IN THE UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

WENDY B. DOLIN Individually and as Independent Executor of the Estate of STEWART DOLIN, deceased,	No. 12 CV 6403
Plaintiff,	
vs.	Chicago, Illinois
SMITHKLINE BEECHAM CORPORATION D/B/A GLAXOSMITHKLINE, a Pennsylvania Corporation,	March 21, 2017
Defendant.	9:15 o'clock a.m.

VOLUME 5 A
TRANSCRIPT OF PROCEEDINGS
BEFORE THE HONORABLE WILLIAM T. HART

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(The following proceedings were had out of the presence of the jury in open court:)

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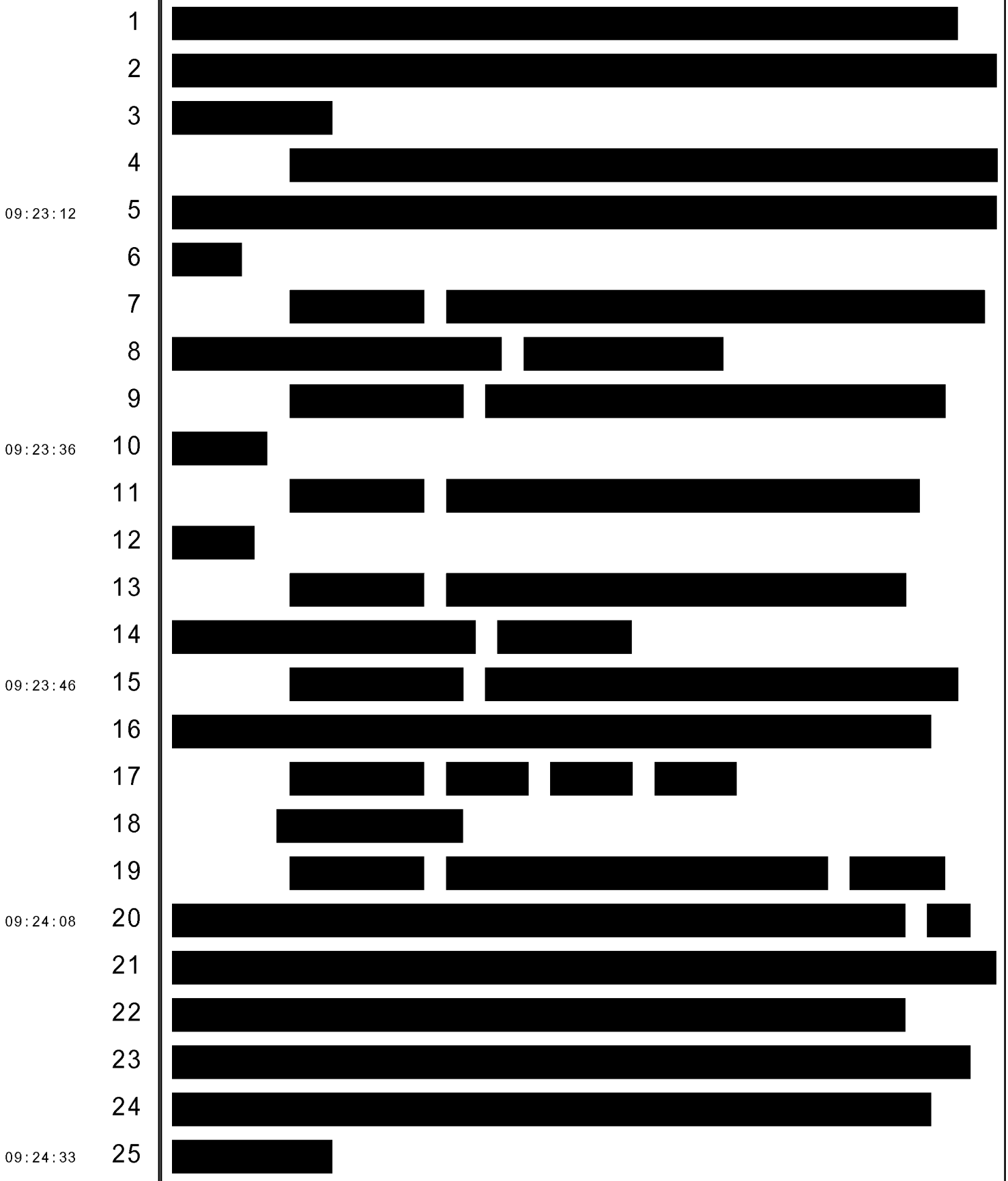
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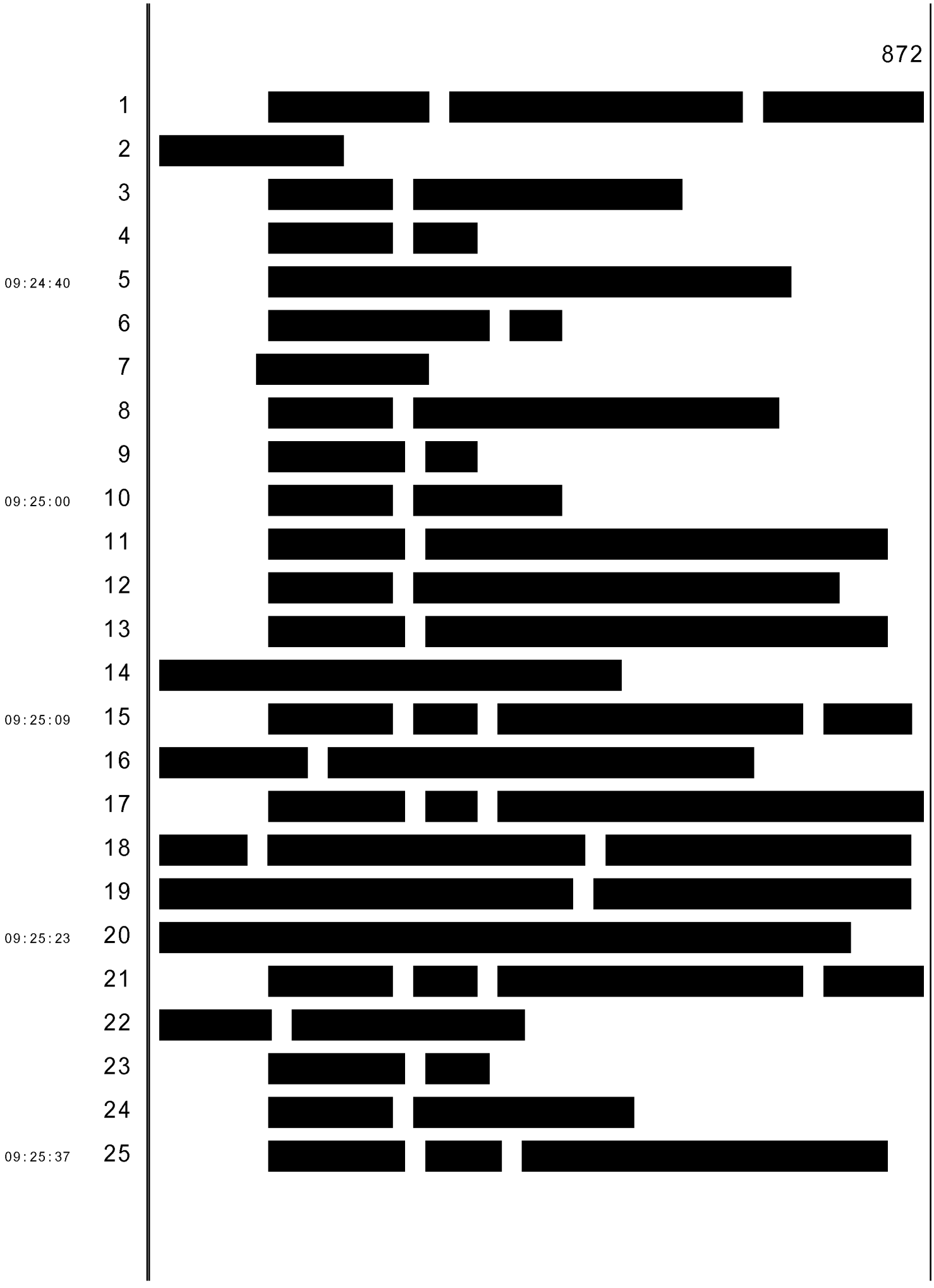
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(The following proceedings were had in the presence of the jury in open court:)

09:26:38 THE COURT: All right. Thank you very much, ladies and gentlemen. Please be seated. And we will proceed.

This morning, ladies and gentlemen, we will begin with the reading of a deposition. And if I haven't said this before I'll say it now, it will apply throughout the trial, that, in 09:26:58 certain instances, the witnesses are not available but their depositions have been taken under oath before the proceedings. And the parties are entitled to read that material to you. And you are to consider it the same as if the witness testified here in court. You've already seen a couple of depositions.

09:27:14 This next deposition, I'm told, will be read by a person who will take the witness stand who obviously is not the witness but is the person who reads with the attorney so that you may hear the testimony. There will, however, be an exhibit, as I understand it.

09:27:32 All right, you may proceed.

MR. RAPOPORT: Thank you very much, Your Honor.

We'll call Martin Brecher, Dr. Martin Brecher to the stand, and his testimony was given on March 13th of 2003.

THE COURT: You have a reader?

09:27:46 MR. RAPOPORT: I did. Sorry. I thought he was back there.

(Brief pause).

MR. RAPOPORT: Here we go.

(Brief pause).

09:28:06 MR. RAPOPORT: All right.

(Deposition read by Mr. Rapoport questioning and Mr. Michael Baum as the witness.)

BY MR. DAVIS:

Q. (Reading:)

09:28:10 "Please state your name for the record, please.

A. Martin Brecher.

Q. What year did you graduate from high school?

A. 1966.

Q. And where did you go to college?

09:28:21 A. MIT.

Q. What did you major in?

A. Biology and philosophy.

Q. And then you went to medical school?

A. That's right.

09:28:28 Q. Where did you go to medical school?

A. Suny Brooklyn.
Q. And you got out in what year?
A. 1976.
Q. And then did you go into a residency?
09:28:36 A. That's right.
Q. Where?
A. Same place.
Q. Are you currently board certified in psychiatry and neurology?
09:28:44 A. Yes.
Q. What year did you become board certified?
A. 1980."
MR. DAVIS: Excuse me. Your Honor, I would just ask that the exact words and the exact answers be read and given.
09:28:55 There's a little deviation here from the transcript.
MR. RAPOPORT: I wasn't aware of deviation. I might've left out an "okay" before the question. I hope not.
THE COURT: Proceed.
BY MR. RAPAPORT:
09:29:09 Q. Let's go back to, I guess, early '89. You applied for a position at the FDA. What position did you originally apply for?
A. A medical officer.
Q. GS?
09:29:23 A. I was a GS14.

Q. GS14. Okay. You were there two years. And a little more detail. If you know, if you now can in this two-year period of what you did at the FDA. And don't tell us who you worked for, I'll get into that later, but from '89 to '91 every job you had at the FDA.

09:29:47

A. Well, it was the same. I was a medical officer in the division of neuro psychopharmacological drug products for the entire time I was there.

From the time I arrived until December of '89, I was primarily involved with the safety evaluation of Clomipramine, which was being reviewed as a treatment for obsessive compulsive disorder.

09:30:03

I had a little bit of work evaluating new IND's in that period of time. After the -- that review was -- after the advisory committee in December of '89 and some follow-up work after that, really beginning in January of 2000, I began work on the Paroxetine NDA and I was responsible for safety and -- for the safety and efficacy reviews of Paroxetine.

09:30:24

Q. You said 2000. You mean 1990?

A. I'm sorry, I misspoke. In January of 1990 I began a review of --

09:30:48

Q. Paroxetine?

A. -- safety and efficacy of Paroxetine. In addition, at that time I begin to -- I received a portfolio of compounds in which I was responsible for the evaluation of post-marketing reports.

09:31:05

These were approved compounds and from that time, January until the time I left, I also reviewed IND's as they came in and as they were distributed to the reviewers.

In addition to the -- to Paroxetine which was the largest piece of work that I had from January of 1990 until the time that I left, I also conducted a review of the efficacy of Phenylpropanolamine. I conducted a review of the efficacy efficacy -- I'm sorry, and the Phenylpropanolamine review was as a treatment for weight loss. I don't recall if -- the major component of that review is efficacy.

I also evaluated fluoxetine for weight gain. Of the -- I mentioned a moment ago that I had a portfolio of products to evaluate the postmarketing surveillance reports. One of those was fluoxetine which was -- there were -- since it was a very popular and growing new drug, there were a lot of reports of adverse events and there were issues involved with fluoxetine.

Q. So from January '90 to June of '91 with the exception of these fluoxetine and other -- and the other weight gain issue you were discussing, your job was almost exclusively Paroxetine?

A. I wouldn't want to have to give an estimate of the total average time spent. It was -- the Paroxetine was certainly the largest project that I had.

Q. Okay.

A. But I was not -- but there came a time when I was pretty much finished and if I -- I think I was largely finished by the end of 1990, as best I can recall.
Q. Okay.
09:33:13 A. But before I left I had to polish up my review prior to leaving so there was some work with that. And there were -- there also came a time when, I don't remember exactly when chronologically, when an electronic NDA became available and I spent several weeks using that platform to further evaluate the
09:33:35 safety of Paroxetine.
Q. Now, you had the NDA and that was submitted in November of '89 and you took over the job in January of '90, correct? So you had had -- this is prior to the Teicher article now in January by month at least and the NDA had been submitted two
09:34:00 months earlier. That NDA had suicide tables and data, did it not?
A. Yes.
Q. And did you, through a matter of course in your regular routine, review that suicide data?
09:34:13 A. I believe I did.
Q. So the data on suicide that you had when the NDA -- let's basically -- that will be Exhibit 15. Take a look at that for a minute.
Ready?
09:34:31 A. Uh-huh.

Q. Now, this table Roman Numeral 11.21 talks about attempted subsides and overdoses worldwide data, and at the bottom it indicates the PAR safety summary of 10 November of 1989. And you'll notice up in the right-hand corner of the worldwide data
09:34:57 that it has all the population that we talked about earlier that you believed I was telling you the truth, and I am, the one that says 2,963 under Paroxetine 1,151 and 554 respectively for placebo, do you see that?
A. Uh-huh.
09:35:22 Q. Okay. Now, here we have attempted suicides on the top line that are further broken down into drug overdose, and I'll save you the time by figuring this out and it's to their benefit anyway, so the drug overdose category is within the top category. It's not -- it's not in addition to, it's a subset
09:35:44 of attempted suicides. And my question is the asterisk of two overdoses during the placebo run-in period. Do you see the asterisk on the side, and of the overdoses, attempted suicide, two were -- occurred during the run-in period. Let me ask you this, based on your procedures at the FDA -- first of all, let
09:36:09 -- let me back up a minute. Based on your procedures at the FDA, what is a run-in period?
A. Prior to randomization, subjects are discontinued from their old medications and given placebo usually for about a week, sometimes shorter.
09:36:29 Q. And how about washout; same?

A. That -- that period also washes out their previous medication.
Q. So the terms are effectively synonymous for purposes of -- okay, now, based on FDA procedure, and I'll even elevator that to scientific procedure that you understood scientific procedure to be when you were at the FDA, is it scientifically legitimate to count a suicidal act occurring during washout and run-in to the placebo count?
A. No, because everybody got placebo.
Q. So it's -- so it's a scientifically illegitimate way to count, correct?
A. Yeah."
MR. RAPOPORT: The next questions are by GSK, unless you want me to read them?
MR. DAVIS: I'm fine. I'll that do.
BY MR. DAVIS:
Q. (Reading:)
"... now, with respect to FDA's role and responsibility, can a manufacturer or a company market a drug in the United States without an prescription medication without FDA approval?"
MR. BAUM: Excuse me. I think you may have skipped a page.
MR. DAVIS: What page is that?
MR. BAUM: I'm at page 314.

MR. BAUM: Okay. Just one second.

(Brief pause).

MR. DAVIS: Oh, thank you.

(Brief pause)

09:38:14 MR. DAVIS: Let me give you some help. I think you need to go back to 308.

Do you need help? Let me give you some help. I think your copy has some pages missing.

MR. BAUM: Okay.

09:38:31 (Brief pause).

MR. WISNER: Your Honor, you sustained our objection to this portion.

MR. DAVIS: I don't believe that's all of it.

Could we go to sidebar, Your Honor, just to get this

09:39:14 cleared up.

THE COURT: Do you have the transcripts?

MR. DAVIS: I do. Excuse me.

(Proceedings heard at sidebar on the record.)

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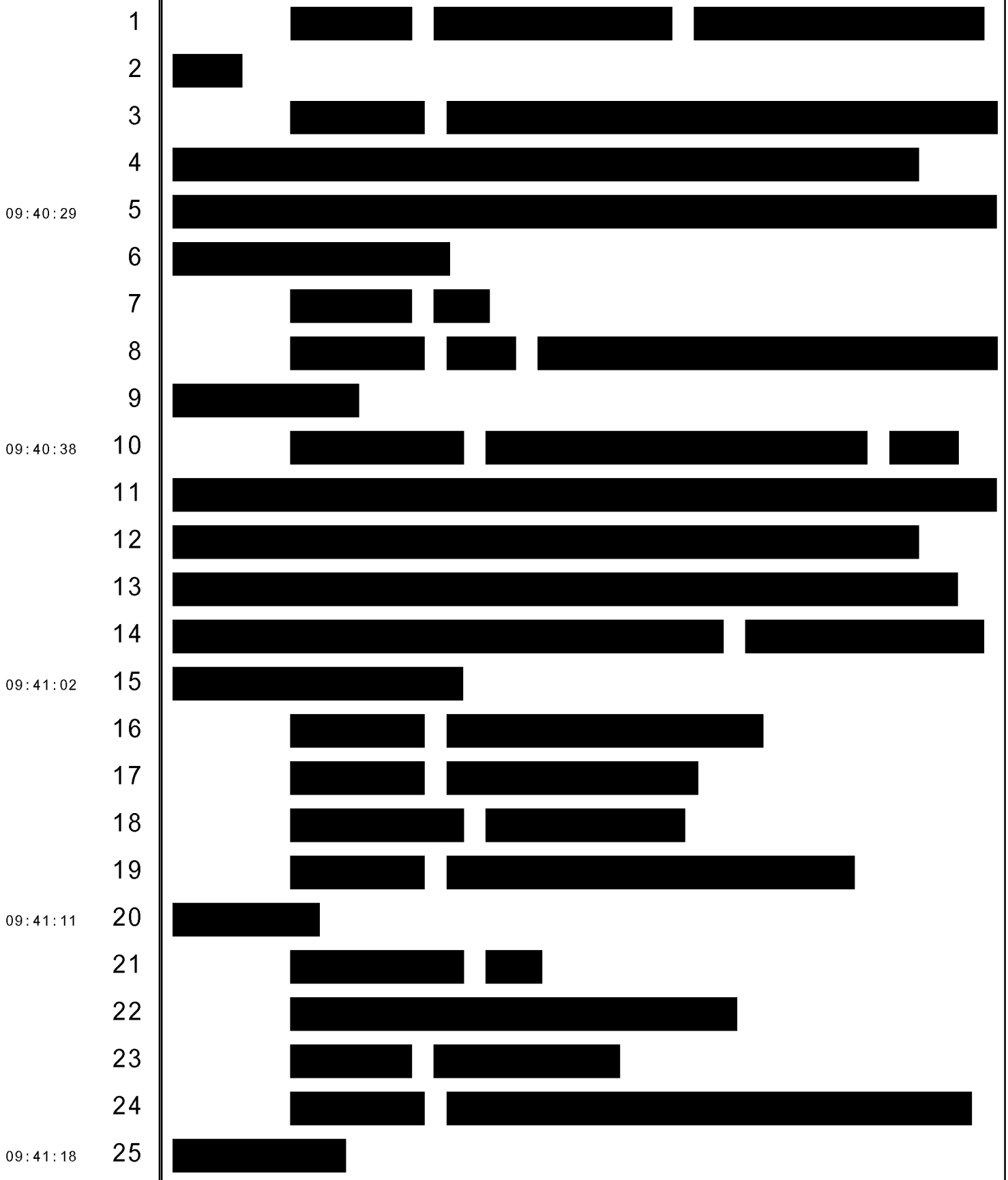

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(Proceedings resumed within the hearing of the jury).

MR. DAVIS: All right. I'm going to pick off where I left off, and since you don't have the transcript, Mr. Baum,

I'm just going to read the answer and the question for the jury.

MR. BAUM: Okay.

MR. DAVIS: I'll pick up right where I left off:

09:42:47 (Reading:)

"Now, with respect to FDA's role and responsibility, can a manufacturer or a company market a drug in the United States without a prescription medication without FDA approval?

"Answer: They cannot."

09:43:09 MR. DAVIS: Do you have page 13, Line 6 through 14 in front of you?

MR. BAUM: No.

MR. BAYMAN: Okay. I'll just read it to speed it up along.

09:43:19 "Question: All right. Now after FDA approves a prescription drug, does its role end there?

"Answer: No.

"Question: Does FDA continue to monitor the drug safety?

09:43:32 "Answer: Yes.

"Question: Does FDA monitor the published literature for issues related to a drug safety?

"Answer: Yes."

Page 314, lines 10 through 14:

09:43:50 "Question: If someone were to suggest to you that FDA

turns a blind eye to what happens after a prescription drug is approved, would you agree or disagree?"

MR. BAUM: "Disagree."

MR. DAVIS: Page 317, lines 13 through page 318 Line 7, do you have it?

MR. BAUM: Yeah.

MR. DAVIS: Thank you.

MR. BAUM: I think I'm with you from this point forward.

MR. DAVIS: Okay.

BY MR. DAVIS:

Q. (Reading:)

"... when you received the assignment to work on the safety review for Paxil, did you understand that it was important for you to conduct a rigorous analysis of the safety data?

A. Yes.

Q. Did you believe you did so?

A. I thought so.

Q. Okay. Did you understand that it was important for you to conduct an independent scientific analysis of the safety data?

A. Yes.

Q. Do you believe you did so?

A. Yes.

Q. Do you understand that other people within FDA would

evaluate and assess your critique and analysis of the safety data with respect to Paxil?
A. I knew that it would be reviewed. Knew that my review would be reviewed.
09:44:53 Q. During the course of your safety review, if you had questions of SmithKline Beecham did you feel comfortable in terms of asking SmithKline Beecham for additional data?
A. Yes.
Q. And did you believe that SmithKline Beecham was cooperative
09:45:06 with you in providing you with that data?
A. I thought they were cooperative.
MR. DAVIS: Page 328, beginning at Line 22.
BY MR. DAVIS:
Q. (Reeding:)
09:45:17 "... as the -- I believe you told us that there were others within FDA who evaluated labeling issues.
A. Yes."
MR. DAVIS: Page 335, Line 6 through 10.
BY MR. DAVIS:
09:45:25 Q. (Reading:)
"... okay, sir, you're familiar with prescribing information or package inserts that accompany prescription medications approved by FDA for marketing in the United States?
A. Yes.
09:45:38 Q. Is it your understanding that FDA considers all the

information and the package insert or prescribing information important information regardless of where it's located?
A. Yes.
Q. Should healthcare providers ignore information that's in the package insert -- package insert just because upon where it is located?
A. No."

MR. DAVIS: Page 344, beginning with Line 16.

BY MR. DAVIS:

Q. (Reading).

"... Mr. Farber asked you some questions about the relatedness determination that sometimes clinical investigators make during the course of clinical trials, do you remember that discussion?"

MR. BAUM: Ah --

THE COURT: What's in the transcript?

MR. BAUM: I think you skipped.

MR. DAVIS: What page is that?

MR. BAUM: 344 starts at Line 1.

MR. DAVIS: May I see it?

(Brief pause).

MR. DAVIS: I think we had a mix-up.

MR. BAUM: Okay.

MR. DAVIS: If you turn to page 344, Line 16.

MR. BAUM: Yes.

BY MR. DAVIS:
Q. (Reading:)
"... Mr. Farber asked you some questions about the relatedness determination that sometimes clinical investigators
09:47:26 make during the course of clinical trials, do you remember that discussion?
A. Yes.
Q. Is that determination dispositive in terms of cause and effect between a symptom or an event in a drug that's being
09:47:36 studied?
A. That determination does not prove that an event is causally linked to the drug."
MR. DAVIS: Thank you, Your Honor.
THE COURT: All right. Call your witness, please.
09:47:48 MR. WISNER: Yes, Your Honor. At this time we call Dr. David Ross to the stand.
May I approach, Your Honor? I have a binder for you.
THE COURT: All right.
(Binder tendered to the Court.)
09:48:34 MR. WISNER: He's on his way, Your Honor. Unfortunately, we're in the witness room all the way at the end of the building. So it would take a minute for the witness to get over here. So he's walking.
(Brief pause).
09:50:39 THE COURT: All right, Doctor, step up here, please.

THE WITNESS: Yes, Your Honor.
(Brief pause).
THE COURT: Please raise your right hand.
(Witness duly sworn.)
09:50:52 THE COURT: You may take the witness stand.
THE WITNESS: Thank you.
THE COURT: Do you have water for the doctor? For the witness?
MR. WISNER: I believe there's a pitcher up there.
09:51:02 THE WITNESS: Yes.
MR. WISNER: It has water in it.
THE COURT: All right. You may proceed, sir.
MR. WISNER: Thank you, Your Honor.

DAVID ROSS, PLAINTIFF'S WITNESS, SWORN

DIRECT EXAMINATION

09:51:06 BY MR. WISNER:
Q. Good morning.
A. Good morning.
Q. Could you please introduce yourself to the jury.
09:51:17 A. Good morning. I'm Dr. David Ross.
Q. Dr. Ross, before we get going I want to be clear. Are you the same David Ross known as Grandpa Ross on the Cubbies?
A. Well, I was a catcher in little league, unfortunately no.
Q. All right. You said you're a doctor. Are you a medical
09:51:42 doctor?

A. I am.
Q. What sort of medical doctor are you?
A. Hopefully a good one. I am an infectious disease physician and a general internist.
09:51:50 Q. And where do you practice medicine?
A. I have clinical privileges at the Washington, D.C. Veteran Affairs Medical Center.
THE COURT: Read his qualifications to the jury, sir.
MR. WISNER: Sure, Your Honor.
09:52:07 THE COURT: It'll save some time.
BY MR. WISER:
Q. Dr. David Ross is the director of Public Health Pathogens Programs with the United States Department of Veteran Affairs and has held this position since 2006.
09:52:23 In his capacity, Dr. Ross supervises the VA's National Human Immune Deficiency Virus Program and the national Virus Hepatitis Program. Additionally, Dr. Ross is frequently called upon to provide guidance of policy programs and products related to the treatment of patients within the VA.
09:52:38 Prior to joining the VA Dr. Ross worked for the FDA for ten years. He served in various capacities as an associate director for regulatory science, deputy director, senior medical reviewer, and medical officer during a ten-year tenure.
At the FDA Dr. Ross was possible for reviewing New
09:52:59 Drug Applications, biological licensing applications, and

investigational new drug applications for many pharmaceutical products across a broad range of therapeutic applications.

Dr. Ross also examined the safety of proposed clinical trials, provided scientific comments, reviewed safety and
09:53:19 efficacy data, and made specific recommendations about ap provability of an application and a sponsor's proposed labeling.

As part of this work, Dr. Ross was also tasked with reviewing postmarketing data for already approved drugs to make
09:53:34 recommendations about regulatory action, including labeling changes. His work included preparing and delivering presentations and briefing packages to FDA advisory committees.

He has completed numerous FDA sponsored regulatory training courses which were specifically designed to teach the
09:53:52 methods and procedures of the FDA review process.

And in his later years at the FDA he actually helped cultivate and develop specific policies about the proper scientific procedures to be used at the FDA.

Dr. Ross has lectured, written, and presented
09:54:07 extensively regarding the approval of new drugs, regulatory issues related to safety, clinical trials, risk-benefit analysis, and has specifically testified before Congress on these important issues.

Dr. Ross is a board certified internist, having been
09:54:24 certified in internal medicine by the New York State Board for

medicine, the State of Connecticut Department of Health Services, and the State of Maryland Board of Physician Quality assurance.

Dr. Ross is also a diplomate of the National Board of Medical Examiners and the American Board of Internal Medicine. He's also currently licensed -- he's currently licensed in infectious diseases by the State of Maryland.

Dr. Ross maintains a clinical practice and has done so since graduating from medical school. Currently in addition to his work as a senior director at the VA, Dr. Ross works as a staff physician in Washington, D.C., at the Veteran Affairs Medical Center where he treats veterans for a variety of conditions.

Dr. Ross graduated cum laude from Yale University with a Bachelor of Science in molecular biophysics and biochemistry. He then attended New York University where Dr. Ross received a Masters of Science and then a Ph.D. in biochemistry. During that same time, Dr. Ross attended and graduated from New York University School of Medicine and subsequently completed his residency at New York University Medical Center.

Following his residency, Dr. Ross participated in a research fellowship at Yale University School of Medicine where he operated as an instructor of medicine at the medical school.

Although he previously served as an instructor at Yale University, he currently is also an associate clinical

professor of medicine at George Washington University School of Medicine and health services.

Finally, in 2012 Dr. Ross obtained an additional master's degree, this one in biomedical informatics from Oregon 09:56:07 Health & Science University as part of Dr. Ross's continuing educational efforts. He has written articles in various procedures and medical journals, such as the New England Journal of Medicine and the Lancet.

THE COURT: All right. You may proceed.

09:56:20 MR. WISNER: Thank you, Your Honor.

BY MR. WISNER:

Q. All right, Doctor, before we get into your opinions that you offered for your case today, I'd like to go over a few things first.

09:56:39 I read to the jury that you worked at the FDA. Can you please explain to the jury the work that you did at the FDA, where you started and where you ended up.

A. Sure. So just to provide a little bit of background. I think everybody has heard about the FDA. It's a federal agency 09:56:58 that's part of Health and Human Services. It's been around for over 100 years. And it regulates products that involve about a quarter of the nation's economy.

So if you brush your teeth this morning with toothpaste, the FDA had a role in that to toothpaste. And if 09:57:19 you had something from Starbucks, Dunkin' Doughnuts, FDA has a

role in that. So the FDA is broken into centers that -- and this is all going to sound maybe a little bureaucratic but it's ultimately about people trying to figure out do drugs work and do they do more good than harm, that's really what it's all about when you get past all the jargon.

09:57:46

So to answer your question, I started out at the center that handles drugs as opposed to -- and you say, well what else is there? Well, there's vaccines, there's animal drugs, there's devices like artificial joints. And I started out in the division that handles antibiotics. And that had to do with my clinical training, but I've certainly worked in a lot of other issues.

09:58:06

And I started out as a medical reviewer. And as the medical reviewer you are part of a team that includes clinical pharmacists, microbiologists, and the like. Doctors always think they're more important than anybody else, but they do designate, it's not always true, but you are designated sort of the first among equals, because it's ultimately about patients. Is this drug -- drugs are meant to do one of two things, make people live longer, make them live better. If a drug can't do that, forget about it.

09:58:26

09:58:49

And some --

Q. Doctor, let's break this up.

A. Sure.

Q. So you started off as a medical reviewer.

09:59:00

A. Yes.
Q. Did you get elevated at any point at the FDA?
A. I did. After 4 years I became a senior medical reviewer and a medical team leader.
09:59:12 Q. Okay. And then after you became a medical team leader, what next?
A. So in 2004 I became deputy office director for the office that handled what are called therapeutic biologics, which are complex drugs, I guess I'll say, but they're really called
09:59:31 biologics that are things that are used to treat diseases like cancer, rheumatoid arthritis, and the like.
Q. And after that did you get elevator even further?
A. I moved over to the office of oncology drug products and I became their associate director of regulatory science.
09:59:49 Q. And in that capacity, what were you overseeing?
A. So at the level of medical team leader, I was overseeing primary reviewers and coordinating with other team leaders: Statistics, chemistry, that sort of thing.

As deputy office director for biologics I was
10:00:12 overseeing division directors, not only primary reviewers and team leaders but also division directors. So there was a team of well over 100 scientists there and I was overseeing. And by overseeing, I mean looking at their analyses and conclusions and saying do I agree.

10:00:30 And then in oncology and cancer drugs, I was doing

that, as well as helping devise policy on regulations involving -- not just cancer drugs but also hematology drugs, drugs involved in x-rays, that sort of thing.

Q. Now, you said you worked in different divisions while you were at the FDA. Are the standards, the scientific standards used by FDA the same across divisions?

10:00:52

A. Yes.

Q. And why is that?

A. So the law that FDA enforces, basically, is called the Food, Drug and Cosmetic Act. And basically it says you have to show--and by "you " I mean a drug's manufacturer--you to show that the drugs works for what you say it can do.

10:01:08

The problem as -- let me just give a little bit of background. Most drugs that get tested end up not working. And that's not anybody's fault per se. It's just, you look at cancer drugs, only about 10 percent actually get approved, and that is usually because they might look good in the initial studies, but then they don't work.

10:01:34

The FDA a couple months ago gave 22 case studies of drugs that looked good early in development and then turned out either not to work, not be safe, or both.

10:01:56

So the law says, and I'll spare everyone the legal language, but you have to show that it's safe and you have to show that it's effective for its intended use, that's number one.

10:02:14

Number two, you have to give what are called adequate directions for use. And by "you" again I mean the manufacturer. You have to say what the drug is used for, at what dose, what the side effects are, what patients shouldn't get it, which patients you could use it if you think the risks are worth it, but you got to say what those risks are.

10:02:33

Q. And while you were at the FDA, did you work specifically on psychiatric drugs?

A. Some of the drugs that I worked on had significant psychiatric side effects that were important in the labeling, but not directly on drugs intended to treat psychiatric and mental health conditions.

10:02:55

Q. And the scientific procedures that were used within the division within the FDA that focused on scientific drugs, are those the same basic scientific principles that you used in your other divisions?

10:03:15

A. Yes. And it's a little bit like if you go to a cardiologist or an infectious disease specialist, they're both going to use a stethoscope to listen to your heart. It's not like you use different methods depending on what specialty you're in.

10:03:27

Q. And as part of your investigation in this case, have you looked at the regulatory interactions between GSK and FDA as it relates to Paxil?

A. I have.

10:03:44

Q. And have you assessed whether or not you believe GSK properly met its regulatory requirements?
A. I have assessed that.
Q. And in doing that assessment, did you use the same principles and methods that people in your field regularly rely upon?
A. By "the field," basically I still have trouble -- I sometimes will say, "well, FDA, here's what we do," and it's a little bit hard for me even though it's been 10 years to remember, well, I'm not there anymore, because I still think of myself that way, but using the same kind of procedures that FDA reviewers would use.
Q. And the opinions that you came to in this case, did you arrive at those opinions with a reasonable degree of scientific certainty?
A. I did.
Q. I understand prior to taking the stand today you actually sat down and wrote out all of your opinions, you summarized them?
A. That is true.
Q. Would you please turn to Exhibit 44 in your binder. Plaintiff's Exhibit 44.
A. You know I realize I do not have my binder. And I apologize to the Court for that.
Q. It is right here (indicating).

MR. WISNER: May I approach, Your Honor?

THE COURT: Yes.

(Binder tendered to the witness).

MR. BAYMAN: I object, Your Honor. If we could have a sidebar?

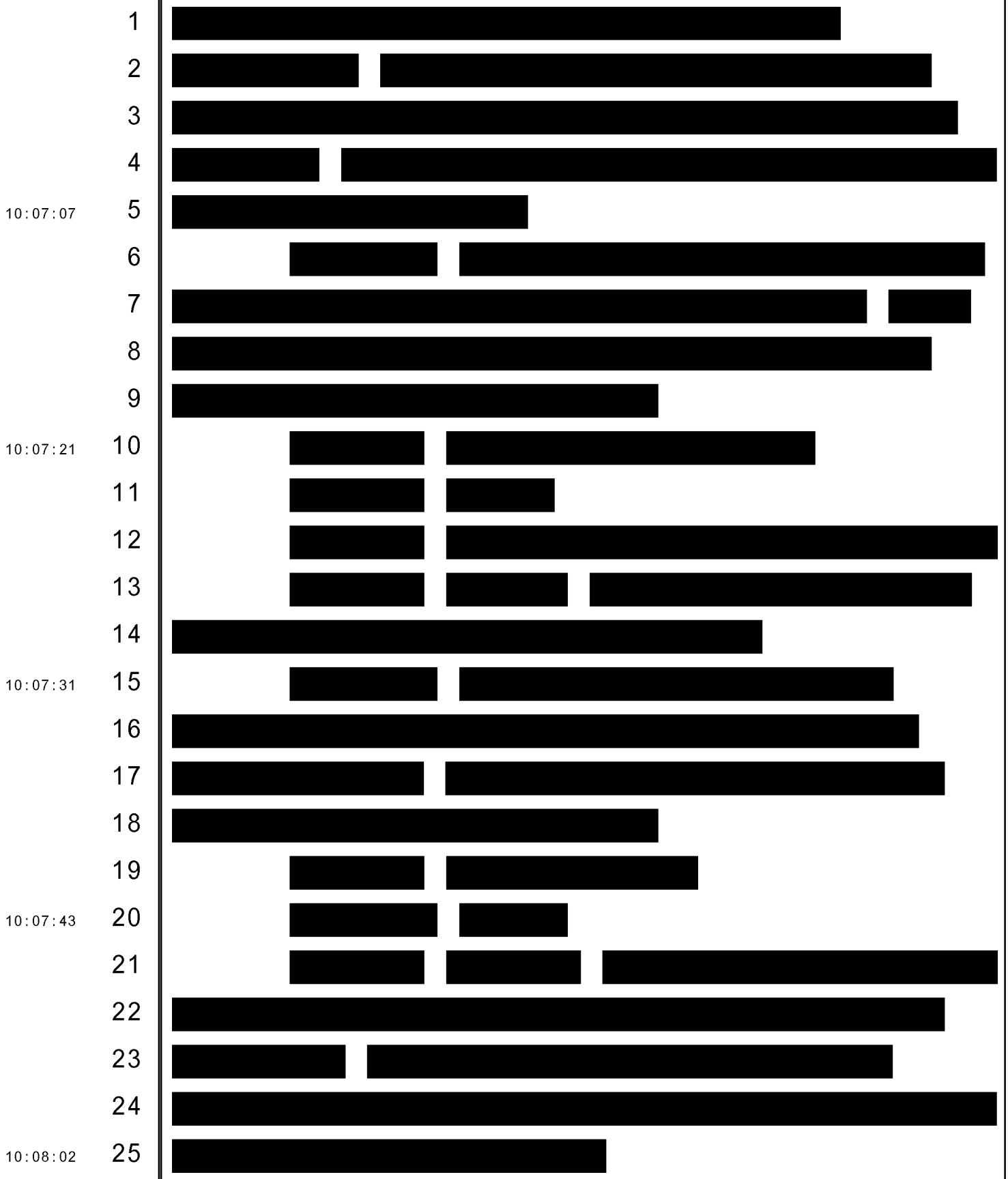
THE COURT: Okay. Does it to have to do with this document?

MR. BAYMAN: Yes, sir.

THE COURT: Okay.

(Proceedings heard at sidebar on the record.)

[redacted]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(Proceedings resumed within the hearing of the jury).

MR. WISNER: Can you hear me now?

THE COURT REPORTER: Yes.

BY MR. WISER:

Q. Dr. Ross, what is Plaintiff's Exhibit 44?

A. So I'm going to take this out of the binder.

So this is a summary of my opinions based on the data that I've reviewed.

Q. Okay. Great. Is this a fair and accurate summary of your opinions?

A. Yes, it is.

Q. And did you prepare, actually write these things out in these sentences?
A. I did.
Q. All right.
10:09:35 MR. WISNER: Permission to publish, Your Honor?
THE COURT: All right. You may proceed.
(Exhibit published to the jury.)
BY MR. WISNER:
Q. All right, Doctor, we have in front of the jury Exhibit 44.
10:09:48 What I want you to do is I want you to just read to the jury these various points and then we're going to discuss what they mean briefly; okay?
A. Okay.
Q. So first, Paxil is associated with an increased risk of
10:10:04 suicidal behavior in adults older than 24. In other words, they're more likely to have suicidal behavior on Paxil than individuals who are not.
Second, GlaxoSmithKline was not upfront about Paxil suicidal behavior risk.
10:10:25 Third, in 2010 GlaxoSmithKline had the ultimate responsibility as any drug manufacturer does for its product for the Paxil label. They're responsible for making sure that hit meets the regulation involving the drug label, and those are that they were responsible for ensuring that the Paxil
10:10:55 label did not contain any false, misleading or inaccurate

information about safety.

Fourth, federal regulations required, and this is true from the time the drug's approval onwards, that GSK had to warn physicians, doctors, about adult suicidal behavior induced by Paxil.

10:11:25

GSK could have warned doctors by changing the Paxil label. There is no evidence, let me say that again, there is no evidence that FDA would have stopped GSK from issuing Paxil specific warning in sections of the label outside of the class labeling. And, in fact, FDA specifically invited GlaxoSmithKline to come in and discuss such changes but GlaxoSmithKline never did.

10:11:53

Lastly, GSK did not warn doctors of the true risk of Paxil-induced suicidal behavior in adults older than 24.

Q. Thank you, Doctor.

10:12:25

Now, we're going to explore the basis for these various opinions you put here on this chart, but here's how I would like to organize your testimony. I want to organize it into three general categories.

First, I want to talk about the FDA, FDA regulations, the way drug makers generally interact with the FDA and how labels are created.

10:12:39

Then I want to talk to you about the chronology of GSK's interactions with the FDA and whether or not, in your expert opinion, those interactions complied with governing

10:12:59

federal regulations.

And, finally, I want to explore, separately from the FDA, how your work in this case has influenced the way that you, as a general practitioner of medicine, use Paxil.

10:13:17 So let's start off at the beginning part. Let's talk about the FDA.

A. I'd love to.

Q. If you want to move the microphone closer to you so you don't have to lean over, you're going to get a back spasm.

10:13:33 A. The reporter -- I assume she will let me know if I'm a little too close, but yes.

Q. We're never too loud. I promise.

A. Okay.

Q. All right. So let's talk about the FDA. When was the FDA

10:13:45 created?

A. So the FDA actually in a way started here in Chicago, and I'll explain what that means. And I'm going to be succinct, I don't want to lecture people. If I do, someone please pick up a blunt object and throw it at me.

10:14:03 (Laughter in the courtroom.)

BY THE WITNESS:

A. So I said before, most drugs don't work, there's a few that do, but most drugs don't work or you find out that they do more harm than good.

10:14:17 And just to give you an illustration, there was a

belief back in the 19th century that tomatoes were poisonous, the reason was that they were related to deadly night shade and other plants in the Belladona family. And in the early 1800's someone actually amazed -- and a lot of this is true, and after
10:14:44 all this is over you can look it up on Wikipedia, he ate a bushel of tomatoes on a courthouse stand and he lived. And everyone was like, oh, my God, they're not poisonous. But people still thought they were very potent and they taking an extract of tomatoes and use it along with a Chinese sauce as a
10:15:06 patent medicine, something that they thought would help cure disease. And believe it or not, this patent medicine is something that is still used and it's called ketchup, or miraculously, tomato ketchup; that's true. You know, right now we just kind of preserved it. We don't use it as medicine,
10:15:27 it's good on stuff like pancakes.

So this went on for a while. And then finally at the early turn of the 20th century, it came more and more clear that the situation was getting out of control. And it really culminated with a publication of a novel set here in Chicago
10:15:48 called the Jungle by a novelist called Upton Sinclair. And he was talking about what would happen in a sausage patent place. And he talked about how they would just shovel in anything. You know, just to get it in there. So talk about roaches, rats, dirt, said sometimes someone would fall into the baths
10:16:16 and become part of the sausage.

This did not go over very well with the public and there as an outcry. And Congress in 1906 passed what's called the Pure Food and Drug Act.

Q. What did that act required of manufacturers?

10:16:28 A. It said you have to say what's in your product. People have to know what they're putting into their bodies.

Q. So we're talking about a list of ingredients?

A. Exactly.

Q. And you said Food and Drug Act, did this apply to both food

10:16:43 and drugs?

A. It did.

Q. All right. So then that's 1906. At what point did the FDA's role sort of expand beyond recurring that people list their ingredients?

10:16:56 A. Well, so it was -- I'm just going to mention a couple of things that why do we have it. I mean, did it just land from another planet? No.

So the law said -- it didn't have to say that the drug was safe. There was kind of a very weak statement that you

10:17:16 couldn't say something about what it did that was false, but it wasn't really something that anybody can enforce. It's very hard to prove that somebody knows that they're doing something that's false with regard to something like that unless you got the details to back it up.

10:17:33 So it was when it started getting out of control

again. And the best example I can think of is a drug called Radafore sold in the late '20s and contained -- it was accurately labeled, according to the law, contained radium, which as you probably know is an incredibly radioactive substance and 1 millimeter of water. It was like the Viagra of the roaring '20s. And there was a very wealthy businessman who would consume it because he really thought it was going to bring him good health.

10:17:54

And the Wall Street Journal summarized the results back in an article in the '30s and they said the radioactive water worked fine until his jaw fell off. They actually exhumed -- and he died from bone cancer and radiation poisoning. And they exhumed his body some 3 or 4 decades later and it was still radioactive. But under the law at that time, that was completely legal.

10:18:14

10:18:33

So the last straw happened in 1937. A company called S. E. Massengill wanted to market a new antibiotic called Sulfanilamide, which is still in use today, but they wanted to not sell it as tablet or pill, they wanted to sell it as a syrup that children can drink.

10:19:02

And so the president of the company went to his chemist and said turn this -- put this into a drug that children can swallow. So the chemist thought about it and he took an compound called Divinyl glycol and he added some raspberry flavoring and it went on sale in these gallon jugs.

10:19:21

And Divinyl glycol is actually a great choice. It's a great solvent, it's cheap, it's chemically stable, and it's sweet so children will drink it. The only problem is that it's about one step chemically, away, from Divinyl glycol is one
10:19:41 step away from antifreeze. It's incredibly poisonous to the kidneys.

So this went on sale. And over 100 people died, most of whom were children. And the FDA actually could not get it off the market even though it was clearly unsafe. The only way
10:19:58 they were finally able to get it off the market was the fact that it was labeled as an elixer, which means that there's some alcohol in it. And the FDA was able to say, okay, that's not accurate, you haven't correctly labeled it, we're going to pull it off the marketing. But that's the only thing -- it was a
10:20:19 little bit like, and I don't know if this has ever happened, for example, in Chicago, someone who is a gangster in a murder and you get him out of there because he hasn't filed tax returns.

So at any rate, there was a huge outcry. And in 1938
10:20:29 Congress replaced the Pure Food and Drug Act with what's called the Food, Drug and Cosmetic Act. And that said, for the first time, you have to show that your drug is safe before you can sell it, and you have to show it to the FDA. You can't just wait for someone to cash up to you and say, oh, it's not safe
10:20:57 and here's why. The manufacturer of the drug has to show that

it's safe, not the FDA has to show it's dangerous.

Q. All right. So let's jump ahead in time. It's 1938, they have to show that it's safe. When did the issue of efficacy emerge?

10:21:22 A. So that came in some years later.

And, by the way, one of the things I want to mention because it's really important is, that the company -- well, going back, the president of the company said, you know, hey, we're selling a legal product, we've complied with the law, you

10:21:36 know, this isn't -- this isn't my fault. The chemist who devised it felt a little differently, and there's tragedy, he felt so guilty about it that he killed himself.

So going to efficacy saying that a drug works, again remember, drugs when they've tested generally don't work. Just

10:21:56 because somebody says it does, doesn't mean that it does. And people oftentimes say, well, a person got better on a drug. Well, if I got a cold and I give somebody penicillin and they get better, did the penicillin cure them? No, penicillin doesn't work against cold viruses. But a lot of times that's

10:22:15 what people would say.

So there was another tragedy -- and historically, there's been tragedies that have driven reform. A company in Germany, in Europe, manufactured a drug called thalidomide and they sold it as a tranquilizer for women who were pregnant.

10:22:40 And the problem was, they actually had never tested it

in pregnant women not only to see whether it was safe, but did it work. They did a test in a couple of animal species, but not the right species and not the right kind of test.

Now, they tried to market it and the FDA -- when I say
10:23:06 market, I mean sell it to pharmacists who can then sell it to people and write scrips for it.

So the reviewer at the FDA, a woman named Francis Kelsey, who had earlier been involved in tracking down these elixir of Sulfanilamide containers and trying to get them off
10:23:26 the market, looked at the information and she said, I feel really, really uncomfortable about this, I do not think this drug has been shown to be safe. I've got concerns about the side effects.

And remember, it's not just, you know, does it have
10:23:39 side effects. I prescribe a lot of drugs that have serious side effects, the question is are they included in the label.

And by "the label," by the way, I just want to be clear, everyone has seen, you know, when you get a prescription you get this thing that's in teeny tiny print. You need a
10:23:58 magnifying glass sometimes to see it. That's what I mean by the label. It has all the technical information about the drug.

So anyway, she said, I'm not going to approve this application. And she came under tremendous pressure to just
10:24:18 approve it. The company that submitted the application hired

private detectives to follow her around in trying to get dirt on her. Her superiors at the FDA at that time threatened her and tried to intimidate her and get her to approve it.

Then information started coming out from Europe that a lot of the women who had taken thalidomide when they're pregnant gave birth to children with horrible birth defects. They had a defect called phocomelia or psyllium in which they would not have arms, or sometimes legs, or sometimes both. They just have these kind of like little stubs or flippers like a zeal. And there were tens of thousands of victims.

So at this point people said, whoa, Dr. Kelsey was right. And it finally dawned on people: Listen, there's no such thing as a drug that is absolutely safe.

The drug has to do something useful to justify whatever risks are associated with it. So we have to know what kind of side effects it might cause in the people who are going to get it, and as importantly, we have to know that it does something worthwhile.

So in 1962 Congress changed the law to say the manufacturer not only have to give the FDA data saying that the drug is safe, but also that it does what the manufacturer says it does. And not just say well, we'll certify it, but actually give the data from clinical trials showing that the drug works.

Q. Is that when clinical trials entered the picture when it

came to drug applications?
A. Yes; pretty much.
Q. Okay. We've heard a lot about clinical trials. We're not going to spend too much time on that here, Doctor.
10:26:13 A. Okay.
Q. Just want to focus on FDA.
A. Sure.
Q. All right. The FDA today, how big is the organization?
A. So the FDA is headquartered in -- actually the main office
10:26:31 is in Silver Spring Maryland, although the technical headquarters is in D.C. It's as I said earlier, a federal agency. It's got about 16,000 employees, the majority of whom are in D.C. but there's actually FDA staff all over the country, and these are people who do things like inspections of
10:26:55 clinical trial sites and manufacturing facilities.
Q. Now, these 16,000 employees, do they all work on prescription drugs?
A. No.
Q. What's the percentage of them that work on prescription
10:27:07 drugs?
A. Roughly -- well, actually I was going to say roughly a quarter, but it's actually somewhat less than that because the center that handles drugs, and the abbreviation that I'll use sometimes is CDER, C-D-E-R, handles not just prescription
10:27:31 drugs, or innovator drugs, but it also handles over-the-counter

drugs.

So if you -- to give an example, if you give a Zantac, if anybody has seen that on the shelf, when I was in training that was actually a prescription medicine. And the FDA said, after a point, the manufacturer came and said is this something you think the risk risks the benefits as such that we could sell it directly to consumers. And the FDA looked at the data and eventually said yes. So it's a quarter handling drugs and the number of handling prescription of drugs is actually lower.

10:27:52

10:28:12

Q. And within that -- I mean, we're talking about 3-, 4,000 employees, Doctor. Has it grown since the '80s and '90s?

A. Not substantially. You actually contract those because the FDA will plug, you know, how many employees it has, they also put up how many applications it's reviewed, and so and so forth. So it's gone up, but not in proportion of the workload.

10:28:35

Q. So for these few thousand people who work on prescription drugs, how many prescription drugs are out there that they're having to oversee and regulate?

A. You know, I have to tell you, I was asked that question once from a friend of mine who is still at the FDA. And this is a long time ago. There's this book called the orange book, and it's called that because it's got this orange cover and it basically lists every drug on the market. And I said how many drugs are in there. And she laughed and said, you know, it's really a little bit hard to tell, I don't know how to figure

10:28:50

10:29:12

out that number. Now, of course, somebody knows it, and the FDA knows it, and it's probably at this point somewhere 16-, 17,000 roughly.

Q. So these few thousand employees have to regulate 16- to 10:29:27 17,000 drugs that are on the market?

A. Well, that's one of the things that they do.

Q. What else do they have to do?

A. So they review applications for drugs and these are called New Drug Applications or NDA's. And if you say, well how many 10:29:47 of those are. There's a lot of work. You know, I'm not talking about that right now, but they did about 175 NDA's last year, that one center. That's just new drugs, drugs that have never been on the market before.

Drugs that are on the market when a manufacturer comes 10:30:07 in and says, well, we want to get approved for use in some other disease, or some other group of people, or we want to add some information of the label, there were over 2500 applications like that. That's in addition to thousands of what are called investigational new drug applications where 10:30:34 somewhere is not asking for approval, but also just try testing the drug.

Q. So if there's 16-, 17,000 prescription drugs that are on the market, how many IND's or investigational of drug applications did the FDA have to run through before we got to 10:30:54 that number?

A. Hundreds of thousands. And remember, these -- most of these IND's end up not for drugs that don't work, but each of these -- well, when you say "what does that mean, they reviewed them," that is huge amount of work.

10:31:12 So somebody comes out -- let's talk really quickly about this with an IND, the drug has never been tried in humans before. The FDA has to say is it reasonably safe to try this drug in humans. And sometimes, you know, it doesn't happen often, but a drug gets tested in humans for the first time and

10:31:29 people die. It doesn't happen often.

The FDA reviewer, because it comes down to a person sitting at a desk has to say, is this drug look safe based on the data. And then if it isn't, they -- they don't think it is. And reviewers take this very seriously, they don't want to

10:31:49 hold up new drugs, but they also don't want someone to die, they'll say you got to bring in more data. So you're talking about every year thousands of new IND's. So that's another thing that reviewers have to contend with.

Q. Now, let's get into these type of applications for a

10:32:06 minute.

A. Sure.

Q. You mentioned an NDA or New Drug Application. You were back in the FDA in the '90s, right?

A. Yes.

10:32:14 Q. Well, were things electronic when you started?

A. Well, we had telephones.
Q. Okay. Give the jury a sense of how much volume of paperwork goes into a New Drug Application for a brand-spanking new drug?
10:32:32 A. Okay. Well, let me start with something that was a brand-spanking new drug, just imagine from there. So the very first application I started with at FDA was a drug that was already in the market and which the FDA -- that manufacturer said we want approval to use this drug in people with cancer
10:32:57 who've got damaged immune systems and who have infections. So that application was over 100 volumes, each of which was about the size of the Chicago telephone book.
Q. So that's what's called a supplemental --
A. That's called a supplement. The original -- and I
10:33:17 sometimes would have to go down to document room to look at various, not a lot, but various aspects of the original NDA, was probably over a thousand volumes.
Q. Okay. So we're talking about NDA's that have all this paperwork, SNDA's. How much paperwork is involved in an
10:33:37 investigational New Drug Application?
A. Well, again, people would come in with -- so the information in that is going to include what is the drug, what's in it. I mean, does it have something -- you can never manufacture a drug that's a hundred percent pure. Does it have
10:33:54 impurities in it, in other words, things that shouldn't be

there. If so, is it a level that's going to cause a problem. What is the data from animals, because these drugs, like it or not, are always tested on animals. What happens to the animals, do they have seizures, do their livers fall out, that sort of thing.

10:34:15

What are they proposing to do. Does it make sense. If somebody says, well, I'm going to test this antibiotic in patients for infection and you look at the information and you say, wait a minute, if you're testing penicillin against a cold vires, that makes no sense, you're exposing patients to risk. Penicillin is a really safe drug, but a few hundred people a year die from allergic reactions.

10:34:27

What dose are you proposing to start at? How are you going to watch these people? What happens if they get into trouble? There's some companies, a lot of companies will do this, when they're first testing a drug they will admit patients to a hospital. And that's not -- it depends on the drug, but that is not overkill, in some instances.

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So you're talking about, you know, not that hundred -- you know, a hundred or thousand volumes, but you're talking about maybe ten or twenty, you've thirty days to review that. If you don't get it, the company can say, well, you didn't say anything, I can go ahead.

10:34:59

Q. So let's be clear, as a medical reviewer who is on the front lines reviewing all this information, how many NDA's

10:35:14

SNDA's an IND's are you responsible for at any given time?
A. So I should explain. The NDA refers both to the original application. It's almost like ever- expanding file. So when people talk about a company owning an NDA, or a reviewer
10:35:40 overseeing an NDA, they mean everything that's going on with the NDA, what's happened in the past and also what's happening in the future.

So, you know, like safety reports. So, for example, last year, CDER received over 1 and a half million safety
10:35:57 reports on drugs, one and a half million. And the division that handles those safety reports is only a small portion of CDER, so there's relatively few employees.

So you've got at any given time, what I had as a primary reviewer, maybe 30 NDA's and each of the NDA's has
10:36:22 regular submissions. So there's going to be an annual report, there's going to be periodic safety update reports, there's going to be information about adverse events, about side effects that come in.

And you're responsible for looking at all that and
10:36:35 saying everything is okay. I mean, if there's a death -- and this has happened, the safety information in the annual reports says, hey, there are these patients who are getting the drug, because once the drug is on the market doctors can do it for anything. They could use antibiotics for treating high blood
10:36:55 pressure, if they want.

And believe me, people, doctors, say, "well, that looks like it makes sense" even though it's not in there.

So if there's deaths because people are using it in a population where it has never been studied, you're responsible for looking at that report.

10:37:08

So maybe 30 NDA's, at any given time maybe about 10 IND's, and each of those has this continuing flow of information coming at it. And it's not casual reading. For example, we had a drug, it's called Ceftin, where a number of reports came in of women who had just given birth, they got Ceftin, they got cesarian sections, and this antibiotic was used just before the cesarian to protect against infection. And these were women in their 20's who some had blood counts drop dramatically. They developed a condition called homoallelic anemia where the drug actually destroyed the red blood cells. Basically an alert reaction.

10:37:37

10:37:59

I happened to have three of these across my desk in a short period of time. So I said, wow, it's unusual to have three of these events, but I happened to notice that. These were not bound up by the company together. They weren't -- there was no report from the company. I just -- it -- if another reviewer happened to be saying, well, I covered for David today and they saw it, I wouldn't have seen all those reports. Or if they come -- and these reports don't come in as soon as the company knows about it. It's the nature of the

10:38:21

10:38:39

beast.

Q. So considering the staggering amount of paperwork that you have to review at any given time as a medical reviewer, what sort of requirements or trust is put on the sponsor in

10:38:58 submitting the information?

A. Well, a lot. I mean, there's no way -- first off, the FDA itself does not do drug trials. We only know what we see from these reports. And, again, I just want to give you a better idea. I was unusual in this, my team leader when I first

10:39:22 started, after a couple of months, she was teasing me a little bit because I didn't just have volumes stacked up on my desk, they were on my bookshelves, they were on my floor. I had to create a path. And that's not unusual. So you have to rely on the company.

10:39:36 Now, it is a crime to intentionally make a false or misleading statement to the FDA, but you have to know that somebody is doing that in order for it to get enforced. So most of the stuff looks reasonable. If you look at it, if you're reviewing, let's say, a 1,000 page study report and

10:40:07 there's a line in there that says, "oh, by the way patients who got this drug were more likely to die than patients who didn't," and I have seen such clinical studies.

So what the manufacturer does when they submit an NDA is they submit a summary of the data. We don't get the

10:40:25 original data. We don't get the raw data. We get their

summary of it and we get a report that they write.

So I do not even -- and those reports are generally, like it's not unusual for them to be over 1,000 pages. And it's not that they're describing the clinical trial protocol, the patients, and so on. If that statement is buried somewhere, I might not actually see it or notice it or might not recognize what's going on, especially if the data are not presented in a clear way.

Now, if the company says up front, page 1, we want to call your the attention to this finding, that's another thing, but just because it's in the report does not mean that I'm going to find it. And they're actually -- again, I know everyone likes to think that the FDA has hundreds of thousands of people scouring at a given application; it doesn't.

Q. Now -- oh, sorry.

A. No, I was just going to say, I've seen applications where the FDA has said, you know, because we didn't think this was relevant, we did not review this particular report even though it came in.

Q. So considering all this work and the limited manpower at the FDA, after a drug has been approved and there are subsequent supplemental applications for approval for various differently conditions, does the FDA reviewer each time a new supplement is submitted review the entire case file from before?

A. No; that's ridiculous. I mean, there may be specific issues that you go back and look.

But just as an example, and I'm going to use Paxil as an example: So after the original approval it's been approved for a number of other indications, such as post-traumatic stress disorder or PTSD and actually I made -- you know, in at least one of these, the reviewer wrote explicitly, well, there was no -- there was no new clinical pharmacy what we call biopharmaceutics information submitted. So there was no review in that area. Now, when we went back and reviewed it, the old stuff, there was no review done at all. I -- unless there's a focused thing you're looking at, when you say, well, I want to see what happened with, let's say, penicillin and allergy in the previous application and join it up with this other one, but that's absolutely ridiculous. And anybody who says differently, I'd like them to show me an example of where the FDA reviewer in a supplement went back and documented that they re-reviewed the whole file. It's not just one reviewer, by the way, it's multiple reviewers. That is -- I'm sorry, I don't mean to be -- you can ask that. It's -- it's -- somebody who says that --

THE COURT: Slow down a little bit there.

THE WITNESS: I'm sorry, Your Honor. I'm sorry. I get a little passionate about this.

By the way, one of the things, I just want to make

sure people understand, I'm not complaining about this. I loved my time at the FDA. And there's people there who I still work with on scientific and clinical level. Some of them see patients at the same clinic I do. So I just want to be clear, 10:43:52 I'm not saying, oh, my God it was horrible. No, it was great, it was just a lot of work.

BY MR. WISNER:

Q. Now, you mentioned that you went back and you looked at one of the reviews for Paxil, is that right?

10:44:03 A. A couple of them actually, yes.

Q. I think you mentioned PTSD, is that right?

A. Yes.

Q. Is that because of the work you do for veterans?

A. Well, it was available, that's one thing. The one thing I 10:44:14 should explain is, the FDA actually posts reviews of its drugs on the web. It doesn't post all of them, but all of them are what's called flyable. You can request them under the Freedom of Information Act.

And so anytime there's an original application, the 10:44:34 reviews, medical statistical and so on, actually get put up on the web. I've gone back and looked at my own reviews which is at least interesting. But yes, I did look at them and also because I am interested in I take care of PTSD patients.

Q. And when you look at the PTSD application, for example, did 10:44:56 you see if they had any exclusion criteria for the clinical

trials?
A. I did.
Q. And I think you mentioned this, what did you notice?
A. Well, when you study a drug you have -- you say who are you going to study and who you are not going to study. And that's actually tied directly to the law. The law says you have to have patients in the study who actually have the condition that you are interested in.
10:45:10
So it terms of who you're going to study with PTSD, you want to use some recognized standard for saying this patient has a diagnosis of PTSD.
10:45:30
Okay. You don't study other patients for a variety of reasons. Let's suppose somebody is allergic to the drug, that would be somebody you wouldn't bring in because it wouldn't be safe. So in this case, I was kind of shocked because they excluded --
10:45:45
MR. BAYMAN: Objection, Your Honor. We're getting into motive. This is far afield.
THE COURT: Yes, I'll sustain your objection.
10:45:59
Move on, sir. Bring us down to the issues.
MR. WISNER: Yes, Your Honor.
BY MR. WISNER:
Q. Let's move on to a different topic. The funding of the FDA.
10:46:08
A. Okay.

Q. Specifically CDER. Where does CDER's budget come from?
A. So this might be the proposed rather than the actual budget, but it's not far off, so CDER is this unit in the FDA that reviews drugs, makes decisions.
10:46:29 So its total budget is about $1.3 billion. And that money is partly from a taxpayer, but most of it is not. Most of it is privately funded by drug companies under what are called user fees. When I say "most," I mean there was in FY16, it was, like I said, about 1.3 billion, $800 million of that
10:46:57 came from pharmaceutical companies.
Q. Let me get this straight, Doctor, are you saying that the majority of the budget for the reviewers reviewing these drugs comes from the drug companies?
A. That's correct.
10:47:08 Q. Doesn't that create some conflict?
MR. BAYMAN: Objection; argumentative, Your Honor.
THE COURT: Sustained.
BY MR. WISER:
Q. Does that create any conflict?
10:47:17 A. Well, there's conflicts and then there's conflicts. So in the 1950's they were the head of the antibiotic division at FDA --
Q. Let's not get into that, Doctor. Answer my question.
A. Sure. Yes, I mean, there's been a lot written about not
10:47:33 whether individual reviewers are conflicted because the money

is going to the FDA, but if some of it is paying you to do a task -- and by the way, the trade-off for that is, the companies pay these fees and in return the FDA says, well, we're going to get the job done and at this point it's
10:47:58 10 months, it's an actual human tendency to want to please people. And that works for --

MR. BAYMAN: Objection, Your Honor. This is now argumentative and beyond the scope of his report.

THE COURT: Yeah, it's very interesting, but I think
10:48:15 we have to stay with the issues in the case.

MR. WISNER: Your Honor, I think this does apply because we're talking about the FDA's review of '89 submission and there's no explanation as to why Dr. Brecher missed all this stuff. And so I think he can provide an explanation as to
10:48:29 the relationship between drug companies and the FDA, that's where I'm going.

MR. BAYMAN: Your Honor, that's entirely speculative.

THE COURT: I'm going to sustain the objection.

MR. WISNER: Yes, Your Honor.

10:48:38 MR. BAYMAN: And I'd ask that his comments be struck, Your Honor.

THE COURT: That may go out.

BY MR. WISNER:

Q. All right, Doctor, putting aside the budget for CDER, is
10:48:48 there cross-pollination between the FDA and the drug

industries?
A. Of course.
Q. And by cross-pollination -- by cross-pollination what are we talking about?
10:49:00 A. Well, there's a couple of ways it happens. I mean, first off, there's -- you know, you interact with people from drug companies at meetings and the life the FDA has. And, you know, somebody would come they're an infectious diseases physician, I'm an infectious disease physician, and we would talk as
10:49:21 colleagues, you see people at meetings, scientific meetings I mean. And, you know, frankly, people will face a problem in terms of maintaining the staff at FDA, and people will say, well, I'm, you know, overworked and underpaid here, I've got all this expertise --
10:49:40 MR. BAYMAN: Objection, Your Honor. We're getting into propensity again.
THE COURT: I'm going to sustain the objection.
MR. WISNER: Okay.
THE COURT: Stay with the issues in the case.
10:49:49 MR. WISNER: Okay.
BY MR. WISNER:
Q. Are you aware if there's any cross-pollination between FDA and GSK?
MR. BAYMAN: I think it's the same topic, Your Honor,
10:50:00 that you just sustained.

THE COURT: Well, I think the jury has heard enough. The jury is hearing the case. The jury is going to learn about how things work. Stay with the issues.

MR. WISNER: Fair enough. Fair enough.

10:50:15 BY MR. WISNER:

Q. Let's move on to a different issue. Let's talk about labels. You mentioned briefly what a label is. Who writes the initial label for a drug?

A. So the application must contain a draft label. And, in

10:50:33 fact, the whole application is really just the scientific support for what the manufacturer wants to say in the label.

So you don't start to your a blind slate. The company comes in and says here is our proposed label and here is the data to back it up.

10:50:51 Q. In that process of proposing a label and having the data support it, is that an artifact of the origins of the Food and Drug and Cosmetic Act?

A. It's an interesting question. I would say -- so I think -- here's the thing, and this is, I think, completely

10:51:11 non-controversial: The manufacturer knows the most about their drug, and that's as it should be, as long as the important stuff gets to the FDA.

They know about studies, for example -- if they do a in another country and it's used in the application, they don't

10:51:33 necessarily have to submit it to the FDA in detail. So they're

going to know about it.

Now, I'm not saying that they're automatically hiding something, I'm just saying they know about it. They know about the exact details of the studies at a level of detail that the
10:51:50 FDA either isn't going to know or may not know it as intimately.

So yeah, the manufacturer starts out with that. So they start out with an initial proposal. And there's a reason that, you know, the FDA and the industry will talk about
10:52:09 labeling negotiations. It's not something that is simply dictated by the FDA to the companies.

One drug I worked on there was concern about interactions with foods and we had this long debate. This may sound ridiculous, but actually it's turned out to be important,
10:52:28 about whether we should include the list of foods, things like aged cheeses or pickles. And so, you know, the FDA might propose, well, let's put this, and the manufacturer says, well, our experience shows X, Y and Z.

Q. At the end of the day, is the label a static document?

10:52:52 A. Absolutely and totally not.

Q. What do you mean by static document?

A. Well, I assume you mean it's set in stone and it never changes; no. Let me give -- and this works in a number of ways, let me -- just indulge me.

10:53:08 So I mentioned thalidomide before. Thalidomide is

still on the market. It's certainly not used as a tranquilizer, but if you look at the label it is now used to a blood cancer called multiple myeloma. So the label has been updated to actually -- you know, obviously you don't give it to pregnant women with this disease, fortunately they're not likely to develop it, but sponsors are constantly, constantly, constantly submitting what are called supplements to the original NDA. And there may be dozens or sometimes even hundreds of supplements. These can be things like how do we manufacturer it, what uses are there for it, or what's going on with side effects.

Q. And as new information becomes available from the drug sponsor or the manufacturer, are they required to update the label to reflect that new information?

A. Yes.

Q. And if they don't update the label, who is responsible? Is it the FDA's responsibility?

A. So it is the manufacturer's. I mean it's a little bit like if I'm -- if I don't have my license plate on my car and a police officer doesn't pull me over, it's still my responsibility, or if I'm speeding and the police officer doesn't notice that I'm speeding, I'm still responsible.

Q. Is there a difference between responsibility and authority when we talk about federal regulations?

A. Well, I think first off, anybody who is in the workplace

certainly knows there's a big difference between having the authority and having the responsibility, unless you work for yourself. But yes, there is.

Q. What's that difference?

10:54:49 A. So the difference is that, and this is under the regs, this is not an issue of morality or ethics or something like that, where does the buck stop.

If the FDA doesn't notice something but the company knows about it, it is the company's -- and when I say "notice," 10:55:10 it can be like a piece of data -- let me give an example. The same drug where I happen to have a debate about the pickles was first drug approved new in about in 50 years and a lot of people were very anxious for it to be approved.

So the company in particular, they called us up one 10:55:35 day, and this was over the most important use for the drug for resistant bacteria, and they said, you know, the site that it's enrolled, the clinical trial site that's enrolled the largest number of patients for this particular infection, we have very serious concerns about how the investigator at that site, so 10:55:58 this some private physician, is running the trial. We wanted to let you know about it. We're stopping, shutting down his site, we're going to do the analysis, including the patients that he's enrolled who are also going to do it without.

Now, the chances that we would've found this out on 10:56:20 our own were pretty low, frankly, because there were hundreds

of sites in this study, many of which for other infections were enrolling other patients. But they did the right thing, they called -- and, you know, that could've -- this was particular infection, they didn't have a lot of cases. So it was important.

Q. So going back to the label --

A. Yeah.

Q. -- we're talking about the responsibility and the authority of the label. Can you please explain to the jury how that works.

A. Okay. So ultimately everything comes from the label. What physicians are told by the company, what advertising goes up. So that all has to be consistent with the label. And by consistent I mean, if somebody -- if the label says well such-and-such is good for -- a label only says it's good for this one infection and the company starts saying, no, no, it's good for all these other things too on its advertisements, that's illegal. So that's number one. Number two, physicians do depend on these labels.

Q. Doctor, doctor --

A. Yes. Sorry.

Q. Focus on my question.

A. I'm sorry.

Q. Okay. Who is responsible for the label and who has the authority over the label?

A. I'm sorry. I'm sorry. So it's the company that has responsibility for it. I'm sorry, I didn't --

THE COURT: All right. We're going to take a recess at this time, ladies and gentlemen.

10:57:43 THE WITNESS: Sure.

THE COURT: The jury may step into the jury room.

Mike, lead the jury out.

(The following proceedings were had out of the presence of the jury in open court:)

10:58:11 [redacted]

10:58:41 [redacted]

10:58:50 (Recess.)

(The following proceedings were had out of the presence of the jury in open court:)

[redacted]

11:19:12 [redacted]

[redacted]

(The following proceedings were had in the presence of the jury in open court:)

THE COURT: All right. Thank you very much, ladies and gentlemen. Please be seated. We will resume.

You may proceed, sir.

MR. WISNER: Thank you, Your Honor.

BY MR. WISNER:

Q. All right. Dr. Ross just before the break I was asking you about the label and labeling responsibility.

Who when it the comes to a drug label is responsible for the content and accuracy of the label?

A. The drug's manufacturer.

Q. Why is that?

A. They're the ones who study the drug. They're the ones putting it on the market.

Q. And is it because -- is there a difference of information available -- known about the drug between the FDA and the manufacturer?

A. Yes.

Q. What's that difference?

A. The company has the raw data. They know what analyses they've done, they know which ones they've submitted to the FDA

and which ones they haven't, and all of those things make them much more able and responsible for writing the label.

Q. Now, the drug label, because of new information, no longer is accurate or is discovered contains inaccurate information, is it the FDA's responsibility to change the label?

A. No.

Q. Whose responsibility is it?

A. The manufacturer's.

Q. You mentioned there's a distinction between responsibility and authority. Who has the authority to take the drug off the market.

A. The FDA.

Q. And what's the difference between authority and responsibility here? What's that distinction?

A. So the manufacturer -- the FDA is in charge of enforcing the law, but the manufacturer is the one, the entity that's responsibility for complying with the law. The FDA enforces that responsibility.

Q. So if the FDA doesn't take any enforcement action against a drug company, does that mean the drug company didn't do anything wrong?

A. No, it does not mean that.

Q. Why not?

A. Because under the law and regulations, the FDA -- sorry, the manufacturer remains responsible. If the example I used

before was, if I'm speeding and I don't get pulled over because somebody doesn't notice it or they're not paying attention and I get into an accident, it's not the highway patrolman who is responsible, I'm responsible.

11:22:52 Q. All right. So I want to look specifically at the regulations that relate to labeling. Are you familiar with those, Doctor?

A. I am.

Q. Did you review those a part of rendering your opinion here

11:23:09 today?

A. I did.

Q. Can you please turn to Plaintiff's Exhibit 45 in your binder.

(Brief pause).

11:23:16 BY MR. WISNER:

Q. And, Doctor, what is Plaintiff's Exhibit 45?

A. So this is part of the regulations that describe what must go into the label, what the manufacturer is responsible for putting in the label.

11:23:43 Q. And does this appear to be a fair and accurate copy of regulation 21C CFR Section 201.80?

A. It is.

Q. And would going through this regulation aid you in your testimony today?

A. Yes.

MR. WISNER: Permission to publish, Your Honor.

THE COURT: All right. You may proceed.

(Exhibit published to the jury.)

BY MR. WISNER:

11:24:20 Q. All right, Doctor, we're looking at here at 21 CFR Section 201.80. Let's start off with the title here:

"... specific requirements on content and format of labeling for human prescription drug in biological products; older drugs not described

11:24:33 in ..."

and there's a citation there.

What is this referring to?

A. So this refers to drugs older than, I believe, I don't remember the exact date off the top of my head, but drugs that

11:24:52 are using old format because they were approved so long ago. The new format came into existence in 2006.

Q. Why don't you try moving the microphone a little bit closer to you. I'm hearing a ringing noise.

Is that helping?

11:25:08 (Brief pause).

BY MR. WISNER:

Q. Okay. Great.

Okay. And what is the purpose of this section?

A. This provides the details on what manufacturers for these

11:25:22 older drugs have to put on the label in order to comply with

the regulations, the details in other words.
Q. All right. And the first thing here says:
"... each section heading listed in ..." and it lists, and it has a bunch of stuff "... shall contain the following information in the following order."
Do you see that?
A. Yes.
Q. And does this describe the various sections that go into a drug label?
A. Yes.
Q. And is this the regulation that applied -- is this the one that applied to Paxil?
A. Yes.
Q. Okay. I want to go into the section warnings.
This is one of the sections, of course, that you've reviewed before right, Doctor?
A. Yes.
Q. It says:
"... warnings: Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revise to do include a warning

as soon as there is reasonable evidence of an association of a serious hazard with the drugs, a causal relationship need not have been proved."

Do you see that?

A. Yes.

Q. All right. Let's break that down a little bit.

What is this warning section referring to?

A. Basically about side effects that could kill or seriously injure a patient taking the drug.

Q. And it says:

".. shall be revised to include a warning as soon as there is a reasonable evidence of an association."

What does that translate to as a responsibility for the drug manufacturer?

A. So as soon as they have, as soon as they have reasonable evidence that there's a link between the drug and the serious side effect, they need to revise the label.

Q. And who is this regulation directed at?

A. The manufacturer.

Q. And failure to comply with this regulation, is that a violation of the regulation?

A. Yes.

Q. So if a manufacturer knows about a risk and doesn't include that on the labeling, who is responsible for that?
A. The manufacturer.
Q. Okay. Great.
11:27:52 Are you also familiar with adverse reaction section of the labeling?
A. Yes.
Q. And what is that versus the warning section?
A. That is a listing of side effects; in other words, things
11:28:07 that -- side effects that occur with the drug but are not as serious as those that lead to a warning.
Q. Why is there a separate section for adverse reactions versus the warnings?
A. So common side effects are common. People get nauseous,
11:28:29 they get a headache when they take a drug, but it's not going to kill them. The warning section is tended to highlight things that you really, really want to know about. And when I say "you" I mean the physician or the patient wants to know about because there's a possibility that they could kill you.
11:28:50 Q. Now, it says here:

> "... the frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to
11:29:04 safe and effective use of the drug, shall be

expressed as provided under the adverse reactions section of the labeling."

Can you please explain to the jury what that means in English.

11:29:14 A. Sure. How often does it happen and how often does it kill people or seriously injure people.

Q. And are these listed with actual rates of occurrence in the label?

A. Yes.

11:29:24 Q. What does that mean, rates of occurrence, Doctor?

A. So if you have a drug that causes liver damage, as it happen once every 20,000 patients who get the drug, once every 2 million, or every time.

Q. And are you aware that there's a standard for frequency

11:29:47 describing them as frequent, infrequent, or what have you?

A. Yes.

Q. What level of risk or occurrence does it have to be for the FDA and for this regulation to require a frequent disclosure?

A. (No response.)

11:30:02 Q. Let me ask that question in another way that's not confusing.

A. Sure.

Q. What is the occurrence rate when it's frequent?

A. I believe, and I'm -- I need to look at the exact

11:30:17 definition, but I believe it's over 1 percent.

Q. So if there's a reaction that happens more than 1 percent, under the regs it's categorized as a frequent adverse reaction, is that right?
A. Yes.
11:30:29 Q. Okay. Great.
Now, one of the things that we've heard about is the authority of the FDA to enforce certain labels. Does the FDA have that authority?
A. Yes.
11:30:42 Q. When did that authority emerge, by the way?
A. Well, ultimately it goes back to 1906 when the initial labeling, but in its modern form 1938 and then again in 1962.
Q. What is the mechanism by which the FDA can enforce something the drug company is not listening to?
11:31:09 So let's say the drug is not properly labeled, what does the FDA have to do to get that drug off the market?
A. So, in general, it has to go to court and, in essence, sue the drug company to compel it to take the drug off the market.
Q. Are you familiar with a concept called misbranding?
11:31:33 A. I am.
Q. What does it mean for it to be misbranded?
A. It means that the label has -- the label is false or misleading.
Q. Are you familiar with that statute, Doctor?
11:31:50 A. Yes.

Q. All right. Please turn to Exhibit 47 in your binder.
(Brief pause).
BY MR. WISNER:
Q. Do you have it in front of you, Doctor?
11:32:02 A. Die.
Q. What is that exhibit, Plaintiff's Exhibit 47?
A. So this is the section of the law that defines what misbranding is in detail.
Q. And this is the statute that you've obviously reviewed in
11:32:15 rendering your opinions?
A. Yes.
Q. And is this the current federal statute as it relates to misbranding, to the best of your knowledge?
A. Yes.
11:32:24 Q. Okay. Great.
MR. WISNER: Permission to publish, Your Honor?
THE COURT: You may proceed.
(Exhibit published to the jury.)
BY MR. WISNER:
11:32:32 Q. Okay. So we have here, Doctor, U.S. code 21USC331, prohibited acts, do you see that, Doctor?
A. Yes.
Q. Sorry. We're on another exhibit.
(Brief pause).
11:32:48 BY MR. WISNER:

Q. Okay. Here we go.

So we have in front of us misbranded drugs and devices, do you see that, Doctor?

A. Yes.

11:33:14 Q. And it defines it here -- can you read that to the jury what I have culled out.

A. (Reading:)

"... a drug or device shall be deemed to be misbranded if it's labeling is false or

11:33:25 misleading in any particular."

Q. What does that mean, false or misleading in any particular?

A. So if there's a specific issue on which there is a statement of the label that is wrong or not substantiated by evidence or it omits something that should be in there, that's

11:33:59 what false and misleading means.

Q. Now, if the FDA concludes that a label contain something that is false, misleading, or omitted, as you said, can the FDA initiate a misbranding proceeding against the manufacturer?

A. Yes.

11:34:13 Q. And what is the ultimate outcome of a misbranding action?

A. If successful the manufacturer has to stop distribution of the product and generally recall any of the product that's out there.

Q. Now, in your experience, how does a misbranding issue

11:34:35 usually get resolved within the FDA?

A. With -- within the FDA itself?
Q. Yes.
A. I'm not sure I completely understand the question.
Q. Let me ask you another question.
11:34:47 A. Yes.
Q. Does the FDA frequently bring misbranding actions against manufacturers?
A. It's not that common but certainly it does happen.
Q. And when an issue about the accuracy of the label comes up,
11:35:00 what is the process that usually happens with the manufacturer?
A. Well, generally the FDA will go to the manufacturer and say we've noticed this, we'd like to you correct it.
Q. And unless the -- and if the manufacturer says I'm not going to fix it, is that then this sort of nuclear option?
11:35:24 A. Fairly unusual to see a misbranding action.
Q. All right. Are you familiar with something called class labeling, Doctor?
A. I am.
Q. What is class labeling?
11:35:33 A. So there are drugs that form a particular chemical or pharmacologic class; in other words, they have the same structure or they work by the same mechanism.
Q. And why is there such thing as class labeling?
A. Well, a lot of times you have a drug or a class of drugs,
11:35:59 as I should say, where they have the same side effect

associated with them, although it's not necessarily to the same degree.

Q. And so why do you have class labeling?

A. Well, you want to warn prescribers that you need to pay attention if this is a drug in that class or if you've previously prescribed the drug in that class or patients had a problem with another drug in that class to make sure you know that an alternative drug in the same class might have a similar issue although the degree may definitely vary.

11:36:24

11:36:47

Q. Now, when the FDA wants to institute class labeling how does it typically go about doing that?

A. Well, typically what will do is send out a request to all manufacturers who market drugs belong to that class.

Q. And you said another request, why would they request it? Can't they just tell the manufacturer what to do?

11:37:07

A. Well, the FDA is a law-based and science-based organization. It does not just runaround telling people what to do. First off, it's the manufacturer's responsibility. The FDA would always prefer that things get done voluntarily. It's very expensive and usually unnecessary to get into conflicts like that if you don't have to.

11:37:34

Q. And so when the FDA sends out a request to initiate class labeling, do manufacturers at that point have the opportunity or even obligation to make counterproposals to that class labeling?

11:37:54

A. Oh, absolutely.
Q. Why is that?
A. Well, as I said, it's not just a matter of ordering people to do things. The manufacturers, as I said, always know more about their drugs than the FDA.
11:38:05
And the manufacturer may have a legitimate reason to say, hey, we're not even a member of this class, or this shouldn't apply to us, and the FDA will listen to those things. It may not agree, but certainly it will listen and will take those arguments very, very seriously.
11:38:31
Q. And in the course of your investigation and research in this case, have you found examples where the FDA has instituted class labeling but specific manufacturers have made changes or additions to that class labeling?
A. Yes.
11:38:47
Q. And why did you look into see if that was possible?
A. Well, you were asking before does the FDA use the same standards throughout, and the answer is yes. And one of the issues here is, can a manufacturer have something in that it's product-specific even if there's class labeling. And the answer is, you know, if that's true that they can, there should be examples, and I found those almost immediately.
11:39:04
Q. Do you recall -- if you could turn to exhibit, Defendant's Exhibit 6335 in your binder.
It's probably the last one there.
11:39:39

A. Yes.
Q. Do you see that, Doctor?
A. Yes.
Q. What is this document?
11:39:46 A. This is a paper written by a group of FDA clinicians and scientists talking about class labeling in a product that's used for MRI's.
Q. Is this a document that you relied upon in rendering your opinions?
11:40:04 A. Yes.
Q. Is this from a reliable journal?
A. Yes.
MR. WISNER: At this time, Your Honor, permission to publish portions of it to the jury for his testimony.
11:40:16 THE COURT: All right. You may proceed.
MR. WISNER:
(Exhibit published to the jury.)
BY MR. WISNER:
Q. All right, Doctor, we're looking at it. Let's start off
11:40:22 with the title. What's the title here?
A. Nephrogenic systemic fibrosis in class labeling of gadolinium-based contrast agents by the Food and Drug Administration.
Q. Now I had you read that because I, in no way, could
11:40:37 possibly have read it out loud.

In layman terms, what does that mean?
A. So gadolinium is a drug that radiologists inject into patients who are getting MRI's. It helps light up areas where there might be infection so they're easier to see.
11:40:54 In some patients who have kidney problems, that's where the word nephrogenic comes from. They can get -- they get gadolinium, they can get an extremely serious side effect that involves scar tissue forming and can potentially seriously injure or kill them.
11:41:18 Q. And did the FDA institute class labeling for this class of drugs?
A. Originally, yes.
Q. Okay. And we have here a group. And who are these people listed here?
11:41:24 A. So, let's see. Lucy Yang, Ira Krefting, Alex Gorovets, Louis Marzella. Marzella, he's a great guy. He was our reviewer supervising in biologics. Jim Kaiser and Dwaine Rieves. Rieves was division director for hematology. These are all FDA reviewers, scientists and supervisors.
11:41:49 Q. How many FDA authors are there on this?
A. I believe 7.
Q. Okay. And you said it's meant to discuss class labeling, is that right?
A. Yes.
11:41:58 Q. Is this issue of class labeling something that you had

experience dealing within some capacity while you were at the FDA?
A. Yes.
Q. Just before we get there, do you have a personal problem with class labeling?
A. I don't have a personal or professional problem with it.
Q. Okay. All right. So I'm going to call this paragraph right here, it reads:

> "... class labeling for an adverse reaction has sometimes been misinterpreted to mean that all drugs within a class have the same magnitude of risk the reaction."

I'll stop right there. What does that sentence mean to you?
A. What that says is that people outside the FDA sometimes think, well, if all the drugs have a class label, then the risk must be the same for all the drugs unless you say something differently, I guess I would say.
Q. And when say something differently, you mean for that particular drug?
A. Correct.
Q. So, for example, the class labeling dealt with a particular risk, when would there be an appropriate circumstance when you'd have specific information about that drug?
A. When you say when there would be an appropriate

circumstance --
Q. Yeah?
A. -- to add that?
Q. Yeah.
11:43:16 A. As soon as you have that information, as it says in the regs.
Q. So, for example, if you got a large study showing that your drug was worse than the others, would that be an example of when you would want to add to the class labeling?
11:43:28 A. Yes.
Q. All right. Well, it goes on to say here that the GBCA -- what is GBCA?
A. GBCA is the name, the abbreviation for this class.
Q. Okay. Great:

> "... the GBCA experience addresses this potential misinterpretation and shows how package inserts can be updated on the basis of new information."

Do you see that, Doctor?

11:43:57 A. Yes.
Q. What does that mean and what is that referring to?
A. So here's a class where the initial information was that all drugs had a risk of causing this problem in people with kidney disease, but as new information came out it became clear
11:44:17 that some drugs more likely than others caused this problem.

And so that was added to the label for the relevant drugs.
Q. Now, if a manufacturer knows that their drug is different than what is being said in the class, do they have a responsibility under these federal regulations to change that or update it?
11:44:38
A. Yes.
Q. Why is that?
A. That is something that gets back to the law we were looking at earlier in terms of misbranding. If the label, the entire content of the label is false and misleading in any particular, it's misbranded, and it's the responsible -- the manufacturer's responsibility to correct that.
11:44:57
Q. All right. Thanks, Doctor. And I appreciate you bearing with me talking about the FDA generally. Let's get to this case now. Let's talk about Paxil, okay.
11:45:15
A. Okay.
Q. All right. You understand that Paxil -- when was Paxil first approved for sale in the United States?
A. I believe it was December of 1992.
Q. And when did -- and you mentioned a New Drug Application. When did GSK submit its New Drug Application for that approval in '92?
11:45:26
A. I believe it was sometime in 1989.
Q. And in presenting that New Drug Application, did they summarize their safety data?
11:45:42

A. Yes.
Q. Why would they do that?
A. Well, that's a requirement under the regulations.
Q. And what does it mean to summarize safety data, Doctor? If you can explain that to the jury.
11:45:55
A. Sure. So when you are studying a new drug, you submit an application. The company is going to do a whole bunch of studies. They're going to do clinical trials involving patients. Even if it's just the same disease, they're going to have multiple trials.
11:46:16
So what the FDA wants and what the law requires is the manufacturer sort of join that, all that data together from all those trials. So you can have an overall view of how many deaths there were, how many serious adverse events there were, serious side effects, how many people had side effects at all, and what the rates were.
11:46:39
Q. And is that a document entitled The Integrated Safety of Summary?
A. Yes.
Q. And while you were at the FDA, did you review those?
11:46:48
A. Yes.
Q. Is that part of your job?
A. Yes.
Q. Okay. And did you review the integrated safety summary, at least portions of it, as it relates to Paxil and suicide?
11:46:58

A. Yes.
Q. Okay. Great. If you can turn to Exhibit 75 in your binder, Plaintiff's Exhibit 75.
(Brief pause).
11:47:21 BY MR. WISNER:
Q. Got it, Doctor?
A. Yes.
Q. Is that a accurate copy of that document?
A. Yes.
11:47:26 MR. WISNER: Permission to publish, Your Honor?
THE COURT: Yes, you may proceed.
(Exhibit published to the jury.)
BY MR. WISER:
Q. Okay. Looking here at the Integrated Safety Summary, do
11:47:34 you see that, Doctor?
A. Yes.
Q. Okay. And then I want to just quickly show a few things there. We have some authors on here. And in particular, do you see this one, Christine Blumhardt?
11:47:43 A. Yes.
Q. Do you know who she is?
A. Well, it gives her title as acting clinical research director for this study.
Q. Do you know if she had a meaningful while preparing this
11:47:55 document?

A. The fact that she signed it means yes.
Q. Okay. And have you reviewed portions of her deposition in preparation your testimony?
A. Yes.
11:48:05 Q. Okay. All right. Let's go into the document.
The jury has already seen this, Doctor, so I don't want to get into the wash-out stuff too in depth, but I do want to talk a minute about it because I understand you did some calculations.
11:48:18 So this is the table 21.7, what does this table reflect, Doctor?
MR. BAYMAN: Your Honor, I just object. This is really now being cumulative. Dr. Healy went through this in detail, this very data and calculations. So I object to it --
11:48:37 THE COURT: You're right, it is somewhat cumulative, but it is a pretty technical area and I think that I'm going to give him some latitude to cover an area that has previously been heard simply to educate all of us, myself and the jury, as to what's in these documents.
11:48:53 So you may proceed, but bear in mind, I don't want to go through all the pages of these documents nor do I want you to unnecessarily take the time with the jury with additional material that's already been presented.
MR. WISNER: Yes, Your Honor. Almost all the
11:49:08 documents that will be shown today are new.

THE COURT: Summary form.

MR. WISNER: Yes.

THE COURT: Okay.

BY MR. WISNER:

11:49:13 Q. So, Doctor, what is this table?

A. So this combines the numbers for all the patients and all the trials. The manufacturer is stating this is what it is. So this says how many deaths were there in all the patients who got Paxil, all the patients who got active control, and all the

11:49:42 patients who got placebo.

Q. Now we have 12 deaths here. We know how many of those were suicides?

A. 5, I believe.

Q. And then we have a placebo here, we have 2. And did 2

11:49:55 deaths occur in the placebo arms in any of the clinical trials?

A. No.

Q. Where did they occur?

A. These occurred before to 2 patients who never entered the treatment phase of the trial. In essence, they were not in the

11:50:12 trial to begin with.

Q. Based on your experience within the FDA, was that a proper analysis of the deaths worldwide?

A. Absolutely not.

Q. Okay. And then, of course, very quickly, there's a similar

11:50:24 table, Doctor, as it relates to suicide attempts, do you

recall?
A. Yes.
Q. All right. Let me get to it.
(Brief pause).
11:50:28 BY MR. WISNER:
Q. And in that chart, which I'm going to show the jury in just a second, did there -- is there a discussion of suicides as well?
A. On attempted suicides.
11:50:55 Q. Yes. Great.
How many are in the worldwide data here?
A. So looking at the 3 columns on the right, there were 42 suicide attempts in Paxil treated patients and then 3 listed in the placebo treated patents across all the trials.
11:51:22 Q. And again, were there 3 suicide attempts in the placebo arms or no?
A. No.
Q. Okay. We've already heard about the wash-outs, so we're not going to get into the accuracy of that. I want to focus on
11:51:34 this 42 here, it says 1.4 percent; do you see that?
A. Yes.
Q. What does that mean?
A. That means of the 2,963 patients exposed to Paxil, 1.4 percent, about 1 out of every 70 attempted suicide.
11:51:49 Q. We talked about the characterization of a frequent adverse

event, do you recall that?
A. Yes, I do.
Q. You said anything over 1 percent?
A. Yes.
11:51:57 Q. So does suicide attempt here qualify as a frequent adverse event?
A. It does.
Q. Now, I understand in your report you actually went back and recalculated what these numbers should've been, is that right?
11:52:11 A. Yes.
Q. And generated from those new odds ratios and you actually did statistical analysis on it, is that right?
A. Yes.
Q. Please turn to Exhibit 49, and actually look at 49 and 50.
11:52:26 We're going to authenticate them one at a time:
A. Okay.
Q. Are these the tables that you created in your report, Doctor?
A. Yes.
11:52:42 Q. Are they a fair and accurate copy of the tables?
A. Let me just look at the second page to make sure.
(Brief pause).
BY THE WITNESS:
A. Yes.
11:52:55 MR. WISNER: Your Honor, permission to publish.

THE COURT: Yes, you may proceed.

BY MR. WISNER:

Q. All right.

(Exhibit published to the jury.)

11:53:02 BY MR. WISNER:

Q. Looking at Plaintiff's Exhibit 49. Doctor, what is this table 2?

A. So this gives the sponsor's numbers for all suicide attempts for patients exposed to Paxil and those who got

11:53:27 placebo.

What the odds ratio was, in other words, how much more common was it for Paxil exposed patients to attempt suicide as opposed to people who got placebo, and then what's called the P value.

11:53:44 Q. And then the second line, that's what actually happened, is that right?

A. That is correct.

Q. All right. So the way it was presented in the summary safety, it suggests it's an odds ratio of 2.6, do you see that?

11:53:57 A. I'm sorry. I apologize.

Q. Right in front of your screen, Doctor.

A. Okay. I'm sorry.

Yes, that is correct.

Q. All right. And you also see that as a P value of 1.0, do

11:54:10 you see that?

A. Yes.
Q. Is that P value of 1.0 statistically significant?
A. By conventional measures, no.
Q. Okay. But now if we actually look at what the data
11:54:22 should've been, the odds ratio is what, Doctor?
A. 7.8.
Q. And does that mean that based on this data at this time, when the drug was submitted for approval, there was a 7.8 times greater likelihood that someone taking Paxil would engage in a
11:54:36 suicide attempt than someone not taking Paxil?
A. Yes.
MR. BAYMAN: Objection; leading.
THE COURT: Proceed.
MR. WISNER: Thank you.
11:54:44 BY MR. WISNER:
Q. Now, the P value here is 0.01, do you see that?
A. Yes.
Q. Is that statistically significant?
A. Yes, it is.
11:54:53 Q. Now, here's something that I want to clarify. Within the FDA, if you have a statistically significant elevated risk, does that rise to the level, in FDA's view, of causation?
A. You have an enormous increase in risk like there, it almost shouts it.
11:55:19 Q. By reporting it as an only 2.6 with a nonstatistically

significant P value, would the FDA look at that and go, oh, that's a real problem?

MR. BAYMAN: Objection. This is now speculation, would the FDA look at that.

11:55:38 THE COURT: Yes. You'd have to bring it down to an opinion, sir.

MR. WISNER: Sure.

THE COURT: The objection is sustained.

BY MR. WISNER:

11:55:45 Q. Dr. Ross, did the FDA, when it saw the data presented by GSK, tell GSK you have a suicide problem?

A. No.

MR. BAYMAN: Your Honor, he doesn't have any causation opinions.

11:55:56 THE COURT: Yes, sustained again.

Does he have an opinion as to how it'll be evaluated. That's all the jury wants to hear.

MR. WISNER: Okay.

THE COURT: Not any speculation.

11:56:09 MR. WISNER: Fair enough, Your Honor.

BY MR. WISNER:

Q. Actually I have two questions, one is factually, based on your review of the NDA, did the FDA seeing this data tell GSK they had a problem?

11:56:23 THE COURT: If you know.

BY MR. WISNER:
Q. If you know.
A. You are referring to the original numbers, the first row?
Q. Yes. That's right.
11:56:30 A. No, it did not.
Q. In your opinion, does that information indicate that there is a problem?
MR. BAYMAN: Objection, Your Honor. He doesn't have causation opinions.
11:56:39 THE COURT: Overruled, sir.
BY THE WITNESS:
A. The second row, which is the real numbers, yes, there is a problem.
BY MR. WISNER:
11:56:47 Q. But the numbers that were reported, in your opinion, do those show a problem?
A. No.
Q. Okay. And I understand -- if you turn to Exhibit 50, which we've already discussed, Doctor, and it's been authenticated,
11:57:02 what is table 3 from your report? What does this reflect?
A. So this has a look at all the suicide attempts or suicides and suicides, combining the two, in patients exposed to Paxil compared to patients who got placebo in the clinical trials.
Q. And, again, we have the sponsor's submission and the actual
11:57:27 submission, is that right?

A. Yes.
Q. And by "actual submission" I mean it's the actual numbers, right?
A. Yes.
11:57:33 Q. All right. And so when you combine both suicide attempts and completed suicides, the number submitted to the FDA show an odds ratio of what?
A. 1.8.
Q. And, again, is that statistically significant?
11:57:45 A. No.
Q. And based upon those statements made to the FDA, did the FDA come back to GSK and say, you have a problem?
A. No.
Q. Based on those statements to the FDA, in your opinion, do
11:57:58 they suggest that there's a problem?
A. You're talking about the actual numbers?
Q. No, I'm talking about what they said to the FDA.
A. Oh, I'm sorry. No, it doesn't seem to say that at all that there's a problem.
11:58:13 Q. Now, if you look at the actual numbers, what's the risk ratio?
A. 8.9.
Q. So what does that mean, in layman's terms, when it comes to suicide attempts and completed suicides?
11:58:25 A. And just to be clear, this is an odds ratio rather than a

risk ratio, but 8.9 is an enormous increase in risk, enormous. It means that people exposed to Paxil compared to patients who got placebo are almost 9 times more likely to either attempt suicide or actually successfully kill themselves.

11:58:50 Q. And the P value here, Doctor, .004, is that statistically significant?

A. Very significant.

Q. In your opinion, if these actual numbers and actual odds ratios had been presented in 1989, would that have indicated

11:59:08 that there was a suicide signal?

A. Yes.

MR. BAYMAN: Objection; speculation.

THE COURT: Overruled.

BY MR. WISNER:

11:59:19 Q. Now, following the submission of the 1989 integrated safety summary, did anything happen in the medical community to raise concerns about the issues of SSRI and suicide?

A. Yes.

Q. What happened?

11:59:35 A. So the publication of papers are reporting very compelling cases of patients who killed themselves or attempted suicide after starting on a SSRI.

Q. And are you familiar with the -- is one of those Dr. Martin Teicher's paper?

11:59:58 A. Yes.

Q. And one of the authors on that was Dr. Cole as well?
A. Yes.
Q. And in response to these publications of case reports, was there an inquiry started within the FDA about the relationship
12:00:12 of SSRIs and suicide?
A. Yes.
Q. And what was that inquiry?
A. So the FDA started asking, can SSRIs induce suicide, and they started looking for information from manufacturers to
12:00:37 answer that question.
Q. Did they specifically ask the manufacturers to submit suicide reports?
A. Yes.
Q. And do you recall reviewing the memorandum summarizing the
12:00:47 conversation between FDA and GSK on that suicide report?
A. Yes.
Q. If you would please turn to Exhibit 79 in your binder, Doctor. Plaintiff's Exhibit 79.
(Brief pause).
12:01:15 BY THE WITNESS:
A. Okay.
BY MR. WISNER:
Q. Okay. Great. Is this a copy of that memorandum of conversation?
12:01:21 A. Yes.

Q. And who was the conversation between, Doctor?
A. The employee of GlaxoSmithKline and an FDA reviewer by the name of Martin Brecher.
Q. All right. Doctor, you can move the microphone closer to you. You're going to get a back spasm if you keep leaning forward.
12:01:39
A. Thank you.
Q. All right. Is this a fair and accurate copy of that memorandum that you reviewed?
A. Yes.
12:01:45
MR. WISNER: Your Honor, this has already been published to the jury. Permission to publish again.
THE COURT: Yes, you may proceed.
MR. BAYMAN: Your Honor, this is not in his expert report. So I would just object.
12:01:53
MR. WISNER: It is cited in his expert report, Your Honor.
MR. BAYMAN: No, it's not, Your Honor.
MR. WISNER: It's in his reliance material. It's been produced through discovery. That's not true.
12:02:01
MR. BAYMAN: That's not accurate, Your Honor.
THE COURT: Well, I'll deal with that at the break. You can call it to my attention then.
In the meantime, this was already received in evidence once before?
12:02:12

MR. WISNER: Yes, Your Honor. I want to show a paragraph that was not shown to the jury.

THE COURT: Okay. And so for that reason I see no harm in going forward, allowing that to be done.

12:02:22 You may proceed.

MR. WISNER: Thank you, Your Honor.

THE WITNESS:

(Exhibit published to the jury.)

BY MR. WISNER:

12:02:26 Q. Previously, Doctor, we reviewed this document with Dr. Healy, but I want to focus on the middle paragraph that we didn't look at, okay.

It says here:

"... he mentioned that one approach would be to

12:02:38 address it from three types of data ..."

and it lists all these different types of ways of looking at the data, do you see that?

A. Yes.

Q. It says "completed suicides," do you see that?

12:02:47 A. Yes.

Q. And it says:

"Acts broadly defined as attempted suicide."

Do you see that?

A. Yes.

12:02:54 Q. And it says:

"... down to events as small as scratches on the wrists."

Do you see that?

A. Yes.

12:02:58 Q. What is that referring to?

A. So in terms of looking at adverse events recorded during a clinical trial, how to break them down according to essentially how serious they were in a hierarchy.

Q. And the first one, the first thing you want to look at is

12:03:24 what?

A. People who actually kill themselves.

Q. All right. And the second one below that?

A. People who tried to kill themselves.

Q. And then the last one is what?

12:03:31 A. Thinking about killing themselves.

Q. All right. And then you see here it says:

"... he said we should also address the kinds of things mentioned in the article by Dr. Teicher, such as obsessional suicidal ideation and

12:03:49 worsening of the suicidal ideation."

Do you see that?

A. Yes.

Q. What is that referring to, Doctor?

A. So that refers to how often people are thinking about

12:03:56 killing themselves and whether thinking about it is getting

worse and worse and worse.
Q. And who is this referring to when it says "he mentioned this one approach"?
A. Dr. Brecher.
12:04:09 Q. Okay. And that's Dr. Brecher of the FDA?
A. Correct.
Q. Did you ever know Dr. Brecher at the FDA, by any chance?
A. No.
Q. Okay. All right. And then it goes down here and it says:
12:04:20 "Dr. Brecher said he's working full-time on the review of efficacy and expects to finish by the end of the year, December 1990."
Do you see that?
A. Yes.
12:04:33 Q. Are these sort of communications between a medical reviewer and the sponsor about when they're going to get their review done, is that typical amongst drug sponsors and reviewers?
A. No.
Q. Okay. At the very end here it says:
12:04:52 "... again he emphasized that the division does not think it is an issue but it needs to be addressed."
In your experience at the FDA, is the issue of suicide considered a serious one?
12:05:07 MR. BAYMAN: Objection, Your Honor. He's not an

expert on suicide and didn't work on these products and now we're getting far afield again.

THE COURT: Overruled.

BY THE WITNESS:

12:05:17 A. Yes, of course.

BY MR. WISNER:

Q. Why is suicide considered a serious problem?

A. It's a death and it's particularly upsetting form of death because, in many instances, it's preventible by doing things or

12:05:36 avoiding things that can increase the risk of suicide.

Q. Now, while you were at the FDA, did you ever think that an issue relating to potentially people dying from a drug was not a serious issue?

A. Never.

12:05:52 Q. Okay. Now, there's been discussion with Dr. Healy about whether or not it is appropriate, this data from 1989, using the washout data was a scientifically appropriate thing to do, and then there was discussion about whether or not looking at data from uncontrolled trials as opposed to just

12:06:14 placebo-controlled trials was appropriate. Are you familiar with that debate?

A. Yes.

Q. In your opinion, do you think it is appropriate to not look at suicides that occurred on Paxil because they did not occur

12:06:28 in a placebo-controlled trial?

A. It is completely and totally inappropriate to ignore that data.
Q. And have you seen any evidence that specifically shows that that was the FDA's view in 1990?
12:06:43 A. Yes.
Q. All right. If you turn to Plaintiff's Exhibit 76 -- sorry. Yes, 76 in your binder.
(Brief pause).
BY MR. WISNER:
12:07:00 Q. Are you there?
A. Yes.
MR. BAYMAN: Objection, Your Honor. This is not in his report and this relates to fluoxetine which is Prozac, I object to it on two grounds.
12:07:11 THE COURT: I don't have -- let me get this document.
(Brief pause)
THE COURT: Once again, your objection?
MR. BAYMAN: That it's not in his report and it relates to fluoxetine which is Prozac, Your Honor.
12:07:31 MR. WISNER: Your Honor, if I may, this document specifically relates to the FDA's review of suicidality and SSRIs and what data they should be looking at and not in 1990 by the senior epidemiologist of the FDA.
THE COURT: You're relying on the document for a
12:07:52 general proposition and not for the application to Prozac or

fluoxetine?

MR. WISNER: That's correct, Your Honor.

MR. BAYMAN: Your Honor, this was not in his report. We never had a chance to question him about it.

12:08:02 MR. WISNER: That's not true. At his deposition I handed them a flash disk that contained every piece of thing he looked at, called his reliance material, and this was on it. So it's not true.

THE COURT: All right. You may proceed.

12:08:16 BY MR. WISNER:

Q. All right, DOCTOR, is this a document that you reviewed before?

A. Yes.

Q. And is this a document that you relied upon?

12:08:20 A. Yes.

Q. And would discussing it aid you in your testimony today?

A. It would.

Q. Okay. Great.

MR. WISNER: Permission to publish, Your Honor.

12:08:27 THE COURT: All right. You may proceed.

BY MR. WISNER:

Q. Okay. Great. So this is a document --

THE COURT: Let's go to sidebar for a minute.

MR. WISNER: Yes.

12:08:30

(Proceedings heard at sidebar on the record.)

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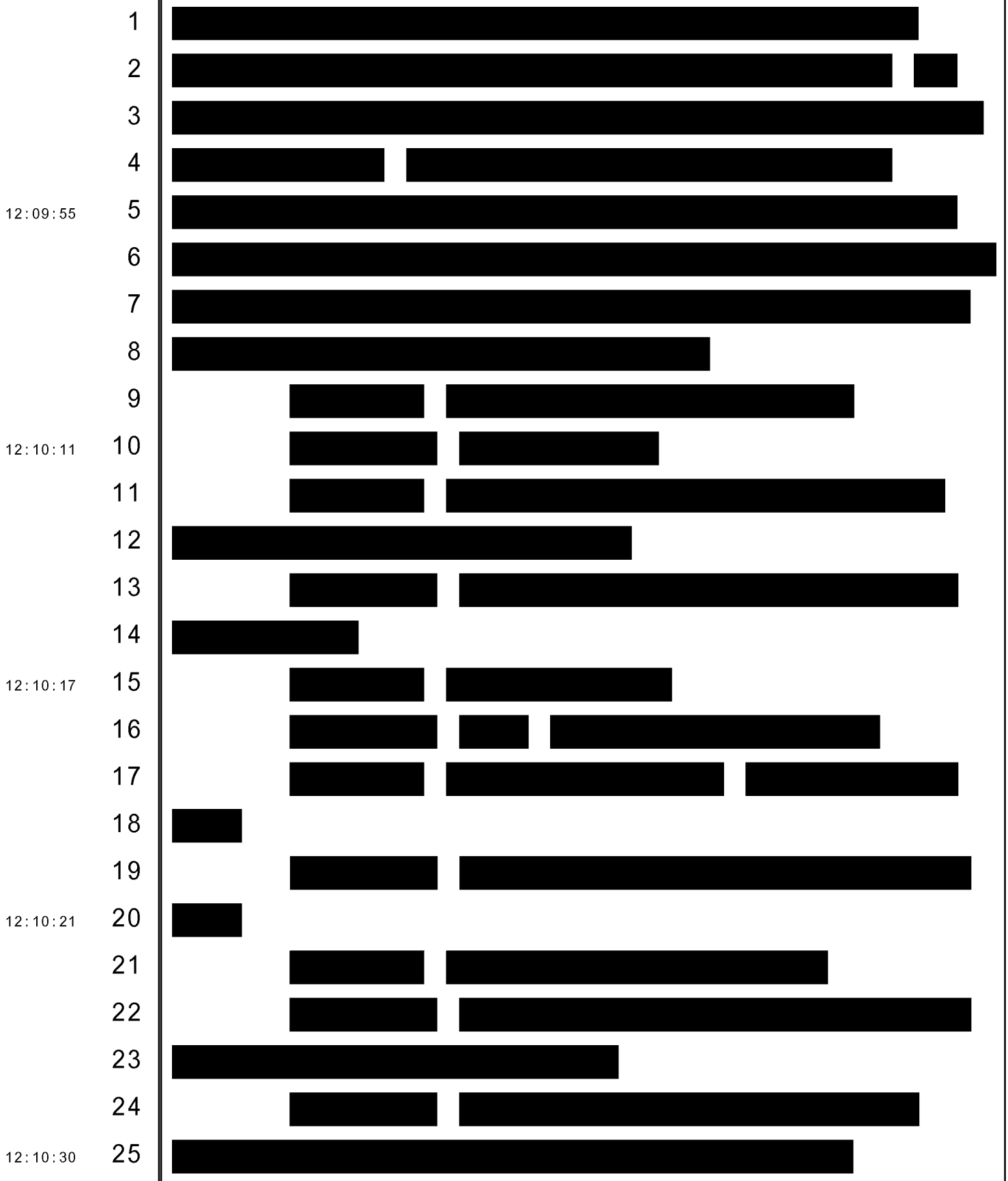
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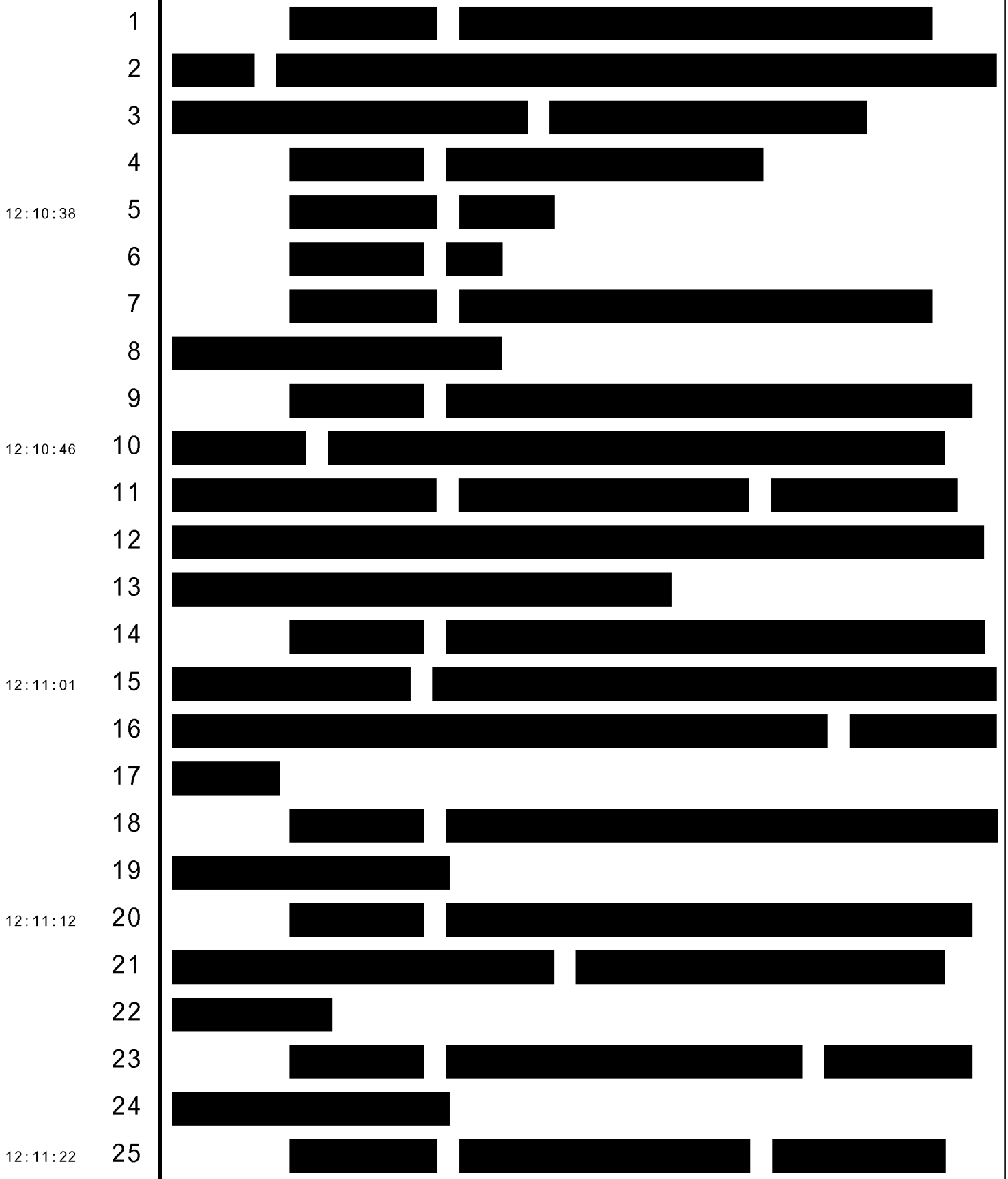
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(Proceedings resumed within the hearing of the jury).

THE COURT: Will you may proceed.

12:11:49 MR. WISNER: Thank you, Your Honor.

BY MR. WISNER:

Q. Looking at Plaintiff's Exhibit 76, Doctor, who is the author of this document and where was it generated?

A. So I just want to make sure I understand.

12:12:01 So there's actually two memoranda here. Are you referring to --

Q. Let's start with the first one.

A. So this is written and signed by Dr. Bruce Savella who is -- sorry.

12:12:35 Q. It appears on the screen.

A. My apologies. He is chief of the epidemiology branch.

Q. And what year is this?

A. 1990.

Q. And you say chief of the epidemiology branch of what

12:12:49 organization?

A. The Center For Drug Evaluation and Research in the FDA.

Q. And the subject here is what, Doctor?

A. So the subject is how to analyze suicide data in this case from fluoxetine -- or for fluoxetine.

12:13:12 Q. And is this around the time that the FDA held a meeting to

discuss SSRIs and suicide, before that, I should say?
A. It's a little bit before.
Q. Okay. All right. I want to call your attention to a paragraph down here, it reads:
12:13:32 "... in the analysis of suicidality, 76 of the total of 97 cases were excluded because they occurred in compassionate use studies or other studies which did not have controls."
What doings that mean, Doctor?
12:13:46 A. So it's that in the application or the data on suicide, around 3/4 of the suicide cases were not included in the sponsor's analysis, leaving only, I would say, fewer than 20 percent -- or maybe around 20 percent, sorry.
Q. And what does it mean they were in compassionate use
12:14:20 studies or other studies?
A. So there are other often many other types of designs that are included in an application besides a randomized control trial. You may have studies where the drug itself is given by itself and then it's compared to historical controls or it's
12:14:45 given compassionate use where it's thought that a patient who's got an untreatable condition could use -- could get this drug even though they're not on the trial. And these are submitted as part of the NDA and are considered in part of, you know, does the drug work.
12:15:05 Q. Okay. And it says:

"... it's inappropriate in a safety analysis to exclude such a large proportion of cases."

Do you see that?

A. Yes.

12:15:14 Q. What does that mean, Doctor?

A. Well, you're --

MR. BAYMAN: Your Honor, I'm going to object. Once again, we're going to what Eli Lilly did, what they included, what they excluded. This is GSK.

12:15:24 THE COURT: I'm going to, at least for the moment, sustain the objection.

And we'll go to lunch now, ladies and gentlemen, and we'll resume about 20 after 1:00. So you are excused for lunch.

12:15:38 And then I'll talk to counsel about this exhibit.

(The following proceedings were had out of the presence of the jury in open court:)

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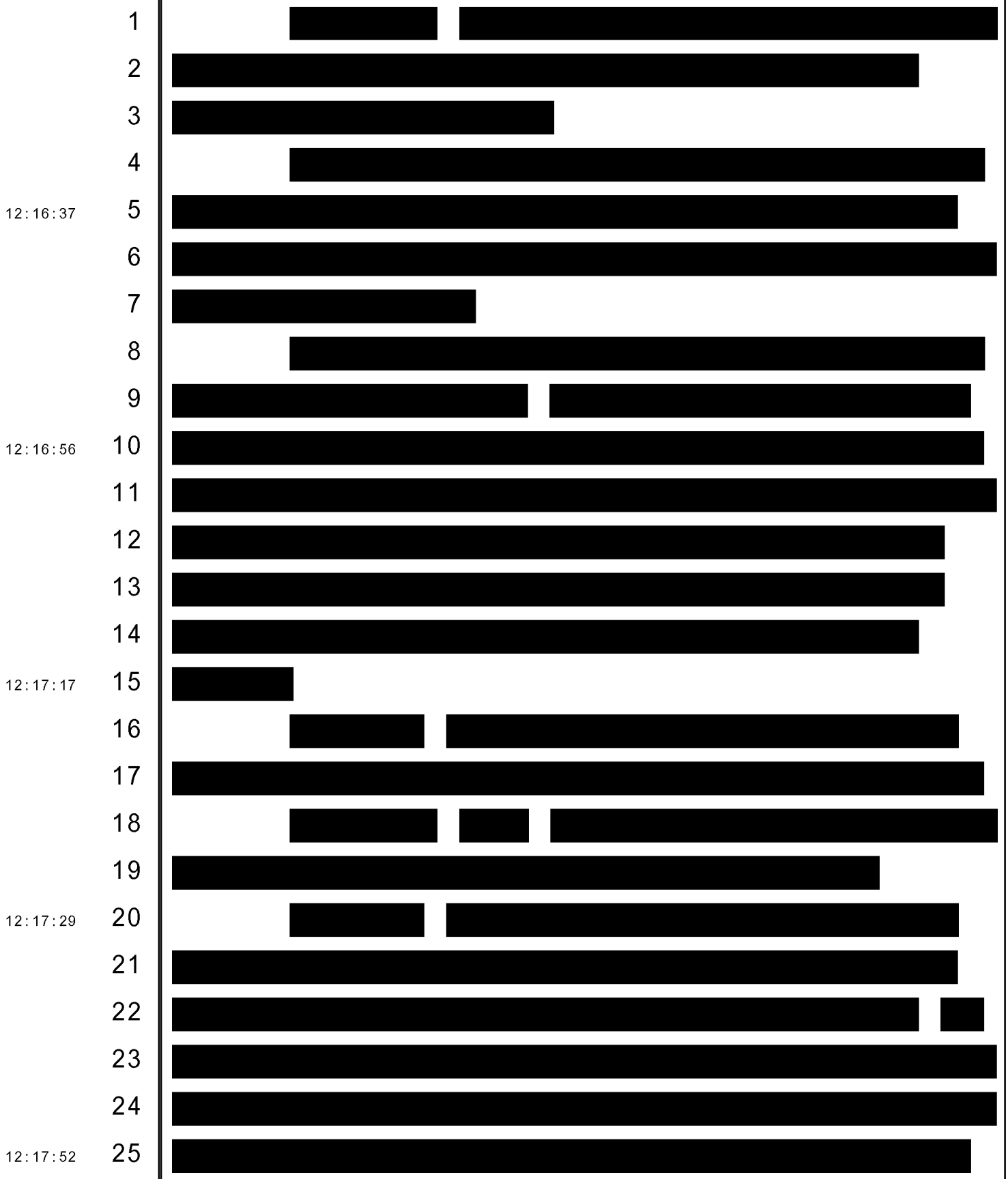
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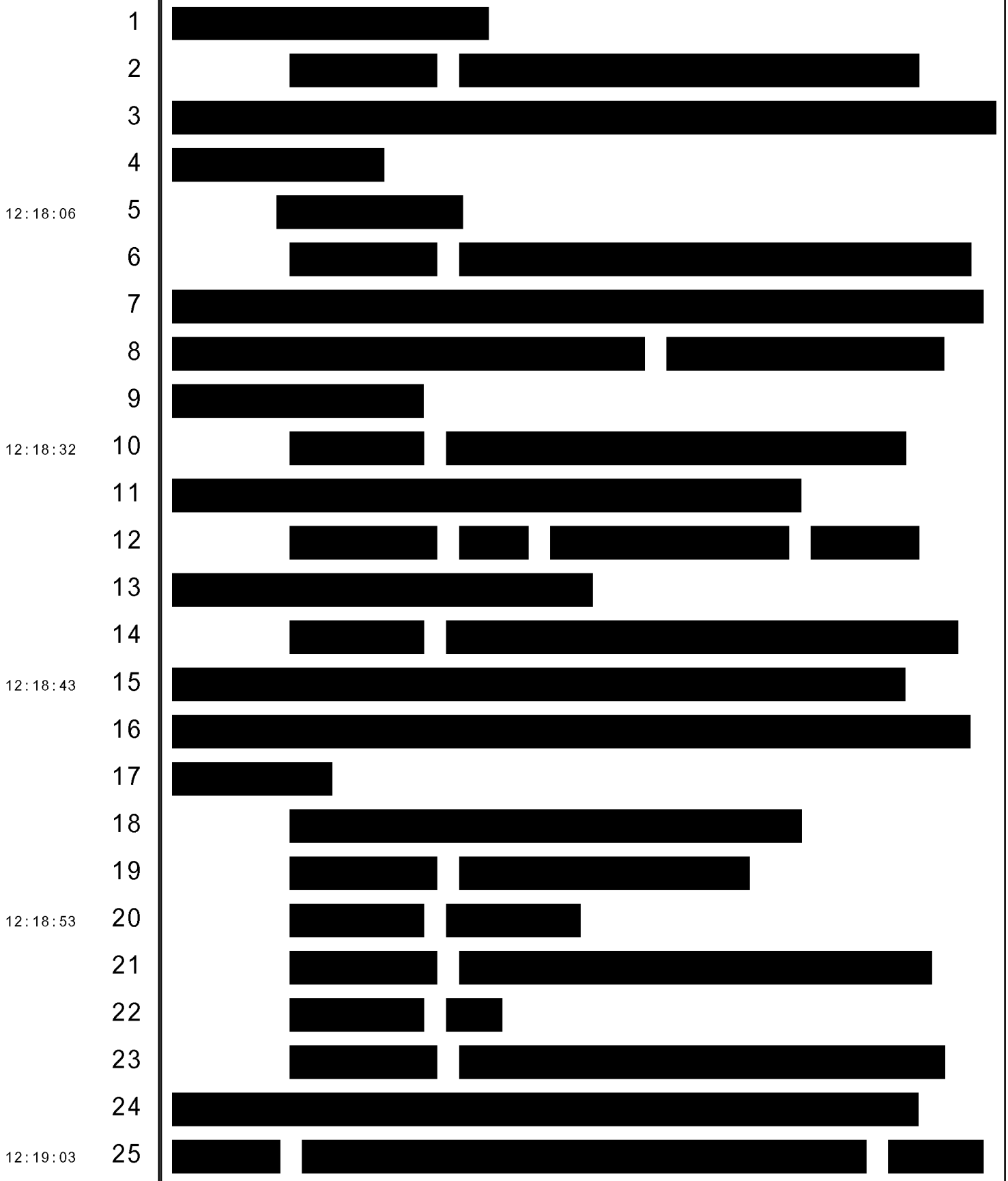
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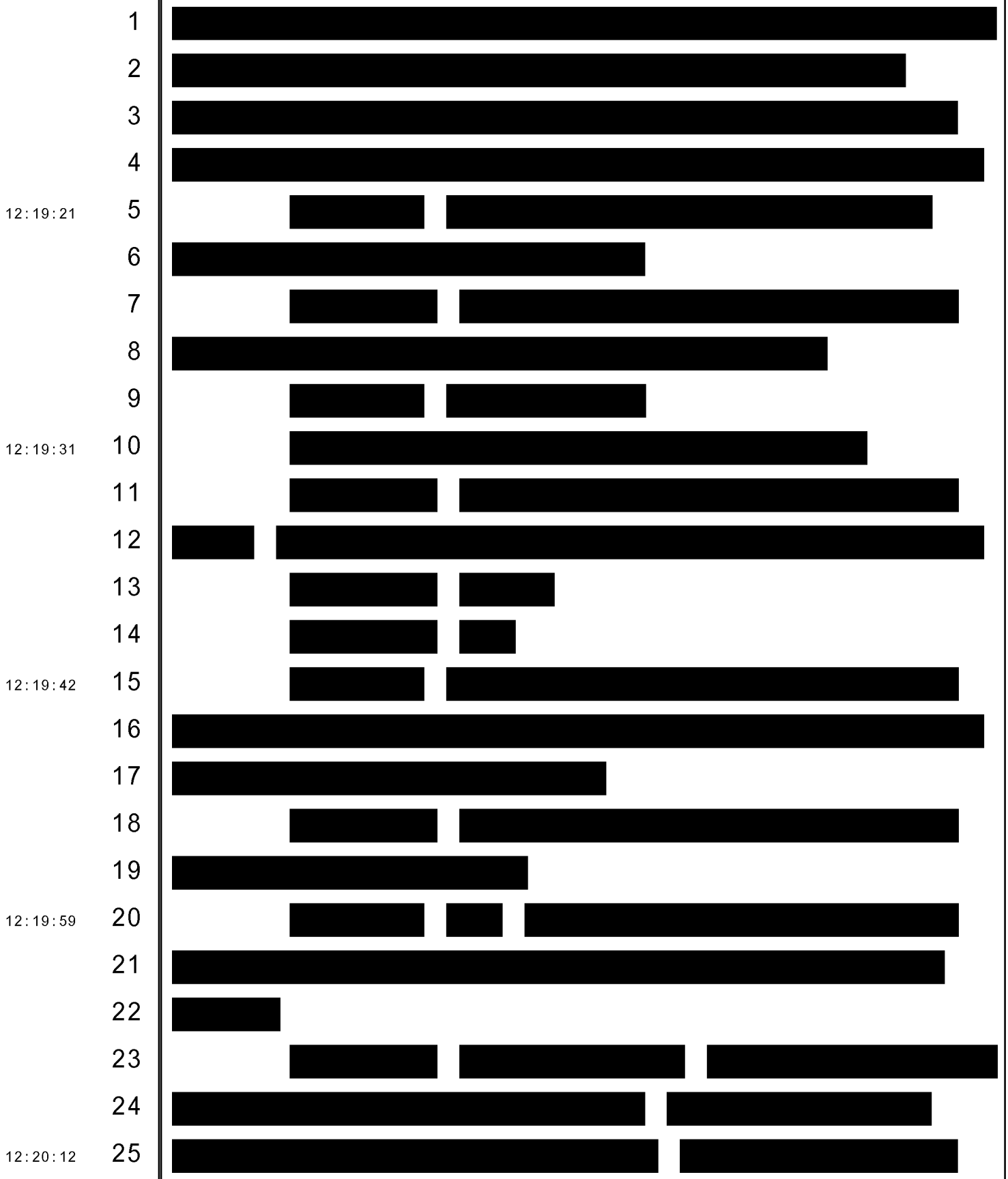
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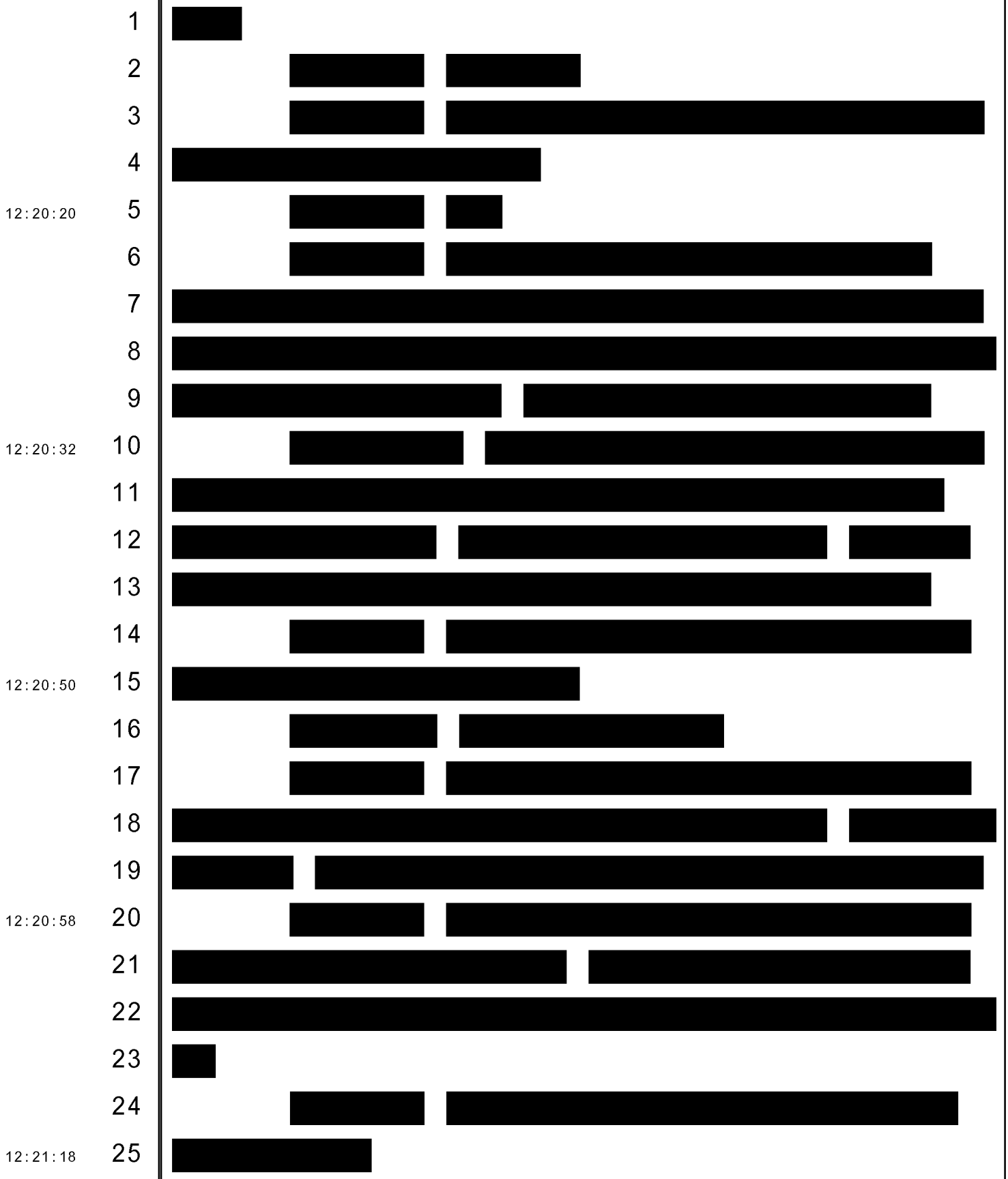
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12:21:30

[redacted]

12:21:44

[redacted]

(Luncheon recess taken from 12:21 o'clock p.m. to 1:45 o'clock p.m.)

* * * * * * * *

I CERTIFY THAT THE FOREGOING IS A CORRECT TRANSCRIPT FROM THE RECORD OF PROCEEDINGS IN THE ABOVE-ENTITLED MATTER

/s/Blanca I. Lara March 21, 2017

12:21:56