 working diligently and is expected to report within the next
4 quarter.
5 [Slide.]
6 This refers to a comment I made earlier about the
7 withdrawal in the EU of virginiamycin, spiramycin, tylosin
8 and zinc bacitracin as growth promoters, a recent decision
9 taken in December 1998.
10 The background to this was that Sweden banned the
11 use of growth promoters in 1986, and when it acceded to the
12 EU in 1995, it received a derogation not to continue the use
13 of growth promoters until the end of 1998.
14 This focused the mind of the commission as we came
15 closer to that date, and the commission came up with a
16 proposal in November to ban four growth promoters, these
17 four growth promoters from the 1st of January 1999.
18 The Council of Ministers met in December, and they
19 agreed that these four growth promoters should be withdrawn
20 from the 30th of January 1999, i.e., in six months time, and
21 that there should be further work carried out to consider
22 how to deal with products from third countries who would, of
23 course, be continuing to use these.
24 I think I would have to say that this decision was
25 not based on a clear risk assessment or any scientific data

1 in that regard except to say that there is a principle that
2 has been operational in the EU since 1969, since the Swann
3 Committee reported about the fact that growth promoters used
4 in animal medicine should not be related to antibiotics that
5 might have a valuable use in human medicine, and that really
6 I think is the background to that particular decision.
7 [Slide.]
8 The next acetate just summarizes the areas where I
9 think we are currently looking at this issue, regulatory
10 approvals, and what changes might be needed to those as a
11 result of the concerns that have been raised, getting better
12 data about how much antibiotics and what sort of antibiotics
13 are used, and how they are used on farm, better surveillance
14 data of resistance preferably using standardized procedures,
15 prudent use guidelines, we just heard from the AVMA
16 representative, and the British Veterinary Association in
17 the UK is carrying forward a similar sort of exercise on
18 prudent use of antibiotics, and particularly getting in
19 close contact with its medical colleagues, realizing that
20 this is a multidisciplinary problem, and then finally,
21 further research on a whole range of issues that are needed
22 to take matters forward.
23 [Slide.]
24 This final acetate just sets out some conclusions
25 that again, I don't think that these have got any blinding

1 insights. Antibiotic resistance is a major issue, it's a
2 global problem. The risks have not been adequately
3 quantified.
4 There are very complex issues, a realization that
5 some of the important problems in human medicine, such as
6 MSRA and TB, have been primarily associated with resistance
7 as a result of human use of the products, but, of course, we
8 must as veterinarians play our full role in order to
9 maintain the efficacy of drugs both for animal treatment and
10 for human treatment, and to safeguard public health.
11 As I say, I don't think there are any blinding new
12 insights in there other than to say that we haven't got
13 quite as far as the framework document and the questions
14 that are being debated today.
15 Thank you very much.
16 DR. STERNER: Does anybody have any questions for
17 Dr. Rutter?
18 DR. ANGULO: I have just a comment and then a
19 question. I think it's an overstatement to say that there
20 is no scientific data to support the withdrawal of the four
21 growth promoters. I think there is strong scientific data
22 to support the avoparcin prohibition or withdrawal, and
23 there was increasing data being built up to support the
24 withdrawal of virginiamycin. I actually think there is
25 convincing scientific data just on the virginiamycin itself,

1 and then when you extrapolate the data on avoparcin, I think
2 it was a very prudent step to just move and follow the WHO
3 recommendation that no antibiotics used in human medicine be
4 used for growth promotion.
5 My question is on the fluoroquinolone resistance
6 situation or I will say fluoroquinolone decreased
7 susceptibility situation in the United Kingdom, and your
8 comment that has come to fairly high level attention, House
9 of Lords' reports and others, and now an impetus to have
10 prudent use guidelines for practicing veterinarians, but I
11 have heard that there is also some active discussion about
12 restricting some usages of fluoroquinolones in food animals
13 in the United Kingdom.
14 Is that the case or to what extent is the
15 discussion on the decreasing susceptibility of
16 fluoroquinolones being held in the United Kingdom?
17 DR. RUTTER: Thank you. If I could just I think
18 comment on the first part, the first comment that you made
19 about the growth promoters. Yes, I think what I meant to
20 say was that it wasn't based on a scientific risk assessment
21 of the impact of the growth promoter use on the risks in
22 human medicine.
23 I think it is quite clear that both for avoparcin
24 and for the other growth promoters, a potential hazard has
25 been identified, the risk has not been adequately

1 quantified. I think that would be the comment that I would
2 make.
3 As far as the fluoroquinolones are concerned,
4 there is, as I say, currently discussion in follow up to the
5 House of Lords Committee, which is being taken forward on a
6 joint departmental basis in the UK, and it would be
7 premature, I think, to make any comments on that.
8 DR. STERNER: Further comments or questions?
9 [No response.]
10 DR. STERNER: Very well. We are moving along
11 nicely on schedule here.
12 From the University of Illinois we have Abigail
13 Salyers. She is going to talk about the importance of
14 commensals and transfer of resistance from animals to
15 humans.
16 Dr. Salyers.
17 **Importance of Commensals in the Transfer of**
18 **Resistance from Animals to Humans**
19 DR. SALYERS: Before I start, I would like to tell
20 you that I brought a small number of handouts which have
21 what is on the transparencies and also an annotated
22 bibliography that some of you might be useful.
23 What I am going to talk about today is a issue
24 that in some sense is much bigger than any of the issues
25 that have been brought up to date. We have heard a lot

1 about the zoonotic pathogens like Salmonella and
2 Campylobacter, but I think we have to address ourselves to
3 the question of is it possible that the use of antibiotics
4 in agriculture could have an adverse impact on resistance in
5 some of the more serious human pathogens like Streptococcus
6 pneumoniae and in enterococcus species.
7 What I would like to do is to address that. This
8 is going to take me, incidently, into the murky realm of
9 horizontal resistance gene transfer, and so I am going to
10 have to qualify my statements in a lot of cases, but I will
11 try to give you a feeling for what people are finding out
12 about horizontal resistance gene transfer and to explain to
13 you how it is possible that agricultural use of antibiotics
14 might have an impact on what we think of as mainly human
15 specific pathogens.
16 So, I am going to be asking the question can
17 commensals, that is bacteria, especially human commensals
18 take up resistance genes, pass them on to bacteria that
19 might be human pathogens, and how likely is this to happen.
20 [Slide.]
21 So, the first question is why is commensals, and
22 human commensals especially, a food safety issue? Well, one
23 example, and I will start with this because it's the easiest
24 one to understand, is the enterococci.
25 Now, in the United States and many other countries

1 in the world, sepsis is a major problem. We are talking now
2 about hundreds of thousands of cases, not just 2500 cases,
3 and vancomycin resistance is a real problem in some cases of
4 enterococcal infections.
5 Now, in the United States, there is no question
6 that that is coming from human abuse of vancomycin, so in
7 the United States, our VRE problem is mostly in hospitals
8 and was brought to us by the overuse of vancomycin by
9 physicians. So, in order to ask the question is it possible
10 that you might get something happening to the resistance
11 levels of VRE through the human food chain, I have to move
12 to Europe where the European physicians were much more
13 cautious than ours were with vancomycin's use in hospitals,
14 and so they have not a problem with vancomycin, but
15 enterococci in hospitals, but they have been conducting an
16 experiment through the use of avoparcin, which has now been
17 discontinued.
18 So, here is a place where if vancomycin resistance
19 would come through the food chain, we might be able to see
20 it.
21 So, let me start with that example and to say that
22 there are some reports coming out recently. These
23 particular figures are from the DANMAP surveillance program,
24 but there are actually some other reports that have come out
25 recently that put the incidence even higher, that the use of

1 avoparcin in Europe has, in fact, produced vancomycin
2 resistant enterococci.
3 So, there are a number of reports of that. Here
4 we have 59 percent of enterococci in chickens supposedly
5 resistant to vancomycin.
6 I would like to caution you a little bit on some
7 of these figures I am going to give you, because people like
8 to play around with the breakpoints between resistance and
9 susceptibility, and moving the breakpoint a little bit
10 either way can cause a big difference in the percent
11 resistance, but when that happens, that's a signal to you
12 that there are a lot of strains built up around the
13 breakpoint and that they may be moving in the direction of
14 resistance.
15 So, what would be the problem here? Well, the
16 first question is could animal enterococci actually colonize
17 humans, because if they could, then, conceivably if you got
18 colonized with VRE, you go in for surgery, your chances of
19 having a postsurgical VRE problem are somewhat increased.
20 How much they would be increased is hard to say.
21 But let's suppose that that can't happen, let's
22 suppose that the animal strains are different enough from
23 the human strains that animal strains don't colonize the
24 human intestinal tract or if they do, they don't cause
25 diseases effectively.

1 Then, the question arises whether, as these
2 enterococci move through your intestinal tract, they could
3 transfer their resistance genes to human pathogens. That is
4 a question I want to ask, and actually, I could substitute
5 Streptococcus pneumoniae later on in that scenario and say,
6 okay, what about vancomycin resistant enterococci coming
7 through the food chain, getting into your intestine, and
8 passing on antibiotic resistance gene to Streptococcus
9 pneumoniae.
10 Now, you might say wait a minute, Streptococcus,
11 the enterococcus faecalis, enterococcus faecium, or the
12 colon, strep pneumo, when it colonizes, it usually colonizes
13 in the throat, how could that possibly happen.
14 Well, the answer is we have evidence that that
15 kind of transfer can happen, so my question is how likely is
16 this sort of thing to occur, and what evidence do we have
17 for or against that.
18 Before I go on to that, let me just show you some
19 data that I got just before I came here. I got this from a
20 European group, Vander Bogard's group.
21 [Slide.]
22 Now, I am not so sure about these figures myself
23 because I haven't seen the data, and they are pretty small.
24 Anyway, I thought I would show these to you because what is
25 interesting is once again, they are saying in that first

1 column on the left is vancomycin resistant enterococci, they
2 are seeing again the high percent of VRE in animals, but the
3 significant figure on here, which I will just read it to
4 you, because I can see it even if you can't, is that in
5 urban adults, they are finding significant, 12 percent they
6 claim, of the enterococci or vancomycin resistant.
7 Now, this is something in the United States that
8 we haven't seen, clinical abuse of antibiotics, of
9 vancomycin in particular, is community carriage of
10 vancomycin resistant enterococci.
11 So, it will be interesting to see -- as I said, I
12 haven't seen the data -- but it will be interesting to see
13 if this trend actually develops and if, in Europe, you begin
14 to see VRE coming through the food chain and colonizing
15 people.
16 But back to the question of horizontal transfer.
17 [Slide.]
18 Now, there is another issue here that needs to be
19 addressed, and we come now to the true human commensals, the
20 bacteria that are the predominant one in your colon, and
21 these are all the colonic anaerobes. Bacteroides is a gram-
22 negative anaerobe, about 25 to 30 percent. The remainder
23 are gram-positive anaerobes, which are not that distantly
24 related to Streptococcus pneumoniae and Staph aureus.
25 So, the question is if the bacterium came through

1 and transferred resistance genes to one of these organisms
2 here, these are rounded, high numbers, they are around all
3 the time, and then a pathogen comes through and another
4 transfer occurs, how likely is this to occur?
5 [Slide.]
6 Well, how are you going to do that? Incidently,
7 if I did a risk analysis on this, if you had asked me before
8 I got the answer that I am going to give you in the
9 transparency after this, I would have said that the risk of
10 this happening are zero, very, very unlikely.
11 So, how do we do this kind of a test? Well, the
12 best way to do it obviously would be to colonize a bunch of
13 people with vancomycin resistant enterococci and see if the
14 gene got transferred or do some of these other studies in a
15 prospective manner, actually watch this transfer occur, and
16 there have been a couple of animal studies where people have
17 demonstrated in real time the transfer of resistance genes
18 between bacteria in a test of mice, just to give you the
19 impression that there is only really two or three cases in
20 which this has been done.
21 So, all of the type of evidence that we have about
22 these gene transfers comes from the second type of study,
23 which is the retrospective study, which is on the second
24 part of the transparency, where you look to see whether you
25 can find the same resistance gene in different kinds of

1 bacteria.

2 So, the argument here is that if you find

3 virtually identical copies of the same resistance gene in

4 two different species of bacteria, that was probably due to

5 horizontal transfer, now, not necessarily between those two

6 bacteria, it might have gone a more circuitous route, but

7 that there is some sort of genetic corridor open between

8 those bacteria.

9 [Slide.]

10 I am not going to go through this whole thing

11 because it's kind of complicated, but this is the type of

12 thing I am talking about. Let's take tetM there, which is

13 the second one down. This is a type of tetracycline

14 resistance gene. I am using this just now as an indicator

15 as to what kinds of horizontal transfer can occur.

16 If you look, there are a lot of different genera

17 and species in which that resistance gene, the same

18 resistance gene has been found. There are some gram-

19 negative ones like human Haemophilus and Neisseria strains.

20 It has been found in Campylobacter. It has been found in

21 Enterococcus, Staphylococcus, Actinomyces.

22 So, what this suggests to us, to me at least, is

23 there is a lot of possibility, a lot more than I would have

24 guessed for horizontal gene transfer. Now, where it occurs

25 we don't know, how it occurs we don't know although probably

1 by conjugation.

2 Incidently, this tetracycline resistance is a

3 chromosomal gene, and it is transferred on conjugative

4 transposons most of the time.

5 The next one down, tetK and tetL, have been found

6 in soil bacteria, on the left, Bacillus and Streptomyces,

7 but also in human commensals of Staphylococcus, so even

8 between soil bacteria and human commensal bacteria, there is

9 some evidence that there have been horizontal transfers.

10 I won't go over all the details of what we know

11 about this, but there is now abundant evidence that

12 horizontal transfers have occurred between oral bacteria and

13 colonic bacteria, as well as between soil and human

14 bacteria, and [Micro] found the first evidence that it was

15 the same gene in Prevotella ruminicola from animals and

16 Bacteroides from humans.

17 Now, sometimes we can't tell what direction this

18 has been in, but sometimes you can, and in our case, by

19 looking around the gene, at the DNA sequences around the

20 gene, we were able to suggest that possibly the transfer of

21 the resistance gene we were looking at, tetQ, between the

22 human Bacteroides and the animal Prevotella, was from humans

23 to animals, and not vice versa. But what ever happened,

24 somewhere there is a genetic conduit open between those two

25 groups of bacteria.

1 [Slide.]

2 Similarly, as is shown in this overhead, there
3 have been efforts to trace vancomycin resistance
4 determinants. What they are doing is -- this group found
5 essentially identical genes in chickens, enterococci from
6 chickens, from pigs, and from humans -- and what they are
7 doing here is using the fact that the genes were almost
8 identical, in some cases there was a single base pair
9 difference, and so they looked at the pattern.

10 Humans had one particular type, was that
11 particular type found in animals, and in some cases, they
12 were actually able to guess that the resistance gene had
13 come from the animal to human, and sort of put this on a
14 more firmer scientific footing.

15 Now, this is just the beginning, and I think you
16 are going to see a lot more reports of this type where
17 people are bringing out very compelling arguments for
18 horizontal gene transfer and actually using more
19 sophisticated tracking means to show the direction of
20 transfer although this is still in its infancy.

21 [Slide.]

22 I used this to make the earlier speakers who
23 complained about the complexity of their slides feel better.
24 I could have made this simpler, but I want to impress you, I
25 want to explain to you what this is.

1 We don't need to go through the thing, but I want
2 to impress you with a number of examples. Now, the examples
3 I have been giving you are not single isolated examples.
4 They have been very easy to find, there have been very many
5 of them, these putative horizontal gene transfer events.
6 This is the one that I think is so far one of the
7 most chilling I have seen. What these people did was to
8 look at isolates of bacteria from food. Over on the very
9 lefthand column we have isolates from cheese, from sausage,
10 and some of them are Enterococcus faecalis, but some of them
11 are Lactococcus lactis, very harmless bacteria.
12 Then, they went in and they asked are these
13 resistant, and where they were resistant, what was the
14 resistance gene. So, they found the resistance gene. You
15 can't see it very well there, but they were identified.
16 Then, they asked, well, where else have we seen
17 this resistance gene, and then over on the right you see
18 human clinical isolates. These are bacteria that were,
19 under some conditions, capable of causing disease, like
20 Enterococcus faecalis obviously was not too surprising, but
21 Staph aureus, other types of bacteria that we associate with
22 human disease.
23 They found in those isolates the exact same gene,
24 and we are talking about identities of 99.8 percent to 100
25 percent in most of these cases.

1 So, this doesn't prove that the resistance gene
2 transferred from the food bacterium to the human bacterium,
3 in fact, it might be that somebody colonized with the
4 resistant bacteria, contaminated the food. We can't rule
5 that out. That is what I was talking about, the problem of
6 direction, but once again, it shows that there is some
7 evidence for a genetic conduit for resistance genes between
8 these two very unlikely partners in an exchange.
9 So, to make a long story short, what I am telling
10 you is that there are an accumulating number of examples of
11 evidence at the genetic level that suggest that antibiotic
12 resistance genes can be transferred, not just across genus
13 and species lines, but transferred very readily in nature.
14 The fact that it has been easy to find these
15 examples suggests that they probably have occurred fairly
16 often, and that this type of evidence is going to continue
17 to accumulate, so it's very important that you think about
18 what this means and to try to figure out how to interpret
19 this information, but it certainly raises the question of
20 whether it is possible that bacteria, antibiotic resistant
21 bacteria from animals coming into the human intestinal tract
22 could transfer their resistance gene to human pathogens, so
23 this is not completely out of thinking about.
24 Many of you probably are very skeptical about this
25 sort of thing. There are lots of caveats that you can make

1 about this type of evidence, but one reason that I want to,
2 that I think even if you don't believe a word of it, that
3 you need to know about it because of what is on the last
4 transparency.
5 [Slide.]
6 Public perception of food safety. Now, I wouldn't
7 have even thought to talk about this except that to my
8 sorrow I was involved in testifying about the safety of
9 transgenic corn where the Europeans were very concerned
10 about an ampicillin resistance gene that was used as a
11 marker gene in corn, and they are obsessing about that while
12 they are using avoparcin in animal feed, but that gives you
13 an idea of the fact that the public isn't always really
14 clear on risks and perceptions.
15 So, if we learn from this, first of all,
16 antibiotic resistance is getting to be a very hot-button
17 issue. This is something that the public is quite concerned
18 about, but the public does not necessarily understand much
19 about antibiotic resistance, tends to identify antibiotic
20 resistance with virulence, and is going to be very confused
21 about subtle arguments like whether human strains of
22 enterococcus can colonize the human body or not.
23 So, I think that you are going to have to think
24 about this from a public safety perception and especially if
25 evidence emerges that some of these agricultural use

1 antibiotics can compel cross-resistance, not just to
2 vancomycin, but also to Synercid and some of the new
3 antibiotics coming through the human use pipeline.
4 So, I think this is an issue, this gene transfer
5 issue is not something that you should just brush under the
6 rug because you personally don't find it too convincing, but
7 really take a look at this, because this information is out
8 in the literature now, it is being paid attention to, and at
9 the very least you are going to have to answer questions
10 about it.
11 I think I will stop there.
12 DR. STERNER: Questions from the committee for Dr.
13 Salyers? Dr. Barker.
14 DR. BARKER: So, is the use of antibiotics in
15 humans more of a hazard to animals than it is the other way
16 around?
17 DR. SALYERS: Well, that is a possibility. You
18 know, there are a lot of issues here. First of all, and I
19 want to make this clear again although I know I said it at
20 the beginning, there is no question that the pressure from
21 physicians to develop resistant strains is the major problem
22 right now, but I think the reason I am raising the question
23 in the context of animal use is that the public is going to
24 be a lot less forgiving for that type of pressure than they
25 will be for human clinical pressure.

1 Another problem that people perhaps should think
2 about is people are handling these antibiotics in
3 agricultural use, and that is something that I didn't
4 address, but it is something that you might think about with
5 respect to people who are colonized with resistant strains
6 just selected by their use of the antibiotic.
7 It isn't impossible, though. I mean our finding
8 that the resistance can go the other way is something that
9 nobody really thinks much about, but is a possibility.
10 DR. BARKER: In terms of the framework document
11 that we are working on, how might we incorporate these
12 issues into our considerations about setting thresholds and
13 determination of whether there really is resistance?
14 DR. SALYERS: I think the document -- incidently,
15 I just want to say that I was impressed with this document
16 in the sense that it showed more of a sophistication in
17 terms of some of these issues like the more complicated ones
18 of gene transfer than one normally sees, but I think that
19 the document does address the issue of gene transfer, are
20 these genes transmissible or not.
21 I think the document does address the issue of
22 gene transfer, and one thing in the document that I think is
23 not right is that you wouldn't expect to get gene transfer
24 between the respiratory pathogen and intestinal bacterium.
25 I think that we are beginning to find is maybe not the case,

1 but I think the issue of whether the resistance is
2 transmissible is a very important one.
3 Now, you have to be careful there, though, because
4 sometimes one type of resistance gives you the idea that it
5 is not transmissible, and I use the fluoroquinolone
6 resistance as an example.
7 You know, people have been telling each other for
8 quite a while that fluoroquinolone resistance is a mutation
9 in DNA gyrase or topoisomerase, cannot be transferred, and
10 yet recently, transmissible fluoroquinolone resistance has
11 been identified. It is just now being studied.
12 So, it is a difficult issue to address because you
13 don't know in most of these natural settings how the gene is
14 being transferred. Probably it is by conjugation. Many
15 conjugation systems are regulated. The one that we work on
16 is stimulated by very low levels of tetracycline. Others
17 are stimulated in other particular ways.
18 I think that what you are going to have to assume
19 is that any resistance gene is transmissible would probably
20 be the safest thing.
21 DR. STERNER: Other questions, comments?
22 [No response.]
23 DR. STERNER: Thank you, Dr. Salyers.
24 Our last speaker before our break this afternoon
25 is Dr. Sherwood Gorbach from Tufts University talking about

1 the importance of in vitro resistance compromising therapy
2 for diarrheal disease.

3 **Importance of In Vitro Resistance Compromising**
4 **Therapy for Diarrheal Disease**

5 DR. GORBACH: My task was to talk about impact of
6 low level antimicrobial drugs on the human intestinal
7 microflora, as well as the changes in resistance that might
8 have a role in the treatment of human diarrheal disease.
9 Let me make a few general comments. I will talk
10 about the microflora first.
11 Antimicrobial drugs cause resistance in animal
12 isolates of human pathogens, and they also create an
13 atmosphere or an environment in the microflora where these
14 resistant genes can be passed to other members of the
15 microflora or to other human pathogens.
16 So, on the one hand, we have the problem of
17 resistance all together.
18 [Slide.]
19 That is the microflora.
20 [Slide.]
21 The second issue has to do with antimicrobial
22 residues, very small amounts of antibiotic that might be
23 present in the human food chain that somehow escaped
24 surveillance, and the effects of these very low levels of
25 antibiotics in terms of possibly inducing resistance.

1 Well, just to remind you about the localization of
2 the microflora, the vast number of microorganisms are
3 located in the colon, and as we go across the ileocecal
4 valve -- I don't have a pointer here, but it is that line
5 all the way on the right -- there is a dramatic increase --
6 these are log changes -- and so that we get to the human
7 colon where anaerobic bacteria outnumber the aerobic or
8 facultative types by a factor of about 1,000 to 1.
9 E. coli and the other gram-negatives are located
10 starting in the mid-ileum and then moving down and are
11 increased in the large bowel. The large bowel is so heavily
12 compacted with microorganisms, 10^{11} or 10^{12} per gram that it
13 approaches the theoretical limit that can fit into that
14 given mass.
15 [Slide.]
16 Now, this is the result of changes in the
17 microflora with therapeutic doses of oxytetracycline. It is
18 obviously well known. These are called Finlandian graphs.
19 These are the resistance of the E. coli strains. The graph
20 all the way on the left is the normal, and the bottom there
21 is the minimal inhibitory concentration. As the graph
22 shifts to the right, there is increasing resistance.
23 [Slide.]
24 This shows that depending on the day as it goes
25 out, that a therapeutic dose will have a tremendous impact

1 on the antibiotic resistance, not very surprising. What is
2 interesting -- these are studies by Tancrede from France --
3 what is interesting is that this is a very low dose, 20
4 milligram dose in a human, which is lastly sub-therapeutic,
5 and again there is a significant shift of the graph, the one
6 on the furthest left being pre-antibiotic, and the one on
7 the furthest right being the changes in the resistance, an
8 increase in resistance even with very low sub-therapeutic
9 doses.
10 [Slide.]
11 These investigators, Tancrede and Barakat, noted
12 that in the French population, 97 percent of normal
13 untreated people are permanent or occasional fecal carriers
14 of oxytetracycline resistant enterobacteriaceae.
15 Enterobacteriaceae, of course, include E. coli and normal
16 members of the flora.
17 [Slide.]
18 So this is a tremendous amount of resistance.
19 This was also shown in the studies of Stuart Levy, which are
20 difficult to see here, but these are several antibiotics,
21 ampicillin on the furthest left, and they show that people
22 carry about 40 percent of the strains in their microflora
23 have a resistance to one or another of these antimicrobials.
24 This is healthy human Americans, so the antibiotic
25 resistance is very common, and these are the resistances to

1 people on or off antibiotics, and the graphs on the left are
2 the people off antibiotics, the controls, and it not only
3 shows the 40 percent figure in people off antibiotics, but
4 also shows that many, up to 10 percent have multiple
5 resistances.
6 [Slide.]
7 So, when people are exposed to antibiotics, they
8 not only get a resistant to one antibiotic, namely, the one
9 they are exposed to, but they develop multiple antibiotic
10 resistances. These are off of treatment, and these are the
11 percent with four antibiotic resistances, 10 percent of
12 their E. coli isolates had four antibiotic resistances.
13 So, antibiotic resistance is very common. Now,
14 how much of this is related to human use and how much is
15 related to agriculture or to veterinarian use? We really
16 don't know that answer. All we can say is that not everyone
17 is exposed to antibiotics, although it seems that way if we
18 look at the antibiotic costs, but nevertheless, not everyone
19 is exposed, and these people were not exposed, at least in
20 the recent past. So, we have to assume that some of this
21 may be coming.
22 [Slide.]
23 Now, what are the effects of a low dose? Well,
24 this is a study done in mice where a very low dose of
25 streptomycin, about 1 milligram, was given to these mice,

1 and it shows the infective dose.

2 In the untreated mice, it required a million cells

3 of Salmonella to produce a 50 percent infection rate.

4 However, with this remarkably low dose of streptomycin, that

5 sensitivity of Salmonella was reduced, the point being that

6 even if small residues of antibiotics make their way into

7 the food chain, they can have a major impact on the

8 susceptibility to infection.

9 [Slide.]

10 The human counterpart was a study reported by the

11 Centers of Disease Control, of an outbreak of Salmonella

12 havana. It's a rather unusual strain, so they were able to

13 track this, and they showed that the susceptibility was 31

14 percent in people who had had prior antibiotic treatment,

15 that is, anywhere from one week to two weeks before the

16 contact with the organism, versus 13 percent with no

17 treatment, so it was about 3-fold increase in the

18 susceptibility to Salmonella infection when people had

19 antibiotic treatment in the past.

20 This relates to the intrinsic resistance of the

21 microflora to infection. So, you perturb the microflora

22 with even very low amounts of antibiotics, and the

23 susceptibility to Salmonella continues for at least one week

24 and possibly more.

25 [Slide.]

1 Now, let me move to human disease. This is WHO
2 data giving you some of the big human pathogens. This is
3 Shigella, 600,000 deaths a year. This is out of a total of
4 2 1/2 million deaths that WHO has tracked. Enterotoxigenic
5 E. coli, 300,000; the rotavirus, a huge number.
6 By the way, not considered a heavy-duty pathogen,
7 mild disease, but nevertheless, it can on a worldwide basis
8 responsible for a huge number of deaths, and typhoid fever
9 for about 600,000.
10 Now, in the United States, the CDC has reported an
11 annual mortality of about 500 cases per year, that is,
12 deaths due to diarrheal disease. In the UK, the
13 corresponding number is about 200 deaths per year. This is
14 probably almost certainly vastly underreported.
15 Community-based studies have shown that acute
16 diarrhea in the USA occurs in adults about one to two times
17 per year. It is not a topic for polite cocktail
18 discussions, but all of us are aware of these occasional
19 intestinal assaults.
20 In children, the number is about twice that, so
21 it's around two to four cases of diarrhea per year, and if
22 the child is in daycare, the numbers can be doubled yet
23 again. Daycare is a veritable cesspool of pathogens. It's
24 almost an immunizing event for a child. That is if daycare
25 is generally over 10 kids in a daycare center.

1 Now, it is important to distinguish the organisms
2 that are of human or environmental sources from those that
3 are of animal sources, so among the pathogens causing
4 diarrheal disease, those of animal sources are Salmonella,
5 Campylobacter, Yersinia, and E. coli 0157.
6 Those of human sources, several of them are shown
7 here. Shigella is human. The primary cases are mostly
8 human to primate. Enterotoxigenic E. coli, as well as some
9 of the other E. coli - enteroaggrative E. coli, and so on,
10 are probably of human origin. Cholera is marine based, as
11 well as most of the other Vibrios.
12 The rotavirus is human. The human strain is
13 uniquely human, and Salmonella typhi is also a uniquely
14 human pathogen. So, everything on this slide is human, but
15 these don't show the figures for the non-typhoidal
16 salmonellosis, which is the major cause of food-borne
17 disease in the United States, at least the bacterial ones -
18 Campylobacter, which is very close to it, and all in all,
19 causes a serious morbidity.
20 [Slide.]
21 It is often said that you really don't need
22 treatment for these, and I have heard that comment, and I am
23 showing you a study that was published about two and a half
24 years ago in the Clinical Infectious Diseases by Dryden from
25 the UK, in which he randomized people with severe diarrheal

1 disease into receiving either placebo or Cipro before the
2 cause of the diarrhea was known, and this is the outcome.
3 You can see the days of diarrhea were cut almost
4 in half by the use of Ciprofloxacin, a fluoroquinolone.
5 The definition of diarrhea, severe diarrhea, in
6 this study was four or more bowel movements per day for
7 three or more days, and that is rather a heroic number of
8 stools.
9 That should be accompanied by one other symptom,
10 such as fever, abdominal pain. So these represent a small
11 piece of the total diarrheal cases, but nevertheless, these
12 are the ones that are sick enough to stay home from school.
13 Diarrhea is probably second only to respiratory disease as a
14 cause of staying home from school or losing time at work.
15 Intestinal indiscretions can cause this, and it is clear --
16 this is the fourth of a series of studies from different
17 places in Europe, and one from Chicago, as well -- that has
18 shown the striking reduction in the symptoms of acute
19 diarrhea by the use of Ciprofloxacin.
20 So, the point of this is Ciprofloxacin is a major
21 -- these are just the pathogens, I won't go through all of
22 those -- but suffice as to say that in this study, 88
23 percent of the cases of diarrhea had an identifiable
24 bacterial pathogen. The leading causes would be as you
25 expect Salmonella and Campylobacter, and that last slide,

1 which is difficult to read, in Salmonella and Campylobacter
2 cases, contrary to popular teaching, there was a significant
3 decline in symptoms in these severe cases.
4 Well, the point is that the fluoroquinolones are
5 very important in treatment of Salmonella, not only the
6 extraintestinal forms of Salmonella, Salmonella bacteremia
7 and local tissue salmonellosis, but also the more severe
8 diarrheal cases, and despite what the textbooks say, not to
9 treat Salmonella, the fact is that practicing physicians,
10 when they see a patient that qualifies with severe diarrhea,
11 which generally means enough diarrhea to come to the
12 physician's office, and you can usually spot them, they are
13 kind of moving around on two legs, when a physician sees
14 this amount of diarrhea that has gone on for three days or
15 more, almost invariably they will treat, and almost
16 invariably they will treat with a fluoroquinolone.
17 The four studies, one of which I have shown you,
18 justify that. I would like to emphasize that while many of
19 our resistance problems are surely related to antibiotics in
20 human medicine, and I would include the pneumococcus and
21 Staph aureus, tuberculosis, and with due respect to the
22 honorable delegate in the front row, Abigail, I also include
23 VRE as a problem of human proportions, at least in the
24 United States.
25 It is rooted in the intensive care units, it is

1 not found in the community, but we can argue that.

2 While those are clearly related to abuses in human

3 medicine, that is not what this meeting is about. What this

4 meeting is about is the problems in the veterinary medicine,

5 and I don't think we can escape from the increasing

6 incidence of Salmonella and Campylobacter resistance to

7 fluoroquinolones, that has been seen in Europe, temporally

8 related to a prior introduction the fluoroquinolones in

9 veterinary medicine.

10 The only way that you get is significant

11 resistances in these organisms is through pressure,

12 antimicrobial pressure at the animal source.

13 We don't yet have it although a recent study from

14 Minnesota, published in The New England Journal of Medicine,

15 suggests that fluoroquinolone resistance is increasing in

16 our Salmonella/Campylobacter strains. In this country, we

17 are still low enough so that a positive action by this

18 committee I think can avert what is, now in Europe, a

19 tremendous problem.

20 Spain is 50 to 70 percent resistance with

21 Salmonella and Campylobacter. Granted, we don't have to

22 treat all of them, but those that are sick enough to treat,

23 we are not going to get a good antibiotic unless we can slow

24 the resistance in these important pathogens.

25 DR. STERNER: Questions from the committee for Dr.

1 Gorbach?

2 I am going to at the risk of demonstrating my

3 ignorance to this entire assemblage ask if you could help me

4 in understanding the issue of increased susceptibility.

5 When I look at antibiotic residues in foods of animal

6 origin, in general, levels are set at the part per billion

7 level, and violative residues that show up commonly would be

8 at less than 100 parts per billion.

9 If I understood your statement on tetracycline

10 dosage, you were giving a 20-milligram dose to a human and

11 then demonstrated increased susceptibility.

12 DR. GORBACH: Increased resistance.

13 DR. STERNER: If you took at 45-kilo adult, you

14 had about 0.44 milligrams per kilogram, so you were at half

15 a milligram or half a part per million dose?

16 DR. GORBACH: I think the problem is it may be a

17 little like the radiation effect, that you may be able to

18 demonstrate resistance with very small amounts, but it gets

19 harder and harder to demonstrate, but there may not be any

20 bottom at which it is completely safe.

21 We don't really know that. All we know is that

22 very small amounts, sub-therapeutic amounts can cause

23 changes in the microflora, and I should say that does not

24 relate to the problem with diarrheal disease.

25 It should be apparent that changes in resistance

1 to the microflora would reflect themselves in increased
2 resistance in urinary tract pathogens, E. coli or in
3 infections, more deep-seated infections that we might see in
4 the hospital, but I don't know what the bottom safety is.
5 I am not disagreeing, in fact, I was part of the
6 speaker at the deliberations on antibiotic residues, and I
7 agree with the position, but we don't know what the lowest
8 level of safety is with antibiotic residues.
9 DR. STERNER: Well, that gets to the heart of the
10 issue of the whole drug approval process as it has existed
11 for every since I have been familiar with it, and the fact
12 that we do, in fact, set some minimal level at which we
13 consider it to be safe or a tolerance setpoint, and the data
14 that you have shown would argue against anything other than
15 what we can detect, in other words, zero. The smaller it
16 gets, the safer we are.
17 DR. GORBACH: I think that is true, but I can't be
18 sure. All I would say is I like the approach of the draft
19 document in that it separates out antibiotics by importance.
20 So, I wouldn't worry as much about the Class II or Class
21 III, but I would worry about even low exposures to Class I.
22 DR. STERNER: So, for example, our AOAC says that
23 they can detect a compound at a part per quadrillion. Even
24 that level then would become unacceptable for a Class I
25 drug?

1 DR. GORBACH: Well, we are talking about different
2 issues now. We are talking about antibiotic residues which
3 may impact the human to microflora.
4 DR. STERNER: Right.
5 DR. GORBACH: There is another aspect of that
6 question that relates to the changes in the intrinsic
7 strains from animals, that is, Salmonella and Campylobacter,
8 and that is a different issue. So, I am willing to accept,
9 for antibiotic residues, a definable low level, but I am not
10 very happy about using what the document defines as Class I
11 drugs, because that in itself may influence the animals'
12 microflora, which includes Salmonella and Campylobacter.
13 DR. STERNER: Then, if I may, by inference your
14 philosophical opinion would be there would be zero Class I
15 approvals then under any circumstance?
16 DR. GORBACH: I don't like the "under any
17 circumstance," because there may be situations in animals
18 where it is lifesaving in an animal, but for routine use,
19 yes, that would be my position.
20 DR. STERNER: Thank you. Other questions?
21 DR. GERKEN: Yes. You stated that Spain has so
22 much Campy and Salmonella resistance, I think it was to
23 fluoroquinolones, is that correct, or was that in general?
24 DR. GORBACH: Yes, to fluoroquinolones -- well, it
25 is actually in general. I mean they have resistance to

1 pneumococcus, it is up to 60 percent. But I referred to
2 Campylobacter/Salmonella.
3 DR. GERKEN: Is there evidence that their food is
4 contaminated with bacteria that have that type of
5 resistance, and that there is a correlation between those
6 two things?
7 DR. GORBACH: I don't know about the food, I am
8 not an expert in it. I can simply say that there are a lot
9 of reports from Spain about resistant cases of salmonellosis
10 and Campylobacter. Maybe some of the experts on the panel
11 could comment.
12 DR. GERKEN: In disease in people.
13 DR. GORBACH: Humans. Yes, in people. They do
14 report increasing levels of resistant strains in people.
15 DR. GERKEN: Maybe you can shed some light on
16 that.
17 DR. ANGULO: One of the background documents for
18 this panel is the report from the WHO meeting last summer on
19 fluoroquinolones in which all the data available then was
20 reviewed, and there is clear evidence of quite marked
21 fluoroquinolone resistance in Campylobacter from several
22 European countries, most notably being Spain, and there is
23 also literature that show fluoroquinolone resistant
24 Campylobacter at retail, from poultry at retail and pork at
25 retail in Spain.

1 The rates that have been just suggested for
2 fluoroquinolone resistant Salmonella have not been seen.
3 There have been case reports of fluoroquinolone resistant
4 Salmonella around the world, but there are no countries that
5 I am aware of that have a notable rate of fluoroquinolone
6 resistant Salmonella.
7 There is evidence of decline in susceptibility to
8 fluoroquinolones amongst Salmonella in several countries in
9 Europe and in the United States, but there is not an
10 emergence of fluoroquinolone resistant Salmonella of note.
11 DR. GERKEN: Does the meat in Spain mostly come
12 from production facilities in Spain, and in those production
13 facilities, are they using more fluoroquinolones than in
14 other countries?
15 DR. ANGULO: That's right, and there are other
16 members in the audience that participate in the WHO working
17 group, and it was my impression the consensus that one of
18 the items of concern was the unregulated use of
19 fluoroquinolones in some southern European countries where
20 there is over-the-counter usage of fluoroquinolones, and it
21 was a conclusion of the WHO consultation on fluoroquinolones
22 that the veterinary use of fluoroquinolones had contributed
23 to the emergence of fluoroquinolone resistant Campylobacter.
24 I should also point out that it was the conclusion, as
25 stated by Dr. Vogel, of the WHO consultation that there was

1 not then evidence of clinical treatment failures from such
2 usage. In other words, the clinical consequence of this
3 emergence, which there was agreement was the consequence of
4 using fluoroquinolones in food animals, the clinical
5 consequence of that emergence had not been seen yet.
6 DR. STERNER: Other questions?
7 [No response.]
8 DR. STERNER: Thank you, Dr. Gorbach.
9 Dick Geyer has some housekeeping announcements.
10 We will at the end of his comments take a 15-minute break.
11 I hope you have noticed we are keeping ahead of schedule, so
12 that there is the prospect of you actually being able to
13 take a meal this evening before every place has closed.
14 When we do break, it will be 15 minutes. You can set your
15 watches, and if you are not in here, we are going to press
16 on regardless. Our next group speaking will be from the
17 Animal Health Institute.
18 [Housekeeping announcements.]
19 [Recess.]
20 DR. STERNER: We are going to go ahead with the
21 Animal Health Institute's presentations, but before we get
22 to Dr. Brendan Fox, Richard Geyer has a few comments,
23 housekeeping details that he needs to address before we get
24 started. So, Richard, with that, we will call the meeting
25 to order.

1 MR. GEYER: Keith, what I had to say applies to
2 our public speakers, so I think I will just hold off until
3 we start that section.
4 DR. STERNER: Our first speaker representing the
5 Animal Health Institute is the president of Elanco Animal
6 Health from Indianapolis, Indiana, Dr. Brendan Fox.
7 **Testimony of Animal Health Institute**
8 **Dr. Brendan Fox**
9 DR. FOX: Thank you, Mr. Chairman.
10 On behalf of the Animal Health Institute and its
11 member companies, we appreciate the opportunity to appear
12 before you today to provide our views on FDA's proposed
13 framework document regarding the approval and use of
14 antimicrobials in food producing animals.
15 As you have just mentioned, I am Dr. Brendan Fox,
16 president of Elanco Animal Health, a division of Eli Lilly
17 and Company. Since joining Eli Lilly in 1974, I have served
18 in several research and management positions within the
19 company, and my current responsibilities include both R & D,
20 drug research and development, as well as the business side
21 of our activities, but I am here today representing the
22 views and concerns, not only of Elanco Animal Health, but of
23 AHI's member companies, and I believe my comments will
24 reflect the views of my fellow CEOs of Animal Health
25 companies, those responsible for directing future investment

1 in the animal health industry and in to antibiotics in
2 particular.
3 Before proceeding, let me take a moment to
4 describe how we would like to use our time this afternoon.
5 I would like to make some opening remarks to give the
6 committee a sense of the overall views of the animal
7 pharmaceutical industry, and following that, I would like to
8 turn to Dr. Richard Carnevale here.
9 Dr. Carnevale is the vice president of regulatory,
10 scientific and international affairs for AHI. He will
11 provide a more detailed examination of some of the specific
12 scientific elements outlined in the framework document, and
13 he will answer all the difficult questions.
14 Then, Alex Mathews, AHI's president and CEO, will
15 offer our views on what we believe are appropriate measures,
16 because we do believe there are appropriate measures to
17 address the issue of antimicrobial resistance in food-borne
18 pathogens.
19 Those sort of steps will included: establishment
20 of an appropriate risk assessment methodology to quantify
21 the potential impacts of food animal antibiotic use on human
22 health; secondly, strengthening and expanding the
23 government's national monitoring and surveillance efforts to
24 assess the potential human exposure to antibiotic resistant
25 food-borne pathogens; additionally, joint government,

1 industry, and producer efforts to educate the industries on
2 judicious use of antibiotics in farm animals; and finally,
3 the appointment of a blue-ribbon panel to advise FDA on the
4 this whole question of antibiotic resistance in both humans
5 and animals.
6 So, we will discuss those ideas later on, and once
7 we complete the presentation of the three speakers, we would
8 welcome the opportunity to take any questions or comments
9 from the panel.
10 In setting out my part of the agenda, I would
11 like, first of all, to state very clearly the worldwide
12 concern over antimicrobial resistance is one which we, as
13 manufacturers of pharmaceuticals for both human and animal
14 medicine, strongly share. Health care both in humans and
15 animals is our business, and it is very important to us to
16 protect human health above everything.
17 From a public health viewpoint, protecting the
18 long-term effectiveness of antimicrobial drugs for human
19 medicine is critical, and obviously from a business
20 viewpoint, we have a clear interest in prolonging the useful
21 life of our products both in humans and in animals.
22 The development of antimicrobial resistance in
23 pathogenic bacteria presents difficult medical challenges
24 requiring both attention and action. To successfully
25 address this challenge, it is critically important to fully

1 understand the nature and extent of the problem in both
2 human and animal medicine. In order to make sure we are
3 proposing sound solutions, we must examine the basic issues
4 in perspective, such questions as:
5 What is the risk to an individual of developing an
6 illness from a food-borne pathogen which developed
7 antibiotic resistance as a result of veterinary drug
8 therapy? And what is the rate of treatment failure in such
9 instances?
10 What is the relative contribution of human
11 antibiotic use to the problem of resistance development
12 compare to food animal use?
13 Finally, what is the cost to consumers and
14 agricultural producers of changing current regulations
15 regarding the approval and use of antimicrobials in animals?
16 Clearly, there are many, many more questions to be
17 examined. And the questions, like this entire debate, are
18 not new. We have known since antibiotics were first used
19 that bacteria can employ defenses that allow them to survive
20 drug therapy and that resistance to antibiotics is a logical
21 consequence of their use in both humans and animals.
22 The questions before the advisory committee today
23 are fundamentally no different than the questions that have
24 been asked repeatedly in scientific circles and debated
25 there for the past 40 years.

1 FDA has indicated that recent resistance data
2 relative to food-borne pathogens have "rekindled concerns"
3 and led to the development of this framework proposal, but
4 as you will hear in our more detailed analysis, we believe
5 the agency is overreacting, it is overstating the
6 conclusiveness and the implications of the data that we have
7 in hand and has put forth a flawed proposal.
8 We believe the framework document is, in practice,
9 unworkable. It is not support by the scientific evidence,
10 and it is based on too many faulty assumptions. In short,
11 it proposes a solution to a problem that is as yet far from
12 clearly understood.
13 The framework is based on five components designed
14 to "evaluate and minimize the potential human health
15 effects" of antimicrobial use in animals. But by starting
16 the examination of this issue from that standpoint, implicit
17 in the framework itself is the assumption that there is a
18 risk to public health from the use of antimicrobials in
19 agriculture. This does not provide a sound scientific
20 objective from which to proceed.
21 There is universal agreement that any use of
22 antibiotics in human and animal medicine represents a hazard
23 that antibiotic resistance can develop. But the framework
24 seems to suggest that the hazard is exactly the same as a
25 risk, which is not the case.

1 Clearly, hazard identification and
2 characterization are only two of the components in analyzing
3 risk. In our view, any proposal for regulatory change --
4 and I would add that this is a major change -- in the
5 approval process for antimicrobials in advance of a full
6 evaluation of the nature and extent of resistance, and the
7 actual risk as opposed to hazard, the actual risk of a
8 public health impact from their use is, in our view, very
9 premature.
10 The key issue is not whether food-borne or other
11 pathogens develop resistance, it is what is the potential
12 for such resistance to have a negative impact on human
13 health, to result in infections that cannot be treated by
14 antibiotic therapy.
15 Addressing this issue requires the establishment
16 of an appropriate risk assessment framework to examine the
17 various uses of antimicrobials in food producing animals and
18 identify and quantify any specific threats to public health
19 caused by their use.
20 Contrary to the assertion in the framework
21 document, this proposal does not set out a conceptual risk-
22 based framework for evaluating microbial safety. It is, at
23 best, a hazard-based framework, based on a potential risk.
24 What is needed first -- before any of the
25 discussion of details of pre- or post-approval studies,

1 resistance thresholds, monitoring thresholds, drug
2 categorizations or pathogen loads -- is a quantitative risk
3 and benefit assessment methodology with a farm-to-table
4 approach to quantify potential impacts and establish
5 acceptable levels of risk.
6 The importance of a comprehensive risk assessment
7 in this equation becomes clear when you examine the number
8 of points along the continuum from farm to table where
9 something could go wrong in order for a food-borne pathogen
10 to cause an antibiotic treatment failure in an individual.
11 Let's look at how the process is laid out in the
12 framework document. I am quoting from page 3 of the
13 document.
14 It says, "If, (1) when using an antimicrobial in a
15 food producing animal, (2) resistance occurs in such
16 bacteria, and (3) the resistant bacteria are then ingested
17 by and (4) cause an illness in a consumer who (5) needs
18 treatment, (6) that treatment may be compromised (7) if the
19 pathogenic bacteria are resistant to the drug used for
20 treatment."
21 So, clearly, there are seven steps even in this
22 document from the treatment of an animal on the farm to a
23 compromised human drug treatment, and I would point out
24 compromised treatment is not quite the same as treatment
25 failure.

1 This example doesn't include the numerous food
2 processing steps which affect pathogen levels, from the
3 slaughterhouse all the way through to food preparation, and
4 things that happen in the home or in the restaurant.
5 This example partially demonstrates the complex
6 nature of the issue of food-borne pathogen antimicrobial
7 resistance and suggests the importance of a more
8 comprehensive risk assessment methodology to assist in
9 making the important policy decisions in this area.
10 In order to develop better risk analysis
11 understanding of food-borne antimicrobial resistance, the
12 Animal Health Institute has provided financial support to
13 Georgetown University's Center for Food and Nutrition Policy
14 in their efforts to develop a comprehensive risk and benefit
15 assessment of the impacts on human health of using
16 antibiotics in food animals.
17 Our understanding is that the development of the
18 risk assessment model is currently underway and that
19 Georgetown Center will share the results with this committee
20 and with the Center for Veterinary Medicine once it is
21 complete.
22 Beyond this issue, however, there are other
23 troubling aspects of the proposed framework document that
24 deserve comment. As someone from a company which looks at
25 this issue both from the context of human and animal

1 medicine, and from discussions with my medical colleagues, I
2 am struck by the difference in approaches within FDA to the
3 problem of antimicrobial resistance in human medicine as
4 opposed to that for animal medicine. This difference is
5 especially striking in light of what we know about the
6 public health impact of human versus animal use of
7 antimicrobials.
8 If I may just depart for a second here. I had
9 some very interesting discussions recently with my
10 colleagues dealing with these issues, but one of the points
11 they have pointed out is there is an increasing use of
12 antimicrobials, antibiotics in humans that is driven by
13 factors in society today.
14 It is driven by the fact there are an increasing
15 number of infections. This was mentioned a little bit
16 earlier here. I think the number of cases of otitis media
17 here in the U.S. has doubled in the past several years, and
18 this is due to child care centers basically.
19 Those do require treatment, and in some cases,
20 child care centers will not readmit children if they have
21 not been treated with antibiotics, a clear example there of
22 changes in society, but I don't think the Secretary or
23 anybody will propose abandoning child care centers. The
24 question is what can we do in that environment to ensure
25 appropriate use.