UNITED STATES DISTRICT COURT

DISTRICT OF MASSACHUSETTS

IN RE: ZOFRAN® (ONDANSETRON))
PRODUCTS LIABILITY LITIGATION) MDL NO.: 1:15-md-2657-FDS

DEPOSITION OF DEREK NEWALL

a witness herein, called for examination, taken by and before Emma White, Court Reporter, at Shook, Hardy & Bacon, Tower 42, 25 Old Broad Street, London EC2N 1HQ, United Kingdom

Wednesday, 28 June at 9.02 am

Wednesday, 28 June 2017

(9.02 am)

VIDEOGRAPHER: Good morning. We are now going on the video record. Please remember that recording will continue until all parties agree to go off-the-record.

My name is Luis Guisbert representing Veritext. The date today is June 28, 2017 and the time is approximately 9.02 am. This deposition is being held at Shook, Hardy & Bacon, located at 25, ,Old Broad Street, London, EC2N 1HQ in the United Kingdom, and it is being taken by the counsel for the Plaintiff. The caption of this case is In Re Zofran® Products Liability Litigation and all cases related.

This case is being held in the US District Court, district of Massachusetts, Case No. 1:15-md-2657-FDS. The name of the witness is Derek Newall. The Court reporter today is Emma White, representing Veritext.

Will counsel please introduce yourselves for the record?

MR AYALA: Good morning. Tom Ayala for the Plaintiffs.

MR SCHNIEDERS: Chris Schnieders for the Plaintiffs.

MR DALY: Mike Daly for the Plaintiffs.

MR SHEEHAN: Tom Sheehan for Derek Newall and GSK.

MS SHAH: Jennifer Shah for Derek Newall and GSK.

MS HENRY: Laurie Henry for Derek Newall and GSK.

MS HALLYBURTON: Elizabeth Hallyburton, GSK.

VIDEOGRAPHER: Can the people over the phone -- can they introduce themselves please?

MS HEIS: This is Jennifer Heis for Teva Pharmaceuticals USA Inc., and also present is Hana Schefer.

VIDEOGRAPHER: Thank you.

Will the Court Reporter please swear in the witness and we can proceed?

DEREK NEWALL,

having been duly sworn,

testified as follows:

Cross-examination by MR AYALA:

BY MR AYALA:

Q Well, good morning. Is it Dr Newall.

A Yes.

Q Dr Newall, my name is Tom Ayala. We just met briefly a moment ago for the first time, correct?

A Yes.

Q Dr Newall, could you state -- just tell us your full name.

A It's Derek Reginald Newall.

Q And where do you work, Dr Newell?

A I'm retired.

Q Dr Newall, have you given deposition testimony before?

A No I have not.

Q Okay.

Well, in light of that I just want to explain the process a little bit to you, because it's somewhat unlike informal communication in that the Court Reporter is transcribing all the words we are speaking, and so I'm going to be asking you questions today, you're going to be answering them under oath, and I'm going to need you to answer verbally as opposed to with the nod of a head or with a, "Mm-hmm", okay?

A I understand.

Q Okay.

Is there any reason you feel that your testimony today cannot be truthful, accurate and complete?

A No.

Q And I'm going to try not to talk over you when you're answering a question, and for the Court Reporter's sake, if, essentially -- we need to try not to talk over each other otherwise she can't take down what we are saying, okay?

A I understand.

Q If you don't understand one of my questions, please feel free to ask me to repeat it, or clarify it, and I'll do my best to do that. If you do answer a question, I'll assume you have understood it and proceed accordingly.

If at any time after you testify today and you take

a break today and come back and realize, "I forgot this", or, "I want to amend an answer", or add to an answer, just let me know and you're free to do that today, okay?

A I understand.

Q You're welcome to take a break. I just ask if there's a question pending, let's finish that question and answer session before we take a break, okay?

A Yes.

Q Dr Newall, did you spend time preparing for the deposition today?

A No. Not specifically, no.

Q Have you spent any time preparing for the deposition at all?

A Yes, I have. I've --

Q Okay.

What have you done to prepare?

A I've had four meetings.

Q And who were your meetings with?

A With the associates who are present here today.

Q Okay.

The lawyers present here today?

A Yes.

Q And over roughly what period of time did you have those four meetings with counsel?

A About two weeks, I think.
Q Roughly how many hours, total, would you say that adds up to in meeting with lawyers?
A Possibly about eight hours.
Q Probably about eight hours?
A Sorry, eight hours.
Q Eight hours total?
A Yes.
Q Did you review documents to refresh your recollection in preparation for this deposition?
A I looked at some documents, yes.
Q Okay.
Do you recall the nature of the documents that you reviewed to refresh your recollection?
MR SHEEHAN: I'll just make an objection and direct the witness not to answer under the attorney work product doctrine.
BY MR AYALA:
Q Were any of those documents used to refresh your recollection?
A No.
Q Okay.
Dr Newall, you mentioned that you're retired. When did you retire?
A I went on gardening leave last February.

Q I'm sorry, I didn't catch that.
A Gardening leave, the February of last year. My retirement date was at the end of May last year.
Q Well, congratulations, and before you retired, where did you work?
A At GlaxoSmithKline.
Q And how long did you work with GlaxoSmithKline?
A About 30 years.
Q Okay.
What did you do before working at GlaxoSmithKline?
A I worked for two years at a contract research organization and, prior to that, I worked -- I was doing research at the Newcastle University. At Newcastle University.
Q Okay.
What was the name of the contract facility?
A It was called, "Life Science Research".
Q Dr Newall, I just want to show you two exhibits. One I've marked for identification as Exhibit 1, which is a notice to take the videotaped deposition today, the other is marked as Exhibit 2 which reads on the front page, "Information About the Expert - Non-Clinical", and on the back page it has a curriculum vitae that appears to be yours, so I'll hand those to you and you can have a look at those.

(Exhibits 1 and 2 marked for identification)
So, as to Exhibit 1 my question is simply; have you received this document? Have you received this document before today?
A I'm aware of this document, yes.
Q Okay.
Roughly when did you receive it?
A Possibly two months ago. I can't be sure.
Q I see.
Well, that would make sense, because it's dated May 11.
A Right.
Q All right.
So you've been aware in other words, since you were made aware of this document that your deposition was going to be today, correct?
A Yes.
Q As to Exhibit 2, if you would, sir, have a scan of the curriculum vitae page, and I'm going to ask you whether this accurately summarises your education and work experience as you just described.
A Yes it does, with the exception that it doesn't specify that I retired, so the last item still says, "To date".
Q I see, and I see from your CV you received degrees from the University of Newcastle, first, is that a Bachelor

of Science?
A It is.
Q In zoology?
A Zoology, yes.
Q Study of animals?
A Yes.
Q Okay, and then a Ph.D. What was the degree in, the Ph.D degree?
A It was about the effects of Vitamin A on inducing cleft palate in mice.
Q But was that your degree, or -- I'm trying to understand what degree were you awarded. What was the nature of the Ph.D degree that you were awarded?
A It was a Ph.D in the Faculty of Medicine based on a research project that looked at Vitamin A effects on mice.
Q So, Vitamin A effects on cleft palate in mice?
A Yes, it was.
Q Would it be fair to say that the topic of Vitamin A -- Vitamin A's association with cleft palate in mice was the subject of your dissertation?
A Not specifically. Its purpose was to look at a technique for analysing data that might differentiate between different mechanisms by which cleft palate was induced.

Q Now, the individuals at Glaxo conducting in-house Reproductive Toxicity Studies, the individuals -- let me withdraw that.

At Glaxo -- when Reproductive Toxicity Studies were performed in-house, the individuals who initially examined the fetuses externally, viscerally or skeletally, who were they? Were they technicians? Were they Fetal Pathologists? Who were they?

A The group was led by a trained Fetal Pathologist and -- who would oversee the process. Specific technicians were employed into that group and they would be trained in fetal pathology and that small group would then be responsible for performing those fetal examinations, and there were SOPs that covered training and there would be training records as well that would document the training process and nobody would be allowed to make final decisions on a fetus unless they had achieved full -- a sufficient status to be able to do that, so -- were accredited -- not accredited, that's the wrong word -- were considered to have reached a standard where they could be allowed to proceed on their own.

Q What were the credentials and qualifications required of a technician at Glaxo who would examine fetuses during Reproductive Toxicity Studies?

A I don't know. You would need to consult with the Fetal

Pathologist to know that.

Q Okay.

During your time at Glaxo you mentioned rats and rabbits being used.

A Yes.

Q Were there specific strains of rats and rabbits that Glaxo used in conducting reproductive toxicology studies?

A There were and they changed during my time with Glaxo.

Q Okay, and what were they?

A Originally rabbit studies were performed in a Dutch Belted rabbit and around about the early/middle nineties that was changed to a New Zealand White rabbit. With respect to rat strains, when I arrived we used an Allen & Hanbury Wistar rat. Over the following years we changed to Sprague Dawleys and then I believe we went back to Wistars but I don't recall the specific strains or when those changes occurred.

Q Was it your understanding that the specific strains used in the rat and rabbit Reproductive Toxicity Studies were used elsewhere throughout the world?

A I'm not aware of that.

Q Did Glaxo maintain data referred to as, "Background data", on the specific strains of animals that it used for conducting Animal Studies and Reproductive Toxicity

Studies?

A Yes it did.

Q Okay.

Where did it maintain the background data?

A I don't recall specifically where it would maintain. It would have been kept with raw data. It was derived by the Fetal Pathology Unit with respect to their evaluations, although other evaluations were included. There was no need, specifically, to keep it separate and secure because it was derived from the control data in all the studies that were performed, and they were subject to rigorous control and GLP, of course.

Q Do you recall whether the background data was maintained in a manner that was specific to each supplier of the animal, or how was it organized?

A Yes, it would have been organized -- it would have been specific to a strain and, yes, it would have been specific to a supplier of a strain as well, because strains of rats are outbred so they're subject to variation. Strains of rats are outbred so they are subject to variation with time.

Q What does, "Outbred", mean?

A They're not -- I might be using the wrong terminology myself. It's a long time since I was involved in this. They're not genetically identical. They are

heterogeneous in their genetic make up, so they may vary over time.

Q Are they inbred as well?

A They are deliberately not inbred. Yes, sorry, I remember now. "Inbred", refers to a mating process which ensures homogeneity, outbred to one that ensures variation. I mean, we are outbred, I guess, so it's very important that background data is kept on individual strains from specific suppliers and also with respect to time as well, so that it's kept chronologically, so that any shifts in patterns within the control can be acknowledged, so if one performs a study, if one looks at a specific study, if one wishes to look at the background data associated with that study it's important not only to go to the strain and the supplier, but also to the time period when those studies were being performed.

Q Okay, and in a Reproductive Toxicity Study you mentioned at Glaxo the background data was derived from the control animals used in the studies; correct?

A Yes.

Q And what's a control animal?

A It's an animal that undergoes exactly the same procedures as all the other animals in the study but is not dosed with the active compound.

Q And presumably the control animal in a given study was delivered from the supplier as part of the same group of animals; correct?
A Yes. It was randomly selected from that group of animals.
Q Do you recall a rodent breeding unit at Glaxo?
A No I don't. No.
Q Do you recall Glaxo breeding its own rats at any point during your time there?
A I don't. No.
Q If you had a question about whether Glaxo ever breeded its own rats, who would you ask?
A I would ask somebody who was involved in animal -- in the supervision of the Animal Technicians and the animal rooms and I can't think of a specific name, people have changed over the years, but there is a separate group within Glaxo who were responsible for the welfare of animals -- for their breeding, for their -- because animals, I think, are specifically bred in some areas for -- but very -- for things like -- yes, which of course contradicts what I just said. I believe it's possible that some animals were -- but I believe there are -- what are they called? You know, the very genetically-specific animals and animals like that, but I'm not sure. But anyway, this group looks after the

maintenance of all the animal facilities, looks after animal welfare, and if there were any breeding they would be -- they would know about it but I'm afraid I'm not aware of any animals that are specifically bred in GSK.
Q Okay.
Were there particular instances where Glaxo wanted to use Allen & Hanbury Wistar rats versus Sprague Dawley rats, and if so, why?
A I don't recall there being Wistar rats -- sorry -- Sprague Dawley rats -- until much later, until the late 1990s, and the primary reason for that was because of the carcinogenicity studies, because background data is very important in the evaluation of carcinogenicity studies. I'm only familiar with the use of the Allen & Hanbury strain in Reproductive Toxicity Studies and I don't recall any stage at which that was questioned.
Q And do you recall instances where Glaxo decided to use Dutch rabbits versus New Zealand White rabbits for particular drugs?
A No. The Dutch Belted rabbits were used when I arrived and they came from a specific supplier, and then at a specific point a decision was made to move to the New Zealand White rabbit, and that, I believe, largely had to do with the availability of those rabbits from

the supplier.
Q Do you recall how many years -- for how many years the Dutch rabbits were used at Glaxo for Reproductive Toxicity Studies during your time there?
A I believe that they were used up until, probably, the early/middle nineties.
Q Okay.
If you were to approximate how many Reproductive Toxicity Studies on all of Glaxo's drugs under development, during your time there, involved the Dutch rabbits, what would your estimate be?
A I have no idea. In the short time it was there I couldn't answer it. I really don't know.
Q Could you estimate how many Reproductive Toxicity Studies were performed at GlaxoSmithKline on its drugs under development from the time you started with the company in 1986 through 1995?
A No I can't.
Q Would it be more than 100?
MR SHEEHAN: Objection.
THE WITNESS: It would be a guess. I don't know.
BY MR AYALA:
Q Would it be more than five?
MR SHEEHAN: Objection.
THE WITNESS: It would be more than five.

BY MR AYALA:
Q Would it be more than 20?
MR SHEEHAN: Objection.
A I would be guessing, I can't answer it.
BY MR AYALA:
Q Do you recall how many Reproductive Toxicity Studies you performed while you were at GlaxoSmithKline?
A No I don't.
Q Do you recall performing any?
A I don't recall any specific study, no.
Q But you recall the fact that you performed Reproductive Toxicity Studies at Glaxo?
A I did, yes.
Q Now, when Glaxo outsources the conduct of an animal study to -- withdraw that.
During your time at the company when Glaxo outsourced Reproductive Toxicity Studies to outside parties, did it always enter a contract for services?
A I don't know the details, but yes. There was an extensive contract existent which covered that.
Q Did Glaxo participate in the design of the studies?
A Yes. Yes.
Q Did Glaxo receive drafts of the study protocols to review and comment on?
A Yes.

Q And did Glaxo receive drafts of the Animal Study reports to review and comment on --
A Yes.
Q -- before they were finalized?
A Yes.
Q Okay.
Just wait until I'm finished with the answer --
MR SHEEHAN: With the question.
A Sorry.
BY MR AYALA:
Q -- or with the question.
Did Glaxo -- was it your understanding that Glaxo had the right to access the raw data generated as part of the contracted study?
A Yes.
Q And was it your understanding that the contract organization maintained the background data and the raw data for the studies consistent with GLP requirements?
A Yes.
Excuse me, can I just get some more water?
VIDEOGRAPHER: We'll go off-the-record. The time is 11.22 am.
(11.22 am)
(Off-the-record)
(11.23 am)

VIDEOGRAPHER: We are going back on the record. The time is 11.23.
Dr Newall, I'm handing you what I've marked as Newell Exhibit 3. I'll ask you to take a look at that.
(Exhibit 3 marked for identification)
(Pause) Dr Newall, do you recognize this document?
A I do.
Q Okay, what is it?
A It is the ICH -- the current, I believe -- ICH guideline for the conduct of Reproductive Toxicity Studies specifically related to male fertility -- oh, sorry, it is the entire guideline, isn't it -- and male fertility. Yes.
Q It relates not only to male fertility but also to Reproductive Toxicity, correct?
A Yes. Yes.
Q Okay?
A Yeah.
Q The parent guideline for this ICH S5 document at Exhibit 3 was published in June of 1993, correct?
A Yes.
Q So it was published when you were at Glaxo conducting Reproductive Toxicity Studies, correct?
A Yes.
Q And when did you become aware of this document? These

guidelines?
A I was aware that they were in progress, I guess in the late eighties, early nineties.
Q How did you become aware that they were in progress?
A I believe that one of my colleagues was involved in their production.
Q Okay.
Did there come a time -- well, who was that?
A Mark Sutherland. He was head of Reproductive Toxicology at the time.
Q Yes. Thank you.
Did there come a time when these S5 guidelines were made applicable within Glaxo with respect to its conducting of Reproductive Toxicity Studies?
A Yes. There was an initiative to align our protocols and, where necessary, relevant SOPs, with the new guidance, and there were decisions -- I said that there is some flexibility within this guideline now, so there was an internal guidance drawn up that described, or gave advice on how best to apply this guideline, what the default study designs would be, and any other relevant information regarding their performance, to support Project Teams and Study Directors.
Q Okay.
The internal guidance that was developed with

respect to the ICH S5 guidelines, that was developed within Glaxo?
A Yes. Well, it was an -- I don't know what you would call it. It was a covering document, if you like, on this that described how Glaxo was going to apply this document. It wasn't a GLP or an SOP or anything like that. It was an advice document, if you like, on how best to apply it, and also, as I say, the other relevant documents were amended as well, where necessary, to ensure compliance with the new guidance.
Q The other relevant documents being the SOPs with respect to --
A Yes.
Q -- Reproductive Toxicity Studies?
A Yeah.
Q Okay.
So, when did Glaxo make the decision, to your knowledge, to apply the S5 guidelines in-house?
A I don't specifically know I'm afraid. I can't answer that.
Q Okay.
Did Glaxo also make the S5 guidelines applicable to its contract --
A Yes.
Q -- organizations? Yes?

A Yes.
Q Do you know whether the S5 guidelines were applied within Glaxo shortly after they were published in 1993?
A I don't know what the delay was. There would have been a delay between the finalization of the guideline and ensuring that all the support necessary for those guidelines was in place before they were actually enacted because it would be -- and they would only be enacted when our GLP group, relevant SOPs, et cetera, were all in place and everybody was absolutely confident that the new studies were being performed fully in line with GLP, so there would have been some transition period.
Q Okay.
Did you have an understanding at or around the time the S5 guidelines began to govern practices at Glaxo, did you have an understanding as to whether the S5 guidelines had also been adopted by regulatory agencies in the United States, Europe and Japan?
A I think -- I can't remember the convention, but I think once a guideline is accepted at a specific step, then effectively it has been adopted by the agencies, and the agencies themselves then bring out their own -- not version, but their own -- okay, I'll use the word, "Version" -- their own version of that guideline written

in their format within their appropriate documentation. I could be wrong about this but I guess for the FDA it might have been published in the is Code of Federal Regulations, something like that. I'm not exactly sure. I don't remember the terminology I'm afraid, but yes, and that would be an acknowledgement that at that stage it was to be applied.
Q Okay.
Do you recall who authored the internal guidance document at Glaxo with respect to the S5 guidelines?
A I don't. Again, I'm guessing it would be Mark Sutherland as he was head of Reproductive Toxicology, so he would have taken responsibility for ensuring that document was in place.
Q Okay.
If you turn, please, to page 1, its page numbers are on the bottom right-hand corner of the document?
A Yes.
Q The introduction reads:
"For the purpose of the guidelines" --
MR SHEEHAN: So not the (i).
THE WITNESS: Yes. Sorry. I didn't realize that. Yes. I have it now.
BY MR AYALA:
Q The purpose of the guideline, mentions:

"There is a considerable overlap in the methodology that could be used to test chemicals and medicinal products for potential reproductive toxicity".
That point is essentially touching on what you testified to earlier --
A Yes.
Q -- that there were different standards and resulting animal waste, correct?
A Not different standards, different designs.
Q If you look down just past -- just below the first paragraph, the guideline reads:
"The actual testing strategy should be determined by:
" - anticipated drug use especially in relation to reproduction".
Do you agree with that statement?
A Yes. It's very general but yes, in principle.
Q And the actual testing strategy should be determined by the form of the substance and relative administration intended for humans?
A Yes.
Q And the actual testing strategy should be determined by making use of any existing data on toxicity, pharmacodynamics, kinetics and similarity to other compounds in structure and activity. You agree with

that statement as well?
A Yes I do.
Q Okay.
What are kinetics?
A It's the disposition of the drug within the animal post-dosing. The amount in the blood, the levels, this sort of thing.
Q Is metabolism a component of kinetics as well?
A Yes it is, yes. A drug disposition, metabolism and kinetics, yes, and all would be considered.
Q Okay, and what are pharmacodynamics?
A The pharmacological action of the drug.
Q What does that mean, exactly, to a layperson?
A Yes. The anticipated effect at a receptor, the response to the drug by the biological system.
Q Okay, and if you look on the next page, page 2, at the top, the guideline S5 reads:
"The aim of reproduction toxicity studies is to reveal any effect of one or more active substance(s) on mammalian reproduction".
Do you agree with that statement?
A I do.
Q Of course, rats are mammals, right?
A Yes.
Q Rabbits are mammals?

A Yes.
Q And humans are mammals?
A Yes.
Q Okay.
Apart from the ICH S5 guideline, did Glaxo adopt all of the other ICH guidelines that covered topics that included Animal Study -- Non-Clinical Studies and Animal Studies?
A Yes they did.
Q What other guidelines, if any, apart from ICH guidelines and guidelines published by regulatory authorities did Glaxo adopt or endeavour to follow?
A With respect to Reproductive Toxicology?
Q Yes.
A None that I'm aware of.
Q Okay.
Do you recall any handbooks or treatizes on Reproductive Toxicity testing that Glaxo maintained, kept, referred to?
MR SHEEHAN: Objection.
THE WITNESS: Within the library there were a number of books that related to techniques used.
BY MR AYALA:
Q Okay, so Glaxo had a library. Describe the library.
A It was a bookcase containing a number of books that were

relevant to toxicology in general.
Q Were they relevant to Reproductive Toxicology specifically?
A Sorry, I interrupted. There were some books that covered topics of Reproductive Toxicology, yes.
Q How -- what was the size of the library in terms of --
A It was small.
Q Small?
A We are probably talking no more than five books or so.
Q Do you remember what the books were, any of them?
A No. One of them is the directory of teratogens which I believe is by an author, Shepherd, who put it together. They were largely reference books, but I can't recall any of the others. I believe there were one or two books on in vitro toxicology as well that would have -- that I would have had because of my particular role at that time.
Q We've spoken about Animal Studies. I want to talk about In Vitro Studies as well.
A Yes.
Q Now, you mentioned, I recall, during your time at Glaxo, you took part in attempting to develop a screening methodology, the purpose of which was to try to identify the potential teratogenicity of drugs; correct?
A Correct.

Q Was that screening methodology -- did it have a name?
A There were a number of different tests that had names, but the overall screening approach was one that was being considered in a number of areas, not just to look at teratogenic effects, but at other possible effects as well.
Q Okay.
What was the methodology called?
A The initial methodology that we looked at was micromass cultures. These are dense cultures of mesenchymal cells derived from rats. Rat limb buds I think, rat fetal limb buds.
Q What's a rat limb bud?
A So, during the development of the limb it starts as a budding, a swelling, on the fetus, and we would remove those from the fetus -- I can't remember which day we did it. I can't remember a lot of the details around this, the test. We would remove those. The cells in that limb bud would be largely mysenchyme cells, the cells that eventually become cartilage and bone and muscle, I believe, and those cells would be disassociated into a cell suspension, and then the cells would be cultured in a dish and under normal conditions -- by, "Normal", I mean using a specific gas regimen, incubating in a specific gas regimen, in the

presence of a specific culture medium -- those cells would differentiate and form dense foci which could be stained, so you would end up with a disc of cells with dark spots in it, and those spots represented differentiation into -- a process differentiation which is important in reproduction and in organogenesis, and the purpose of the test was to see if chemicals disrupted that process of differentiation, so some groups of cells were incubated with various chemicals and then a staining technique and an evaluation technique was used to look at the number of differentiated foci. At the same time we determined whether or not the cells were killed by the chemical, so we measured the proportion of cell death. All of this was done at a range of doses and was related to a control which was untreated, and the purpose was to look for chemicals that appeared to specifically affect differentiation without having any other deleterious effect on the cell culture, so a cell -- a system that, at the time we were developing those, was considered to be a possible indicator of a teratogen.
Q How did you determine whether the differentiation of the cells was impeded?
A By -- it was a very simple process. The cells were stained, I think it was a blue stain, I can't quite

summary tables that would provide group changes, mean changes, this sort of thing. Those data would then be collated into a report, a textual report would be written that would summarize those results intake, so they would describe the results as they were presented in the tables and the appendices, and they would draw conclusions specifically with respect to a specific type of finding, and those are some of the end points that are described in this particular document, the ICH document.

Then a conclusion would be produced which would make conclusions about the data in the study with respect to what it did to the animals, basically, the outcomes of the animals. Those reports would then go to a project representative on a Project Team who was concerned, or who was leading for that particular compound, and it would be that individual's responsibility to prepare a summary description of the reproductive effects of that compound to go into an appropriate regulatory document, an IND, a marketing application or whatever, or a Clinical Trials application, and they would do that in consultation with all relevant experts and when one is assessing reproductive data, it isn't solely done by Reproductive Toxicologists. When you read out those particular considerations, that shows the breadth that

is considered, so you might talk to the chemists about the structure, you might talk to the pharmacologists. You would certainly talk to the drug metabolism specialists who would provide data on the exposure of the animals, and maybe the metabolites. Are the metabolites the same as you see in humans? You would look for all the relevant data that enabled you to determine the degree of reassurances these data provided for human safety, and then there would be a conclusion that would go into whatever the relevant document was to support a specific Clinical Trial, or, ultimately, to support a Marketing application that would include those conclusions, and as you progressed through the development of the drug and got more and more data from various sources, not just -- I mean, once the reproductive studies are completed, it doesn't end there. The interpretation of those data and their putting into a clinical context is something that continues throughout the lifetime of the drug from the INDs, the Clinical Trials applications, through to the Marketing application and beyond.

MR SHEEHAN: Tom, that was a very long answer, obviously, and you've probably got questions. We've been going again, about an hour and 20. I don't know when would be a good time to take a break but in the not so distant

future that would be appreciated.

BY MR AYALA:

Q Yes, that sounds good. I just have a few more and then we can break in a couple more minutes to follow up on that answer.

Now, you mentioned the appendix component of the study reports. The appendix is derived from the raw data, correct?

A It should be a transposition, an entirely accurate transposition of the raw data. In fact, of course, in modern systems that's exactly what it is. It is derived from the entered data. One thing I can add is that, of course, the data within the reports is subject to a quality assurance check which is performed by the group I referred to before who were responsible for ensuring that GLP is adhered to within the company, and they would do an independent check to ensure that the data accurately represented the data within the report, both tables and summaries accurately reflected the original raw data.

Q But the Quality Control people aren't having a second look at the specimens, are they?

A I don't know. It's possible that under some circumstances that might occur, but I don't know.

Q You mention that the interpretation of the Reproductive

Toxicity Study results continues as the drug goes to market and after the drug is sold on the market, correct?

A Yes. I mean, it doesn't -- it is -- not the interpretation. The interpretation may remain the same throughout, but data is always looked at in the light of new data, so occasional reappraisals might occur in the light of new data. That's always possible, and not just possible, that's important that that should occur.

Q Sure, because after the drug is marketed and sold, the individuals like yourself at Glaxo have the benefit of reports from the clinical experience with the drug, correct?

A Correct.

Q And reports from peer-reviewed literature studying the drug, correct?

A Absolutely, yes.

Q And the post-market information, whether it's from the clinical experience or peer-reviewed literature should be factored in in the reassessments of the studies as that information becomes available to the company, correct?

MR SHEEHAN: Objection.

THE WITNESS: It's important that all safety data is reviewed in a timely manner, yes.

MR AYALA: Now, I just want to close the loop on -- well, let me just check my notes here for a second. (Pause) Okay. Now is a good time to break. A good stopping point.
VIDEOGRAPHER: We are going off-the-record. The time is 12.05 pm.
(12.05 pm)
(Off-the-record)
(1.00 pm)
VIDEOGRAPHER: Here begins Media No. 3. The time is 1.09 pm. We are back on the record.
BY MR AYALA:
Q Dr Newall, I'm handing you what's been marked as Exhibit 4.
(Exhibit 4 marked for identification)
A Thank you.
Q Exhibit 4 is a document entitled, "Glaxo Company Report No WPT/85/145, GR38032F: Effects of Intravenous Administration on Pregnant Dutch Rabbits and Their Progeny (Study No L10873)". Do you recognize this document, Dr Newall?
A I don't know whether I've read this before, no, because I was not involved in its production, nor in its review at any stage.
Q To the extent that you don't recall being -- you don't

recall reviewing this document?
A I don't recall reviewing or -- no. I don't.
Q Do you recall seeing this document at any time in the last couple of weeks?
A This particular document?
Q Correct.
A No I don't.
Q No?
For the benefit of those on the phone, we just went back on the record. One document has been marked for identification as Newell Exhibit 4. It is Glaxo company report WPT/85/145 and it has a title indicating that it is a study of the effects of intravenous administration on pregnant Dutch rabbits and their progeny.
Now, earlier during our conversation you mentioned that as part of your role at GlaxoSmithKline from 1995 forward, and perhaps even earlier, you were involved in interpreting Animal Studies conducted by or on behalf of the company. Do you recall that?
A Yes.
Q And as part of your work on the Labeling committee as the Non-Clinical Representative of that committee, that committee, the members of the committee, looked to you for insight and interpretation of various Non-Clinical Studies for their drugs that were the subject of their

committee meetings, correct?
A No. That's not the way it worked. The Labeling committee was approached by teams that represented the Project Team for a particular drug, for example, and they would do all the interpretation, the presentation of the data, they would make proposals as to the appropriate wording. My purpose on the committee was to facilitate that that occurred, and then to be involved in the final discussion as to what was specifically included in the label, and it was very rare that Non-Clinical data were discussed in that way. Most of the work of the Labeling committee is clinical.
Q But you were consulted by the Project Team as a Reproductive Toxicologist within the company, and where Non-Clinical Studies were discussed in the context of a label you offered insight; correct?
MR SHEEHAN: Objection.
THE WITNESS: No. It didn't work like that. The Project Team would -- I wasn't there as a consultant. I was there as a -- to represent Non-Clinical on the Labeling committee, so it was more a role of a facilitator rather than a consultant, and the Project Team would consult with relevant experts which may -- would not have necessarily included myself. I don't recall them ever doing that, and they would then present a series of

documents which I would review and where we were dealing with a Non-Clinical issue I would review that, and on the basis of the information provided I would advise the -- at the Labeling committee -- I would advise on whether or not I thought it was appropriate, based on those data, in conjunction with input from other members of the committee.
BY MR AYALA:
Q Okay, and so your review and input of the clinical data provided to you was part of your role on the Labeling committee, correct?
MR SHEEHAN: Objection.
THE WITNESS: The team provided me with the conclusions. They did the review. I did not.
BY MR AYALA:
Q But you did review -- you just testified you reviewed the material. Do you recall that?
A I read the material that they provided. Yes.
Q Okay.
Were there instances where you were called upon to either draft or review and comment on Non-Clinical data for a drug label?
A I was asked to review and comment on text that was proposed to go into the label.
Q And by whom was the text typically proposed?

been Clinical Pharmacologists who would have had input into who went in, so it wouldn't have simply been their analysis that would have been taken into account, but I'm not an expert in that field whatsoever, so I wouldn't have felt in a position to contribute.
BY MR AYALA:
Q Okay.
Do you recall offering any input into the issue of whether Herg effects of Zofran® should be included in the Zofran® label?
MR SHEEHAN: Objection.
THE WITNESS: I don't.
MR AYALA: What's the objection?
MR SHEEHAN: I think, "Herg effects", is vague and ambiguous.
MR AYALA: I'm sorry, I didn't hear the answer.
A No I don't. I think -- could you repeat the question then?
Q Sure. Sure. Do you recall offering any input with regard to whether the Herg effects of Zofran® on the human body should be included in the label for Zofran®?
MR SHEEHAN: Objection.
THE WITNESS: I do not.
BY MR AYALA:
Q Do you recall when you were asked for input on the topic

of Herg effects?
A I think I was -- I can't remember exactly. I think it was early 2000 that the issue first arose.
Q Okay.
Do you recall whether the topic of Zofran®'s Herg effects on the human body were ultimately adopted in the United States label for Zofran®?
A I don't.
Q Do you recall whether the topic of Herg effects of Zofran® on the human body was included in any label for Zofran® throughout the world?
A I don't recall any dates, no.
Q Okay.
Do you recall any instances in which anyone at GlaxoSmithKline asked you to draft or review and comment on proposed language for the Zofran® label with respect to Reproductive Toxicity?
MR SHEEHAN: Objection.
THE WITNESS: Could you be more specific with regard to, "Zofran® label"?
BY MR AYALA:
Q I'll ask it again and be more specific, yes.
Do you recall anyone at GlaxoSmithKline asking you to draft or review and comment on proposed label language with respect to Reproductive Toxicity in the

United States label for Zofran®?
MR SHEEHAN: Objection.
THE WITNESS: I don't, no. I don't think so, no. No.
BY MR AYALA:
Q Okay Dr Newall, I'm handing you three exhibits now. These exhibits have been marked as Newall 7, 8 and 9.
(Exhibits 7, 8 and 9 marked for identification)
A (Pause) Thank you.
Q I'll ask you to take a look at those and I'm going to direct you to some specific portions of that. (Pause)
Exhibit 7 is -- first of all, do you recognize Exhibit 7?
A No I don't.
Q Okay.
It is an email from Amy Ebel to various people at GlaxoSmithKline, not including yourself.
A No.
Q But it attaches an attachment entitled, "2014-11-10 Zofran® Oral Draft Proposed.doc", and Amy Ebel writes:
"Here is current draft labeling - still a few things in the works that can hopefully be advanced via email before Monday's meeting. Thanks for team's comments/inputs thus far ... getting there".
Attached is a draft label for Zofran®, and it's a red-lined version of the label, and if you turn,

Dr Newall, let's see, to section 8.1 of the label, it appears on ZFN00098170 -- you see that?
Okay, and do you see the heading, "Use in Specific Populations", 8.1, "Pregnancy?
A Yes.
Q And under that there is a subheading called, "Animal Data"?
A Yes.
Q And a paragraph, and underneath the paragraph is bracketed language that says:
"[FDA Note to sponsor: Please provide full details of animal reproduction studies]".
Do you see that?
A Yes I do.
Q And then underneath that notation, the FDA note to sponsor, there is a notation that says:
"[GSK: Amy to contact Derek Newall regarding FDA changes to text. Action pending]"?
A Yes.
Q Do you see that? Okay.
Does this document refresh your memory with regard to whether anyone reached out to you to seek your input on Zofran® labeling in the United States?
A Yes.
Q Okay.

A Yeah.
Q So now, if you turn to Exhibit 8 there is an email from you, Derek Newall, to Amy Ebel on January 29 2015, and it -- the subject is, "Comments from FDA: Zofran® US Labeling, PLR conversion for oral formulations", and you write to Amy:
"Amy details of reproductive studies as requested, basically it had no effects of any significance. I've included a rabbit iv study that was not referred to in the original label. Not sure if this is required here. Best regards, Derek".
Do you recall writing that?
A I do now, yes.
Q Okay.
Then there is an attachment to your email at the top of that chain, and if you turn to the attachment, which is ZFN00583515, it says, "Confidential", and then it has a heading of, "Animal Data", and then some text and a list of some reports.
A Yes.
Q Did you create this document, ZFN583515?
A Yes.
Q Okay, and did you create this document on or around January of 2015?
A You said January? It's dated March. 25 March.

Q I see it. Okay. Right there. Drafted March 25, although it's attached to an email that says -- that's dated February 25, 2015?
A Oh right.
Q But it says the draft on ZFN583515 says March 25 '04.
A Oh right. I understand. Yes. Sorry about that. Yeah.
Q Okay so --
A That makes sense.
Q So let me ask it again to clean it up. Did you create ZFN00583515, the animal data summary, on or around January of 2015?
A Yes.
Q Okay, and how did you go about creating this document?
A I can't recall specifically the events around this, but the original document that you provided said that -- what was it -- within 8.1 Amy Ebel said that -- let me just find it again, that the FDA required us to provide full details of animal reproduction studies, and ,"Full details of reproduction studies", is a very vague term. There are a lot of studies, and I would almost certainly have clarified that, .in fact I'm sure I clarified it. It was my habit to clarify by telephone. I found that it was much easier to contact people by phone and to discuss through exactly what was required. I'm assuming that Amy had a document from the FDA, or had

a transcript of a conversation with the FDA specifying what she -- what they required, and on that basis I generated this document, and the fact that I produced this document suggests to me that this document fulfilled the requirements of the FDA as told to me by Amy when I contacted her.
Q When did you contact Amy and ask her for clarification?
A I don't know because -- I don't know.
Q Where were you when you contacted her?
A I would have been in my office at the time in Ware.
Q How long did you have a conversation with her where you sought clarification?
A Sufficiently to feel that I had clarified it to the best of my ability and that I knew what the FDA required.
Q Do you remember how long that took?
A I don't, no.
Q Did she give you an answer right away?
A I imagine she would have done, yes, because I would have continued until I got an answer, unless she had to go back to the FDA to seek further guidance which she may have done. I can't recall what the sequence of events was.
Q Do you recall whether you had more than one phonecall with her?
A I don't, no.

Q Do you recall when the phonecall was?
A No.
Q Do you recall what she said to you?
A No. No I don't, other than the document that I produced was in response to whatever she said. That, presumably, fulfilled the requirement that the FDA had made.
Q Is there anything that you believe would refresh your recollection of what your understanding of the FDA requirements were, as relayed to you by Amy?
A I can't think of what would do that, no.
Q Now, earlier you testified that when an issue arose with regard to analysis of Reproductive Toxicity data, that the company would always consult an appropriate expert. Do you recall saying that?
MR SHEEHAN: Objection.
THE WITNESS: Not in those specific terms, no.
BY MR AYALA:
Q Okay.
What did you say?
A I can't recall what I specifically said, but I don't believe I said that we would always consult an appropriate expert. Do you refer to an external expert or somebody internally?
Q Either one.
A Yeah, any new information would be reviewed by

appropriate experts within the company.
Q Amy's request to you with regard to Zofran® and analyzing Animal Study data, was that the first request you received in your almost 30 years at GlaxoSmithKline to analyze and comment on Reproductive Toxicity data?
MR SHEEHAN: Objection.
THE WITNESS: That's not what they state. I believe they --
MR SHEEHAN: Are you talking about any Reproductive Toxicity data or are you talking about Zofran®?
BY MR AYALA:
Q Any Reproductive Toxicity data.
A Okay. Could you rephrase?
Q Yes.
Amy Ebel emailed you, or contacted you in or around November 2014 and asked you to interpret Reproductive Toxicity data and studies for Zofran®; correct?
A No she did not. She asked me to provide full details of animal reproduction studies which was so vague I required clarification. My clarification ended in my producing this particular document, so I can only assume that this is what was requested, but not what you were saying in your question.
Q Now, in order to provide full details of the Reproductive Toxicity Studies you had to interpret them first, correct?

A No. Not at all. The studies on Zofran®, the Reproductive Toxicity Studies on Zofran®, were performed to GLP. Those studies were analyzed at the time that they were recorded. They were robust studies. They involved doses that were sufficiently high to produce quite severe maternal toxicity. They were very thorough studies. They were reviewed by the experts in Glaxo who produced them, who performed them. They were reviewed by other experts during the insertion into regulatory documents, and the conclusions that were made of those studies were provided in summaries. Those reports and those studies have also been reviewed by the FDA, by the European agencies and by the Japanese authorities, all of whom reached exactly the same conclusions that Glaxo experts arrived at. Those conclusions are included in summary documents --
Q Okay, I'm --
MR SHEEHAN: Hold on, hold on, just let him finish.
A -- additional data. There is absolutely no need for me to go back and rereview data that has been so extensively reviewed and the reviews of which have been accepted by regulatory authorities during marketing applications.
BY MR AYALA:
Q Objection, move to strike as completely non-responsive.

Okay.
Earlier today you testified that you had no involvement in conducting any of the Reproductive Toxicity Studies for Zofran®. Is that still your testimony?
A It is. It still is.
Q Okay.
So, you have no personal knowledge, you have no first hand knowledge of what activities went in to conducting the Reproductive Toxicology Studies studies for Zofran® because you weren't there. You weren't involved, correct?
MR SHEEHAN: Objection.
THE WITNESS: I don't need to have that first hand data. I know that they were performed to GLP. I know the integrity of the people who reviewed them. I know the integrity of the regulatory agencies like the FDA that reviewed them. I have complete confidence in those summaries.
BY MR AYALA:
Q You have confidence in it but you don't know because you were not personally involved in them, correct?
MR SHEEHAN: Objection.
THE WITNESS: My personal involvement is not necessary for me to have confidence. I'm aware of the process and I

know that the process was followed and that gives me confidence.
BY MR AYALA:
Q But the basis of your testimony about the Reproductive Toxicity results of Zofran® is what somebody else wrote down in a document and what somebody else told you, correct?
MR SHEEHAN: Objection.
THE WITNESS: It's what experts wrote in documents and it's what experts have reviewed and concluded and agreed with. It's perfectly reasonable for me to accept what is in those summaries based on all I know of the quality and integrity of the people who have reviewed those data in the past.
BY MR AYALA:
Q I understand you feel it's reasonable for you to accept the results. My question is; when you accept the results, you are relying on what other people wrote and what other people told you about the conduct of the Reproductive Toxicity Studies; correct?
MR SHEEHAN: Objection.
THE WITNESS: I disagree. I'm not relying on it. I know it to be the case. I have complete trust in the integrity of the people who performed those studies. There is no reason whatsoever why I should in any way disregard what

they wrote simply because I was not directly involved in them.
BY MR AYALA:
Q I understand that's what you believe but you actually think it's possible to know something as a fact without observing it or witnessing it first hand?
MR SHEEHAN: Objection.
THE WITNESS: If you trust the people who witnessed it, yes.
BY MR AYALA:
Q Very well. Very well. That's fair.
So, back to Exhibit 8 which contains Derek Newall's summary document created on or around January 2015 of the Zofran® Animal Study data; correct?
A Correct.
Sorry, could you repeat that question? I think I didn't quite hear you.
Q Sure. This document, Exhibit 8, contains your summary of the Animal Study data, Reproductive Toxicity data for Zofran®, correct?
A No. This document contains -- to my recollection, this document contains extracts from summaries prepared by others of the Zofran® data, selected paragraphs that contain the information that I had confirmed was required by the FDA.
Q Okay.

When Amy Ebel reached out to you to prepare this summary of Zofran® Animal Study data, the Reproductive Toxicity data to be precise, was that the first time that anyone at the company asked you to prepare a summary of Reproductive Toxicity data for a drug of GlaxoSmithKline?
A I can't recall whether that's the case. It is possible in the past I've been asked to do that. I don't know.
Q And it's equally possible that you had never been asked to do that?
MR SHEEHAN: Objection.
THE WITNESS: It is possible.
BY MR AYALA:
Q Okay.
What resources did you consult in creating the Animal Study summary at Exhibit 8?
A I requested the Non-Clinical overview, the current version of the Non-Clinical overview. That is the summary -- Non-Clinical summary document contained in a current marketing application under ICH.
Q Okay.
A I asked for the most recent of that because I assumed that that would have the information that was required.
Q Okay.
Let me -- so you provided the summary in response to

the FDA's request for full details of the Reproductive Toxicity Studies without reading any of the primary source Animal Studies; correct?
A Correct, because I had already clarified that what the FDA wanted, and what, "Full details", referred to, was additional information to that which was included in the document that they provided.
Q Did Amy Ebel tell you that the FDA asked you to only look at the clinical -- Non-Clinical overview?
A No. She would not have done that. That would have been my decision.
Q Did she tell you that the FDA did not want you to consult the full Animal Study reports.
MR SHEEHAN: Objection.
THE WITNESS: I have no idea what the discussion was, but I think that would be very unlikely that she would have said anything like that. That would have been my decision, based on what she told me was required of the FDA.
(Dial tone)
MR SHEEHAN: It's happened before. We've just got to dial back in. We've got the info.
MR AYALA: Let's go off-the-record for a few minutes.
VIDEOGRAPHER: We are going off the record. The time is 1.55.

(1.55 pm)
(off-the-record)
(1.57 pm)
VIDEOGRAPHER: Going back on the record. The time is 1.357 pm.
BY MR AYALA:
Q You mentioned something earlier about reproductive studies, toxicity studies, being provided to the FDA. Did you provide any Reproductive Toxicity Studies to the FDA?
A No.
Q Did you have any communications with the FDA about Reproductive Toxicity Studies?
A I don't believe so. Not that I'm aware of.
Q Do you have any first hand knowledge -- did you see anybody provide Reproductive Toxicology Studies to the FDA?
A No.
Q So the basis and the only basis for your testimony that Reproductive Toxicology Studies were provided to the FDA is what somebody else told you, correct, or what you inferred?
MR SHEEHAN: Objection.
THE WITNESS: I would infer that from the fact that Marketing applications were put in and the reports would

be contained within those documents.
BY MR AYALA:
Q Okay.
Did you look at those documents to confirm that all Zofran® Reproductive Toxicity reports were in there?
MR SHEEHAN: Objection.
THE WITNESS: I was not involved in the process behind the submitting of the Marketing application so I would not have done that.
MR SHEEHAN: Again, just give me a moment to register my objection.
THE WITNESS: Sorry. Yes.
BY MR AYALA:
Q But along the lines of what you just testified to, you would expect that all relevant Reproductive Toxicity reports for Zofran® or any other Glaxo drug would be provided in a timely fashion to regulatory agencies, correct?
MR SHEEHAN: Objection.
THE WITNESS: I would expect that those reports that were necessary under current guidance and regulations were provided but I'm not aware of exactly what the requirements are for inclusion of reports in a marketing application, so...
MR AYALA: Okay, so...

A So I would have expected that they would have been provided in line with that guidance.
Q Do you have an understanding that it's Glaxo's policy and practice to provide Reproductive Toxicity Studies to regulatory agencies only when asked?
MR SHEEHAN: Objection.
THE WITNESS: As I say, I'm unaware of what the specific guidance is regarding that. Whatever the guidance is I would imagine that GSK complies with it.
BY MR AYALA:
Q You would expect GSK to comply with it, correct?
A I would expect GSK to provide what was necessary. Yes.
BY MR AYALA:
Q I'm handing you what has been marked as Exhibit 5, Dr Newall. It's a large document.
MR SHEEHAN: Can we sort of put the other ones to the side or do ...
MR AYALA: I would keep them out, actually. I'm sorry, that's the wrong one.
MR SHEEHAN: You do not want -- sorry.
MR AYALA: I'm a little bit out of order. I need to do 4 before 5. I just need to find 4.
MR SHEEHAN: We have 4.
BY MR AYALA:
Q Excellent. Okay. So, I'll refer you to the document

that has been marked Exhibit 4, and this is Glaxo company report WPT/85/145, Effects of Introvenous Administration on Pregnant Dutch Rabbits, and as I understand, Dr Newall, you have never seen this document before, correct?
A No I haven't.
Q And in preparing your response to the FDA's request for full details this was not one of the reports you consulted?
MR SHEEHAN: Objection.
THE WITNESS: I did not consult any reports, as I said.
BY MR AYALA:
Q Okay.
Now, you did list reports in your response to the FDA, correct?
A I did, yes.
Q And WPT/85/145 at Exhibit 4 is one of the reports you listed, correct?
A Correct.
Q And you listed that report as support for the language, the proposed language in the US Zofran® label, correct?
A I did. Correct.
Q In fact, you drafted a statement in Exhibit 8, your response to the FDA's request that says, with regard to report WPT/85/145:

"In an intravenous study in rabbits no adverse effects on embryofetal development was seen at doses up to 1.5mg per kilograms per day, but at the high dose 4mg per kilograms per day, there was a slight increase in the incidence of early fetal death".
Do you see that?
A I do.
Q And that was language that you crafted yourself?
A I can't recall. I may have taken it from another source.
Q You noted with respect to the report of an increase in the incidence of early fetal death, you noted to Amy Ebel in your cover email that you included a rabbit iv study that was not referred to in the original label, correct?
A Yes, I state that.
Q Okay.
So the finding in the study that there was a slight increase in the incidence of early fetal death was significant enough in your mind to propose including it in the Zofran® label for the United States, correct?
MR SHEEHAN: Objection.
THE WITNESS: No. Not at all. I believe that what happened was that I referred back to a version of the Non-Clinical overview, a recent version of the

Non-Clinical overview, where the text had been considerably paraphrased and that I felt that given I had determined what the FDA required, that the current version of the Non-Clinical overview did not give me the appropriate text, and what I think I did at that point is that I went back and asked for earlier versions of the same document, and I believe that at some point I found a version that included this particular text and given -- that was not in the current label -- and therefore included it for completeness.

My -- I'm sure that the reason why it was not in there was because the FDA had chosen not to have it in there, because they regarded the finding as of no significance, and -- but I provided it for completeness because I had been asked -- at the time I was aware what I had been asked for. I can't recall exactly what that was, so I put it in there for completeness, not because I thought there was any significance in this particular text, and they were writing -- reformatting the whole label, so therefore I thought it appropriate to do that.

However, in the reformatting of the label, which I guess is the format of the current label, I don't know whether or not they have included this particular sentence, whether, given that they originally considered it to be of no relevance and therefore excluded it from

the label, they continue in that belief and that therefore it is not in the current label.

Q First of all the Zofran® label is GlaxoSmithKline's label, correct?

A No. It's -- the GDS is ours. The labels, I believe, are -- certainly the US label is written by the FDA based on information we provide.

Q And so GlaxoSmithKline does not accept responsibility for the Zofran label in the United States, correct?

MR SHEEHAN: Objection.

THE WITNESS: GlaxoSmithKline accepts responsibility for the data that underpins the label in the US.

BY MR AYALA:

Q But not for the label itself, correct?

MR SHEEHAN: Objection.

THE WITNESS: The label itself, the finalling wording, is agreed with the FDA but the FDA, as far as I'm aware, and it's not my field, have final say in what that label should contain.

BY MR AYALA:

Q Okay.

So you're speculating, really?

A I'm not a regulator. I am to some extent. I'm not in Regulatory and I should not have engaged in that particular conversation, yes.

Q Okay.

With regard to your statement that the FDA must have concluded that your clause about increased incidence of fetal death should not go into the label, you're speculating about that too, aren't you?

A I'm speculating that -- yes I am.

Q Okay.

Would you agree, Dr Newall, that a dose-related increase in the incidence of embryonic death during a reproductive organogenesis study is a finding that should not be taken lightly?

MR SHEEHAN: Objection.

THE WITNESS: No. There are circumstances where -- it is a finding and it should be considered, but whether it has any relevance depends on context and a range of other factors.

BY MR AYALA:

Q Okay.

A It has to be put in context before one could arrive at that conclusion.

Q Okay.

Can you turn -- Exhibit 4 -- to the page that's -- has the Bates number on the bottom right ZFN00079162?

MR SHEEHAN: Take your time to familiarize yourself with the document, doctor, if you need to. (Pause)

THE WITNESS: Yes.

BY MR AYALA:

Q Are you at ZFN79162?

A I am, yes.

Q Do you see the section at 2,2 entitled, "Incidence of Early or Late Foetal Death (Table 2)"?

A Yes I do.

Q Okay, and there's a statement by the author of this document from GSK that states:

"There was significant evidence of an increasing dose related trend in the number of early or late deaths".

Do you see that statement?

A I do.

Q Okay.

Do you presume that the author of this document from GSK was a person of integrity of the sort that you described earlier today?

A I do.

Q Okay, and are you in a position, sitting here today, to disagree with this author's finding that the evidence of increasing dose-related trend was significant evidence?

A It was statistically significant, yes.

Q But they didn't write, "Statistically significant", did they? They wrote that there was significant evidence of

an increasing dose-related trend in the number of early or late deaths. Do you see that?
A Yes I do.
MR SHEEHAN: Tom, you're starting to yell a bit. I mean, we are right here. We can hear you.
MR AYALA: I'm not yelling.
MR SHEEHAN: I sounds like you are to me.
THE WITNESS: It's followed by a statement with a P value. I would assume that -- but it is an assumption -- that the use of the word, "Significance", refers to the statistic that is provided immediately below the sentence.
Q Okay.
Are you familiar with Wilson's Principles of Teratology?
A I was. I'm not sure I can remember them at the moment.
Q Do you recall that one of his principles refers to manifestations of deviant development?
A I can't recall specifically.
Q Okay.
Do you recall that fetal death is one of the four manifestations of deviant development in a Reproductive Toxicity Study?
MR SHEEHAN: Objection.
THE WITNESS: I don't recall that, no, but ...

BY MR AYALA:
Q Okay.
Dr Newall, I hope handing you what has been marked as Newell Exhibit 28 which is a summary of James Wilson's Six Principles of Teratology by the Embryo Project Encyclopaedia. If you turn to the third page out of 6, the second full paragraph, it reads:
"Wilson's fifth principle, 'The Four Manifestations of Deviant Development are Death, Malformation, Growth Retardation and Functional Deficit'".
Do you see that?
(Exhibit 28 marked for identification)
A I do.
Q Okay.
Does this refresh your memory as to whether fetal death is one of the four manifestations of deviant development under Wilson's principles?
A What it states here is that death is a manifestation of deviant development, but it doesn't say that death in all cases is a manifestation of deviant development. Deaths could be for a number of different reasons, not necessarily because of malformations. It could, for example, relate to the condition of the dam.
Q Okay.
If you can turn to page -- I'm going to go by Bates

number, in Exhibit 4, ZFN00079165?
A I don't have a 79165, do I?
MR SHEEHAN: Is this an incomplete ...
THE WITNESS: It is, yes. Oh sorry. What? There is something else attached to it, is there? I'm sorry. Oh I see. Yes. Sorry. That was a report. Right. I'm there now. Yes.
BY MR AYALA:
Q Okay.
ZFN00079165 is entitled, "Table 2, Incidence of Early or Late Fetal Death", and this is a table listing the incidence of early or late fetal death in both controls on one hand, and, on the other hand, rabbits who were administered intravenous Zofran® at three dose groups, 0.5, 1.5 and 4.0mg/kg/day. Do you see that?
A Yes I do.
Q Okay.
First of all, do you know whether any one at GlaxoSmithKline analyzed the fetuses, these dead fetuses listed in Table 2, to determine whether their death was caused by a malformation or whether it was caused by something else?
A I don't know that, although I would say that I don't believe it's possible, depending on the state of the deaths and the time they occurred, in most cases it

would be very unlikely one could interpret -- get any meaningful data from a resorption in a rabbit.
Q Do you know whether anyone at GlaxoSmithKline conducted a follow-up in vivo study in an effort to determine whether these reported fetal deaths could be replicated?
A One thing I would say about these fetal deaths is that four of them occur in one litter. In the absence of that one litter the incidence of fetal death amongst other litters within the high dose group are unremarkable. That's an immediate flag that there is something specifically of concern with that dam.
Q I want to talk with you about that, but first --
A Okay.
Q -- I'm going to ask you to answer my question, which was do you know whether anyone at GlaxoSmithKline conducted another intravenous study of these rabbits in an effort to replicate these findings?
A I'm not aware of that because I had nothing to do with the early development.
Q Okay.
A So I can't comment on whether or not --
Q Okay, so now back to you point.
A There was another study.
MR SHEEHAN: Don't talk over him. Let him finish his answer.

BY MR AYALA:
Q So now back to your point. You said if you take away the four embryonic deaths from one litter, that that would significantly alter the results. Is that what you said?
A That's what I said. Yes.
Q Okay.
So as it stands now, you have nine -- in the dose group of 4 mg/kg you have nine litters out of 14 litters that have reports of embryonic death, correct?
A Yes.
Q Okay.
If you take away four from that litter you have five litters out of fourteen litters that have embryonic death, right?
MR SHEEHAN: Objection.
THE WITNESS: I'm sorry, I don't ...
MR AYALA: You're objecting right now but I don't know ...
MR SHEEHAN: I think so. I'm not following it at all, but...
A No. No.
BY MR AYALA:
Q If you take away the four that you just mentioned, if you take away the four from the nine then you end out with five out of fourteen litters that have --
A You're talking about the number of litters affected?

Q I am. I am.
A Yes.
Q Five out of fourteen litters affected is 35 per cent of the litters affected with embryonic death.
MR SHEEHAN: Objection.
BY MR AYALA:
Q Is it your testimony that that is not significant evidence of fetal harm?
MR SHEEHAN: Objection.
THE WITNESS: I'm suggesting that these deaths have to be taken in the context of the study and have to be taken in the context of other studies performed in rabbits with ondansetron, if they exist, and that any conclusion about embryofetal deaths within this study has to be taken broadly in the context of all studies performed. I'm not aware of the results in other studies, although I believe they're referred to in here, but based on the fact that all these studies have been reviewed, as I said, by experts in whom I have complete trust, and that their conclusion was that these results were not significant overall, then I have no concerns for these particular data.
Q Okay, and am I correct that you also have complete trust in the integrity of the author of this document who stated that there was significant evidence of an

increasing dose-related trend in the number of early or late deaths?
A He was stating a fact.
Q He? Do you know whether it was a he?
A I think I read -- oh no I don't. No. I was looking at another report. Sorry. I don't know who wrote this.
Q Okay.
A They were still --
Q But you presumed that they were at GlaxoSmithKline?
A Absolutely.
Q You have complete trust in their integrity, right?
A And they were stating a fact. There is an increase in the number of deaths in those groups which shows statistical significance. Those are facts. Their interpretation is another matter, and they can only be interpreted in the light of other data -- maternal toxicity, for example -- what were the body weight findings at that group? Can you -- can we look at those data?
Q Assume for a minute that there were body weight findings.
A Yes.
Q That would still represent an indirect effect of fetal harm in the --
MR SHEEHAN: Objection.

BY MR AYALA:
Q -- in the embryonic deaths, correct?
A It would show that if there was severe maternal toxicity in the high dose group where those deaths occurred, which were primarily in one litter, it would show that perhaps that dam in particular was severely affected by the drug.
Now, if there was general toxicity induced in the drug, the mother would have loss of condition, and under those circumstances she might not have been able to sustain a normal pregnancy. It doesn't indicate anything wrong with the fetuses, but perhaps a fault -- a problem with the mother because she was unable to sustain those, because of her loss of condition, because of maternal toxicity, and as I say, this study, and the findings in these studies, such as this finding you're referring, has to be taken in the context of all the other studies that were performed within ondansetron and ...
Q I understand, and I'll ask you just to assume that some of the embryonic deaths -- assume for the sake of the discussion that some of the embryonic deaths were contributed in part by maternal weight loss. Even with that assumption, the fetal deaths represent at least -- if not conclusively, I'm not saying it's conclusive

Page 154

WPT/86/021. Do you see that?
A Yes.
Q This is entitled:
"GR38032F: Effects of intravenous administration on pregnant AHA rats and their progency)Study No R10937)".
Do you see that?
A Yes.
Q Okay.
Now, this was a study, we know, that was sponsored by the Glaxo entity in Ware UK, correct?
A Yes.
Q And we know that by the study number. You see that?
A Yes.
Q Okay.
Have you ever seen this study before?
A No I haven't.
Q Okay. You can set it aside.
Okay, I'm handing you what have been marked as Newall Exhibits 14, 15 and 16.
(Exhibits 14, 15 and 16 marked for identification)
Let's turn to Exhibit 15 if we can here.
MR SHEEHAN: 14 or 15 did you say?
BY MR AYALA:
Q This is -- forgive me, this is Exhibit 14. Okay.
Dr Newell, do you have handy Exhibit 33? No, I'm

Page 155

sorry, I'm going by the wrong numbers. Do you have handy Exhibit 8 as well, if you could get that out so you can cross-reference?
A Yes.
Q Exhibit 8 is the response to the FDA. Okay. All right.
So Exhibit 14 is a Glaxo company report WBP -- do you know what, "WBP", stands for?
A It refers to the drug metabolism section, but I don't know why "BP".
Q Okay.
WBP/88/039. This is distribution of radioactivity in the pregnant rat following oral administration of C-GR38032 (GR38032K) at a dose level of 15 mg/kg whole body autoradiography (MET 435). Have you ever seen this report before?
A No I haven't.
Q Okay.
Do you have an understanding from the title of what kind of non-clinical Study Report this is?
A I do, yes.
Q Okay.
What is it?
A It shows the distribution of labeled ondansetron in the rat following a dose of 15 mg/kg, at least it shows the distribution of a radioactivity derived from that dose,

Page 156

so it may include metabolites as well as the parent compound.
Q As well as the parent compound?
A Yeah.
Q What are the metabolites of Zofran®?
A I'm not aware of that.
Q Okay, and it shows not only the distribution of radioactivity in the rat-administered Zofran® but it shows the distribution of radioactivity and the degree of placental transfer --
A Yes.
Q -- after a single dose of Zofran® to 12, 13 and 19-day pregnant albino AHA rats. Do you see that?
A Yes.
MR SHEEHAN: Are you reading from somewhere? I'm not --
BY MR AYALA:
Q If you look just at the very first page inside the cover.
The fourth paragraph on that page summarizes the results in saying:
"The results of this study show that the rat fetus will receive exposure to ..."
Paraphrasing, Zofran®:
"... and its metabolites following oral administration of the drug to pregnant females".

Page 157

Do you see that?
A I do.
Q Okay.
Now, this was a finding in a Glaxo report of placental transfer of Zofran® and exposure to a fetus during pregnancy, and that finding was made in 1988, and I asked you to pull out Exhibit 8 so that you could cross-reference the studies that you listed there, and you can tell from the report numbers on that page that the Reproductive Toxicity Studies listed in Exhibit 8 were conducted in years 1984, '85 and '88. Do you see that?
A Yes.
Q As the -- as an individual with responsibility for Reproductive Toxicity testing and Non-Clinical affairs at Glaxo for roughly 30 years, have you seen instances other than this one where a placental transfer study was performed after the Reproductive Toxicity Study?
MR SHEEHAN: Objection.
THE WITNESS: I can't recall any particular case.
BY MR AYALA:
Q Does it make sense to you as a person experienced in conducting and overseeing Reproductive Toxicity Studies to perform a Reproductive Toxicity Study before you have the information about placental transfer?

A It does make sense because the assumption is that placental transfer takes place. It's incredibly rare that it doesn't, and, in fact, under current guidance, I don't think placental transfer studies are done any more.
Q You're assuming that the drug crosses the placental barrier, but if you don't do the placental transfer study first, then you don't have any information about the extent and duration of the exposure to the embryo or fetus, do you?
MR SHEEHAN: Objection.
THE WITNESS: You do, because you have kinetic data that shows the residence of the drug, its rate of metabolism, the kinetics we talked about earlier, and the frequency of dosing, for example, in order to ensure that animals are properly exposed are based on those data, not on the longevity of radioactivity. This is a relatively crude system. There are far more precise ways of determining how long a drug remains in a system by measuring the drug itself directly in the blood of the animals.
Q In the blood -- measuring the drug in the blood of the mother animal, correct?
A Of the mother animal, and assuming the worst case that the drug is freely transferred across the placenta, so you are assuming a worst case when you analyze the data,

so one could argue that a placental transfer study is unnecessary, and, in fact, as I say, I don't believe they're done any more because there are so few examples of drugs that are not transferred, and with our current understanding of the physicochemical transfer -- the characteristics of compounds that transfer across the placenta, I believe it's possible to make determinations like that simply from understanding their structure and the structural implications.
Q Do you believe that -- I'm trying to understand what you just said. Do you believe that the placental transfer of Zofran® was obvious in -- the placental transfer of Zofran® in mammals was obvious to GlaxoSmithKline researchers back in the '80s when these Reproductive Toxicity Studies were performed?
A I don't know whether it was but they would have assumed that there was placental transfer. I mean, had they -- sorry. Carry on. I apologize.
Q Well, go ahead how did they --
A No, it's okay.
Q Somebody -- some of the researchers at GlaxoSmithKline felt it important to conduct a placental transfer study, correct?
A It's possible that -- in fact it is probable that it was a requirement at the time, and that it was done for

completeness, but that it didn't inform the design of the study because the study was going to be performed anyway with the assumption of complete placental transfer, so at the very -- the only influence this could have had on the interpretation of those studies was if it didn't cross the placenta. The fact that it did doesn't in any way affect the interpretation of these studies because that assumption was made anyway.
Q Unless the results of the placental transfer study add additional information about the rate, extent and duration of the placental transfer, correct?
MR SHEEHAN: Objection.
THE WITNESS: As I've said, I believe -- these particular studies are not particularly accurate -- "accurate" is the wrong word -- they're very simple studies. They involve dosing the animals and then sectioning them and you taking autoradiographs, and then measuring drug related material, and there are better ways of determining the information that you have just mentioned than performing a study like this. In fact, by measuring the kinetics of the drug within the maternal animal one would get more precise data than one would here, which is why it's no longer required.
BY MR AYALA:
Q Okay, and we discussed earlier the S5 ICH guidelines --

A Yes.
Q -- that mentioned the relevance of kinetic data --
A Absolutely.
Q -- in conducting In Vivo Studies, and we established that those guidance, the parent guidelines were implemented in 1993 and in Glaxo some time after that. Do you remember that?
A Yes.
Q And so the Reproductive Toxicity Studies that you listed in your response, your proposed labeling language for Zofran®, were all conducted in the '80s before the ICH guidelines referencing kinetics were implemented.
MR SHEEHAN: Objection to the characterization as proposed labeling language --
A I would just amend -- yes, exactly. That is not proposed labeling language. That's information requested by the FDA.
BY MR AYALA:
Q Okay, so your response to the FDA listing the Reproductive Toxicology Studies lists the Reproductive Toxicology Studies from the '80s, correct?
A Yes.
Q And those studies, when conducted in the '80s, were not conducted with the benefit of implementation of the S5 ICH guidelines; correct?

Page 166

2015 you served in that capacity and you also were serving on Labeling committee and the pregnancy Outcome Advisory Panel?
A Yes.
Q Okay, and at no point during those eleven years -- well, I shouldn't say that. At no point during the nine years from 2006 to 2015 did the finding from is placental transfer of ondansetron during early human pregnancy come to your attention, correct?
MR SHEEHAN: Objection.
THE WITNESS: Correct.
BY MR AYALA:
Q All right.
His published conclusion was that:
"A significant amount of ondansetron was present in all embryonic compartments of the human embryo. The developmental significance of this drug exposure requires further investigation, ie whole embryo culture".
My question is; from 2006 until your time retiring from the company as director of Worldwide Non-Clinical Safety, did you ever have any discussions with anyone about additional study of Zofran® in light of the reports that it was being widely used to treat morning sickness in pregnancy?

Page 167

MR SHEEHAN: Objection.
THE WITNESS: There was no need to repeat what were already robust studies performed at high doses that caused toxicity, and that showed no evidence of teratogenicity, with the assumption during the risk assessment performed that there would be placental transfer. This -- so this does not change any of the considerations that were made when the original assessment was made.
BY MR AYALA:
Q Okay.
Earlier -- well, that didn't answer my question though.
A Okay.
Q My question was; from 2006, when this finding was reported forward, until you retired from the company as director of Worldwide Non-Clinical Safety in 2015, did you have any discussions with anybody at the company about conducting additional safety assessments of Zofran® in light of the finding that it was being widely prescribed for use to treat morning sickness in pregnancy?
MR SHEEHAN: Objection.
THE WITNESS: There were no discussions because they were not necessary. Such studies were not necessary, and would have not provided any additional data of value, so

Page 168

the original studies, which, as I say, showed no evidence of teratogenicity at high doses that caused maternal toxicity and where maternal transfer via the placenta to the fetus was assumed.
BY MR AYALA:
Q And those were the same studies, the reports of which you have not reviewed, correct?
MR SHEEHAN: Objection.
THE WITNESS: As we've said before there were reasons why I was perfectly happy to accept the results of those studies as reported in summary documents by my colleagues.
BY MR AYALA:
Q Do you believe that the finding that a drug -- pharmaceutical drug crosses the human placental barrier and results in embryonic exposure in significant amounts is a finding that would be important to healthcare providers or patients considering whether to use Zofran® to treat morning sickness in pregnancy?
MR SHEEHAN: Objection, calls for speculation.
THE WITNESS: Yes -- I can't speculate on that.
BY MR AYALA:
Q Do you think it would be reasonable to include a finding of placental transfer of a pharmaceutical drug during pregnancy in a warning label for a pharmaceutical drug

Page 169

at GlaxoSmithKline?
MR SHEEHAN: Objection.
THE WITNESS: As I said, the assumption is that it will transfer.
BY MR AYALA:
Q Then why not just say that in the label?
MR SHEEHAN: Objection.
THE WITNESS: This is completely outside my area of expertize and responsibility because this study is a clinical study, so it may be that clinical discussion might determine that there is a place in the label for it, but from a safety point of view, and a Non-Clinical safety point of view, this does not add anything to the existing risk assessment and, as I say, I can't comment on how a Clinical Pharmacologist or -- might handle this, and how Regulatory might handle a label in respect of this paper.
BY MR AYALA:
Q Okay.
A I'm sorry if I may take a bathroom break?
MR AYALA: Sure.
VIDEOGRAPHER: Going off-the-record. The time is 3.40 pm.
(3.40 pm)
(Off-the-record)
(3.53 pm)

19. This is a product information label for Zofran®. If you look at the back, the last page, the last two pages actually, numbered 14 and 15, this is a Zofran® label with the most recent amendment of February 21, 2005 and the manufacturer is GlaxoSmithKline Australia. Is this -- this is the label that was used at the time for Zofran® products in Australia, okay? I'll ask you to turn, please, to page 2 of the document and look at the first full paragraph where it reads:

"A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. The clinical relevance of this finding is uncertain".

Okay? Do you recall in or around 2005 or before being involved in discussions among the Label committee where the committee proposed that language to the effect of that which I just quoted be included in Zofran® labels worldwide?

MR SHEEHAN: Objection.

THE WITNESS: I don't recall any specific discussions, no.

BY MR AYALA:

Q Let's move on to the next document. Okay Dr Newall, I'm handing you what has been marked as Exhibit 20.

(Exhibit 20 marked for identification)

This is an email from Jane Bacon and you, Dr Newall, are cc-ed among the members cc-ed on the email --

A Yes.

Q -- dated November 11, 2008. Do you recall who Jane Bacon is?

A Yes. She was in INCR and she was, presumably, the INCR member who was responsible for documentation relating to Zofran®.

Q I see, and it appears from her cover email that she is attaching a revised GLC briefing document with expanded suggested text to be included in the label for ondansetron Zofran® and more detailed supporting information, and she attaches the Global Labeling committee briefing document. You see that?

A Yes.

Q And it's titled, "Non-Clinical Update from November 2008"?

A Yes.

Q And in the executive summary under the first heading, it reads:

"The current GDS [Global Datasheet] wording indicates that the potential to affect cardiac repolarisatin via blockade of hERG potassium channels is only relevant to the injection formulation. We propose that this data is pertinent to all formulations and

requests that the GDS is updated to reflect this".

Okay?

A Yes.

Q Do you recall being involved or hearing discussions about the proposal of the Labeling committee in 2008 to include data on Herg effects in labeling worldwide for all formulations of Zofran®?

A I do not recall that discussion, no.

Q Okay.

If you can go to the last paragraph of the same page, the briefing document reads:

"Comparison of the hERG IC50 (808 nM equivalent to 235mg/mL) of ondansetron determined by Kuryshev (2000) with systemic exposures obtained in the clinic confirmed that effects in vitro could be clinically relevant - an oral dose of 24mg achieved a maximum plasma concentration of 194.4 ng/mL".

Question; what is your understanding of the term, "The clinic", as used in that sentence?

A I would be speculating. I would assume it meant in clinical use.

Q Have you ever seen the concept of clinical use referred to as, "The clinic"?

A I don't recall having so, or ...

Q Okay, but you don't know and you would be speculating?

A I don't know. Yeah.

Q Okay, and in the conclusion the committee recommended -- I'll read it:

"We recommend that the Non-Clinical information section of the ondansetron GDS be revised as follows, and subsequent Global Core Texts for each formulation be amended appropriately", and then the new proposed label deletes the word, "Injection", presumably because it's now going to apply to all formulations, and it goes on to say:

"A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via a blockade of Herg potassium channels at clinically relevant concentrations. In vivo, a lengthening of the QT interval has been observed in anaesthetised cats following intravenous dosing, but at doses exceeding 100 times those effective pharmacologically. Similar effects were not seen in cynomolgus monkeys. Transient ECG changes have been reported in the clinic (see Warnings and Precautions)".

And then the language that previously was there, "The clinical relevance of this finding is uncertain", is now deleted, and so the question is; do you recall raising any objection to this proposed language in November 2008 when that Labeling committee proposed it?

Page 182

A I do not recall objecting to that language, no.
Q Okay, and if you just take a look at the references, there is a reference to an article by Lorenzi in 1994, there's a reference to an article by Kuryshev in 2000, there's a reference -- and then there are references to two company reports, one from -- well, both are from 1991, and this Labeling committee in November 2008, as the basis in the references for proposing a label about the Herg effects of Zofran® and QT prolongation effects, are referring to studies that occurred at least 14 years -- no, no, forgive me, at least eight years prior to the date that the committee is recommending the label change; correct?
A Correct.
Q Do you recall thinking at the time, "Why has it taken the committee eight years to propose a warning label about Herg effects in QT prolongation when the basis for the proposal are studies that happened at least eight years prior to the proposal?"
MR SHEEHAN: Objection.
THE WITNESS: I do not recall.
BY MR AYALA:
Q Okay.
Let's move on.
Q I'm handing you what has been marked as Exhibit 22.

Page 183

(Exhibit 22 marked for identification)
Exhibit 22 is an email from Barbara Munch at GSK to you, Derek Newell, among others that forwards a safety announcement from the FDA dated June 29, 2012, and the announcement reads that the US Food & Drug Administration, FDA, is informing healthcare professionals and the public that preliminary results from a recently completed clinical study suggests that a 32 mg single intravenous dose of ondansetron, also known as Zofran®, may effect the electrical activity of the heart QT interval prolongation which could predispose patients to develop an abnormal and potentially fatal heart rythm known as Torsades de Pointes.
And -- and then it goes on to say that:
"GSK has announced changes to the drug label to remove the 32 mg single intravenous dose".
My question for you is, in or around July 2012 when you received this document, first of all, who is Barbara Munch?
A She still works for GSK. She worked for -- in RTP and I think she was responsible for documentation. I'm not sure specifically why she would have circulated this.
Q Do you recall being involved in any discussions with anybody about this, do you recall?

Page 184

A I do not recall anything around this. I'm afraid, no.
Q Set that aside.
Okay, Dr Newall, I'm handing you two more exhibits. They have been marked as exhibit numbers 23 and 24.
(Exhibits 23 and 24 marked for identification)
Exhibit 23 appears to be an email from Patrick Wier to various folks at GlaxoSmithKline, including you, dated Wednesday, November 28, 2012, and Dr Wier attaches a document entitled, "Pregnancy 'pilot' for POAP November 2012", so that's for the Pregnancy Outcome Advisory Panel, correct?
A Yes.
Q And from reviewing the list of recipients of this email on Exhibit 23, does it appear to you to be an email to the members of the Pregnancy Outcome Advisory Panel?
A It does, although there are some people here who I'm not familiar with, so I suspect it was the POAP and others were included for reasons I don't know.
Q Okay, and so if we turn our attention to Exhibit 24, Exhibit 24 is the attachment, one of two attachments, Exhibit 24 is the attachment entitled, "Pregnancy 'pilot' for POAP, November 2012". Okay?
A Yes.
MR SHEEHAN: I think it's called, "Pregnancy Pilot Update"?

Page 185

BY MR AYALA:
Q I was reading from the file name in Exhibit 23, but no, if we turn to Exhibit 24, thank you, we can see that the title of the document is, "GSCP Pregnancy 'pilot' Update by Greg Powell, GSCP". What is GSCP?
A I think it's Global Clinical Safety and Pharmacovigilance.
Q Do you remember Gregg Powell?
A No I don't I'm afraid.
Q Do you remember the existence of a pregnancy pilot team in November of 2012?
A I don't recall it, no.
Q Okay.
Presumably its function overlapped at this moment in time with the Pregnancy Outcome Advisory Panel, since you and the members of that panel were getting a copy of this?
A Patrick clearly considered we should be aware of it, yes.
Q Okay.
I just want to review some of the information in these slides that went to the panel and you, including you. In the first slide the presentation -- just a moment. Greg Powell, just for the record, is gregoryepowell@gsk.com, so he's an employee of GSK?