

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

ORIGINAL

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: In the Matter of: :  
: : :  
Enrofloxacin for Poultry: Withdrawal : FDA DOCKET NO.  
of Approval of Bayer Corporation's : 00N-1571  
New Animal Drug Application (NADA) :  
140-828 (Baytril) :  
: :  
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Monday, May 5, 2003

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The hearing in the above-entitled matter commenced at 9:00 a.m., pursuant to notice.

BEFORE:

DANIEL J. DAVIDSON  
Administrative Law Judge

**Diversified Reporting Services, Inc.**  
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00N-1571

TR 6  
TR 14

Corrected as per OR 46 6/13/03

634

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## C O N T E N T S

WITNESSES:	DIRECT	CROSS	REDIRECT	RECROSS
Marja-Liisa Hanninen	639	644	718	--

EXHIBITS:	DESCRIPTION	MARKED	RECEIVED
G-624	Document		637
G-1458	Written direct testimony of Dr. Hanninen	639	--
G-1803	Protocol		637
B-589	Document		637
B-1936	Abstract	713	--

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## P R O C E E D I N G S

(9:00 a.m.)

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JUDGE DAVIDSON: Be seated.

Before I get to ruling on your various motions, whatever you call them, anything you have preliminarily?

MS. AMBROSE: No, Your Honor.

MR. NICHOLAS: I just have one small matter, Your Honor.

JUDGE DAVIDSON: Okay.

MR. NICHOLAS: I wanted to let the Court know that tomorrow's cross examination will be conducted by one of my other partners, Jeffrey Bates. He's been part of this matter for some time, and he's going to be conducting the cross examination.

JUDGE DAVIDSON: Remind me at the beginning of the session to have him make his appearance on the record.

MR. NICHOLAS: Thank you, Your Honor.

JUDGE DAVIDSON: Okay. Thank you for making my weekend so nice with your motions that I had to deal with. The responses came in at 4:30 or 4:15.

1                   Anyhow, here's what I've decided.

2                   With respect to the reinstatement of Exhibit  
3 G-624 and B-589 into the evidentiary record, that is  
4 granted.

5   (Exhibits G-624 & B-589 were  
6   reinstated into evidence.)

7                   JUDGE DAVIDSON: The testimony of Dr. Angulo  
8 is not reinstated in the record.

9                   Primarily, I take responsibility for that  
10 myself, because at the time he was on the stand, that  
11 was not in the record, stricken, and therefore, counsel  
12 for Bayer is correct they had no obligation to cross  
13 examine him on that portion of his testimony.

14                   With respect to the additional motion to  
15 include Exhibits G-1802, 1803, and 1804 into the  
16 evidentiary record, I find that only Exhibit G-1803,  
17 which if I'm not mistaken, is the protocol, will be  
18 admitted.

19   (Exhibit G-1803 was received  
20   into evidence.)

21                   JUDGE DAVIDSON: The others are not. They  
22 will remain in the 1285.

1           In the case of 1802, I don't know what that  
2 will remain as, but 1804 will be like underlying  
3 documentation in case there's further disagreement as  
4 to what was and wasn't asked for and received, but as  
5 of now, I don't see that as an issue.

6           What I've decided with respect to the exhibits  
7 themselves and the materials themselves is that the  
8 objections really go to the weight, not the  
9 admissibility.

10           It's incumbent upon me to ferret out what's  
11 worthwhile and what's not, based on your arguments.

12           All right. If there's nothing else, mark this  
13 down. Take a moment please.

14           We still have 1801 pending, I believe.

15 Correct?

16           MR. NICHOLAS: That's correct, Your Honor. We  
17 will be filing a reply this afternoon.

18           JUDGE DAVIDSON: Thank you.

19           All right. I believe we're ready for the  
20 witness.

21           MS. AMBROSE: Call Dr. Hanninen to the stand.

22           (The witness was sworn by Judge Davidson.)

1 JUDGE DAVIDSON: Please be seated, give your  
2 full name and address to the reporter, and then await  
3 counsel. Full name and address to the reporter. You  
4 have to give it orally.

5 MS. AMBROSE: Say your name and address.

6 THE WITNESS: Yes. I'm Marja-Liisa Hanninen.  
7 I am working at the faculty of Veterinary Medicine at  
8 the University of Helsinki, Finland.

9 MS. AMBROSE: Your Honor, may I approach the  
10 witness?

11 JUDGE DAVIDSON: Surely.

12 MS. AMBROSE: I'm handing Dr. Hanninen Exhibit  
13 G-1458.

14 (Exhibit G-1458 was  
15 identified.)

16 Whereupon,

17 MARJA-LIISA HANNINEN  
18 was called as a witness and, having been first duly  
19 sworn, was examined and testified as follows:

20 DIRECT EXAMINATION

21 BY MS. AMBROSE:

22 Q Dr. Hanninen, do you recognize this document?

1 A Yes. It's mine.

2 Q Is that your written direct testimony?

3 A Yeah, that's it.

4 Q Would you please turn to Page 9?

5 A Yeah.

6 Q Is that a copy of your signature on Page 9?

7 A Yeah, that's it.

8 Q Have you had an opportunity to review your  
9 testimony since you've signed it?

10 A Yes, I have.

11 Q Are there any corrections or typographical  
12 errors to the testimony that you would like to correct?

13 A There are a few.

14 Q Would you please point out where they are?

15 A On Page 2, there are, the years when the  
16 enrofloxacin was approved in different countries, and  
17 I -- yeah.

18 JUDGE DAVIDSON: What's the change?

19 MS. AMBROSE: Your Honor, when Dr. Hanninen  
20 was reviewing her testimony, she realized that some of  
21 the dates in the table for some of the countries are  
22 inconsistent with what's in the joint stipulations, and

1 Dr. Hanninen has agreed, and opposing counsel has  
2 agreed to substitute the dates in the joint  
3 stipulation, to the extent that they are different, for  
4 the dates of registration for the various countries in  
5 the table.

6 JUDGE DAVIDSON: So the joint stipulations --  
7 okay.

8 MS. AMBROSE: Yes.

9 JUDGE DAVIDSON: Okay. Move on.

10 BY MS. AMBROSE:

11 Q Are there any other corrections, Dr. Hanninen?

12 A Yeah, there are, on Page 4, Chapter 5, Sweden.

13 On Line 6, was not approved, I want to change it that  
14 the agent was not used for treatment of chickens in  
15 Sweden.

16 Q Okay. Dr. Hanninen, are there any other  
17 corrections?

18 A There are also on Page 6, in Chapter 2, on  
19 Line 3, I would add, on the sentence, "who had been  
20 traveling in Spain or Portugal," I would like to add  
21 "who had been traveling, for example, in Spain or  
22 Portugal."

1 JUDGE DAVIDSON: I'm sorry. I don't find it.  
2 What are you talking about? Page 6, did you say,  
3 ma'am?

4 THE WITNESS: Yes.

5 MS. AMBROSE: Yes, Page 6.

6 JUDGE DAVIDSON: Page 6, Chapter 3?

7 THE WITNESS: Chapter 2.

8 JUDGE DAVIDSON: On Page 6, I have Chapter 9.

9 THE WITNESS: Yeah. This is --

10 MS. AMBROSE: She means the second paragraph,  
11 Your Honor, the first full paragraph.

12 JUDGE DAVIDSON: Okay.

13 MS. AMBROSE: The third line.

14 JUDGE DAVIDSON: Okay.

15 THE WITNESS: Third line, yeah.

16 JUDGE DAVIDSON: She wants to say what, now?

17 MS. AMBROSE: She wants to say, "for example,  
18 in Spain or Portugal," where it says -- add "for  
19 example."

20 JUDGE DAVIDSON: Okay. Go ahead.

21 THE WITNESS: And can I return back on Page 4?

22 MS. AMBROSE: Yes.

1 THE WITNESS: And there, back to Chapter 5,  
2 Sweden, the paragraph in conclusion, I would, the  
3 sentence, "In Sweden, the fluoroquinolone resistance  
4 among domestic poultry Campylobacter isolates was low,"  
5 I would delete the end of this sentence.

6 JUDGE DAVIDSON: In other words, "because  
7 Baytril has not been approved"?

8 THE WITNESS: Yes.

9 JUDGE DAVIDSON: All right. It's deleted.

10 BY MS. AMBROSE:

11 Q Are there any other corrections, Dr. Hanninen?

12 A (Examining) Okay. There is --

13 Q I believe you mentioned when you and I were  
14 discussing that you wanted to make a correction to Page  
15 7?

16 A Yeah. It's Page 7. And there was some --

17 Q In Section 12?

18 A Yeah. (Examining)

19 Q Line 2?

20 A Okay. Yeah. There was also a mistake. I  
21 want to replace the word "norfloxacin" with  
22 "enrofloxacin."

1 Q Any further corrections, Dr. Hanninen?

2 A No.

3 MR. KRAUSS: I'm sorry, Your Honor. Excuse  
4 me. I did not catch where that last change was made.

5 JUDGE DAVIDSON: Paragraph 12, Page 7, second  
6 line, changing "norfloxacin" to "enrofloxacin."

7 MS. AMBROSE: Thank you, Your Honor.

8 JUDGE DAVIDSON: I'm going to write that down.

9 MS. AMBROSE: The witness is ready for cross  
10 examination.

11 JUDGE DAVIDSON: Okay.

12 CROSS EXAMINATION

13 BY MR. KRAUSS:

14 Q Good morning, Dr. Hanninen. My name is Greg  
15 Krauss, and I will be conducting your cross  
16 examination.

17 Before I begin, let me just set some  
18 parameters.

19 I would like for you, if you don't understand  
20 any of my questions, to please let me know so that I  
21 can rephrase them, and we can have an understanding of  
22 what I'm asking. Is that okay?

1 A Yeah.

2 Q Similarly, so we have a clean record, if you  
3 could please wait until I finish asking a question  
4 before you answer, and I will give you the same  
5 courtesy, I will wait for you to answer before I ask my  
6 next question. Okay?

7 A Okay.

8 Q In order for the court reporter to be able to  
9 take down what you're saying, you need to be answering  
10 audibly and loudly enough for the court reporter to  
11 hear. Okay?

12 A Yeah. Okay.

13 Q Now, Dr. Hanninen, CVM's counsel referenced  
14 you to your testimony. Did you draft your testimony  
15 yourself?

16 A Yes.

17 Q All of it?

18 A All of it.

19 Q When you signed it, on or about December 2,  
20 2002, you signed it declaring that the foregoing was  
21 true and correct under penalties of perjury, didn't  
22 you?

1 A I did.

2 Q Dr. Hanninen, let me just briefly explore your  
3 professional background.

4 You are a veterinarian; is that right?

5 A Yeah, that's right.

6 Q You are a professor in food and environmental  
7 hygiene?

8 A I am professor in environmental hygiene. The  
9 department where I work is Food and Environmental  
10 Hygiene.

11 Q So you're not a professor in food hygiene?

12 A No.

13 Q I understand that you have a Ph.D., but I  
14 couldn't tell from your testimony or your CV what your  
15 Ph.D. is in? What do you have your Ph.D. in?

16 A It was associated with characterization and  
17 detection of *Campylobacter jejuni* and *Campylobacter*  
18 *coli* from foods.

19 Q That was your thesis?

20 A Yes.

21 Q Okay. What subject matter is your Ph.D. in?  
22 In other words, is it a Ph.D. in epidemiology, or is it

1 in microbiology?

2 A It's in food hygiene.

3 Q Are you a medical doctor, licensed to treat  
4 humans?

5 A No.

6 Q Do you have any advanced degrees in  
7 microbiology?

8 A Advanced?

9 Q Like a Master's or a Ph.D.?

10 A Yeah. My Ph.D. is associated in microbiology,  
11 because Campylobacter is bacterial, and it's in  
12 microbiology.

13 Q Are you a poultry veterinarian?

14 A Not actually.

15 Q Are you a Diplomate of the American College of  
16 Poultry Veterinarians?

17 A No.

18 Q Are you a member of the American Association  
19 of Avian Pathologists?

20 A No.

21 Q Now, Dr. Hanninen, referring to your testimony  
22 at Page 8, you referenced temporal and spatial

1 evidence, and I would like to get your definition,  
2 please, so I have an understanding of what it is that  
3 your testimony relates to.

4 What is temporal evidence?

5 A Temporal, I mean in this context, that strains  
6 of humans and chickens are collected at the same time  
7 when they are compared.

8 Q Anything else?

9 A That's for temporal.

10 Q In terms of spatial evidence, what do you mean  
11 by that term?

12 A In this context, I mean that, for example, the  
13 strains are collected in a certain area, for example  
14 Finland, or in Denmark or in Spain, so that the strains  
15 are collected in the same area.

16 Q When you say strains, are you referring to  
17 both human and animal strains?

18 A Either, depending on what topic, either from  
19 human or animal strains, but because in that case we  
20 are comparing human and animal isolates in most cases,  
21 the temporal and spatial association can be -- is  
22 associated to both strains, both to animal and human

1 strains.

2 Q Now, Dr. Hanninen, from what I understand from  
3 your testimony, correct me if I'm wrong on this, you  
4 say that there is a, in certain countries, there is a  
5 temporal relationship between the approval of  
6 enrofloxacin for use in poultry and a subsequent  
7 increase in the levels of resistance in Campylobacter  
8 in humans, fluoroquinolone resistance; is that right?

9 A Yeah, that's right.

10 Q Would you agree with me that a temporal  
11 relationship is not the same thing as a causal  
12 relationship?

13 A Yes.

14 MR. KRAUSS: Now, Your Honor, may I go to the  
15 whiteboard? Thank you.

16 JUDGE DAVIDSON: Just remember that the record  
17 doesn't reflect the board.

18 MR. KRAUSS: Yes, Your Honor. I'm going to  
19 try to be careful about that. Thank you.

20 BY MR. KRAUSS:

21 Q Dr. Hanninen, I have tried to simplify, if I  
22 could, the temporal relationship that you've mentioned

1 in your testimony. I want to see if I get this right.

2 Essentially, if I understand your temporal  
3 relationship right, in your model, you say that  
4 resistance in poultry and humans before enrofloxacin  
5 was approved in many countries was low, fluoroquinolone  
6 resistance in Campylobacter; am I right?

7 MS. AMBROSE: Excuse me, Mr. Krauss. I can't  
8 see with you -- thank you.

9 THE WITNESS: Yes, I am saying that before the  
10 era of years of enrofloxacin in chickens, the  
11 resistance in chickens and in humans was low.

12 BY MR. KRAUSS:

13 Q Right. So that's the first part of your  
14 temporal relationship, am I right?

15 A Mm-hmm.

16 Q And then, in some countries that you've  
17 observed, there was an approval of enrofloxacin for  
18 poultry, right? That's the second step in the temporal  
19 relationship; am I right?

20 A Would you repeat?

21 Q In your analysis of the temporal relationship,  
22 the second step is that enrofloxacin was approved for

1 poultry?

2 A Yeah.

3 Q Then, you've observed, based on your  
4 testimony, an increase in fluoroquinolone resistant  
5 Campylobacter, that's FQRCP here --

6 A Mm-hmm.

7 Q -- an increase in poultry that you say leads  
8 to an increase in human fluoroquinolone resistant  
9 Campylobacter in humans; am I right?

10 A Yeah.

11 Q Do you agree that this is a fair  
12 representation of your temporal relationship that  
13 you've testified about in your testimony?

14 A A simplified model, yes.

15 Q A simplified model? But you agree that, even  
16 though it's simplified, this accurately reflects what  
17 your model is?

18 JUDGE DAVIDSON: There were two thises.

19 MR. KRAUSS: I'm sorry, Your Honor.

20 JUDGE DAVIDSON: You have your statement, you  
21 have your testimony -- excuse me. You have your  
22 statement, her agreeing that it's correct. I think you

1 can't go much further than that, because you can't put  
2 that in the record.

3 MR. KRAUSS: Okay. Thank you, Your Honor.

4 BY MR. KRAUSS:

5 Q Now, Dr. Hanninen, would you agree that if  
6 there are situations, there are countries where there  
7 is an increase in human fluoroquinolone resistance in  
8 Campylobacter, but there's not an approval for  
9 enrofloxacin for poultry, that that would not -- would  
10 you agree that that circumstance would not fit your  
11 temporal association model?

12 A No.

13 Q Why not?

14 A Because my own country is one example of that,  
15 so that in Finland we have not approved enrofloxacin,  
16 but we have increase in human, increase in the  
17 resistance of human isolates, and in that instance, we  
18 need to know where the humans have been infected. That  
19 means -- that is the spatial association.

20 Q The spatial association?

21 A Yes, because some humans acquire the  
22 enrofloxacin while they are traveling to countries

1 where enrofloxacin has been approved for treatment of  
2 chickens.

3 Q So in the example, you say Finland is an  
4 example of this circumstance, but it's your opinion  
5 that the increased human resistance that's being seen  
6 in Finland is coming from foreign travel to countries  
7 where there are approvals in poultry?

8 A Yeah. That's part of case -- yeah, that's  
9 true, yeah.

10 Q We'll get to that in a minute. Let me ask you  
11 about another situation.

12 In the circumstance where there is an approval  
13 for enrofloxacin for use in poultry, and  
14 fluoroquinolone resistant *Campylobacter* in poultry is  
15 low, but fluoroquinolone resistance in *Campylobacter* in  
16 humans is high, that would not fit your temporal  
17 association model, would it?

18 A I don't know such countries.

19 Q But if there is an example of such a country,  
20 that would not fit your temporal model, would it?

21 A But we have so many practical examples, and we  
22 don't have these kind of examples, so far as I know.

1 JUDGE DAVIDSON: Right. But answer the  
2 question that's been given to you.

3 We have your explanation on the record  
4 already, but counsel would like you to say that would  
5 not fit your model, and I think you'll agree that  
6 situation does not fit your model.

7 THE WITNESS: Yeah, that's --

8 BY MR. KRAUSS:

9 Q Okay. One more example.

10 In a situation where -- if there are countries  
11 where fluoroquinolone resistance in Campylobacter in  
12 poultry is high, and fluoroquinolone resistance in  
13 Campylobacter in humans is high, where there's no  
14 approval for poultry, and in fact where it's so far  
15 back in time that there's not an approval for  
16 enrofloxacin in poultry and there's -- it's even before  
17 the time of ciprofloxacin use, say 1981 or 1983, that  
18 would not fit your temporal association model, would  
19 it?

20 A No.

21 Q Dr. Hanninen, going back to this condition,  
22 which was the circumstance where there was no

1 enrofloxacin approval for poultry and there's increases  
2 in fluoroquinolone resistant Campylobacter in humans,  
3 have you looked at countries where this is the case and  
4 you've looked at the domestically acquired cases of  
5 Campylobacteriosis?

6 A Yeah. For example, in Finland, we have done  
7 many studies where we have shown that in humans who  
8 have not traveled away from Finland and have  
9 Campylobacter infection, the resistance among those --  
10 in strains isolated from those patients -- is very low.

11 Q Now, Dr. Hanninen, at Pages 2 through 6 of  
12 your testimony, you mentioned six countries in  
13 particular, and those are Finland, Sweden, Denmark, The  
14 Netherlands, the U.K., and Spain.

15 Are those all the countries where you've  
16 analyzed the temporal association between -- and the  
17 spatial evidence -- between fluoroquinolone use in  
18 poultry and the levels of fluoroquinolone resistant  
19 Campylobacter infections in humans?

20 A I think not. I chose only these countries,  
21 because they are European countries. I didn't speak  
22 anything about U.S. situation, because you have so many

1 experts here who can discuss on this topic.

2 Q Right. So my question is, are those six the  
3 only ones that you analyzed?

4 A No. I, of course, I know the situation also  
5 from some other countries, but this is what I know the  
6 best, of course.

7 Q How did you pick the six that you did testify  
8 about?

9 A Finland is my own country. I know the  
10 situation, I think, very well.

11 Sweden is our neighbor country, and there the  
12 situation is quite similar as in Finland.

13 Denmark has very good statistics on antibiotic  
14 susceptibility in humans and in animals, and also  
15 associated fluoroquinolone susceptibility in animals,  
16 and they have also epidemiological data on human  
17 Campylobacter infections.

18 And Netherlands was chosen because it was one  
19 of the first countries who was reporting on increased  
20 resistance to fluoroquinolones in, both in humans and  
21 poultry.

22 United Kingdom has also quite good database on

1 this topic.

2 Spain was chosen because it is the country  
3 from where both Finnish people, Swedish people, English  
4 people will catch infection with resistant --  
5 fluoroquinolone resistant Campylobacter strain.

6 Q Now, with respect to each of the six countries  
7 that you testify about, how did you choose the  
8 literature? How did you go about choosing the  
9 literature to examine for each of the six?

10 A Because I have been working in Campylobacter  
11 research quite a long time, and I know the studies from  
12 these countries, what they have been doing, and we had  
13 a very good database provided by the CVM.

14 Q What do you mean by that, you have a -- you  
15 had a very good database provided by the CVM?

16 A They have been sending references for  
17 different applications associated to Campylobacter.

18 Q Did you do any literature search yourself for  
19 these countries, besides the literature that CVM sent  
20 you?

21 A Yeah, of course. There are coming old and new  
22 -- new studies associated to these questions and also

1 on epidemiological questions. Of course, I did.

2 Q Now, Dr. Hanninen, in your analysis of the  
3 temporal and spatial evidence, did you observe any  
4 countries in which human fluoroquinolone resistance  
5 rates have increased after enrofloxacin was introduced  
6 for use in poultry, but not after ciprofloxacin was  
7 introduced in human medicine?

8 And I can repeat that question if you need me  
9 to, because I know it's complex.

10 A Yeah.

11 Q Do you want me to repeat the question?

12 A Please repeat.

13 Q Okay. Did you observe any countries in which  
14 human fluoroquinolone resistance rates increased after  
15 enrofloxacin was introduced, but not after  
16 ciprofloxacin was introduced?

17 A I don't remember.

18 Q Isn't it true that, for every country that you  
19 examined where you saw an increase in human  
20 Campylobacter resistance, that increase occurred after  
21 ciprofloxacin was approved for use in human medicine?

22 A No.

1 Q In what situation did that not happen?

2 A In Sweden, in Finland, in Spain. Of course --  
3 yeah, in Spain, all these countries it was the  
4 situation, so that we must make distinctions between  
5 countries which never have been using enrofloxacin in  
6 chickens and countries which have been using, approved  
7 use of enrofloxacin, because, for example, in Finland  
8 and Sweden -- in Finland, we didn't have almost any  
9 resistant Campylobacter -- enrofloxacin resistant  
10 Campylobacter strains before at the end of '90s,  
11 beginning -- '80s, beginning '80s, and according to  
12 studies of Rautelin, et al.

13 Q I think you might have misunderstood my  
14 question, so let me ask it again.

15 In your analysis, did you find any countries  
16 where you observed an increase in human resistance in  
17 Campylobacter where there was not a prior approval for  
18 use of ciprofloxacin in human medicine?

19 JUDGE DAVIDSON: I couldn't answer that  
20 question.

21 MR. KRAUSS: Okay. Let me -- I'm sorry, Your  
22 Honor.

1 JUDGE DAVIDSON: You said have you observed  
2 anywhere that was not -- I mean, you know, that's like  
3 a double negative.

4 MR. KRAUSS: Okay. I'm sorry, Your Honor.  
5 Let me clarify.

6 BY MR. KRAUSS:

7 Q You've looked at six countries, and you've  
8 observed increases in human fluoroquinolone resistance  
9 in Campylobacter; am I right?

10 A Mm-hmm.

11 Q Okay. Now, for those countries where there  
12 has been such an increase in human resistance in the  
13 Campylobacter, ciprofloxacin was approved for use in  
14 human medicine, right?

15 A Yes.

16 Q In your analysis of the temporal and spatial  
17 evidence, did you observe any countries in which  
18 domestic human Campylobacter resistance increased where  
19 there was not a ciprofloxacin approval for human  
20 medicine?

21 A No.

22 Q Now, Dr. Hanninen, in your testimony at

1 Paragraph 18, you mention --

2 JUDGE DAVIDSON: Do you want to put a page on  
3 that?

4 MR. KRAUSS: Yes, Your Honor. It's the last  
5 page, Number 9.

6 JUDGE DAVIDSON: Thank you.

7 MR. KRAUSS: Yes.

8 BY MR. KRAUSS:

9 Q You mention in your testimony that  
10 ciprofloxacin is frequently used to treat human  
11 diarrhea, including diarrhea caused by Campylobacter.

12 Now, isn't it true that most cases of  
13 Campylobacteriosis are not treated with antimicrobials?

14 A Yeah, that's -- I think so, yeah. Of course,  
15 I'm not medical doctor, but I have been reading.

16 Q Would you agree that the use of ciprofloxacin  
17 or another fluoroquinolone to treat Campylobacteriosis  
18 in humans can lead to the selection of fluoroquinolone  
19 resistant Campylobacter in humans?

20 A I have been reading such reports, that that's  
21 possible.

22 Q So you would agree that that can happen?

1           A     That can happen.

2           Q     Now, in your analysis, Dr. Hanninen, did you  
3 examine whether fluoroquinolones are used for, in the  
4 countries that you looked at, did you examine whether  
5 fluoroquinolones are used for prophylaxis to prevent  
6 traveler's diarrhea?

7           A     I was trying to look at that, but there was  
8 quite few remarks that it can be possible in certain  
9 cases.

10          Q     Did you examine that issue in the six  
11 countries that you looked at, Dr. Hanninen?

12          A     Yes, I was trying to look at that.

13          Q     Did you draw any conclusion with respect to  
14 any of the six countries on that issue?

15          A     Yeah. It can be possible that it's in quite  
16 low level, if you compare to whole number of human  
17 Campylobacter patients appearing annually, so the  
18 number of patients who may have prophylactic treatment  
19 is, for diarrhea, is quite low.

20          Q     But with respect to resistant cases, did you  
21 examine whether the frequency of use of a  
22 fluoroquinolone for prophylaxis while traveling was

1 high or low? Did you look at that?

2 A I was trying to look. It was low, usually, in  
3 most cases, low, if it was indicated. It was not  
4 always indicate, any prophylactic use.

5 Q How did you undertake looking at that issue,  
6 Dr. Hanninen?

7 A I was reading the text. Sometimes in some  
8 papers they said that, or at least were discussing that  
9 topic, in discussion part.

10 Q Dr. Hanninen, in your analysis, did you  
11 examine for each of the six countries that you looked  
12 at, did you examine what other fluoroquinolones besides  
13 ciprofloxacin might be used in the various countries  
14 for treatment in humans?

15 A This was not possible for me.

16 Q That was not possible?

17 A Because statistics for medicine use is not  
18 available from all countries.

19 Q Were you able to determine what  
20 fluoroquinolones are used in human medicine in Spain,  
21 in your analysis?

22 A Yeah, I don't remember that. I need to have

1 this original document. I need to check from the --

2 Q What is it that you're looking for, Dr.  
3 Hanninen?

4 A I have this -- there was actually three  
5 papers, at least -- Reina, Reina, et al., '92, '94,  
6 Saenz, et al., 2000 where they may have described what  
7 kind of antimicrobial agents are used in these  
8 countries for human treatment.

9 Q Did you incorporate in your analysis for  
10 Spain, in formulating your opinions, the other  
11 fluoroquinolones that are available for use in Spain?

12 A Of course, it's impossible for me. I must  
13 rely on the data of the scientists describing their  
14 results, in discussion or result or introduction part.

15 Q Did you, in your analysis, examine what other  
16 fluoroquinolones are available for use in poultry  
17 medicine in Spain?

18 A I was mostly following enrofloxacin use.

19 Q With respect to Spain, did you examine the  
20 conditions of use for the human medicine, the human  
21 fluoroquinolones, and -- let me break it down.

22 Did you examine the conditions of use for

1 human fluoroquinolones in Spain as part of your  
2 analysis?

3 A On the basis of the data that was available in  
4 the publications that I was using for my references.

5 Q Are you aware that, in Spain, fluoroquinolones  
6 are available over the counter --

7 A Yes.

8 Q -- for human medicines?

9 A Mm-hmm. They are.

10 Q Are you aware that in Spain fluoroquinolones  
11 are available over the counter for veterinary medicine?

12 A Yes. And they became earlier available,  
13 according to this data I have here, which is accepted,  
14 than in human medicine.

15 Q Do you know what other fluoroquinolones are  
16 available for treatment of humans in The Netherlands  
17 besides ciprofloxacin?

18 A Depending, all these questions are dependent  
19 on the time that we are discussing. I think so.

20 I don't know exactly, of course, what kind of  
21 medicines they have in The Netherlands, but in  
22 quinolones, it's associated with the time, because in

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1 earlier time, in human medicine, ~~norfloxacin~~<sup>norfloxacin</sup>, for  
2 example, was used more than ~~ciprofloxacin~~<sup>ciprofloxacin</sup>.

3 Q Dr. Hanninen, in examining the temporal and  
4 spatial evidence, did you incorporate the approvals of  
5 other fluoroquinolones besides, say, ~~ciprofloxacin~~<sup>ciprofloxacin</sup>,  
6 into your analysis in here? I'll broaden it to all the  
7 countries in your analysis.

8 A Of course, because the cross-resistance  
9 exists.

10 Q So you mentioned, for example, in The  
11 Netherlands, norfloxacin is available, and you said  
12 that that could have happened at various points in  
13 time.

14 Did you incorporate the introduction of  
15 norfloxacin, the approval of norfloxacin in human  
16 medicine in The Netherlands into your temporal study  
17 for The Netherlands?

18 A I was not able to do that, but I was believing  
19 on the documents represented by Endtz, et al., because  
20 he was analyzing them, I think quite well.

21 Q Did you, in your analysis of The Netherlands,  
22 consider other fluoroquinolones that are available for

1 use in The Netherlands, in doing your temporal  
2 analysis?

3 MS. AMBROSE: Objection, Your Honor. I  
4 believe that Dr. Hanninen already answered that  
5 question.

6 MR. KRAUSS: That was on the human side. I'm  
7 doing the poultry side, veterinary side.

8 JUDGE DAVIDSON: All right.

9 THE WITNESS: On the basis the documents  
10 described the fact -- on the Jacobs-Reitsma paper  
11 related to veterinary use, it was described.

12 BY MR. KRAUSS:

13 Q So if I understand you correctly, if it's in  
14 the Jacobs-Reitsma paper, if discussions of other  
15 fluoroquinolones that might be available in The  
16 Netherlands for treatment of poultry are in the Jacobs-  
17 Reitsma paper, you looked at it, but if it's not in the  
18 Jacobs-Reitsma paper, then you didn't look at it. Is  
19 that right?

20 A There were also some other papers. Endtz'  
21 paper was published regarding the same time period. I  
22 think they were discussing that quite well.

1           Q     So if it's in the Endtz paper or the Jacobs-  
2 Reitsma paper -- and by "it" I mean a discussion of  
3 other fluoroquinolones that are available in The  
4 Netherlands in veterinary medicine -- then you looked  
5 at it, but if it's not in those papers, then you didn't  
6 look at it. Is that right?

7           A     It's quite impossible to have data from other  
8 countries about their antibiotic use was 10 years ago,  
9 or like that.

10          Q     Dr. Hanninen, did you examine what other  
11 fluoroquinolones, other than ciprofloxacin, are  
12 available for use in human medicine in the United  
13 Kingdom when you did your analysis of the temporal and  
14 spatial evidence?

15          A     On the basis of data represented in the  
16 publications I was reading.

17          Q     So if it's -- if a -- strike that.

18                    You didn't look beyond the papers that you  
19 read to determine whether there's other  
20 fluoroquinolones that might be used and available for  
21 use in human medicine in the U.K.; is that right?

22          A     I think it came out from the papers which for

1 the first time described an increase in -- of  
2 fluoroquinolone resistance in human strains.

3 Q And for the U.K., with respect to  
4 fluoroquinolone use in veterinary medicine, did you  
5 examine whether there's other fluoroquinolones  
6 available besides enrofloxacin?

7 A I think the enrofloxacin is the most  
8 important, in any case.

9 Q In the U.K.?

10 A Yes. And it came '93, approval came '93.

11 Q Why is that the most important in your  
12 analysis?

13 A Because I don't think, in my -- in analysis,  
14 but also to use in animals, or in animal medicine, the  
15 most extensive, more extensive than other -- most  
16 extensive.

17 Q What did you look at to make that  
18 determination, Dr. Hanninen?

19 A It was based on the documents, what I was  
20 reading.

21 Q With respect to Denmark, did you examine what  
22 other fluoroquinolones besides ciprofloxacin might be

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1 available for use <sup>in human</sup> ~~inhuman~~ medicine in Denmark, in doing  
2 your analysis of the temporal and spatial evidence?

3 A I think also in this country ciprofloxacin has  
4 been the most important fluoroquinolone in human  
5 medicine.

6 Q Do you know whether that was the  
7 fluoroquinolone that was first approved in Denmark for  
8 human medicine?

9 A I don't remember at the moment. I have been  
10 looking at.

11 Q With respect to your temporal and spatial  
12 analysis of the evidence for Denmark, did you look at  
13 what other fluoroquinolones besides enrofloxacin might  
14 be available for treatment in poultry, if any?

15 A I think there was very little use of  
16 ~~cerafloxacin~~ <sup>sarafloxacin</sup>, maybe, or some other fluoroquinolones,  
17 before they approved enrofloxacin. It was of minor  
18 significance.

19 Q For Sweden, did you examine what other  
20 fluoroquinolones besides ciprofloxacin are available  
21 for use in human medicine as part of your temporal and  
22 spatial evidence analysis?

1           A     They were speaking about norfloxacin. They  
2 have done studies on norfloxacin resistance, also.

3           Q     Now, with respect to Sweden and the veterinary  
4 use of enrofloxacin in poultry, I believe you changed  
5 your testimony on that point from, "The agent was not  
6 approved for use in Sweden" to, "The agent was not used  
7 for treatment of chickens in Sweden." Is that right?  
8 Is that --

9           A     Yeah, that's right. That's right, because  
10 this was taken from the paper of Eva Berndtson, from  
11 1996. She used that terminology, that it was used for  
12 treatment.

13          Q     Dr. Hanninen, what's your -- in terms of  
14 analyzing the temporal and spatial evidence for Sweden,  
15 what is your basis for your statement that the agent  
16 was not used for treatment of chickens in Sweden?

17          A     It's in the document of Eva Berndtson --

18          Q     And that --

19          A     -- in her doctoral thesis, as well as in the  
20 abstract.

21          Q     That study was from 1996, if I'm not  
22 mistaken?

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1           A     It has been published then, but the strains  
2 were collected a little bit earlier.

3           Q     In your analysis of the spatial and temporal  
4 evidenced from Sweden, did you examine levels of use of  
5 enrofloxacin in poultry in Sweden after 1996, as part  
6 of your analysis?

7           A     I think they have not been used.

8           Q     What is your basis for that statement?

9           A     They said. That's only oral <sup>statements</sup> ~~statement~~ from  
10 Swedish veterinary medical experts. I don't have any  
11 written documents for that.

12          Q     Who did you consult with for that? Who did  
13 you consult with, Dr. Hanninen, for that?

14          A     Would you please repeat?

15          Q     Yes. I was asking you whether you had looked  
16 at the levels of use of fluoroquinolones in poultry in  
17 Sweden after the 1996 Berndtson article, and you said  
18 that you consulted with practicing veterinarians  
19 orally, and I'm asking you who did you consult with?

20          A     They weren't practicing veterinarians, they  
21 were working at the state Veterinary Medical Institute,  
22 and they are responsible over the medical issues in

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1 Sweden.

2 And we have also now new data which is not  
3 included in this testimony, where it shows that there's  
4 very low resistance.

5 Q You can't get into that, Dr. Hanninen.

6 In the Berndtson article, where she mentions  
7 that fluoroquinolones were not used for treatment of  
8 chickens, isn't she referring only to the ~~flock~~<sup>flocks</sup> that  
9 she examined, where she found resistance?

10 A I think she was speaking the whole chicken  
11 production, because for this data she was using in this  
12 article, what I refer here, she was studying most of  
13 the Swedish chicken flocks for use during that period,  
14 so that it was quite extensive databsae.

15 MR. KRAUSS: Just a minute, Your Honor. I'm  
16 going to find --

17 JUDGE DAVIDSON: Sure.

18 MR. KRAUSS: Thank you.

19 (Pause.)

20 BY MR. KRAUSS:

21 Q Dr. Hanninen, let me hand you G-62, which is  
22 the Berndtson article, and right under "Methods" on

1 Page 1, doesn't it say that for the flocks that she  
2 looked at, no chicken flocks had been treated with  
3 anti-microbial?

4 A Mm-hmm. So it says, "No chicken flocks had  
5 been treated with anti-microbials."

6 Q And doesn't she limit that to the flocks that  
7 she was looking at as part of her study?

8 A I think she said that she studied 6,297  
9 chicken flocks. She mentioned all these flocks. They  
10 are most of the flocks which were slaughtered in Sweden  
11 during that time.

12 Q In this study where Dr. Berndtson was looking  
13 at chicken flocks that had not been treated with  
14 antimicrobials, she found some fluoroquinolone  
15 resistance, didn't she?

16 A Yes.

17 Q Now, Dr. Hanninen, turning your attention to  
18 your testimony, G-1458, Page 2, at the bottom, it's  
19 your opinion, isn't it, that risk factors for acquiring  
20 Campylobacteriosis are different in different  
21 countries?

22 A At least, yeah, that's my opinion.

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1 Q Would you agree that risk factors for  
2 acquiring fluoroquinolone resistant Campylobacteriosis  
3 is also different in different countries?

4 A Yeah. Yes.

5 Q Would you agree that the conditions of use of  
6 fluoroquinolones in food animals, such as whether they  
7 are strictly regulated or not strictly regulated, can  
8 influence the risk factors for acquiring  
9 fluoroquinolone resistant Campylobacteriosis from food  
10 animals?

11 A I would think so, if you think you cannot rule  
12 out <sup>dose</sup> ~~these~~ response.

13 Q Sorry. I did not understand what you said.

14 A So that the -- I was speaking about <sup>dose</sup> ~~these~~  
15 response.

16 Q In your analysis of the spatial and temporal  
17 evidence, did you observe any differences in the levels  
18 of fluoroquinolone resistant Campylobacter in food  
19 animals between countries in which fluoroquinolone use  
20 for food animals is strictly regulated and those in  
21 which it is not strictly regulated?

22 A Yeah, if you think about that, for example, in

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1 Spain, it's not strictly regulated. I don't exactly  
2 know how the situation is in Spain; and it is strictly  
3 regulated in Denmark, for example, I think.

4 So there is difference in the level of  
5 resistant strains in chicken production, so that in  
6 Spain it, at the moment, is close to 100 percent, and  
7 In Denmark it was, in 2000, about 8 percent.

8 But it's also a question, maybe a question of  
9 how long a time it has been used in certain countries,  
10 because in Spain, it has been used since '87, and in  
11 Denmark it has been maybe used since '93, or approved  
12 in '93.

13 Q Your analysis of the temporal and spatial  
14 evidence, say between Spain and Denmark, the two  
15 countries you just mentioned, did you compare the  
16 levels of resistance at certain -- at intervals after  
17 approval to see whether the length of time on the  
18 market for poultry <sup>fluoroquinolones</sup> ~~fluoroquinolone~~ does, in fact,  
19 impact the levels of resistance that are seen in  
20 poultry?

21 A Would you please repeat this question?

22 Q Sure. If I understand your testimony, when I

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1 asked you, you know, comparing and contrasting Spain,  
2 where animal fluoroquinolones are less strictly  
3 regulated, and Denmark, where they are strictly  
4 regulated, you said, well, it may also have to do with  
5 time on the market that they've been using them,  
6 because Spain was '87 and Denmark was '93.

7 Am I right that that's what your point was,  
8 first of all?

9 A Mm-hmm.

10 Q Yes? Okay. In doing your analysis of the  
11 temporal and spatial evidence in this case, did you  
12 compare the levels of resistance after given periods of  
13 time between countries -- for example, Spain, the level  
14 of resistance after five years on the market and use in  
15 poultry versus Denmark, five years after approval in  
16 poultry? Did you examine that?

17 A That's quite impossible to follow, because  
18 documents from Spain are <sup>based</sup>~~placed~~ on results made in  
19 individual universities and individual laboratories.  
20 They are not systematic on following anything, what is  
21 happening in resistance, so that -- and in Denmark, the  
22 systematic monitoring is more, much more available from

1 the last end of '90s, so that you can't compare these  
2 two countries so exactly.

3 Q So you didn't conduct such an analysis, and  
4 you're saying that you couldn't do that?

5 A Yeah.

6 Q Right? I'm sorry, Dr. Hanninen. You have to  
7 be audible, so that the court reporter can take it  
8 down.

9 A Yes.

10 MR. KRAUSS: One second, Your Honor. I'm  
11 scratching some things off here.

12 JUDGE DAVIDSON: Okay.

13 (Pause.)

14 BY MR. KRAUSS:

15 Q Dr. Hanninen, would you agree that the use of  
16 fluoroquinolones for prophylaxis during international  
17 travel -- I don't think I asked this -- can increase  
18 the rates of fluoroquinolone resistant Campylobacter  
19 isolated from humans?

20 A It's possible.

21 Q Let me turn your attention to your discussion  
22 of Finland in your testimony, Page 3, Chapter 4.

1           Now, Dr. Hanninen, isn't it true that before  
2 the introduction of fluoroquinolones onto the Finnish  
3 market, there was some natural fluoroquinolone  
4 resistance occurring in Campylobacter?

5           A     In human, in human Campylobacter?

6           Q     Yes.

7           A     Yeah, that came out from the paper, Rautelin  
8 et al., from '91, where they compared human strains  
9 from '78 to '80 and then from strains isolated in '90,  
10 and in the strains from '87 to '90 -- '87 to -- '78 to  
11 '80, they were not able to find any ciprofloxacin  
12 resistance and very low resistance to norfloxacin, and  
13 they were trying to trace where these patients who had  
14 this norfloxacin resistant strain, where they have --  
15 if they had been acquired infection in Finland or while  
16 traveling Spain or some other countries, and in most  
17 cases, they were able to trace the resistance to  
18 traveling to Spain, but because it was quite old data,  
19 it was not able to -- they were not able to trace all  
20 patients from where they had possibly acquired the  
21 infection.

22           Q     Now, this was -- these were isolates from 1978

1 to 1980, am I right?

2 A Mm-hmm.

3 Q And if I understand your testimony correctly  
4 here today, these researchers tried to tie the  
5 resistance that they saw, the natural resistance, to  
6 travel to foreign countries, in particular Spain; is  
7 that what you're saying?

8 A It was natural, not natural resistance. They  
9 didn't say that it's natural resistance. It was  
10 resistance to norfloxacin, but no resistance to  
11 ciprofloxacin. I don't believe natural norfloxacin  
12 resistance.

13 Q Well, let me turn your attention to G-524,  
14 Page 4, the upper left. These researchers do refer to  
15 it as natural resistance, don't they, Dr. Hanninen?

16 A (Examining)

17 Q This is the paper you were referring to,  
18 Rautelin, et al., isn't it?

19 A Yes. Yeah, if they say natural resistance, I  
20 don't believe in that.

21 Q Okay. Now, Dr. Hanninen, do you know whether  
22 fluoroquinolones were used in poultry in Spain in 1978

1 to 1980?

2 A They were not officially approved at that  
3 time.

4 Q Do you know whether they were used?

5 A Of course, I don't know.

6 Q Now, in this Rautelin study, G-524, if I'm not  
7 mistaken, they define resistance as a breakpoint  
8 concentration of greater than or equal to 8 micrograms  
9 per milliliter; am I right?

10 A Yeah, it seems to be so, yeah.

11 Q Now, wouldn't it be true, Dr. Hanninen, that  
12 if resistance was defined with a lower breakpoint, say  
13 for example, 4 micrograms per milliliter, as it's often  
14 defined here in the U.S., that on this data here, you  
15 would have an even higher level of natural, or of the  
16 resistance found in this study, whether it's natural or  
17 not?

18 A There were very few patients who had higher  
19 than 4 micrograms per milliliter in the material from  
20 '87 to -- '78 to '80.

21 Q Right. But --

22 A It doesn't make a big difference.

1 Q Well, let me ask you this. If you look at the  
2 graph in the upper right-hand corner of G-524, Page 2,  
3 right, Rautelin, et al., they draw their line between  
4 susceptible and resistance between 4 and 8, right, and  
5 they find 4 resistant isolates out of 102 and they say  
6 4 percent; right?

7 A Mm-hmm.

8 Q If you include the isolates that are above the  
9 4, that would give us a different number, wouldn't it?

10 A Yes.

11 Q In fact, if you do that, and you look at their  
12 graph, that would be 6 of the strains out of the 102  
13 that have an MIC of greater than or equal to 4  
14 micrograms per milliliter, wouldn't it?

15 A Yes.

16 Q So that would be about 6 out of 102, 5.8  
17 percent resistance?

18 A Yeah, that's it.

19 Q And that resistance, if it was 1978 to 1980,  
20 if that's the time frame that the isolates were taken,  
21 that would be before fluoroquinolones were approved in  
22 Finland in human medicine, right?

1 A Yeah, that's it. Yeah. That's true.

2 Q And fluoroquinolones were not used in poultry  
3 medicine in Finland, were they?

4 A No.

5 Q Right, they were not used?

6 A They were not approved to use, and they were  
7 most probably not used, but I don't, because this is a  
8 very long time ago, and we don't have any statistics,  
9 but certainly probably that they were not used.

10 Q Now, continuing to look at the Rautelin study,  
11 if you take a look at Table 1, upper left-hand page of  
12 -- Page 2 of G-524 -- for ciprofloxacin, the isolates  
13 from 1978 to 1980 had a range of 0.03 to 4 micrograms  
14 per milliliter. Do you see that, Dr. Hanninen?

15 A Yes, I see.

16 Q Now, if we define ciprofloxacin resistance as  
17 4 micrograms per milliliter instead of 8, like Rautelin  
18 does, there would have been at least one -- we don't  
19 know how many from the data, but at least one --  
20 ciprofloxacin resistant isolate out of those 102,  
21 wouldn't there be?

22 A It's possible, yeah.

1 Q Well, isn't it more than possible, Dr.  
2 Hanninen, because they give the range of .03 to 4, so  
3 there was at least one that was at 4?

4 A Yeah, I think there was one which had 4.

5 Q At least one?

6 A Yeah.

7 Q We don't know, there could have been more than  
8 one? Right?

9 A Yeah, that's right.

10 Q Dr. Hanninen, isn't it true that in Finland,  
11 the percentage of ciprofloxacin resistant Campylobacter  
12 strains isolated from humans almost doubled between  
13 1990 and 1993, despite no enrofloxacin use in poultry?

14 A 1990 --

15 Q 1990 to 1993, in Finland, I'm talking about  
16 resistance -- ciprofloxacin resistant Campylobacter  
17 strains from humans?

18 A You speak now about this --

19 Q I'm sorry, Dr. Hanninen. No. I'm not on that  
20 paper anymore. I'm sorry.

21 A You were speaking about '90?

22 Q Yeah.

1 A '93?

2 Q Yeah. Now that you know I'm not looking at  
3 that paper, let me re-ask the question.

4 A It depends. I don't know now the data what  
5 you are referring in that case, but -- can you tell me  
6 what --

7 MR. KRAUSS: Sure, Dr. Hanninen, I'd be happy  
8 to.

9 Let me hand you Exhibit B-881. It's an  
10 article, another article by Rautelin. I believe it's  
11 the same author we were just discussing.

12 (The witness examined the document.)

13 BY MR. KRAUSS:

14 Q Have you seen this article before, Dr.  
15 Hanninen?

16 A I have seen it, yes.

17 Q My question for you was whether it was true  
18 that, in Finland, the percentage of ciprofloxacin  
19 resistant Campylobacter strains almost doubled from  
20 1990 to 1993, despite no enrofloxacin use in poultry?

21 A I need to first look at this paper, because I  
22 don't remember --

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1 Q Okay.

2 A -- so well.

3 (The witness examined the document.)

4 THE WITNESS: I think, if I look at the  
5 materials and methods of this paper, they say that they  
6 studied 60 human ~~fetal~~<sup>fecal</sup> isolates.

7 They don't tell if the strains were isolated  
8 from patients who had been infected in Finland or from  
9 patients who had been infected while abroad.

10 That's --

11 BY MR. KRAUSS:

12 Q Okay. But they do report, don't they, that  
13 the percentage of ~~ciprofloxacin~~<sup>ciprofloxacin</sup> resistant  
14 Campylobacter strains that they isolated here in  
15 Finland, in fact, their comparing to their 1990 data  
16 almost doubled from 1990 to 1993?

17 A Yeah, they tell so; and I think the reason is  
18 that it included strains which were isolated from  
19 patients who were traveling abroad.

20 Q Is that what they say in the paper, Dr.  
21 Hanninen?

22 JUDGE DAVIDSON: The paper does speak for

1     itself.

2             MR. KRAUSS:   Okay, thank you, Your Honor.

3             BY MR. KRAUSS:

4             Q     Now, isn't it true, Dr. Hanninen, that by 1996  
5     in Finland, fluoroquinolone resistance in Campylobacter  
6     had doubled again, or nearly doubled again, to 32  
7     percent, despite no enrofloxacin use in poultry?

8             A     Can I see data you used for that?

9             MR. KRAUSS:   Yes.   Let me hand you document B-  
10    44, and, in particular, I'm looking at the table on  
11    Page Number 9.

12            (The witness examined the document.)

13            MS. AMBROSE:   Objection, your Honor.   The  
14    document speaks for itself, and it's already in the  
15    list.

16            JUDGE DAVIDSON:  I believe so, but still, I'm  
17    waiting.

18            Again, like we talked about five or six days  
19    ago, you're getting the witness to look at documents,  
20    state what's in the document; and I want to know what  
21    comes next.

22            Because, you know, it goes on and on, and then

1 many times you've disappointed me. You haven't got the  
2 next.

3 MR. KRAUSS: I'm sorry, Your Honor.

4 JUDGE DAVIDSON: If there's something in the  
5 paper that's different, or -- you know, I don't  
6 understand. You keep doing this.

7 The paper does speak for itself, and you're  
8 making a statement that the incidence has doubled  
9 between this date and that date, now the incidence has  
10 doubled according to another paper, between another  
11 date and another date.

12 And let's assume, for the sake of argument,  
13 that your characterization is correct. What's the next  
14 question?

15 MR. KRAUSS: The next question is whether she  
16 considered that in her analysis.

17 JUDGE DAVIDSON: Okay.

18 THE WITNESS: I have considered it, because  
19 all these data where we show increasing number of  
20 resistance in human isolates in Finland, they are based  
21 on isolates where most probably are isolated from  
22 patients who have infection in -- not in Finland, from

1 during their foreign travel.

2 In none of these papers have been described  
3 the background of patients, and that's one of the most  
4 important points, if we are discussing about the  
5 increase of fluoroquinolone resistance in human  
6 isolates in Finland.

7 BY MR. KRAUSS:

8 Q Now, Dr. Hanninen, isn't it true that the  
9 association between resistant Campylobacter in humans,  
10 in patients from Finland, the association with foreign  
11 travel could be from the prophylactic use of  
12 fluoroquinolones while traveling, as opposed to that  
13 they're traveling to countries where they use  
14 fluoroquinolones in poultry?

15 A Of course, we don't know the risk factors  
16 existing in countries where people are traveling, but  
17 prophylactic use, in any case, cannot explain the  
18 increase that we have seen, the numbers we have seen in  
19 resistance of human Campylobacter isolates in patients  
20 who have been traveling to Spain or Thailand or  
21 Portugal, assuming I would document from Rautelin --  
22 2000, B-934.

1           Q     Right; and in B-934, you mention prophylaxis  
2 of travelers diarrhea with fluoroquinolones as one of  
3 the potential causes for an increase, don't you?

4           A     Not for increase, but it can explain part of  
5 the resistant strains.

6           MR. KRAUSS: Thank you.

7           Your Honor, is this a good place for a break?

8           JUDGE DAVIDSON: It's up to you.

9           MR. KRAUSS: Yes.

10          JUDGE DAVIDSON: Okay.

11          MR. KRAUSS: Thank you.

12          JUDGE DAVIDSON: How much time do you think  
13 you need?

14          MR. KRAUSS: For the break?

15          JUDGE DAVIDSON: Yes.

16          MR. KRAUSS: Ten?

17          JUDGE DAVIDSON: Okay.

18          MR. KRAUSS: Thank you.

19          JUDGE DAVIDSON: We'll be gone until 20 of  
20 11:00.

21                 (A brief recess was taken.)

22          JUDGE DAVIDSON: What's the last exhibit you

1 were referring the witness to? I must have written it  
2 down.

3 MR. KRAUSS: Yes, Your Honor. The very last  
4 one we discussed, I believe the witness brought up, was  
5 B-934.

6 JUDGE DAVIDSON: 934. All right. That's all  
7 I need.

8 MR. KRAUSS: Your Honor, on these B exhibits  
9 that I've used with the witness, I can't represent to  
10 you right now whether they've been moved into evidence  
11 or not. May I clear that up tomorrow?

12 JUDGE DAVIDSON: Sure, but could you give me  
13 copies of them if you're going to talk about them?  
14 Because I haven't been able to locate them right now.

15 MR. KRAUSS: Yes.

16 (Pause.)

17 JUDGE DAVIDSON: Okay.

18 BY MR. KRAUSS:

19 Q Dr. Hanninen, let me turn your attention to  
20 Sweden, and I only have a short on Sweden.

21 To your knowledge, is enrofloxacin still  
22 approved for use in poultry in Sweden?

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1 A No, I don't know the situation on approval,  
2 no.

3 Q You don't know one way or the other?

4 A No.

5 Q Now, turning your attention to Denmark --  
6 which begins on the bottom of Page 4 of your testimony  
7 -- in Denmark, if I understand your testimony,  
8 enrofloxacin was approved in 1993, and there's reports  
9 of resistance in poultry of 8 percent for ciprofloxacin  
10 and 7 percent for nalidixic acid in the year 2000, and  
11 in humans, 6 to 7 percent in 1998, and 22 to 25 percent  
12 in 2000.

13 Is that right?

14 A Yeah, they are taken from <sup>DANMAP</sup>~~Denmark~~, 2000.

15 Q And for the DANMAP, isn't it true that, in  
16 Denmark, they defined a resistance breakpoint for an  
17 MIC of greater than or equal to 1 microgram per  
18 milliliter?

19 A I need to check that.

20 (Pause.)

21 MR. KRAUSS: Your Honor, I'm going to hand her  
22 G-151, which is the DANMAP 2000 report that we were

1 talking about.

2 (The witness examined the document.)

3 BY MR. KRAUSS:

4 Q Dr. Hanninen, could I direct you to a table  
5 for that proposition, that they used 1 as a breakpoint?

6 A Yes.

7 Q Page 45 of G-151; and this is with respect to  
8 Campylobacter isolated from animals.

9 A You said page 45?

10 Q Yes, and when I'm saying --

11 A Yes, there is the middle.

12 Q Right. And DANMAP defines resistance with an  
13 MIC of greater than or equal to 1, right?

14 MS. AMBROSE: Objection, your Honor. The  
15 document speaks for itself.

16 MR. KRAUSS: Your Honor --

17 JUDGE DAVIDSON: I assume it's a preliminary  
18 question.

19 MR. KRAUSS: Thank you, your Honor.

20 (The witness examined the document.)

21 THE WITNESS: In Table -- okay, yeah, that's  
22 Campylobacter. You are right. It's 1, what they used,

1 yeah.

2 BY MR. KRAUSS:

3 Q That's for animal isolates, and in fact, they  
4 report, for poultry for 2000, 8 percent resistance for  
5 ciprofloxacin and 7 percent for nalidixic acid, right?

6 A Yes.

7 Q My question is, if the breakpoint for Denmark  
8 was 4 micrograms per milliliter instead of 1, that  
9 resistance for poultry Campylobacter isolates might  
10 even be lower than the 7 or 8 percent reported, right?

11 A It might be, but because the distribution of  
12 resistance is a little bit like on-off system, so that  
13 most strains usually have a higher level of resistance  
14 than 1 microgram, if they are resistant.

15 Q Well, in the 2000 report, the range, the high  
16 end of the range was 16; isn't that right? Page 45  
17 again.

18 A (Examining)

19 Q That's for the ciprofloxacin.

20 A Yeah. Yes.

21 Q So going back to my question, if the DANMAP  
22 data in G-151 were reported on a basis with an MIC of

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1 resistance being defined as a MIC of greater than or  
2 equal to 4 micrograms per milliliter instead of 1, the  
3 reported resistance from poultry isolates could be even  
4 lower than the 8 percent for ciprofloxacin resistance.  
5 Right?

6 A MIC 90 percent for chicken isolates was ~~0.15~~<sup>0.5</sup>.

7 And, yeah, 16 -- yeah, it could be a little  
8 bit higher -- lower, excuse me -- if you use breakpoint  
9 level 4 micrograms per milliliter.

10 Q Now, do you know whether enrofloxacin is still  
11 approved for use in poultry in Denmark?

12 A At the moment, I don't know. I think it; but  
13 it's not question of this testimony to speak today --  
14 today's situation.

15 Q Let me direct your attention to The  
16 Netherlands.

17 Isn't it true that in The Netherlands the  
18 emergence of fluoroquinolone resistance in human  
19 Campylobacter occurred after the introduction of  
20 fluoroquinolones for use in human medicine?

21 A I don't now remember exactly what year they  
22 were taken, used in -- would you tell me the year when

1 ciprofloxacin was taken in use in human medicine?

2 MR. KRAUSS: Yes. Just one second, your  
3 Honor.

4 JUDGE DAVIDSON: Yes.

5 (Pause.)

6 BY MR. KRAUSS:

7 Q For The Netherlands, ciprofloxacin was first  
8 registered in August of 1988 and enrofloxacin was first  
9 registered in April of 1987.

10 Does that help you be able to answer that  
11 question?

12 A So the date that they have in the paper, they  
13 saw that, after the years of enrofloxacin started in  
14 The Netherlands, the increase in human isolates came at  
15 the same time, or a little bit after the resistant  
16 isolates came from poultry.

17 Q Right, but my question is, it was also after  
18 the use of ciprofloxacin in human medicine; isn't that  
19 right?

20 A I don't know how much they have been used at  
21 that time in human medicine. I don't know. So even if  
22 it was approved, I don't know how much it was in use in

1 practice.

2 Q Do you know how much was used in poultry?

3 A I think it -- I don't know exactly the amount,  
4 of course, but I think they started to use that after  
5 the approval.

6 Q In examining the spatial and temporal evidence  
7 for The Netherlands, did you consider the amounts and  
8 extent to which fluoroquinolones were used in human  
9 medicine and fluoroquinolones were used in poultry  
10 medicine?

11 A I don't have such data, database, but on the  
12 pages that we -- even the times when they were approved  
13 for human use and for medicine, medical use in poultry  
14 are quite closely related.

15 We know from practice that resistance in human  
16 strains after treatment, human treatment, treatment or  
17 human clinical Campylobacter, diarrhea is quite low.

18 It's, in any case, we know that it's quite  
19 uncommon, first, because most human campylobacter cases  
20 are not treated by ciprofloxacin, or any other  
21 antibiotics, erythromycin or anything else, so that  
22 that's only minority of cases which are treated by

1 antimicrobials.

2 MR. KRAUSS: Let me --

3 JUDGE DAVIDSON: Mr, Krauss, excuse me. Do you  
4 have the stipulations handy?

5 MR. KRAUSS: Yes, your Honor.

6 JUDGE DAVIDSON: Look at No. 61 and see if  
7 that -- explain to me how that, why that appears to be  
8 different than what you've just read into the record.

9 I know it doesn't say human use, and it says  
10 Bayer ciprofloxacin.

11 MR. KRAUSS: Your Honor, I didn't know that. I  
12 was looking myself at 61, so if I misrepresented  
13 what --

14 JUDGE DAVIDSON: Well, maybe I just heard it  
15 wrong. I thought you said '87 and then a later date  
16 for the poultry use.

17 MR. KRAUSS: No, your Honor.

18 JUDGE DAVIDSON: I could be wrong. 61 is  
19 correct?

20 MR. KRAUSS: Yes.

21 JUDGE DAVIDSON: Okay. So whatever it was,  
22 that will be --

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1 MR. KRAUSS: And I was looking <sup>at that</sup> ~~ahead~~, your  
2 Honor, when I asked the question, or gave the witness  
3 the information.

4 JUDGE DAVIDSON: You aren't supposed to ask  
5 questions from the seat, are you?

6 MR. KRAUSS: Yes, your Honor.

7 JUDGE DAVIDSON: Okay. But the witness did  
8 ask you, so I'll allow it this time.

9 MR. KRAUSS: Thank you.

10 BY MR. KRAUSS:

11 Q Let me, Dr. Hanninen, go back to what I was  
12 trying to ask you about on The Netherlands.

13 The Endtz study, if I recall Endtz, compared  
14 human isolates from a time in the late '80s to human  
15 isolates that were gathered in the early '90s; is that  
16 right?

17 A Yes.

18 Q And he saw an increase in resistance in the  
19 human isolates that he had gathered in the early 1990s,  
20 right?

21 A Yes.

22 Q So my question was, isn't it true that in The

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1 Netherlands, the emergence of the fluoroquinolone  
2 resistance that was seen in the human Campylobacter  
3 isolates occurred after the introduction of  
4 fluoroquinolones for use in human medicine in The  
5 Netherlands?

6 A Yeah, if you think about these two things,  
7 it's true --

8 Q Okay. Now --

9 A -- without consideration of the whole  
10 situation.

11 Q Dr. Hanninen, in performing your analysis on  
12 the temporal and ~~spacial~~<sup>spatial</sup> evidence related to The  
13 Netherlands, did you review the work of Han ~~Deneeling~~<sup>deNeeling</sup>?

14 A No.

15 Q Now, with respect to The Netherlands, is  
16 enrofloxacin still approved for use in The Netherlands,  
17 do you know?

18 A If you speak about today's situation, I don't  
19 know.

20 Q Let me turn your attention now to the U.K.  
21 First of all, do you know Dr. ~~Diana~~<sup>Diane</sup> Newell?

22 A I know, yes.

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1 Q You do?

2 A Yes.

3 MS. AMBROSE: Objection to the form of the  
4 question. Never mind.

5 BY MR. KRAUSS:

6 Q Do you understand that she's a researcher who  
7 has studied the risk factors for campylobacteriosis in  
8 the U.K.?

9 A In poultry.

10 Q In poultry?

11 A Yes.

12 Q In fact, you cite to a Sentinel study --

13 MR. KRAUSS: I just want to make one thing  
14 clear here, your Honor.

15 BY MR. KRAUSS

16 Q -- there's a U.K. Sentinel study, okay, done  
17 by Dr. Newell's group, don't you? She's a member of  
18 that group?

19 A I don't remember if she is. I want to see  
20 the list of the writers in this Sentinel study, because  
21 I don't remember if she is building that study.

22 MR. KRAUSS: I'm going to withdraw the

1 question, your Honor.

2 JUDGE DAVIDSON: Okay.

3 BY MR. KRAUSS:

4 Q Now, Dr. Hanninen, with respect to the United  
5 Kingdom, you cite a handful of studies, and here I'll  
6 just for the record give the G numbers: G-240, G-633,  
7 G-634, G-1665, and G-1772.

8 Now, in your review of these studies, did you  
9 examine the representativeness of the populations that  
10 were studied to be able to compare one study to the  
11 other?

12 A What studies you are now speaking about?

13 Q The ones that you --

14 A I'm thinking all these studies or --

15 Q All the ones that you looked at for the U.K.,  
16 Dr. Hanninen, the ones that are identified in your  
17 testimony.

18 A Yes.

19 MS. AMBROSE: Your Honor, I ask that she be  
20 provided with a copy of the studies that counsel is  
21 referring to.

22 JUDGE: If she doesn't have it already, right.

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1 Does she have copies of it?

2 MR. KRAUSS: Not -- I can give them to her,  
3 Your Honor, for the U.K.

4 (Pause.)

5 BY MR. KRAUSS:

6 Q I'm handing the witness G-1665, G-505, G-240,  
7 G-633, G-1772, and G-634.

8 A Thank you. Would you please repeat your  
9 question?

10 Q Yes.

11 In formulating your opinion with regard to the  
12 U.K., in your analysis of these studies, did you look  
13 at the representativeness of the populations within the  
14 studies in order to be able to compare one study to the  
15 other, and to the extent there was a trend, whether  
16 that trend was accurate?

17 A I think some of them are quite extensive  
18 studies.

19 For example, the Sentinel study is quite  
20 extensive study; and also the study of Gaunt and  
21 Piddock, 96, they were collecting 2,209 Campylobacter  
22 isolates from patients in the ~~Pement~~ <sup>Plymouth</sup> area; and ~~Twitz~~ <sup>Thwaiter</sup>

1 and Frost collected also quite -- studied quite a large  
2 number of human Campylobacter isolates, 5,800, and they  
3 are working at National Public Health Institute  
4 Laboratory, so that they have quite extensive data  
5 collection for use.

6 So that it looks for me that there are quite  
7 big materials in all these studies.

8 Q So the answer to my question on that one is  
9 yes, you did consider the representativeness of the  
10 various studies?

11 A Yes.

12 Q Now, you mentioned that U.K. Sentinel study.  
13 I think you said it was quite extensive.

14 Do you agree with the conclusions of that  
15 study?

16 MS. AMBROSE: If counsel could direct the  
17 witness to what page he's referring to in that study.

18 THE WITNESS: Yeah, I have it.

19 JUDGE DAVIDSON: And the exhibit number.

20 MS. AMBROSE: The exhibit number and the page.

21 JUDGE DAVIDSON: Well, she has it, but the  
22 record doesn't have it.

1 MR. KRAUSS: G-1772.

2 (The witness examined the document.)

3 THE WITNESS: I think it is quite extensive,  
4 and it includes several other topics also, not only  
5 this antimicrobial resistance study.

6 It also includes typing of the isolates and  
7 the epidemiological points of view. So it's a quite  
8 extensive study.

9 BY MR. KRAUSS:

10 Q Do you find it to be a reliable study?

11 A Of course.

12 Q Dr. Hanninen, with respect to your analysis of  
13 the studies that you looked at with respect to the  
14 U.K., did you compare the isolation culture and  
15 speciation methods that were used in those studies in  
16 order for you to be able to compare the results between  
17 studies and see if there was a trend?

18 A Yes. As the all the titles say, some studies  
19 were done for Campylobacter species and some studies  
20 were concentrated on Campylobacter jejuni; but as we  
21 know, also in U.K., as in most other countries,  
22 Campylobacter jejuni is the most common pathogen,

1 representing about 90 percent of isolates; I don't now  
2 remember how is the situation in U.K., but in most  
3 countries, so that jejuni is the most important part.

4 Q Now, back to my question.

5 In analyzing the U.K. studies, did you look at  
6 the isolation culture and speciation methods that were  
7 used in the multiple studies that you refer to and rely  
8 on for your opinion regarding UK in order to allow you  
9 to compare the studies to each other?

10 MS. AMBROSE: I object, your Honor. That's  
11 beyond the scope of her testimony.

12 JUDGE: I'll overrule the objection. You may  
13 answer.

14 MR. KRAUSS: Thank you, your Honor.

15 THE WITNESS: I think they were using such  
16 common methods for speciation of Campylobacters in all  
17 studies, if they were speciating, because we have quite  
18 common methods which we use for speciation for jejuni,  
19 coli level, at least.

20 BY MR. KRAUSS:

21 Q My question for you, Dr. Hanninen, was, in  
22 formulating your opinion, did you look at that issue?

1           A     I was looking just very superficially how, so  
2 not in a very detailed way.

3           Q     Now, Dr. Hanninen, in your analysis of the  
4 temporal and spatial trends relating to the United  
5 Kingdom, and in analyzing the exhibits that you looked  
6 at for the United Kingdom, did you compare the  
7 antimicrobial susceptibility tests that were used in  
8 the various studies in order to determine whether the  
9 results were comparable to each other?

10          A     I think in studies made at the National  
11 Public Health Laboratory they use always the same  
12 methods -- or I suspect.

13          Q     And was that true over the period of time that  
14 you studied?

15          A     I need to -- (examining)

16          Q     Dr. Hanninen, the question is, at the time you  
17 formulated your opinion regarding the U.K., did you  
18 look at that issue?

19          A     I was not truly looking at that issue, so I  
20 was not truly looking at the methods which were used  
21 for assessment of susceptibility for ciprofloxacin.

22          Q     Now, Dr. Hanninen, in your review of the

1 studies from the U.K. did you examine the interpretive  
2 criteria used to define in vitro resistance in the  
3 various studies so you could compare them?

4 A I think they were using 4 micrograms per  
5 milliliter, at least at the National Public Health  
6 Laboratory studies; and also, the strains from the  
7 Gaunt and Piddock studies were sent for further studies  
8 to the Antimicrobial Agents Research Group at the  
9 University of Birmingham, and some of them were sent to  
10 the Campylobacter Reference Laboratory, the Public  
11 Health Laboratory.

12 I think at National Public Health Laboratories  
13 they are using the same breakpoints.

14 Q So it's your understanding that in all the  
15 U.K. articles they were using a common breakpoint as an  
16 interpretive criteria for in vitro resistance?

17 A Seems at least from these papers, what I had  
18 time to check here.

19 Q Now, Dr. Hanninen, do you know whether, in the  
20 U.K., enrofloxacin is still approved for use in  
21 poultry?

22 A If you speak at moment, I don't know.

1 Q Let me turn your attention to your testimony  
2 regarding Spain.

3 Would you agree that the conditions of use of  
4 fluoroquinolones in poultry in Spain are quite  
5 different than the conditions of use in the United  
6 States?

7 A I can't compare these two countries.

8 Q You can't compare the two countries?

9 A I don't have such documents and data; and in  
10 my testimony I left U.S.A. away because I was thinking  
11 here -- own expert to discuss the situation here in the  
12 United States.

13 Q Very well, thank you.

14 Now, Dr. Hanninen, have you examined  
15 fluoroquinolone use in Canada in veterinary and human  
16 medicine to determine if it supports your temporal  
17 trend analysis?

18 MS. AMBROSE: Objection, your Honor. That's  
19 beyond the scope of Dr. Hanninen's testimony.

20 JUDGE DAVIDSON: Is Canada listed here?

21 MS. AMBROSE: No.

22 MR. KRAUSS: Your Honor, on Page 2 of her

1 Exhibit B-1468, she lists Canada on the table.

2 JUDGE DAVIDSON: It says, "very limited use."  
3 Overruled. I thought I saw Canada. Go ahead.

4 BY MR. KRAUSS:

5 Q Now, Dr. Hanninen, have you examined  
6 fluoroquinolone use in Canada in veterinary and human  
7 medicine to determine if it supports your temporal and  
8 spacial evidence analysis?

9 A Not for this purpose, because as I told, I  
10 left the whole continent, America, away from my -- both  
11 U.S.A. USA and Canada. As you see, I don't have any  
12 data on Canada.

13 Q Dr. Hanninen, in your analysis of the temporal  
14 and spatial evidence in countries in Europe that you  
15 testified about, did you examine fluoroquinolone use in  
16 Switzerland in veterinary and human medicine to  
17 determine if it supports your temporal trend analysis?

18 A No, I left it.

19 I was reading some papers, but I didn't use it  
20 in my testimony so much. The --

21 JUDGE DAVIDSON: There's all right, Doctor.  
22 It's no. You've answered the question.

1 BY MR. KRAUSS:

2 Q Dr. Hanninen, in your review of the spatial  
3 and temporal evidence in Europe, did you examine the  
4 emergence of quinolone resistance in Germany relative  
5 to fluoroquinolone use in veterinary and human  
6 medicine?

7 MS. AMBROSE: Objection, your Honor. That's  
8 outside the scope of her testimony.

9 JUDGE: Why don't you just ask her if there  
10 are any other countries she examined instead of going  
11 through each one of them in Europe?

12 MR. KRAUSS: Your Honor, this is my last --

13 JUDGE DAVIDSON: There are a lot of other  
14 countries in Europe. Aren't you going to ask her about  
15 Italy?

16 MR. KRAUSS: I did not, your Honor.

17 JUDGE DAVIDSON: I said, aren't you going to?

18 MR. KRAUSS: I will, if you want me to.

19 (Laughter.)

20 JUDGE DAVIDSON: All right. Let her answer  
21 this question.

22 Did you examine the evidence from Germany?

1 THE WITNESS: A little bit, but there was so  
2 little published data available from Germany.

3 BY MR. KRAUSS:

4 Q Little data available?

5 A Yeah. I left it.

6 Q Dr. Hanninen, if in Germany, as far back as  
7 1983, there was 15 percent resistance to nalidixic acid  
8 in Campylobacter jejuni and Campylobacter coli  
9 isolates, that would not be supportive of your temporal  
10 trend analysis, would it?

11 A I don't understand that question.

12 MS. AMBROSE: It's beyond the scope of her  
13 testimony.

14 JUDGE DAVIDSON: I'll let her answer. What  
15 did your answer say?

16 THE WITNESS: I said that I can't answer your  
17 question.

18 JUDGE DAVIDSON: Okay.

19 BY MR. KRAUSS:

20 Q You can't answer my question?

21 A No.

22 Q Is there a reason why you can't answer my

1 question?

2 JUDGE DAVIDSON: That's enough.

3 MR. KRAUSS: Okay, sorry, your Honor.

4 JUDGE DAVIDSON: Move on.

5 MR. KRAUSS: Your Honor, may I approach the  
6 witness?

7 JUDGE DAVIDSON: Go ahead.

8 (Exhibit B-1936 was marked for  
9 identification.)

10 MR. KRAUSS: Let me hand you what I've marked  
11 as B-1936 for today's purposes. It's an abstract. I  
12 ask you to please take a look at this document.

13 I ask you to please take a look at this  
14 document.

15 (The witness examined the document.)

16 THE WITNESS: May I comment on that?

17 BY MR. KRAUSS:

18 Q Well, I have a question.

19 A But may I first comment on that?

20 Q Absolutely, Dr. Hanninen.

21 A First, it is abstract, and it is not said, are  
22 there isolates from humans or from animals.

1           It's not -- the background of isolates is  
2 quite unknown; so in a few sentences, I don't think I  
3 have capacity to comment on this -- this thing.

4           Q     At the time that you were examining the  
5 temporal and spatial evidence in Europe, were you aware  
6 of reports from Germany that there was 15 percent  
7 nalidixic acid in chemotherapeutic agents isolated from  
8 feces, Campylobacter isolated from feces?

9           A     This kind of document, I can't see if they  
10 are human or animal isolates. It's -- I cannot get any  
11 information of that.

12          Q     Dr. Hanninen, do you understand  
13 chemotherapeutic agents to be agents that are used --  
14 that's a term used in human medicine?

15          A     I think we can use the same term in veterinary  
16 medicine, as well.

17          Q     Dr. Hanninen, in analyzing the temporal and  
18 spatial evidence in this case, did you undertake any  
19 analysis of time series data for human Campylobacter  
20 resistance rates in any of the countries you looked at?

21          A     We have data from Finland where we know that  
22 we have, we have in our domestic human isolates, we

1 have very low resistance. It has not changed during  
2 the whole period of time when ciprofloxacin has been  
3 used in human medicine.

4 But in isolates which have been isolated from  
5 humans who have a foreign travel background to Spain or  
6 Thailand, we have seen the trend of increasing  
7 resistance in '90s, if you compare the resistance in  
8 the beginning of '90s and in '99.

9 Q Is the answer to my question that you looked  
10 at time series data and analyzed time series data in  
11 Finland?

12 A Yes. Also on these other countries, if it  
13 was available.

14 As I said, that systematic collection of  
15 antimicrobial susceptibility data has not been the case  
16 in many countries. Denmark is one of the countries  
17 where they have had this system since '95, as far I  
18 remember right. Also in Sweden they have had it for a  
19 few years, but it's pretty new system in Sweden.

20 But most countries that we are now speaking  
21 for, especially in the early '90s, they didn't have a  
22 systematic surveillance system for looking at

1 antimicrobial resistance.

2           So that the documents we are using are based  
3 on studies made by laboratories or university level,  
4 but not by official monitored programs where the trends  
5 of antimicrobial sensitivity is the special target of  
6 studies.

7           Q    Dr. Hanninen, when you analyzed time series  
8 data, did you use any statistical analytical programs,  
9 computer programs?

10          A    No.

11          Q    Dr. Hanninen, at Paragraphs 11 and 17 of your  
12 testimony, on Pages 7 and 9 of G-1458, you refer to  
13 serotyping and genotyping.

14                Would you agree that genotyping of  
15 Campylobacter species alone, genotyping between the  
16 poultry isolates and human isolates, genotyping alone  
17 cannot show a causal relation? Do you agree?

18          A    Yeah, now we need to speak at species level.  
19 First we need to speak about Campylobacter jejuni and  
20 compare Campylobacter jejuni strains from humans; but I  
21 agree -- I agree that it doesn't tell causal  
22 relationships.

1 MR. KRAUSS: Your Honor, I have no further  
2 questions for the witness at this time.

3 JUDGE DAVIDSON: Do you need a break to change  
4 positions or --

5 MS. AMBROSE: Yes, please, your Honor.

6 JUDGE DAVIDSON: All right. Before you do,  
7 just simply the -- it could wait 'til later, but as  
8 long as you're going on break right now, on the 28th,  
9 Bayer filed a motion to add to the record. I haven't  
10 heard a response.

11 Do I have to shorten the time so you people  
12 will respond before we adjourn, or are you going to  
13 give me an answer, or a position tomorrow?

14 MS. AMBROSE: We'll give you a position  
15 tomorrow, your Honor.

16 JUDGE DAVIDSON: Thank you. We'll go off the  
17 record for five minutes, and then continue.

18 (A brief recess was taken.)

19 JUDGE DAVIDSON: Are you ready, Ms. Ambrose?

20 MS. AMBROSE: Yes, I am, your Honor.

21 JUDGE DAVIDSON: Okay, go right ahead.

22 MS. AMBROSE: Okay.

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Corrected as per OR 46 6/13/03

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1 REDIRECT EXAMINATION

2 BY MS. AMBROSE:

3 Q Dr. Hanninen, could you explain why, in your  
4 testimony, you stated that risk factors for acquiring  
5 Campylobacter is different in different countries?

6 A This, my sentence is based on epidemiological  
7 studies done in different countries, and they show that  
8 the products -- they speak to poultry only, so that  
9 poultry can explain, let's say, 10 to <sup>50</sup>~~15~~ percent of  
10 human Campylobacter cases.

11 It means that the level -- Campylobacter  
12 positive chicken as a risk factor for human  
13 campylobacter infection is not same in all countries.

14 Also, some other risk factors associated with  
15 human Campylobacter enteritis may vary between  
16 different countries.

17 And because, if you look at chicken, because  
18 we are now speaking chicken and human resistant  
19 Campylobacter strains, so we need to look at the whole  
20 food chain, starting from the beginning, because we  
21 have differences in the contamination level of chicken  
22 in different countries, how much the production is

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1 contaminated.

2 In some countries it's only a 10 percent  
3 level, as in Finland, Sweden; and in some countries  
4 it's 50 percent, and in some countries; it's maybe 70,  
5 80 percent of poultry is contaminated.

6 So it means that it's higher exposure  
7 possibility.

8 And then, if you go to products available at  
9 shops, they are also different in different countries.

10 In some countries, chicken is still sold as  
11 deep frozen products, and in some countries, as in our  
12 country, it's sold as marinated consumer packages.

13 So that if you think about that, when  
14 housewife buys and goes home and prepares food in  
15 Finland, she just goes home and opens the package and  
16 put it in oven. There is very little possibility for  
17 cross-contamination, or contact with contaminated  
18 chicken.

19 But in countries where a lot of chicken is  
20 sold as deep frozen or fresh products, it means quite a  
21 lot of preparation at home. It means that there is  
22 much bigger possibility for cross-contamination at

1 home.

2 And I think these facts explain the  
3 differences in the level of risks in different  
4 countries, even they have been not yet so well-defined.

5 Q Thank you.

6 Now, Dr. Hanninen, are you aware of any  
7 studies after the approval of ciprofloxacin in humans  
8 where enrofloxacin has not been used in poultry, but  
9 domestic fluoroquinolone resistant Campylobacter in  
10 humans, infections has remained low?

11 A Please repeat?

12 Q Are you aware of studies after the approval of  
13 ciprofloxacin in humans where enrofloxacin has been  
14 used in poultry, but domestic fluoroquinolone resistant  
15 Campylobacter infections has remained low?

16 A Ciprofloxacin resistant human infections have  
17 remained low?

18 Q Fluoroquinolone resistant Campylobacter human  
19 infections have remained low.

20 A Finland is one example, and Sweden is also  
21 another example.

22 MS. AMBROSE: Thank you.

1 JUDGE DAVIDSON: I didn't hear the last part  
2 of her answer.

3 MS. AMBROSE: She said, "and Sweden is also  
4 another example."

5 JUDGE DAVIDSON: Okay.

6 BY MS. AMBROSE:

7 Q Based on your review of literature and  
8 research studies, do you conclude that enrofloxacin use  
9 in poultry is a major contributor to human  
10 fluoroquinolone resistant campylobacter infections?

11 A I think so.

12 Q Do you agree that the way --

13 A But may I continue?

14 JUDGE DAVIDSON: Certainly. Continue your  
15 answer.

16 THE WITNESS: So there can be also some other  
17 animal sources, but if we speak about at moment major  
18 sources.

19 JUDGE DAVIDSON: All right. Next question.

20 BY MS. AMBROSE:

21 Q Do you agree that, based on your review of the  
22 literature, including genotyping, leads you to believe

1 that fluoroquinolone use in poultry contributes to  
2 fluoroquinolone resistant campylobacter infections in  
3 humans?

4 MR. KRAUSS: Objection, your Honor. She's  
5 just repeating what's in her direct testimony.

6 JUDGE DAVIDSON: Right. Sustained.

7 MS. AMBROSE: No further questions, Your  
8 Honor.

9 JUDGE DAVIDSON: Thank you.

10 MR. KRAUSS: I'm going to surprise you, Your  
11 Honor. No questions.

12 JUDGE: I'm in trouble now.

13 You're excused, Doctor.

14 (The witness was excused.)

15 JUDGE DAVIDSON: Is Dr. Cox going to be here  
16 tomorrow?

17 MR. KRAUSS: Your Honor, I believe we have  
18 cross-examination --

19 JUDGE DAVIDSON: I know you should have some.  
20 That's why I asked the question. Do you know if Dr.  
21 Cox is going to be here tomorrow?

22 He's here every other day. I mean, he's

