ORIGINAL

UNITED STATES OF AMERICA
BEFORE THE FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

In the Matter of:	:	
Enrofloxacin for Poultry: Withdrawal of Approval of Bayer Corporation's New Animal Drug Application (NADA) 140-828 (Baytril)	:	FDA DOCKET NO. 00N-1571

Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland

Tuesday, April 29, 2003

THE HEARING in the above-entitled matter commenced at 9:32 a.m., pursuant to notice.

BEFORE:

DANIEL J. DAVIDSON, Administrative Law Judge

Diversified Reporting Services, Inc.
1101 Sixteenth Street, NW Second Floor
Washington, DC 20036
(202) 467-9200

00N-1571

~~FR 2~~
FR 10

APPEARANCES:

On behalf of the Center for Veterinary Medicine (CVM):

NADINE R. STEINBERG, ESQ.
ROBERT M. SPILLER, JR., ESQ.
CLAUDIA J. ZUCKERMAN, ESQ.
U.S. Food and Drug Administration
Department of Health and Human Services
Office of the General Counsel
Office of the Chief Counsel
5600 Fishers Lane, GCF-1
Rockville, Maryland 20857
(301) 827-5050

On behalf of Respondent Bayer Corporation:

GREGORY A. KRAUSS, ESQ.
ROBERT B. NICHOLAS, ESQ.
McDermott, Will & Emery
600 13th Street, N.W.
Washington, D.C. 20005-3096
(202) 756-8263

Also present:

Dennis D. Copeland, D.V.M., Director
Stewardship - Government/Industry Relations
Research & Development
Bayer HealthCare Animal Health Division
Bayer HealthCare, LLC
P.O. Box 390
Shawnee Mission, Kansas 66201-0390
(913) 268-2522

C O N T E N T S

Corrected as per OR 46 6/13/03

P R O C E E D I N G S

JUDGE DAVIDSON: Okay, on the record. Do we have any preliminary matters?

MR. NICHOLAS: We do. On behalf of Bayer, I'm Robert Nicholas, and I want to respond to CVM's motion yesterday with respect to the Sentinel County study.

As I mentioned yesterday, Your Honor, Bayer has still not received the complete documentation for the Sentinel County study, and critical information is still missing.

For instance, Your Honor, the data set provided by ~~CVC~~ CDC -- and this is the data set provided in the SAS format -- identifies 471 isolates; however, the ~~turnover~~ Tenover article, G-624, identifies 700 isolates in that study.

Another article by Patton, which is B-589, describes the survey as 298 isolates; and another article by Sobel identifies the study, or identifies 460 isolates.

So without complete documentation, Your Honor, we can't even tell what the study is, much less understand what's been done there.

Corrected as per OR 46 6/13/03

Neither the data set, the protocol, nor the questionnaire that we did obtain identify all the variables in the data set. They don't identify -- neither the data set, the proto-formula, or the questionnaire identify the species of each campylobacter isolated.

We can't tell when the organisms were tested, whether they were tested more than once, and we have not seen the laboratory test sheets -- data sheets -- so we're still expecting a reply.

I had a conversation with a lawyer from ~~CVC~~ CDC as recently as three weeks ago and he promised that we would have the information and response to our reply within a week. He then called me back and said he could not make that representation any more. He believed we would get additional information, but he couldn't let me know when.

So that's the current status, Your Honor; therefore, we object to the introduction of this exhibit at this time.

JUDGE DAVIDSON: As I said yesterday, I haven't seen any of this. I don't -- I don't know what

it is that's there and what's not there. I've seen what's been put in the record. I only have your representation that there are things missing, and I don't question that.

So what I'm going to do is I'm going to require the parties, by close of business -- and close of business means whenever we adjourn the hearing on Friday -- to present me with the detailed information that I need to rule on this. In other words, what is there and what's not there. If you can't agree as to what is there and what's not there, then I'll take separate representations in writing from both of you so that I can then mull it over over the weekend and decide what I want to do with it.

As of now, I don't know. I ruled earlier because I took your representation at face value that they hadn't presented the information; and now they claim they have, and I don't know. So I'll have to -- that's it. By the time the hearing adjourns on Friday, I expect a written representation from both sides, or jointly, explaining to me what is missing, if anything is missing, and what is included; and if you want to

add the import of that if your argument is that it's not important. Okay?

MR. NICHOLAS: Thank you, Your Honor.

JUDGE DAVIDSON: All right. Any other preliminary matters? Do you have enough chairs today? Looks that way. Okay.

I think we're ready for Mr. Walker now.

MS. STEINBERG: Dr. Walker --

JUDGE DAVIDSON: I apologize. They -- okay, Dr. Walker. I meant no disrespect; it's just the way they sent this list up to me. Sometimes they put the doctor in front and sometimes they don't.

Whereupon,

ROBERT D. WALKER

was called as a witness and, having been first duly sworn, was examined and testified as follows:

JUDGE DAVIDSON: Give your full name and address to the reporter.

THE WITNESS: Work or home?

JUDGE DAVIDSON: It doesn't matter, as long as you can be contacted there.

THE WITNESS: My name is Robert D. Walker; I

Corrected as per OR 46 6/13/03

work at 8401 ~~Merkirk~~ Muirkirk Road, Laurel, Maryland 20708.

DIRECT EXAMINATION

BY MS. STEINBERG:

Q Dr. Walker, can you state your position at CVM for the record, please?

A I'm the director of the Division of Animal and Food Microbiology in the Office of Research.

MS. STEINBERG: Your Honor, may I have permission to approach the witness?

JUDGE DAVIDSON: Certainly.

BY MS. STEINBERG:

Q Dr. Walker, can you identify what I'm handing you, please?

A This is my written direct testimony.

Q And the exhibit number?

A ~~G-141~~ G-1481.

Q Okay. And can you turn to page 10 of that exhibit? Is that a photocopy of your signature on that page?

A Yes, it is.

Q Thank you. Since the time that you signed that testimony and submitted it, have we had a chance

Corrected as per OR 46 6/13/03

to talk about that testimony?

A Yes, we have.

Q And have you identified to me a correction that you would like to make for the record?

A Yes, I have.

Q And what is that correction?

A On page 7, beginning on line 3, where I state that the surveillance system has used these values in the past, but in 2001 lowered their resistance ~~rate~~ break- points for Ciprofloxacin to equal ~~two~~ to or less or equal to or greater than one microgram per mil? That is an error. They raised their resistance rate point to greater than 2.

Q Thank you. Is there anything else that you would like to correct?

A No.

Q Thank you.

MS. STEINBERG: Your Honor, Dr. Walker is ready for cross-examination.

JUDGE DAVIDSON: Thank you. Mr. Nicholas?

CROSS-EXAMINATION

BY MR. NICHOLAS:

Q Good morning, Dr. Walker. I'm Bob Nicholas. I represent Bayer in this matter, and I'm going to be doing the cross-examination this morning.

Now as I reviewed your testimony, attached to that was your curriculum vitae. And as I reviewed that, it said that you have a Doctor of Philosophy in veterinary microbiology and pathology. Is that correct?

A Yes.

Q And prior to joining the Center for Veterinary Medicine in 2000, you were primarily at the College of Veterinary Medicine at Michigan State University for about 15 years? Is that correct?

A Fourteen years.

Q Fourteen. And you described yourself in your testimony as a veterinary diagnostic microbiologist with research interests in bacterial pathogen post antimicrobial interagent interactions and research interests involved in developing and validating standardized laboratory tests. Is that correct?

A Yes.

Q So if I understood correctly, you're not a medical doctor -- either a D.V.M. or an M.D., is that correct?

A That's correct.

Q I also note on your CV, attached to the government's Exhibit 438, selected research support. You have many activities there, many projects that you worked on involving various animals, primarily companion animals and cattle.

So it would be accurate to say that the primary research focus is veterinary medicine and not human medicine and that your research experience does not include a significant focus on poultry. Is that correct?

A That's correct.

Q I also noted on that same Exhibit G-1438, under Professional Societies and Activities, you listed the Subcommittee on Veterinary Antimicrobial Susceptibility Testing for NCCLS. In fact, you're one of the founding members of that, is that correct?

A That's correct.

Q And also that you're the liaison between that committee, the veterinary committee, and the subcommittee on antimicrobial susceptibility testing. Is that correct?

A That's correct.

Q And if I understand this, NCCLS has these two separate committees -- the veterinary committee, the one that you're on, basically looks at the development of antimicrobial susceptibility testing for organisms isolated from animals; whereas, the human -- the other committee, the susceptibility testing committee, focuses most on human medicine. Is that correct?

A Would you rephrase -- repeat the first part of the question? In other words, I'm --

Q What are the two different committees, or --

A Yeah, the functions of the first one.

Q Well, let me do this. Would you tell me what the veterinary -- the subcommittee on antimicrobial -- the veterinary -- the subcommittee on veterinary antimicrobial susceptibility testing does?

A The subcommittee on veterinary animal antimicrobial susceptibility testing is involved in

generating appropriate testing methods and interpreting criteria for vet meds specific to antimicrobial agents.

Q By the way, is Ciprofloxacin a vet med specific to antimicrobial agents?

A (No audible response.)

Q It's approved -- do you know if it's approved for human medicine?

A Yes, it is.

Q All right. Would you expect that it would be used in poultry?

A I would expect it would not be used.

Q Thank you. Now the subcommittee on antimicrobial susceptibility testing primarily has similar functions but with respect to human pathogens isolated from humans. Would that be a fair statement?

A With antimicrobial agents used to treat pathogens isolated from humans.

Q Thank you.

Now I'd like to ask you a few questions about NCCLS. As I understand it, that stands for the National Conference -- I'm sorry -- Committee on Clinical Laboratory Standards --

A For the National Committee for Clinical Laboratory Standards.

Q For the committee for clinical laboratory standards. And there's a joint stipulation in this matter. I'm not -- I don't know whether you're aware of it, but there's a joint stipulation between the parties and I can provide you a copy. These are joint stipulations between the parties to this matter, the parties that agreed to these matters.

And if you look at numbers 11, and 12, and 13, and those stipulations describe in general the functions of NCCLS. Number 11 says, "The National Committee for Clinical Laboratory Standards, NCCLS, is a standards-developing organization that develops and disseminates standards, guidelines, and best practices for medical testing in clinical laboratories."

Is that correct?

A That's correct.

Q And number 12, one stipulation -- "NCCLS has established guidelines for susceptibility testing of certain bacteria, certain antimicrobial agents."

And number 13 reads: "FDA is a member of

NCCLS and uses the NCCLS standards where feasible." Is that correct?

A Yes.

Q Now you've worked with NCCLS for a number of years, have you not?

A Yes, sir.

Q And can you tell me how NCCLS defines a standard?

A A standard is a method that needs to be followed as described with no variation, as opposed to a guideline.

Q And NCCLS also has guidelines that it --

A Guidelines, yes.

Q And guidelines sometimes describe how one develops a standard, but once a standard is in place, the standard becomes the manner of doing business. Is that correct?

A Guidelines describe how one generates data that can be fed into the standards.

Q So for the purposes of several documents I'm going to show you now, which are NCCLS guidelines and/or standards, let me give you Exhibit 1796 --

Corrected as per OR 46 6/13/03

that's G-1796. I believe most of these were referenced in your testimony. 1796, 1797.

Now this is 1797, and this is entitled, "Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters -- Veterinary Antimicrobial Agents Approved Guidelines -- Second Edition," is it not?

A Yes, sir.

Q So that would be the guideline that would be used to generate data, if I understood what you said correctly, that would feed into the standard to the extent that there was a standard developed as a result of that guideline.

A This would be the procedure for the guidelines that a pharmaceutical company would follow if they had a product that they wanted to present to the NCCLS for either development, establishing quality control ranges, or establishment of ~~interpreting~~ interpretative criteria, yes.

Q And 1796, would you please tell us what that document is?

A A performance standard for antimicrobial disk and dilution susceptibility testing for bacteria

isolated from animals, approved standards, second edition.

Q And when was that standard approved?

A The standard was approved, I believe, in 2002.

Q There is a joint stipulation between the parties, number 29, that reads: "An NCCLS-approved method for animal origin campylobacter susceptibility testing was not available to May 2002, when NCCLS published N-31-A2, Performance Standards for Antimicrobial Disk and Dilutions Susceptibility Tests for Bacteria Isolated from Animals."

Is that that standard?

A I think that's correct.

Q Now there are no NCCLS standards for isolation of -- I'm sorry -- NCCLS standards for antimicrobial susceptibility testing for isolates isolated from people, is there, for campylobacter?

A Are you saying that there are no NCCLS-standardized susceptibility testing methods for campylobacter isolated from people?

Q That's correct.

A That's incorrect.

Q Would you tell us what standard that is?

A That is in the M-100-S-13 document, which deals -- which is a supplement for the M-7 -- I think -- A-6 document.

Q Is it correct to say then that there's no NCCLS interpretive criteria for campylobacter and Ciprofloxacin?

A That is correct.

Q Now could you tell us why it's important to establish standards; why people spend a lot of time and effort and energy developing standards such as the one we've been talking about?

A There a lot -- there are a number of different laboratories that have the capability of performing susceptibility tests. In order for those laboratories to compare results of one set of data to another, there needs to be a common ground.

The development of standardized testing methods enables those laboratories to test under identical conditions and thus compare data generated under identical testing conditions.

Q Now the methods go to how you prepare various

Corrected as per OR 46 6/13/03

reagents
~~free agents~~, to quality of the materials -- basically, a fairly detailed methodology with respect to how you conduct these tests. Is that generally true?

A There is some variation, but basically that's true with some exceptions.

Q So in the absence of a standard, it is difficult to compare tests from one laboratory to the next, even though they may be testing organisms of the same species against the same antimicrobial? I believe that was your testimony.

A No. Two laboratories testing identical isolates against the same drug can always compare the data; but if there is not standards, then you don't know of the reliability of the data they're comparing.

Q And in the absence of standards, is that potentially the same problem in a single laboratory, which is known as intra-laboratory?

A Absolutely.

Q Now in your testimony, you basically address, if I understand it, two aspects of antimicrobial susceptibility. The first aspect you deal with the test, the development of laboratory standards or

Corrected as per OR46 6/13/03

laboratory standards to test various ~~micro-organisms~~ microorganisms for susceptibility to different antibiotics.

Is that correct?

A No.

Q Does your testimony address that issue?

A The first thing -- would you repeat your -- repeat your question.

Q Well, what I was asking you was whether there -- I was looking at your testimony and I was trying to summarize that it essentially addresses two issues. One is laboratory tests used to test the antimicrobial susceptibility of ~~micro-organisms~~ microorganisms to various antibiotics; and two, how to interpret test results from laboratory tests in terms of characterizing the organisms basically as susceptible or resistant.

A The first step would be to develop a testing method.

Q So your testimony describes various laboratory tests and talks about the development of an acceptable laboratory -- the development of a method that would be standardized?

Corrected as per OR 46 6/13/03

A My test --

MS. STEINBERG: Your Honor, instead of summarizing written direct testimony which is already in evidence, if Mr. Nicholas would ask a question of the witness, it might go faster.

JUDGE DAVIDSON: Is that an objection?

MS. STEINBERG: It is an objection, Your Honor.

JUDGE DAVIDSON: Okay. The testimony speaks for itself, Mr. Nicholas. I'm going to sustain the objection.

BY MR. NICHOLAS:

Q Now as I understand it, Dr. Walker, prior to testing the organism to determine the ~~micro-organism~~ microorganism -- in this case campylobacter -- to determine whether it's resistant or susceptible to a particular antimicrobial, the organism has to be isolated, the organism has to be speciated so that there are other standards that are available to deal with the isolation culture of the organism -- and your testimony does not primarily address those issues.

A That's correct. There is not -- that's

correct.

Q And when you test organisms for -- against various antimicrobials, you want to be sure that you're testing a pure culture. Is that correct?

A It depends on what you're defining as a pure culture.

Q Well, I'll turn it around. Could you please define pure culture?

A A pure culture may mean that there is a single species involved. And that's what you always want to do is test a pure species or a single species.

But within a single species there may be different bio-types; and if you look at the NCCLS document, the NCCLS documents say that you pick four to five well-isolated colonies, put those into a broth suspension incubator for a short period of time, make the dilution, and do the testing.

Now of those four to five well-isolated colonies with the same cloning morphology, are they exactly the same bio-type? Is that the question?

Q But you're looking for the same species?

A The same species.

Corrected as per OR 46 6/13/03

Q Okay. Thank you. So at least for the purposes of your testimony, you're not dealing with the isolation of organisms in order to test them; you're dealing with the test -- starting from the testing of the organisms; and your testimony doesn't deal with the source of resistance, does it?

You can't determine from your work what the, what the -- from your testimony where the organism came from, how it developed its resistance to the extent it was resistant. You are just testing -- you're receiving a sample basically to test for antimicrobial susceptibility?

A That's correct.

Q And your testimony doesn't deal principally with whether one uses the Ciprofloxacin, or ~~Amacrolyte~~ macrolide (phonetic), or other antibiotics to treat human cases of campylobacteriosis, does it?

A It does not deal with the clinical aspect.

JUDGE DAVIDSON: I'm sorry, I didn't hear that.

THE WITNESS: It does not deal with the clinical aspect.

JUDGE DAVIDSON: Thank you.

BY MR. NICHOLAS:

Q Now I'd like to turn to your testimony directly in a minute, but before I do that, I'd like to ask you the definitions of several terms that are used in your testimony and ones that I think I want to make sure I understand accurately.

An antimicrobial susceptibility test, it's a laboratory method?

A It is a laboratory method.

Q So it doesn't involve studies of how people respond in clinical settings, it's a laboratory method?

A Susceptibility testing efforts are not --

Q And could you define for us minimum inhibitory concentration, or MIC?

A Minimum inhibitory concentration is the minimum concentration of an antimicrobial agent required to inhibit the growth of an organ susceptible for an organism.

Q And with respect to what you term ASTs, or Antimicrobial Susceptibility Tests, the MIC is recorded how?

A In terms -- quantitative --

Q Quantitative --

A Right.

Q And the quantitative number that you get from conducting one of these tests will tell you, if I understand correctly, that the organism has a certain response in that test system. It won't tell you anything without interpretative criteria as to whether that organism will be clinically resistant or not -- is that correct?

A It will give you an indication as to how much drug is required to inhibit the growth of that organism under those testing conditions.

Q Could you define for us, please, breakpoint?

A In regards to susceptibility testing?

Q That's correct.

A Okay. Breakpoint in regards to susceptibility testing is that point at which an organism is determined to be susceptible for the susceptible breakpoint, intermediate for the intermediate breakpoint, or resistant for the resistant breakpoint.

Q Now when I asked you to define breakpoint, you

Corrected as per OR 46 6/13/03

asked me to clarify with respect to antimicrobial susceptibility testing. Is there another breakpoint known as the clinical breakpoint?

A Generally speaking, these breakpoints are clinical breakpoints.

Q Is there -- I thought you testified earlier that there was no NCCLS-established clinical breakpoint for campylobacter and Ciprofloxacin.

A I did not.

Q So similarly, there is no established breakpoint for antimicrobial susceptibility tests that define something as susceptible, intermediate, or resistant with respect to clinical outcome, is that correct?

A It is not correct.

Q Let me come back to that. Let's -- the -- let's talk about campylobacter from there. Would you agree that campylobacter, which principally causes gastroenteritis ~~gastral enteritis~~ an ~~and~~ infection of the gastro-intestinal tract, frequently is self-limited?

A I would agree.

Q And it is what's known as a fastidious organism?

A I would agree.

Q And why is it characterized as a fastidious organism?

A Because it requires unique growth requirements and it also is not an organism that is capable of surviving for a prolonged time outside a well-defined environment.

Q That would be one of the reasons that it would be important to standardize testing of campylobacter isolates, is that correct?

A Any time you have an organism that has unique growth characteristics, it is important that you develop standardized testing methods for that organism and its unique growth characteristics.

Q Now I'd like to direct you to page 3 of your testimony, Exhibit 1481. And on that page, at line 15 to 17, you describe the standardized susceptibility testing methods used -- one of three methods. Is that correct?

JUDGE DAVIDSON: It's self-explanatory. That's what it says.

BY MR. NICHOLAS:

Q And would you describe -- you described those tests as agar dilution, the gold standard of susceptibility testing; broth dilution; and agar diffusion.

Would you tell us briefly please what agar dilution is? What an agar dilution antimicrobial susceptibility test is.

A An agar dilution antimicrobial susceptibility testing method is where the antimicrobial agent is incorporated into the agar, and the organisms -- the test organisms are then placed on the surface of that agar.

And it generally -- the drugs are incorporated into the agar at two-fold dilution -- using a two-fold dilution scheme and the -- test --

Q And what's broth dilution? Would you describe that, broth dilution?

A Broth dilution can be macro or micro and it's where the antimicrobial agent is incorporated into a broth medium -- again, using the two-fold dilution -- generally, using the two-fold dilution scheme.

Q And disk diffusion?

A Disk diffusion is where an antimicrobial agent is incorporated into some carrier device, like a paper disk, and placed on the surface of a medium that's already been seeded with a micro-organism and allowed to diffuse into the medium, radiating out from the point of contact.

Q And you listed agar dilution as the gold standard. What makes it the gold standard?

A It's -- in many circles, it is referenced as the gold standard because it's what everything -- all the other testing methods are referred back to. In other words, if you test by a broth-dilution testing method, you want to compare the broth-dilution testing method back to the agar-dilution testing method for comparability because the agar dilution would be the more accurate of the testing methods.

Q And did you list these in sort of order of accuracy, from most accurate in descending order?

A No.

Q Now as you describe these tests, they basically have somewhat different characteristics.

Tell me how a laboratory, the FDA for instance, would choose which test method it would use generally, and then I want to ask you to be specific --

A In our laboratory, the first -- it depends on the -- what you are trying to accomplish, what your end point is. In our laboratory, because of our end point, the first thing we would look at is using standardized testing methods. The second thing we would look at is volume.

And, of course, this is all being with the understanding that their accuracy is equal.

Q Would you look at cost?

A We're a government lab, we don't have to.

Q Well, I think that Congress might think otherwise, but I don't presume to speak for the Congress.

A No --

Q We all operate within budgets.

A -- because of what we do, we're more concerned with accuracy; but cost is a consideration.

Q How about ease of use, practicality?

A In our laboratory we cannot sacrifice accuracy

for ease of use.

Q So you would use the gold standard?

A We do use the gold standard.

Q Would you use it most of the time?

A Are you -- in reference to?

Q Well, you were describing your laboratory and your mission, so I want to talk generally and then I'll ask you specific --

A For all organisms, no, we would not, because there are other testing methods that have been shown to be as accurate, or equally, in terms of accuracy and have a greater throughput.

Q Now a throughput is a question of speed of --

A Volume.

Q Volume.

A Volume of what you get --

Q Now let's talk about campylobacter in your laboratory. Do you use the agar-dilution testing?

A Yes, we do.

Q And when you describe your mission, could you tell me what your mission is? Meaning CVM's mission in your laboratory.

MS. STEINBERG: Objection, Your Honor, that is an awfully vague question. Could Mr. Nicholas narrow the scope to that question?

JUDGE DAVIDSON: You can answer the question, but only to the extent that it is not already covered in your testimony.

THE WITNESS: We have in our division a mission statement. I am not -- I cannot recall exactly what that mission statement says at this point in time.

BY MR. NICHOLAS:

Q I wasn't trying to put you on the spot from that perspective. I was trying to understand what it is you were talking about when you said that you would use a particular standard given our mission -- accuracy is important to me -- sometimes there are screening tests, sometimes there are enforcement methods. So FDA has many different missions and many different standards. I was trying to understand your context.

A In this respect, our mission is to provide accurate antimicrobial data to support CVM's mission for the approval of safe and effective drugs for use in humans.

Corrected as per OR 46 6/13/03

Q So for the screening of campylobacter to various antimicrobials, your center routinely uses agar dilution?

A Yes, sir.

Q Now the NCCLS committee that you served on that finalized the performance standards identified as G-1796, that standard did not adopt disk diffusion, did it, as the standardized method?

A When you said that I served on, am I ~~offered~~ off of it?

Q I'm sorry?

A That I served on. Am I ~~offered~~ off of it?

Q You'd be in a better position to know than I would, sir.

A Okay. What do you mean it does not?

Q Well, being adopted as the reference standard, I believe -- standardized agar dilution as the antimicrobial susceptibility standard for campylobacter, did it not?

A Yes.

Q All right. And it did not adopt any of the other kinds of tests as the standardized test for

campylobacter, did it?

A At this point in time, it has not.

Q So at least at this point in time, meaning May of 2002, when the standard was published -- is that correct -- the committee did not adopt as a consensus standard disk diffusion, or any other method. It adopted agar dilution, is that correct?

A As the reference method, yes.

Q Now if I understood your testimony correctly earlier, your oral testimony, you were describing reasons for standardizing tests and test methodologies, and essentially you testified that, if I have this correctly, that it was important to standardize tests so that one could have confidence in the accuracy of the data coming out of different laboratories so that one could rely on it, compare it, use it in whatever fashion that would be appropriate; but that basically standardization was important to be able to use the data. Is that correct?

A Standardization -- if parties are going to compare intra/inter-laboratory data, there needs to be a common basis by which they do their testing method.

And that is -- that common method has been defined by NCCLS as standardized testing.

Q So prior to May of 2002, because there was no standardized NCCLS method, it would be difficult to rely on data coming from different laboratories if they did not use the standardized method as standardized by NCCLS?

MS. STEINBERG: Your Honor, is that a question? I want to object to the form.

MR. NICHOLAS: I thought it was. My voice went up at the end.

JUDGE DAVIDSON: You can answer.

THE WITNESS: That's an interesting question.

BY MR. NICHOLAS:

Q Well, let's -- could we start off with a yes or no and then I could -- I'd like to hear more.

A Okay, would you repeat the question?

Q That's an interesting question.

Well, I'm basically saying that you testified earlier that standards were important so you could have the ability to compare -- you would have the ability to rely upon data from other laboratories that was

developed in the same way -- the results were comparable, if you would -- and that before there was a standard, an NCCLS standard, it would be difficult to do that laboratory to laboratory -- that different laboratories, in the absence of standards by NCCLS, would perhaps be doing tests differently -- even the same test.

A That's true.

Q And this would have been true prior to 2002, May, for disk diffusion, or micro-growth dilution, and growth dilution as well. Is that correct?

A Sure.

Q Now could you tell us about the E-test? You referenced an E-test in your testimony. I'm sure you remember --

A Yes, sir.

Q -- and you've used the E-test frequently -- did frequently?

A We use it frequently.

Q Okay. And when you say we use it frequently, now you're talking about in your laboratory --

A My laboratory --

Q -- in the FDA, performing your functions and -- is that correct?

A For -- to a limited extent, yes.

JUDGE DAVIDSON: I'm sorry?

THE WITNESS: To a limited extent, yes.

JUDGE DAVIDSON: Thank you.

BY MR. NICHOLAS:

Q And you -- did you use the E-test previously, when you were at Michigan State?

A Yes, I did.

Q Now when did the E-test become available?

A I'm not sure when it was first marketed. I think probably back in the early '90s.

Q And the E-test -- when you use the E-test, do you also use the campylobacter -- testing campylobacter susceptibilities to various antimicrobics?

A Yes, we do.

Q Okay. And you do that as a routine part of your mission and work for CVM?

A No.

Q Could you tell me the difference?

A For the vast majority of the organisms that we

Corrected as per OR 46 6/13/03

do susceptibility testing on, we use broth micro-dilution. Because we are involved in an inter-laboratory collaboration, we use the E-test for campylobacter isolates that pertain to those inter-laboratory collaborations, but we also do the agar dilution on those same isolates.

Q And who are the laboratories that collaborate with you on this effort?

A ARS and ~~CVC~~ CDC.

Q And do ARS and ~~CVC~~ CDC use -- if you know -- use the E-test?

A Yes, they do.

Q And they also do agar dilution?

A I don't know.

Q Now could you tell me -- the E-test has the scale for reading the MICs of various antimicrobials that it's formatted for -- and what's the upper end of that scale for Ciprofloxacin?

A Jeez, I'm just guessing. I'd probably say 256, but I couldn't tell you for sure.

Q This is the E-test?

A Yes.

Q And how about agar dilution?

A Agar dilution can be -- the upper end of that scale can be determined within the laboratory on any particular testing day. In our laboratory we frequently or routinely use 8 micro-grams per --

Q But is it -- could it be used for higher?

A If we chose to we could go higher.

Q Now the E-test is not validated as the gold standard, is it, by NCCLS?

A No, it is not.

Q Now there was a study done in your laboratory, I believe. And let me -- it's Exhibit Number 763, G-763, by NCCLS. Is that correct?

A Yes.

Q And you're listed as an author on that?

A Yes, sir.

Q And when was that study commenced, do you know?

A Probably in the year 2000, late 2000/early 2001.

Q And was that study done as a result of the NOOH published by FDA?

A No.

Q And what was the purpose of the test -- I'm sorry, the study?

A We had gone to the NCCLS with a standardized testing method for campylobacter using the agar dilution. We had gotten -- received tentative approval of the testing method and QC organism; and I knew that a lot of labs were doing the E-test and I wanted to know how well the E-test compared to the agar dilution.

Q Is the E-test difficult to use? Does it have some features that make it difficult to use?

A Susceptibility testing in general, when properly performed, is not necessarily an easy testing procedure.

Q And it's more difficult with fastidious organisms such as campylobacter, is that correct?

A Not necessarily once you define the conditions.

Q Well, I thought campylobacter were difficult to grow, for instance.

A They are.

Q And indeed, in this study that I've handed

Corrected as per OR 46 6/13/03

you, there were some difficulties in growing campylobacter, were there not?

If you'll turn to page 10. Let me read to you. It says: "Certain fastidious bacteria and campylobacter present difficulties in antimicrobial susceptibility testing due to both unique requirements and test conditions. The methodology has proved relatively accurate methods to test antimicrobial susceptibility of fastidious organisms."

And on page 11, at line 7, it says, "A technical problem that arose during this study was the poor growth of some campylobacter isolates on E plates, causing difficulty in interpreting the results."

So there are difficulties in using the E-test, would you acknowledge that?

A For testing campylobacter, once you define the testing conditions, ~~then~~ when you have a fastidious organism that will not grow under normal testing conditions, in which case the results would be not appropriate; but once you define those testing conditions, those are testing conditions under which the organism performs very well.

So under those conditions, the E-test should work basically the same for campylobacter as it would for E-coli, but there are some, as indicted here -- there are always some isolates that may not be as easy to cultivate in the laboratory as other isolates.

Q Thank you. But in the absence of standardization, you would expect to see, or likely would see, variability lab to lab in the use of the E-test?

A The purpose of standardization is to demonstrate that you do have experience --

Q I would think the purpose of standardization would be to eliminate the variability so that you set standards and you eliminate the variability -- not to -- not to establish variability. So is that my misunderstanding, sir?

A You define a standardized testing method. Then, because you have those standards, if you have -- if you're doing a test and you're testing and you do not meet those standards, that tells you that there's a problem within your testing environment.

Q And in the absence of those standards, you

really can't tell, can you?

A It's difficult. It's difficult.

Q Now on page 4 of Exhibit G-763 -- the reference is page 3, I'm sorry -- at line 18, it says, the study indicated "The E-tests were not in complete agreement with the agar dilution tests. Although the E-test has proven to be a satisfactory testing method, its use for campylobacter susceptibility testing requires further standardization."

Now it says it's not in complete agreement and it says it's a satisfactory -- and in order for it to be proven to be satisfactory, it requires further standardization.

Would you disagree with that?

MS. STEINBERG: I'm sorry. Can you clarify where you are on the document?

MR. NICHOLAS: Page 2, line 18 to 20. I'm sorry.

MS. STEINBERG: And I'm sorry. Now that we have the right page, could you repeat your question?

BY MR. NICHOLAS:

Q Dr. Walker, on page 2, line 18 to 20, it says

the study indicated the E-tests were not in complete agreement with the agar dilution test. "Although E-test has proven to be a satisfactory testing method, its use for campylobacter susceptibility testing requires further standardization."

Do you disagree with that statement?

MS. STEINBERG: Your Honor, I object. It's -- this -- I withdraw the objection.

THE WITNESS: I agree with that statement.

BY MR. NICHOLAS:

Q I'd also like to direct your attention to page 8. On Page 8, lines 14 to 15, it states, "On the other hand the E-test tended to yield much higher resistant MICs than those measured by agar dilution at the resistant end of the ranges."

Is that correct?

A (No audible response.)

Q And it further goes on to say "The Ciprofloxacin-MIC agreement between the two methods was 85.2 percent."

MS. STEINBERG: Objection, form of question, Your Honor.

JUDGE DAVIDSON: Yes, I mean, Mr. Nicholas, you're reading material that's already in the record again into the record. And then I want a question. And if you have a question -- if you just want the witness to agree with all this, why don't you ask him if he has any problems with the study?

I mean, this is -- I know you like to see it again and again and again and again if it proves a point you'd like to get across, but once is enough for me.

MR. NICHOLAS: Thank you, Your Honor. Appreciate that.

BY MR. NICHOLAS:

Q Dr. Walker, if in this study one was looking at the performance of -- the performance of two different tests, you would -- well, let me rephrase the question.

MR. NICHOLAS: Excuse me a minute, Your Honor.

JUDGE DAVIDSON: Certainly.

BY MR. NICHOLAS:

Q Let's turn to interpretive criteria, if we may.

JUDGE DAVIDSON: Are we talking about his testimony now?

MR. NICHOLAS: Yes, Your Honor.

JUDGE DAVIDSON: Thank you. Do you have a page and line number for us?

MR. NICHOLAS: Beginning on line 23 on page 4, and going on to page 5.

BY MR. NICHOLAS:

Q Now as I understand it, there are no interpretive criteria for interpreting the antimicrobial susceptibility results from a test testing campylobacter to Ciprofloxacin. Is that correct?

A There are no NCCLS-approved interpretive criteria.

Q Are there other criteria approved that have been established in the same fashion as an NCCLS criteria?

A Not that I'm aware of.

Q So the British standard that you mentioned on page 6, line 39, and -- the British report, I'm sorry, that you mentioned on that page; and the French

proposal, or tentative standard that you mentioned on line -- beginning on line 44 on page 6 and going over onto page 7 -- neither of these proposals, or tentative criteria, were promulgated in the same fashion as NCCLS would have been on the standardized criteria for interpreting antimicrobial susceptibility of campylobacter. Is that correct?

A I'm not sure how they determined that.

Q Well, would it surprise you to know that the British standard is based on disk diffusion?

MS. STEINBERG: Objection.

JUDGE DAVIDSON: Sustained.

BY MR. NICHOLAS:

Q Do you know whether the British standard was based on disk diffusion?

A No, I do not.

JUDGE DAVIDSON: Do you need some time?

MR. NICHOLAS: No.

JUDGE DAVIDSON: Okay.

BY MR. NICHOLAS:

Q When you were mentioning the British standards, is that the document you make reference to?

A Yes.

Q And would you take a moment to look at it and tell me whether it is based on the standard of agar dilution testing?

JUDGE DAVIDSON: While he's doing that, do you want to give it a number?

MR. NICHOLAS: I'm sorry? Yes.

JUDGE DAVIDSON: It's going to be in the record. You're referring to it. It has to have a number, as petty as that may seem.

MR. NICHOLAS: B-1939.

JUDGE DAVIDSON: Okay. Thank you.

MS. STEINBERG: Your Honor, excuse me, I think that's also Government Exhibit G-776, that Mr. Nicholas --

JUDGE DAVIDSON: Well, if it is we can strike 1930 and just call it -- it's the same document.

MS. STEINBERG: It does look to be the same document. It has the same citation.

JUDGE DAVIDSON: Well, unless someone can show me otherwise, it's Exhibit G what?

MS. STEINBERG: 776.

JUDGE DAVIDSON: 776. And the next number for Bayer will be 1930.

MR. NICHOLAS: Thank you, Your Honor.

(Government Exhibit 776 was marked for identification.)

BY MR. NICHOLAS:

Q Mr. Walker, Have you previously read this document?

A I have looked at it; I have not read it in detail.

Q On page 79, it speaks about campylobacter.

A Yes, sir.

Q And if you read the -- well, it says here, does it not, that susceptibility tests for campylobacter species are not standardized and therefore there is some variability. I'm reading now in paragraph 1, where it talks about campylobacter in this document.

A Mm-hmm.

Q "Susceptibility tests for campylobacter species are not standardized and therefore there is some variability in the susceptibility data reported in

the literature." And then they go on to discuss disk diffusion, do they not?

A They do.

Q Is there any discussion of clinical data or any of the other extensive requirements that NCCLS would use in setting a standard?

A No, there's not.

Q Okay. Thank you. Are you familiar with the French standard that's cited in --

A No, I'm not.

Q So if I told you that that standard -- you said you're not familiar with it, so let me find it and -- it is cited in your testimony, is it not?

A Right.

Q If you are not familiar with this document, Dr. Walker, could you tell us why you cited it in your testimony?

A I was familiar with other -- with breakpoints being set. And you can be familiar with breakpoints being set without reviewing all the literature that pertains to them.

Q Let me give you this document. Let's see, it

looks like we may have B-1930, Your Honor.

This was pulled off the Web site and cited in the testimony. And I believe campylobacter is discussed in the back of that document. If you turn to the table of contents, it lists campylobacter on page 44.

JUDGE DAVIDSON: Do you have a copy for the reporter?

MR. NICHOLAS: Yes, Your Honor.

(Respondent Exhibit 1930 was marked for identification.)

BY MR. NICHOLAS:

Q And on page 44, where it discusses campylobacter, is there any discussion of clinical data or the other types of data that NCCLS would use to establish a standard?

A No, there's not.

Q And I think you said earlier in response to a question by Ms. Steinberg that your reference with respect to the Danish surveillance system was incorrect.

And that's on page 7, line 3 to 6, where you

Corrected as per OR 46 6/13/03

state that it was lowered, but in fact it was raised.

A Yes, sir.

Q Now in paragraph 17, on page 7 of your testimony, you discuss the NCCLS interpretive criteria for ~~enterobacteriosis~~ Enterobacteriaceae, is that correct?

A Yes, sir.

Q And this is a standard established by and adopted by NCCLS; and it is Exhibit 1794. Is that correct? I think I gave you that, but if I didn't, please let me know.

Now this is an NCCLS-approved interpretive criterion, is that correct? Adopted?

A This 1794?

Q Right. Yes.

A Yes, sir.

Q And would you tell us whether this standard, by its terms, covers campylobacter?

A In this particular document, it does not. It does not.

Q Now would you describe how one would go about setting a standard for campylobacter, a breakpoint for campylobacter resistance to Ciprofloxacin?

A The NCCLS protocol for establishing interpretive criteria for an organism is, number one, develop or identify a testing method, including the appropriate QC organisms and QC testing ranges.

Number two, to determine the susceptibility of -- type organisms to that drug, using the approved testing method, and in conjunction with the QC organisms that have been developed.

The next would be looking at the pharmaco-kinetic/pharmaco-dynamic parameters associated with that drug in the target animal species.

And the fourth would be looking at the clinical response of the patient when treated with the approved dosing regime against organisms, against the target organisms.

Q And, as I understand from what you've said, this is both organism-specific and antimicrobial-specific. So that if one wanted to develop an interpretive criteria for -- and a breakpoint for campylobacter resistance to Ciprofloxacin, you would basically have to go through all of these steps for NCCLS approval. Is that correct?

Corrected as per OR 46 6/13/03

A Generally speaking. There are some exceptions.

Q Now if you are looking at, in the NCCLS process, developing such interpretive criteria -- you mentioned clinical response. This is essentially data from clinical studies or from patients participating in the studies -- and if you are looking for a clinical response, you would be looking at infections -- you would be looking at response to different kinds of infections. Is that correct?

Or would you just, for instance, look at responses to respiratory infections, or would you look at ~~gastro-enteritis~~ gastroenteritis, for instance?

A If a drug were being marketed for treating respiratory tract infections caused by a specific organism, that would be the target of the study. It would not address other organisms associated with --

Q Let's go back to ~~pharmaco-kinetic~~ pharmaco-kinetics -- okay. Now you've worked in this area. You've done these kinds of studies with respect to various antimicrobials, have you not?

A I've done some PK-PD studies, yes.

Q And in your testimony, I believe, you go through a calculation with respect to how you might set a resistance breakpoint for the clinical response of campylobacter to Ciprofloxacin.

I'm looking now on page 7, paragraph 17.

A Could you repeat your question?

Q Well, looking at paragraph 17, on page 7 in your testimony, you describe a calculation based on, I believe, MIC -- I'm sorry, based on PK data and PD data that would result, in your estimation, when someone is dosed with 500 milligrams of Ciprofloxacin and they have a campylobacter infection -- you describe an MIC ratio of 8 to 12 would be necessary in order to have a clinical response to the --

MS. STEINBERG: Objection, Your Honor.

JUDGE DAVIDSON: Is that a question?

MR. NICHOLAS: Is that correct?

JUDGE DAVIDSON: The exhibit speaks for itself.

BY MR. NICHOLAS:

Q Is this -- the question was is this how you would go about establishing a resistance breakpoint for

campylobacter -- Ciprofloxacin?

A Yes, it is one part of the equation.

Q Right. But it's not the complete part of the equation?

A No.

Q And you have not done the complete part of the equation, have you?

A By myself --

Q That's correct.

A -- have I done all aspects of it?

Q Yes, sir.

A No, I have not.

Q Has NCCLS reviewed all of these criteria? They haven't have they? They have not published a standard?

A For?

Q For interpretive criteria for Ciprofloxacin resistance to campylobacter.

A NCCLS cannot initiate establishing interpretive criteria on their own.

Q A pharmaceutical company is required to initiate those efforts?

A If, in human medicine, a pharmaceutical company is desirous of having an NCCLS interpretive criteria, it is their responsibility to put together a package, following the M-23 guidelines, and present that information to the NCCLS for their review for establishment of NCCLS interpretive criteria.

Q So would you tell me how you derived -- how you reached your conclusion that, based on these values, one would expect that a resistant breakpoint -- I'm reading on page 7, line 25 to 26 -- "that one would expect that a resistant breakpoint for bacterium should be no higher than one microgram per milliliter." And this is for campylobacter specifically.

A This is my opinion, based on using PK-PD analysis. It does not incorporate clinical trials. And, while this is my opinion, if we were to do clinical trials and demonstrate that I am right or wrong -- whichever it may be -- those are the values that we would accept because that is the method the NCCLS has defined for generating that information.

Q All right, but clinical studies have not been done?

A The sponsor of Ciprofloxacin has not provided the clinical studies.

Q Does FDA require, if you know, in the drug-approval process, the human drug-approval process, require such standard?

A If a drug, as far as I know -- if a drug is -- has FDA approval for a specific disease entity, there must be clinical data to support that claim.

Q And Ciprofloxacin is an approved drug, is that correct?

A Is what?

Q Is an approved drug?

A It is an approved drug for treating a number of disease entities, but I don't know if it has specific FDA approval for treating campylobacteriosis.

Q But if it did have approval for treating campylobacteriosis, then it -- according to your testimony -- you would expect to find those data in the NDA?

A I would have expected that the sponsor would have provided FDA with appropriate clinical trials to support that claim.

Corrected as per OR 46 6/13/03

Q Now let's talk about how you arrived at your calculation using PK and PD data. You measured -- you looked at certain concentrations, is that correct?

A That's correct.

Q Now you stated earlier that gastro-enteritis -- will you agree with my statement that gastro-enteritis is primarily a disease of the gastrointestinal tract?

Is that correct?

MS. STEINBERG: Your Honor --

JUDGE DAVIDSON: Preliminary --

MS. STEINBERG: Thank you, Your Honor.

JUDGE DAVIDSON: Let him answer.

BY MR. NICHOLAS:

Q I'm sorry, campylobacteriosis --

A It is an inflammation of the epithelial cells lining the gastrointestinal tract.

Q And when you look at the activity of the drug in order to determine -- antimicrobial -- in order to determine whether that an antimicrobial is likely to be effective, you typically tend to look at the site of the infection, don't you? The concentration of the

drug at the site of the infection?

A That's part of the PD package.

Q Now in your calculation you use serum concentrations, is that correct, and not blood-level concentrations?

A In my calculations, I did use a ratio associated with serum concentrations.

MR. NICHOLAS: I have no further questions, Your Honor.

JUDGE DAVIDSON: Okay. We'll take a brief, brief, brief -- unless, does anybody need a pit stop or break? If not, we can get to the redirect by changing sides.

MS. STEINBERG: How about a five- or ten-minute break?

JUDGE DAVIDSON: All right. We'll take a ten-minute recess. When we come back, we'll switch tables.

MS. STEINBERG: Thank you very much.

(A brief recess was taken.)

MS. STEINBERG: Thank you, Your Honor.

REDIRECT EXAMINATION

BY MS. STEINBERG:

Q Dr. Walker, I want to go back to some of the issues that were raised on cross examination. Specifically, I want to ask you a few questions about the E-test. In your opinion, is the E-test a sufficient method for detecting Ciprofloxacin resistance in campylobacter --

A I would say that it is an adequate method, yes.

JUDGE DAVIDSON: Sorry, I didn't hear.

THE WITNESS: I would say that it is an adequate method.

JUDGE DAVIDSON: Thank you.

BY MS. STEINBERG:

Q And can the E-test be used to monitor changes in the prevalence of Ciprofloxacin resistance in campylobacter?

A I think in this day and age it can be.

Q Are there any advantages to using the E-test in a clinical test setting?

A In a clinical situation where a lab may have a

single isolate, it would be to their advantage to use something like the E-test as opposed to the agar dilution, mainly because of the ease of operation.

Q Turning to agar dilution, is that method a practical method for routine clinical --

A No, it is not.

Q Why?

A In order to use the agar dilution -- to run the agar dilution, a series of plates need to be made and on those plates you can run up to 35 isolates; and, if the lab has a single isolate, it is not worth -- it doesn't make sense for them to use that much material to test a single isolate.

Q Have there been any tests or studies that compare results obtained through use of E-test and use of agar dilution for campylobacter, specifically for Ciprofloxacin and tests against campylobacter?

A Have there been any tests that have compared E-test and agar dilution results when testing campylobacter against Ciprofloxacin? Yes, there have been.

Q And what did those tests show in terms of a

correlation? What did those studies show as -- in terms of a correlation between these two testing methods -- antimicrobial susceptibility testing --

A The ones that I'm familiar with there's any where from an 85 to about 88 percent agreement.

Q And are you referring to an agreement with the MIC?

A I think in some of those papers they talk about an agreement and whether it is an agreement in interpretations or actual MIC values. I'd have to go back and refresh my memory on that. In some of the studies that we have done, we find that the agreement is within the interpretation.

Q And just to clarify so that I make sure that it is clear -- in terms of comparability, are there two ways you can compare results?

A There are two way that you can interpret -- there are two ways that you can use the data generated by the E-test versus the agar dilution. One is in terms of the interpretation -- susceptible versus resistant. The other is the actual MIC value.

And I think the studies that -- where they

Corrected as per OR 46 6/13/03

talk about the correlation, it is an interpretation for susceptible versus resistant.

Q And do you recall the correlation? Was there a good correlation?

A A reasonable correlation. Like I said, 85 to 88 percent, I think. Yeah.

Q What is a bimodal population ~~discrimination~~ distribution?

A A bimodal is where you have two peaks, and those two peaks could be side by side --

MR. NICHOLAS: Your Honor, we object to this question. It's outside the scope of the questions on cross-examination.

JUDGE DAVIDSON: Okay. Respond?

MS. STEINBERG: I am trying -- can we have a sidebar?

JUDGE DAVIDSON: Now the response you have to give me on the record is whether or not you believe it is or is not within the scope of cross?

MS. STEINBERG: I'll withdraw the questions and ask the next question.

JUDGE DAVIDSON: Thank you.

BY MS. STEINBERG:

Q Is there anything special about campylobacter MIC results that would help determine the usefulness of certain antimicrobial susceptibility testing methods --

A Are there certain criteria about susceptibility testing -- about the susceptibility testing of campylobacter -- would you repeat the question?

Q Yes. I'll rephrase it. Are there certain characteristics noted about campylobacter MIC results that would help you interpret the usefulness of antimicrobial resistance testing methods -- certain ones that --

A One of the things that we've noticed about campylobacter is that we're either dealing with a very susceptible population or a very resistant population. We don't seem to see a lot in the middle. And when you have a population of organisms that exhibits that type of susceptibility testing results, you have more degrees of freedom in the type of testing methods that you use because you're not held to a one-dilution difference in interpretation.

Q And is that observation of the MIC levels in

campylobacter commonly referred to in any way?

A What we're seeing with the campylobacter and what is referred to as a bimodal distribution in terms of susceptibility profiles.

Q And with a bimodal distribution, is it -- does it -- with observation of a bimodal distribution, does it make it easier to use in several different antimicrobial-resistant methods when you are trying to determine susceptible versus resistant?

A When you have an organism that displays the bimodal distribution pattern that campylobacter displays -- and the reason I make the distinction there is because you could have bimodal where you have two peaks side by side. In this case, you would have two peaks that are a great distance apart. When you have those peaks such a distance, then it allows greater flexibility in your testing methods. It's not a correct statement really. It provides you with -- I guess that's what you'd say -- it provides you with increased flexibility in your testing methods.

MS. STEINBERG: May I have one minute, Your Honor?

Corrected as per OR 46 6/13/03

JUDGE DAVIDSON: Certainly.

(A brief recess was taken.)

BY MS. STEINBERG:

Q Dr. Walker, is there any precedence in using serum concentration of an antimicrobial agent to determine clinical ~~applicacy~~ efficacy of that agent against enteric pathogens?

A In the NCCLS document there are antimicrobial agents that have been approved for use in treating organisms belonging to the family ~~enterobacteracin~~ enterobacteriaceae. Some of those organisms may be associated with soft tissue infections, but some other are associated with enteritis.

And the NCCLS document does not necessarily make a distinction between, say, a salmonella that's associated with a pneumonia versus a salmonella that's associated with ~~and~~ an enteritis. In fact, it specifically talked about using extra-intestinal and inter-intestinal interpretations. It specifically mentioned that you can use that.

Q Was the answer yes?

A Yes.

Corrected as per OR 46 6/13/03

Q Thank you. Turning to the standards setting organizations in the UK and in France -- and this follows up on some questions that Mr. Nicholas asked you about your written testimony -- page 6 and 7. The bottom of page 6, starting at line 42: "Are the British Society for Inter-microbial -- Therapy and the French Society" -- if I can pronounce this in French -- are these two societies the standards-setting societies ~~of~~ or organizations in their respective countries?

A They are as far as I know. It's -- I think that that -- they are, but there's a new organization that has come into play within the last three years and that's EUCAST -- European Community -- European Communities of Antimicrobial Susceptibility Testing, I think is what it stands for.

And EUCAST is trying to unite the European communities into a common organization in terms of susceptibility testing.

Q As far as you know, are there ongoing attempts to bring forward other antimicrobial susceptibility testing methods for NCCLS approval?

A Yes, there are.

Q Turning to Exhibit G-776, page 79. The second column under campylobacter solutions -- when, during cross examination, Mr. Nicholas had you agree that the middle part of that first paragraph under campylobacter species indicated what it said -- however, he stopped before the next sentence and I would ask you to read that sentence now.

A "However, disk diffusion methods are -- for detecting resistance to the commonly used antimicrobials."

Q I have one further question. Who is the sponsor of Ciprofloxacin?

A Bayer.

Q Thank you.

MS. STEINBERG: No further questions, Your Honor.

JUDGE DAVIDSON: Mr. Nicholas?

MR. NICHOLAS: Two short questions.

RECROSS EXAMINATION

BY MR. NICHOLAS:

Q Dr. Walker, you discussed the concordance between the E-test and several other types of

Corrected as per OR 46 6/13/03

antimicrobial susceptibility testing. And was that with respect to solely antimicrobial susceptibility testing of Ciprofloxacin -- campylobacter -- campylobacter -- Ciprofloxacin --

A What are you saying?

Q You replied to Ms. Steinberg's question about how comparable E-test results were to other kinds of antimicrobial susceptibility testing.

A The E-test is a drug-dependent testing method. In other words, the correlation of -- with the E-test and the agar dilution for Ciprofloxacin in our laboratory is around 86 percent -- 85 - 86 percent. But for other drugs, i.e., ~~Gentamiacin~~ Gentamicin, the correlation is about 92 percent. For other drugs, it's not as -- it may not be as good.

Q So your reply to Ms. Steinberg's question was not based solely on Ciprofloxacin and campylobacter, but was more general with respect to other kinds of organisms and antimicrobials, is that correct?

A No, I think I was answering her question in regards to Ciprofloxacin and campylobacter.

Q In those studies that you were relying upon

when you answered that question, do you know whether any of those studies looked at comparing agar dilution to the E-test at the upper end of the MIC range of 32?

A No, am not aware of whether that they did that or not.

Q And in your own -- this -- the G study, G-763, you did not look at the upper end of the MIC range, did you?

A No, we only looked at up to 8 micrograms.

Q So, based on the G study, and the other studies, you cannot say that there is good comparability between the upper level MIC range between the E-test and the agar dilution or disk diffusion?

A I think the comparability was in the interpretation in terms of susceptible and resistant. But in terms of whether or not we would, in an agar dilution, try to test up to 256 micrograms -- I'm not familiar with anybody that would -- has done that or would do that.

Q Well, Table 2 of the study, which I believe you still have -- if I'm interpreting this correctly, the Ciprofloxacin --

JUDGE DAVIDSON: What study are you talking about?

MR. NICHOLAS: It's Table 2. This is Exhibit G-763.

JUDGE DAVIDSON: 763?

MR. NICHOLAS: I believe there are two numbers from this exhibit, Your Honor. This is the study that was put into evidence by FDA before it appeared in a published journal.

MS. STEINBERG: What page are you on?

MR. NICHOLAS: I'm on Table 2 on page 21.

MS. STEINBERG: Thank you.

JUDGE DAVIDSON: You still haven't answered my question.

MR. NICHOLAS: Yes, well, I have that as Exhibit 763, Your Honor. Is there another exhibit number?

MS. STEINBERG: I think that's correct.

JUDGE DAVIDSON: Okay. Thank you.

BY MR. NICHOLAS:

Q If I'm interpreting this correctly, if you look three lines down under antimicrobials agents, it

says Ciprofloxacin and then there are -- it's a little hard to interpret, but it looks like with the agar dilution test, it was run to -- by an MIC of 4. Is that correct?

A An MIC -- the dilution scheme went out to 4.

Q Four. And with the E-test, the MIC went out to 32? The dilution went out to 32?

A I'm not sure how far that went out. We call it greater than 32, so one would think that it might have gone to 32.

Q Okay. So there's no comparison between -- you can't make a comparison of what would have happened if you had run your agar dilution test out further, can you?

A That's correct.

Q Thank you. Now when Ms. Steinberg asked you whether there was precedent to use serum levels for establishing interpretative criteria for gastro bacteria, you discussed salmonella, I believe. Do you know whether the clinical data used in the establishment of that standard, interpretive standard, related to cases of gastro-enteritis, or whether it

just related to respiratory disease?

A I was not there when those -- when discussions took place, so I'm not aware.

Q So you don't know that that's actually a precedent?

A The only thing you can do is assume.

JUDGE DAVIDSON: Is that it?

MR. NICHOLAS: No further questions, Your Honor.

MS. STEINBERG: I've got a couple more.

JUDGE DAVIDSON: Well, if your couples are as long as his couple, we'll never finish here.

No disrespect, Mr. Nicholas. I understand exactly what happened.

Go right ahead.

MS. STEINBERG: Thank you.

REDIRECT EXAMINATION

BY MS. STEINBERG:

Q Dr. Walker, can you explain why, in Exhibit G-763, that study, you did not get to a higher MIC level? You did not test to a higher MIC level with agar dilution?

Corrected as per OR 46 6/13/03

A Two reasons, I would suspect, or three maybe. One is the -- like I alluded to earlier -- the number of the amount of materials involved in performing this test. Then two is the number of isolates that we had to run. And number three, because we were interested in looking at susceptibility or MICs around what were being looked at as a susceptible breakpoint.

Q And given your testimony earlier about the ~~fine little~~ bimodal nature of campylobacter, is it necessary to bring the -- to test for an MIC level 256, or -- is it necessary to bring -- to test for a high MIC level?

A I see no practically in doing that.

MS. STEINBERG: If I can have one more minute.

JUDGE DAVIDSON: Sure.

MS. STEINBERG: No further questions, Your Honor.

JUDGE DAVIDSON: Okay. Is that it, or do you want more?

MR. NICHOLAS: No further questions, Your Honor.

JUDGE DAVIDSON: Okay, you're excused then.

Anything else you have to dig up really quick? Between housekeeping and -- we have a number of exhibits that have been identified and some of them are awaiting my rulings, I know; and some have not been moved into evidence -- they're just identified.

Just -- not do it now, but before we quit, I want to make sure all that's taken care of.

MR. NICHOLAS: Yes, Your Honor.

JUDGE DAVIDSON: So if I forget, you remind me, all right? Okay. I'm sure you'll all be very unhappy to know that we're going to start at 9:30 again tomorrow morning. And we're adjourned until 9:30 a.m., tomorrow in this room.

(Whereupon, the hearing was adjourned, to reconvene on Wednesday, April 30, 2003 at 9:30 a.m.)

* * * * *