IN THE COMPETITION APPEAL TRIBUNAL

Case No: 1524-1525/1/12/22

Salisbury Square House
8 Salisbury Square
London EC4Y 8AP

Monday 6th November – Friday 1st December 2023

Before:

The Honourable Mr Justice Marcus Smith
Eamonn Doran
Professor Michael Waterson

(Sitting as a Tribunal in England and Wales)

BETWEEN:

Appellants

Pfizer Inc. and Pfizer Limited & Flynn Pharma Limited and Flynn Pharma (Holdings) Limited

V

Respondent

Competition & Markets Authority

A P P E A R AN C E S

Mark Brealey KC, Robert O'Donoghue KC & Tim Johnston (Instructed by Clifford Chance LLP) on behalf of Pfizer

Jemima Stratford KC, Tom Pascoe & Alastair Richardson (Instructed by Macfarlanes LLP) on behalf of Flynn

Josh Holmes KC, David Bailey, Jennifer MacLeod, Julianne Kerr Morrison & Conor McCarthy
On Behalf of the Competition & Markets Authority

Monday, 13 November 2023

(10.00 am)

(Proceedings delayed)

(10.12 am)

THE PRESIDENT: Good morning. Before we proceed to Dr Fakes, two points: I think we understand there may be some issues with LiveNote. We are very happy to proceed without that, and we can make it good as and when. Secondly, you may have been told, you should have been told, that there is what is called a full building evacuation tomorrow. That does not include us, but you will have to be in the building before 10.00, I think conservatively 9.50, which I think probably means before 9.45, otherwise you are going to be stuck outside, unable to get in. So can everyone make sure that they are here in good time.

That may mean, I know it is not in the timetable, but that a 10.00 start might be pointful since we will all be here and there is no point in us twiddling our thumbs, but we will leave that to the parties because of course witnesses are being called tomorrow, but the witnesses absolutely need to know that we do not want them standing outside watching things go on from outside rather than being here. So if that could be communicated to them, that would be very helpful.

MS STRATFORD: Yes, thank you. Assuming the timetable stays roughly according to plan, they are not my witnesses, but shall we see how we get on today?

THE PRESIDENT: Let us see how we get on, but I think we just need to know that things are not going to be quite as they normally are tomorrow.

MS STRATFORD: Absolutely, thank you very much.

So, sir, may I proceed, then?

THE PRESIDENT: Of course.

MS STRATFORD: Thank you.

I call Dr Fakes, Dr David Fakes.

DR DAVID WILLIAM FAKES (affirmed)

THE PRESIDENT: Dr Fakes, good morning. Do, please, sit down.

A. Thank you, sir.

THE PRESIDENT: You should have some water there.

A. Thank you.

THE PRESIDENT: I think you have a file which has your witness statements in. We deal with documents electronically here, and I just want you to be happy that if you want to see more of a document that is shown on screen, do say and counsel will take you to it, because the ability to leaf through lever-arch files is not granted to you.

A. Thank you very much.

THE PRESIDENT: But I do want you to be able to find context if you need it, so do not hesitate to ask as and when and we will find the document that you need.

A. Thank you, sir.

THE PRESIDENT: You will have now some questions.

Examination-in-chief by MS STRATFORD

MS STRATFORD: Thank you, sir.

So Dr Fakes as well as the hard copy bundle I hope you have in front of you which should be called "Flynn's factual evidence", then you should also have a copy of a letter dated 10 November from Macfarlanes.

A. Yes, I do.

Q. I will come to that in a minute.

So if you could open the bundle, please, and go to tab 1 of that bundle.

A. Yes.

Q. You see there it says "First witness statement of David William Fakes"?

A. Yes, I do.

Q. If you could go to page 41 of that tab, please?

A. Yes, I am there.

Q. Is that your signature, Dr Fakes?

A. Yes, it is my signature.

Q. Thank you. If you go to the third tab in that bundle, tab 3.

A. Yes, I am there.
MS STRATFORD: Sir, I do not know, sorry, is it helpful for the Tribunal if I give Opus references as well?
THE PRESIDENT: It probably is. I mean, we access them. I have it in front of me electronically, but it is probably best if you do that.
MS STRATFORD: I am now at {XC1/2/1}.
THE PRESIDENT: Thank you.
MS STRATFORD: I am sorry, I should have said that earlier.
THE PRESIDENT: Not at all, no, we have them here, but it is probably best for the record that you do that.
MS STRATFORD: So Dr Fakes you can see there it says "Second witness statement of David William Fakes?
A. Yes, I do.
Q. Could you look at page 19 of that tab, so for Opus that will be page {XC1/2/19} of the same tab.
A. I am there.
Q. Is that your signature, Dr Fakes?
A. Yes, it is my signature.
Q. Thank you. Turning for a moment to the letter that you have, that is a letter from Macfarlanes. I am afraid I do not have the Opus reference for that as yet, but if you could look at the annex to that letter which is a table, and can you see there, there are five sets of minor corrections -- it is to your first statement?

A. Yes, I can.

Q. Are you familiar with those?

A. I am, yes.

Q. Subject to those minor corrections, does the evidence in those two witness statements remain your evidence to the best of your knowledge and belief?

A. Yes, it does.

MS STRATFORD: Thank you.

I will hand over now to the CMA. I am not sure who from the CMA?

THE PRESIDENT: I am grateful.

Just to check, Mr Brealey, you do not have any questions for the witness?

MR BREALEY: I do not, thank you very much.

MS STRATFORD: I am sorry, I should have checked that.

THE PRESIDENT: No, not at all.

MS STRATFORD: Thank you, Dr Fakes.

Cross-examination by MR MCCARTHY

MR MCCARTHY: Sir, we have, for convenience, prepared a hard copy bundle, cross-examination bundle, containing the documents which I propose to take Dr Fakes to in the course of the cross-examination. If it assists the Tribunal I could hand those up and also hand a copy to Dr Fakes.

THE PRESIDENT: That would be very helpful, yes, thank you.

Q. Good morning, Dr Fakes.
A. Good morning.
Q. As I have said, you have two bundles in front of you: one is the bundle containing your witness statements that you have provided in this matter, and the other bundle is a bundle of documents which contain a number of documents which I will take you to in the course of cross-examination today, and I have some questions for you about those documents.

Now, you prepared two witness statements in these proceedings. For clarity, you did not prepare a witness statement or provide a witness statement in the original proceedings in this case, did you?
A. No, I did not, no.
Q. Your evidence was given by -- it was evidence on behalf of Flynn was given by Mr Walters who was Flynn's CEO at the time?
A. David Walters was codirector, we ran the company jointly. He gave two witness statements at the first proceedings.
Q. Yes. You heard also previously an application -- witness statements in support of Flynn's application for interim relief, but we do not need to concern ourselves particularly with those statements today.

I just want to begin by asking you a number of

questions about your professional background and your role in the management of Flynn. I want to begin, just by profession you are a registered pharmacist, is that not right?

A. I am, yes.

Q. And you began working for Flynn full-time in 2006 having first invested in the firm in 2004?

A. That is correct, yes.

Q. Your first witness statement in October 2022 explains that you were the CEO of Flynn at the time?

A. That is correct, yes, I was.

Q. When did you commence your role as CEO, it is just a point not picked up in the statement?

A. It was approximately about five years before that, so around 2017 when Dave Walters began to step down towards retirement.

Q. Yes. So as you pointed out, since 2004 you have led Flynn alongside David Walters and you are both -- you have both been executive directors in the course of your leadership of Flynn?

A. That is correct, yes.

Q. You were the only two executive directors, the other directors have been non-executive directors?

A. Yes, that is also correct.

Q. Now, I understand from your witness statements that you

and Mr Walters effectively split responsibilities in the management of Flynn. Mr Walters took responsibility primarily for commercial and financial matters, and you took responsibility, you say, in relation to scientific and technical matters?

A. That was broadly the case at the time, but obviously since his retirement I have been singularly responsible for most functions, all functions.

Q. Yes, but was that the division of responsibility in relation to the period that we are particularly concerned about which is the period between 2012 and 2016?

A. Yes, it was, yes.

Q. Now, in your first statement, you also explain that you shared an office with Mr Walters and would agree between you all significant decisions in respect of the running of Flynn; is that correct?

A. Yes, that is correct.

Q. And presumably this will have also included significant decisions in relation to the arrangement between Flynn and Pfizer?

A. Yes, that is also correct.

Q. In Flynn's evidence to the CMA, Flynn explained that the relationship between you and Mr Walters as executive directors and Flynn's board as follows, Flynn said

yourself and Mr Walters would discuss and agree strategies relating to particular supply arrangements and plans before they were put to the board for approval. Do you agree that that was the broad approach that you adopted?

A. Yes, that was generally the case, yes.

Q. Standing back from the detail for a moment, you would agree that yourself and Mr Walters were longstanding colleagues over a long period of time?

A. Yes, I do.

Q. You would work in close collaboration with one another in the management of Flynn and in significant decision-making in respect of Flynn?

A. Yes, that is true, we have.

Q. Moving on, in your first witness statement you deal with the characteristics of phenytoin capsules. Now, I will take you to your statement in a moment, but I just want to ask you a few brief questions about that before we do.

Now, Pfizer's expert, Professor Walker, points out that [phenytoin] was first prescribed as a treatment for epilepsy in around 1938, and that phenytoin was one of the oldest medications available for epilepsy, so it is common ground, is it not, that phenytoin was a very longstanding medication?

A. Yes, it is.
Q. It had been prescribed for a period of in and around 85 years or more?
A. Yes, 95 perhaps, I think the number is.
Q. Professor Walker also points out that for a significant time it was one of the most commonly prescribed AEDs worldwide, although since then of course its use has declined. That is also uncontroversial, is it not?
A. It is uncontroversial that its use has declined and continues to decline.
Q. And also that it was one of the most commonly prescribed AEDs for a long period of time?
A. Originally perhaps going back 50, 60 years, yes.
Q. So you would accept, would you not, there is a very great deal of data available in relation to the risks and side effects of phenytoin?
A. With the qualification that insofar as if you go back to the 1930s, the 1940s, it was a very light touch oversight of product safety in real life. So there was probably very little data collected, so you would put much more emphasis on the more recent data when you have got systematic and organised arrangements for pharmacovigilance for safety monitoring.
Q. But you would accept, I think -- subject to that qualification you accept that there is nevertheless

a very great deal of data available through that long history of prescription in relation to the risks and side effects of phenytoin?

A. Yes, there is a lot of data, but still new concerns are arising. There is the congenital defect concern, hypothyroidism, these are new issues which have arisen within recent years.

Q. Now, can I ask you to turn to a document which is contained in the bundle that I have provided in front of you?

A. Yes.

Q. It is at tab 3. It is a document entitled: "Flynn Pharma Communication Plan for the Introduction of Phenytoin Sodium Capsules". If you could turn to page 2 of that document, please.

A. Yes, I am there.

Q. Just to give the Opus reference also in relation to that document, it is {G/163}.

If we look at this document in section 1, we see at the bottom of section 1 the purpose of this document is explained. It is a communication plan, the purpose of which is:

"... to mitigate [healthcare professional] and patient concerns over the name change and to ensure seamless supply chain transition to the Flynn product."

Do you agree?

A. Yes, I see that, yes.

Q. And then if we look at the fourth paragraph down, we see that it says the following:

"In the case of the switch from Epanutin to Flynn Pharma Phenytoin Sodium Flynn Hard Capsules, there are no formulation changes to the product and the site of manufacture remains the same. It remains qualitatively and quantitatively identical in all but product name."

So you accept, do you not, that, as this document indicates, that there was no substantive change at all in relation to the -- in relation to the formulation of phenytoin sodium when Flynn first began to supply the product?

A. At that time, yes, that is the case, yes.

Q. It is right, is it not -- and I think this is just uncontroversial -- that it follows from that that Flynn did not incur any research or innovation costs in respect of phenytoin during the period that we are concerned with, 2012 to 2016?

A. That is true.

Q. Now, can I ask you to turn to tab 4 of the cross-examination bundle, please. This is the remittal decision and the Opus reference is {XA1/1/93}.

A. I am sorry, the page reference?
Q. Apologies, page {XA1/1/93} in the bundle.
A. Ah yes, I am there.
Q. Now, if we look at table 2.2, this is a table I think you are familiar with.
A. Yes, I am, yes.
Q. Yes. This table provides a taxonomy of Flynn and Pfizer's various activities in supplying phenytoin capsules in the UK during the relevant period, and it is obviously produced by the CMA.
A. Yes, that is right, and I do remember it.
Q. Now, in your first statement you object to the presentation of the table, but you accept that the table is accurate in its categorisation of the commercial activities which Flynn undertakes in the supply of phenytoin capsules.
A. I think what I said was it is accurate insofar as it goes, but it does not provide a balanced picture, and it does not separate out or distinguish, differentiate, activities from responsibilities, and I also said that the way they have aggregated some of the activities into a single line made it, in our submission, somewhat misleading.
Q. But you accept, I think -- for present purposes you accept that the crosses or the ticks are in the correct

places on the table?

A. In the context of that table, yes, but I did not agree with the balance of the table.

Q. That is understood. Now, I just want to consider this table for a moment. So we see then at the top of the table "Manufacturing", Pfizer continued to have exclusive responsibilities for all tasks in relation to the manufacture of the capsules which Pfizer continued to undertake at its plant in Germany?

A. No, I do not. They are physical responsibility -- they are physically responsible for the activities, but we are responsible for their conduct in accordance with the MA or the marketing authorisation: we subcontract the activity but not the responsibility, and that is quite an important differentiator.

Q. Yes, so I am focusing here on the actual activity in question. I appreciate you make your point about your overarching responsibility, but just focusing on the activities, I think you accept, then, that the manufacturing responsibility was that of Pfizer. That is clear, is it not?

A. In regard to the activities, yes.

Q. Yes.

THE PRESIDENT: Just to be absolutely clear, when you use the word "responsibility", that is absolutely ambiguous

between liability and conduct. What you are putting is who in fact did these tasks, irrespective of where the legal responsibility lies.

MR MCCARTHY: Yes, precisely, yes.

Looking down then, we see -- and I think you accept -- that the storage, processing, delivery and invoicing of orders in terms of the activities involved continued to be undertaken by wholesalers and a pre-wholesaler. Do you agree that is also correct?

A. I do agree, yes.

Q. It is correct, is it not, I think that during the relevant period, so this is 2012 to 2016, Flynn itself did not in fact have warehousing or delivery facilities?

A. Flynn has never had its own warehousing or delivery facilities, so like many other functions or activities, we contract them out, and in this matter we contracted them out to what was at the time known as UDG, but is now Alloga, and Pfizer, coincidentally, used the same company but different facilities within UDG.

Q. Yes. So at no point did Flynn actually take receipt of or dispatch of the capsules it ordered from Pfizer?

A. Not physical receipt, but financial receipt, ownership, yes, we did.

THE PRESIDENT: So just to be clear, and differentiating between who actually did something and who was

responsible for making sure that it was done, you are accepting that Flynn did not do these things, but are you happy with the tick under the Pfizer box in regards to these activities?

A. Insofar as it goes with the physical conduct of the activities, yes. I think where we differ is in terms of the legal responsibility, the complainant's responsibility.

THE PRESIDENT: Because I read -- and it may be my mistake -- from your last answer that you were coincidentally with Pfizer using the same contractor for warehousing, in which case I am just seeking clarification as to whether the tick in that regard under the Pfizer column is actually the one that you are agreeing with?

A. Perhaps if I try and clarify.

THE PRESIDENT: Please do.

A. Both Pfizer and Flynn happened to both use the same pre-wholesaler which was UDG or now Alloga. That was a coincidence, not that there is great choice. We in turn sent our stock which was held at UDG to our chosen wholesalers, which varied over time, but Pfizer -- I am unsure, they perhaps went with the direct to pharmacy model, but it was stock in a Flynn location and not stock in a Pfizer location, so it was our stock, our

responsibility, we managed it.

MR MCCARTHY: Sir, it may just help to point out that looking at the storage, that tick is in the pre-wholesaler column?

THE PRESIDENT: Yes, I see.

MR MCCARTHY: So, Dr Fakes, I put to you that the receipt and dispatch of the capsules was not an activity undertaken by Flynn, and you agreed with that.

A. I agree with that. Those are activities which we contracted out and paid the pre-wholesaler to fulfil on our behalf. They are far better and far more efficient than we could possibly be.

Q. That is understood, it was a subcontractual arrangement?

A. Yes.

Q. So essentially thinking about the route to market for the product after Flynn became involved in the supply chain, you accept that the route to market for capsules was essentially largely the same as that which existed prior to September 2012?

A. Yes, but there is only a limited number of ways really where the physical product can get to the patient, so the pharmacy will order from a wholesaler, and it could be a short line, a full line, there is quite a range of them, and they would make deliveries on the pharmacy, so there is no other way you can really do that.

Q. It was not the case where Flynn innovated in relation to the route to market, there is no suggestion of that?
A. No, we did not.
Q. The central difference really in relation to the route to market was simply that Flynn then became an additional element in that route to market?
A. No, I disagree. We were more than an element, we were legally responsible for all aspects of the product.
Q. Again, just thinking about the activities rather than responsibilities and distinguishing those two things, in relation to the activities which are involved in bringing the product to market, the essential difference was that Flynn became an element in that?
A. An element in the sense that we displaced the Pfizer element which existed prior to that, yes.
Q. Yes. Now, Dr Fakes, I would like to turn to the question of continuity of supply. If you could turn to your first statement, please.
A. Yes, I have it.
Q. And paragraphs 39 to 43, please. The Opus reference for the first statement is {XC1/1/17}.

Now, looking at your statement at paragraphs 40 and 41 you note that phenytoin sodium is characterised by a narrow therapeutic index and non-linear pharmacokinetics, and you accept that?

A. Yes, I do, yes.
Q. You then acknowledge that these features, ie the NTI -- I am looking here at paragraph 41, the NTI and non-linear pharmacokinetics:
"... makes prescribing the medicine and altering the dosage [what you describe a as] a more complicated process."
A. Yes, that is my view.
Q. Now, when you say "a more complicated process" I infer that what you have in mind, or at least part of what you have in mind is the principle of continuity of supply.
A. No, not at all. Continuity of supply is something quite different. What I am referring to when I talk about the NTI or the non-linear kinetics is it makes the whole management of the patient being treated with that drug more complicated, because the prescriber has to take into account those two factors, so it is really nothing at all to do with continuity of supply.
Q. You say nothing at all to do with continuity of supply, but when you refer to the implications of those two factors as resulting in a more complicated process, that is what I am asking about. Am I right to --
A. I am sorry, I perhaps misunderstood your first point.
Q. No, that is fine.
A. The continuity of supply is more of a concern where you

do have concerns about narrow therapeutic index in that there is a reluctance that you do not unnecessarily or without consent or foreknowledge, change from one source to another, but I think there is a lot of evidence on the file about this whole subject.

Q. Yes. So the implication of those two characteristics of phenytoin is an inhibition or an inability for patients to switch between different brands of the same phenytoin product?

A. It is not an inability because the fact is this switching was a reality in practice, and I think there is a lot of data which would show that, and I also say in I think paragraph 40 that there is nothing particularly special about phenytoin being an NTI drug. I say it is one of, I think, 240 such drugs.

Q. Dr Fakes, can we turn -- to be clear what we are referring to when we are talking about continuity of supply, can we turn to the MHRA guidance which is at tab 8 of your bundle.

A. Yes, I have found it.

Q. We see that this guidance was issued in November 2013, and if you look at approximately halfway down the page we see Category 1, and it says there phenytoin is listed as a Category 1 drug and it says there that for these drugs, doctors are advised to ensure that their patient

is maintained on a specific manufacturer's product.

A. I read that, yes, and it goes on also to give guidance to pharmacists, dispensing pharmacists which gives them the latitude to dispense any source.

THE PRESIDENT: Dr Fakes, just before you answer specific questions in relation to this, I wonder if you could assist us in whether this was something you were aware of at the time.

A. Thank you, sir. Absolutely not.

THE PRESIDENT: Are you seeing it for the first time in these proceedings?

A. Absolutely not, we were not aware. This guidance was issued in November 2013 and it followed a period of consultation on the part of the MHRA with various stakeholders which did not include Flynn. So we were unsighted, and the first hint of this that we got was when we were having discussions about the product naming in 2012 and the MHRA said: no, this cannot be a simple generic, it has to have some invented name or some qualifier.

When asked why, we were told this reflects emerging policy, a policy we had not seen until fully 13, 14 months after we launched.

THE PRESIDENT: So just so that I am absolutely clear, you were not involved in the framing of this document but

shortly after it was promulgated you would have seen its effects or its wording?

A. Yes, we saw it in November 2013, and I think as earlier submissions we have made say, it has always been Flynn's view, my view, that the guidance was loosely followed and in fact it had no teeth, and I think subsequent practice in prescribing and dispensing shows that -- it is NICE statements but they are not enforced, it does not have the power of regulation.

THE PRESIDENT: Thank you.

MR MCCARTHY: So you have accepted that when this guidance was published which was November 2013, you were aware of it at the time it was published?

A. That I was aware at the time it was published?

Q. You were aware of it after it was published?

A. Yes, yes.

Q. Yes. Now, this principle of continuity of supply was also reflected, was it not, in earlier guidance given by NICE in 2004?

A. From memory I think the guidance you refer to might have been SIGN which was the Scottish equivalent of NICE, Scottish Intercollegiate Guidelines Network, but it is certainly true to say the principles behind continuity of supply were not new in 2013, they were not new in 2004, and they had been in the literature for some

years.

Q. No, and can I ask you then to turn to tab 7 of the bundle, please. The Opus reference is {G/121/149}.

A. Yes, I have it.

Q. If you could turn to page 149, please, of this. It is an excerpt rather than the whole document which is very lengthy.

A. Yes, I am there.

Q. Now, we see there at the middle of the page that the 2004 National Institute of Care Excellence recommendation is set out and it states as follows:

"Changing the formulation or brand of AED is not recommended because different preparations may vary in bioavailability or have different pharmacokinetic profiles and, thus, increased potential for reduced effect or excessive side effects."

So that was actually the National Institute of Care Excellence's recommendation from 2004. Is that not right?

A. Yes, that is right. I believe there was also a Scottish equivalent around the same time, but --

Q. Yes, and you would have been aware of this guidance as of 2012?

A. Yes, I would. Yes, we would.

Q. Yes. So to be clear, you were aware of clinical

guidance in 2012 and in fact, to this effect, that essentially switching between brands is inadvisable?

A. Yes, we were aware, and we were also aware that, as I said earlier, it was not followed in practice, even to this day, within the last year, generic products have been approved as being interchangeable with the Flynn product.

Q. Then we see at 81, this is recommendation 81, this was the National Institute of Care Excellence's recommendation which we see there, it is new in 2012.

A. So this is, sorry, recommendation 81 you are referring to?

Q. Recommendation 81, and the recommendation states that:

"Consistent supply to the child, young person or adult with epilepsy of a particular manufacturer's AED preparation is recommended, unless the prescriber, in consultation with the child, young person or adult considers that this is not a concern."

A. Yes, that is what it says, yes.

Q. Yes. Then subsequently, to be clear about the chronology, the MHRA --

THE PRESIDENT: Again, what -- you may not be able to answer this, Dr Fakes, and if so, please do say, but what is the nature of the concern about tying the prescribed medicine to that of the particular manufacturer?

A. That is a good question. The concern is that you can test two products, A and B, and show them to be equivalent in a simple bioequivalence study where you are looking at the blood levels, the area under the curve, the maximum concentration, and the way you deal with that for narrow therapeutic index products is to use tighter limits statistically to, if you like, satisfy the hypothesis that the two products are the same, but there remains a concern that bioequivalence may not be enough to demonstrate beyond doubt therapeutic interchangeability, but the actual evidence for this in epilepsy is modest. I think one of the reasons that we have this continuity of supply principle reflects the understandable sensitivity of patients with epilepsy, because if you have a seizure it has a massive impact. If you go from a period of control to a period of less control, it is very traumatic, so there is a strong psychological element in deference to the patient as well, if you like, the scientific point at issue. I do not know if that helps.

THE PRESIDENT: Well, no, that does. The reason I was asking is because if there was a material difference in terms of the difference of the pharmacological product as manufactured one would expect that to be dealt with at the doctor's level --

A. Yes.

THE PRESIDENT: -- rather than by the pharmacy in consultation with the patient. Frankly, if I am going to a doctor wanting the best form of treatment, I do not expect to be consulted by the pharmacist, I expect to be told by the doctor what is best for me. So I was inferring from that, and you have confirmed, that the concern is a psychological one that you have the same manufactured product being given to you week in, week out by the pharmacy?

A. Yes, there is a strong psychological element. It is not the only aspect, and I think the experts who address you later will be able to speak better than I on the finer points.

PROFESSOR WATERSON: Can I check, since Pfizer manufactures these drugs as we have already established, that supposing the product came from -- as a parallel import would it be exactly the same product?

A. It is a good question, but one I cannot answer. At the moment, we took over responsibility in September 2012, and counsel took me to the communications plans. We could say with confidence that this product was one and the same, was to all intents and purposes identical.

As time has moved on, Flynn is responsible for the marketing authorisations in the UK, before them it was

Pfizer, it is now actually Viatris, I believe, who is responsible for the authorisations in other markets, so it is quite possible that the nature of the product or the nature of the authorisations diverges over time, and we have no insight to that, no visibility of that. So I cannot say today that, let us say, Flynn phenytoin is 100% identical to a parallel import from Spain. It may be, but I do not know.

PROFESSOR WATERSON: Thank you.

MR MCCARTHY: Now, Dr Fakes, I was asking you about the NICE guidance in 2004 and then subsequently the guidance that was issued in 2012, and you confirmed that you were aware -- Flynn and you were aware of that guidance, fully aware of that guidance?

A. Yes, I did, yes.

Q. Can I ask you to turn to tab 10 of your bundle, please, and these are the minutes of a Flynn board meeting held in December 2010. I will just give the Opus reference which is {G/84/1}, or {XG/84/1}, apologies.

I just want to place this document in context. So you agree that discussions between Pfizer and Flynn in respect of the supply of phenytoin, they began in around March 2010?

A. Yes, I agree. I was not actually party to those discussions, but I was aware of them.

Q. You were aware of them. Do you recall that Flynn then provided a draft heads of terms document to Pfizer in around July of 2010, so several months later?
A. Yes, I have seen that, I believe that was a document which Dave Walters prepared and took to Pfizer.
Q. Detailed proposals were then, at Pfizer's request, submitted to Pfizer in October of 2010?
A. That is my understanding, yes.
Q. So by the end of 2010, the discussions between Pfizer and Flynn were substantially under way in relation to the deal in respect of phenytoin?
A. Yes, they were, albeit it was probably a further 15 months before the deal was done, so to speak.
Q. Yes. With that context in mind, can I ask you to look at section 5 which is on page 3 of this set of board minutes {XG/84/3}. We see under section 5 bullet point 2:

"Pfizer."

The document says the following:

"The planned meeting on 6th December of the Pfizer UK leadership group was postponed ... They had raised a small number of questions which have been addressed. If our proposal is accepted by Pfizer, the product rights will be acquired by Flynn and a profit sharing agreement will be drawn up. Epanutin capsules & tablets

are not interchangeable, so the number of scripts should be maintained when the product is sold generically."

A. Yes, I read that, yes.

Q. And so it is clear, is it not, that not only was Flynn aware in 2010 of this issue of the lack of interchangeability of the products but that Flynn considered that an important consequence of that would be that script numbers would be maintained when it began to supply the product?

A. No, that is not quite the case. What this is saying is that -- it says Epanutin capsules and tablets are not interchangeable, but the same could be true of drug X capsules and tablets. If the prescription is written for drug X capsules, that is what must be supplied. If it is for tablets, that is what must be supplied. So that is all that is saying.

Q. You accept, though, do you not -- and we discussed this a moment or two ago -- that capsules are not interchangeable between brands, you accept that?

A. Yes, I do, but unless I am mistaken that was not quite the point that counsel was making.

Q. I think the point that emerges from this is that script numbers will be maintained, and that was Flynn's view, was it not?

A. It was Flynn's view that the number of scripts for

capsules would be broadly maintained, save for the caveat this is in a declining market which I think we talk in terms of it declining 5%, 6%, 7% year-on-year as phenytoin becomes less and less popular or important in epilepsy treatment.

THE PRESIDENT: Dr Fakes, again, do say if this is outside your area of factual understanding, but when a doctor is writing out a script or prescription for sodium phenytoin, to what extent will they, in the prescription, specify that the product to be dispensed ought to be capsule or tablet, or do they leave it as a matter of choice to the pharmacy?

A. Well, to the second part first they could not leave it as a matter of choice, so the script would never be issued which just said phenytoin strength X. It would say formulation type and dose.

THE PRESIDENT: So it would say, amongst other things, the tablet versus capsule choice?

A. That is right.

THE PRESIDENT: To that extent, I appreciate open and closed is a somewhat moveable feast, but they would be closed prescriptions to that extent?

A. Yes, but in regards to tablets, there is only one strength, the 100mg, so if the prescriber wished to use doses which were not multiples of 100mg or were less

than, then they would have to use capsules either alone or capsules in conjunction with tablets. Now, they may hypothetically prefer capsules if there is a swallowing issue for a patient, because they allow the facility to empty the contents and take with water or even a (inaudible), albeit that is off-label.

Having said that, most of the prescriptions, let us just talk about the phenytoin capsule prescriptions, most of those prescriptions are written as open prescriptions, and even as of, I think, last year which was the last time I checked, there was no more than 15% written as closed, ie which specified a particular manufacturer's source. So it follows that 85% continue to be open, and that allows the opportunity at the pharmacy level for switching or moving from one source to another to take place.

THE PRESIDENT: Between sources, yes.

A. That is what the evidence of previous (inaudible) of NRIM has shown us.

THE PRESIDENT: Just so I can put a little bit of meat on the bones, let us suppose the treatment regime for a patient is largely tablet, and you have told us that that is one 100mg dose.

A. Yes.

THE PRESIDENT: But I, as a doctor, want to prescribe a 150

dose each time you take the treatment. Would the prescription say 100mg tablets and 50mg capsules or would it be left open to that extent?

A. No, it would be the first, sir, it would actually be a prescription for two items: one would be the 100mg tablet and the second item would be the 50mg capsule.

THE PRESIDENT: Thank you very much.

A. Open or closed.

THE PRESIDENT: Open or closed, yes.

A. Yes.

THE PRESIDENT: Thank you.

MR MCCARTHY: Now, Dr Fakes, I want to take you to another document. This is in your bundle at tab 12, if you could turn to tab 12, please.

A. Yes.

Q. Before I deal with this document, I want to just deal with some context first.

In the period of around 2011 to 2013 Flynn's shareholders were giving consideration to selling Flynn's business, is that not right?

A. In late 2011/2012, yes, we were having those discussions, yes.

Q. Looking at this email -- oh, sorry, apologies, I keep forgetting to give the Opus reference. {XG/268.1}.

We see here that this is an email. I think, sir,

I can identify the sender of the email. It is Warren Roiter who was a non-executive director at Flynn.

A. That is correct, yes, he is.

Q. And he is attaching in this document a script, and this is what he says about it. He says:

"I feel we should have such a document agreed between us which becomes a script for whoever we talk to about the product."

The product he is referring to, as we will see is phenytoin. Now you were copied on that email, but do you have a recollection of this correspondence?

A. Only a vague recollection. I mean, it would be helpful perhaps if I could see the document to which he was referring to.

Q. Of course, I will take you to that in a moment, I just wanted to set the context. Just looking at this email we see that the purpose of the document is essentially to agree a script between yourself, David Walters and Warren Roiter in relation to phenytoin?

A. That is what the email says, but I am missing the context of the document.

Q. Of course, I will take -- now, we then see if you turn over to tab 13, please --

A. Yes, I see it.

Q. -- and I will give the Opus reference for this document.

It is {XG/268.2}. We see in the response David Walters responds, he copies you into the response and he says this:

"I have added [David Fakes'] comment, slightly reworked to fit in with the flow of the discussion, to the document."

So you would agree from this email it is -- I will take you to the script in a moment, but the email indicates that it is a document that you have seen?

A. Yes, it does.

Q. I want to take you to the script, but apologies, I just need to find the reference. It is at tab 11, if we turn back to tab 11, please. The Opus reference is {XG/499}.

A. Yes, I have found the document.

Q. We see the document begins by discussing some of the clinical characteristics of phenytoin, and then if we can turn over to the second page of the document, it is unpaginated, but just the second page {XG/499/2}, we see it says this in the first sentence just below "Oral liquid":

"Phenytoin capsules and tablets dominate the market. Whereas the product is no longer a first line of treatment for epilepsy, the market is stable in volume terms ..."

Then there is some volume data given below. Do you

see that?

A. Yes, I see that, yes.

Q. This document is dated in April of --

A. 2013.

Q. Yes. It is clear, is it not, that the position as far as Flynn were concerned and the position that they were setting out to those who were interested in phenytoin, who they were in discussions with, was that the capsules dominated the market, but that the market was stable in volume terms. That was Flynn's view in relation to the outlook of phenytoin?

A. It was our view, but if I may I think this is a document where context is all, and having seen it, I am now reminded of who produced it and why. So you mentioned earlier we were in discussion with Jefferies investment bank. We entered an agreement with them I believe in late January 2013, if you like, to promote us with a view to a sale or a merger of some sort.

As a result of that, we also retained IMS, the statistical and consulting firm, to conduct what is in effect a validation report of the portfolio and the forecasts that we were constructing for prospective buyers of Flynn.

Now, as part of that process, we had to -- you say a script, but we had to compile relatively short, simple

statements about each of the product assets within the business and what you are looking at in this document is the phenytoin one.

So this was written with a prospective purchaser in mind, it was not written with a regulator in mind, it was not written with Flynn's board in mind, because they knew all of this. How can you tell the story simply and succinctly? If I may come back to the point about where we do say it was a stable market, I think the data in the table at the top of {XG/499/2} indicate it was declining even on those data.

Q. Yes. You say it was written with the purchaser in mind, and you say that is an important aspect of the context.

A. Yes.

Q. But you accept of course that you would not provide -- you are going to provide accurate information to potential purchasers in discussions, you are certainly not going to provide misleading information on outlook or your perception of outlook?

A. Of course counsel is correct, we would -- we are obligated to provide accurate information, but in the sale process we would not warrant the content of such statements, and the purchaser would be expected to do their due diligence.

Q. Yes.

A. Sorry, if I may, just one point, the clue in this document, I say this was related to the sale process, is the figure on {XG/499/3} where you see the red line shows the word "Frontier", Frontier being the project name that we were given by Jefferies. Frontier was Flynn.

Q. Yes, and so going back to the point that we were speaking about a moment ago, you accept that the position that Flynn was explaining to purchasers as you have explained was that the outlook for phenytoin was one of stable volume?

A. On the face of this document, yes, but, as I said a few moments ago, you can see some evidence of decline, and you have always got to bear in mind in a sale process a lot of it is a question of presentation on the part of the seller: you make your house look the best it can be and you describe it in the neatest of terms, but then the buyer will take a contrary view and look more critically, and you get to, if you like, the reality somewhere in the middle.

THE PRESIDENT: In this case, Dr Fakes, the term "stable" is being used in the context where the figures immediately below are showing minus 3, minus 5, minus 1 in 2009, 2010, 2011 respectively.

A. I accept that, which is why I flagged the point.

THE PRESIDENT: Well, indeed.

A. You could argue with hindsight we should perhaps not use the word "stable". It would have been perhaps more accurate to put: there is some evidence of a continuing or modest decline, but I do not think anyone would buy the business on the basis of that difference in wording. Thank you.

MR MCCARTHY: Dr Fakes, I want to move on to a separate issue which is the question of Flynn's efforts to obtain an alternative active pharmaceutical ingredient.

A. Yes.

Q. Can we first look at what Mr Walters said about this in his witness statement which you cross-refer to in your statement at paragraph 26. So, Mr Walters' statement, the Opus reference is {C2/3/1}. Dr Fakes, the reference is at section 14, tab 14 of the bundle you have in front of you.

A. Yes, I have found it.

Q. You have found it?

A. Yes, I do.

Q. I am grateful. If you could please turn to paragraph 41 of that statement, please, {C2/3/14}.

Dr Fakes, I want to ask you some questions about these paragraphs, but first could I first ask you to read paragraphs 41 through to 43, please, before I ask

you some questions about it. (Pause)

A. Yes, I have read them, thank you.

Q. I just note there is some confidential information in these paragraphs which is highlighted. You can see that, but you do not need to refer to that highlighted information when I ask you questions in giving your answers.

What Mr Walters is explaining here are the steps taken by Flynn to identify an alternative source of active pharmaceutical ingredient, and the first step he identifies at 41 is that he says that you identified two potential suppliers, the names are given on the page, but I will not read them out, you identify them as potential suppliers, so that was the first step at paragraph 41. Do you agree?

A. Yes, that is correct.

Q. Then at 42 he deals with the second step which is that he explains that there was email correspondence which he sets out between yourself, a colleague at Flynn and an Italian agent discussing a possible arrangement with one potential supplier.

A. Yes.

Q. That is at 42.

Then we see between paragraphs 43 and then just over the page at 46 he says that several meetings were held

with Pfizer to discuss the possibility of a second source of active pharmaceutical ingredient {C2/3/15}.

A. Yes.

Q. So those are the three steps he identifies in relation to sourcing an alternative active pharmaceutical ingredient. Do you agree?

A. Sorry, when you say the three steps, could you clarify?

Q. The three steps that I have taken you through.

A. So that is paras?

Q. From paragraphs 41 through to 46.

A. Oh right, yes, yes.

Q. Do you agree?

A. Yes, yes, I agree.

Q. We then see that Mr Walters explains at paragraph 48 that -- he says this, just the very first sentence:

"Ultimately, Flynn has not yet been able to implement its plan to identify a second API source because of the uncertainty created by the CMA's investigation."

That was his point. So beyond those steps, Mr Walters says, effectively, Flynn has not been able to implement its plan. Do you see that?

A. Yes, I see that, and that is what we have always said, I think, as early as, I believe, July 2013 when we had I think a state of play meeting with the authority, we

had said that the investigation and then in due course when it became public with the issue of the statement of objections in August 2015, I think we described it as having a paralysing effect on the business, and in fact phenytoin became more akin to Kryptonite for a while.

Q. You agree with Mr Walters' account in relation to that?

A. Yes, I do. We did not feel in a position to advance the development of a second source for the API or additionally a second source for the finished product because we were in a situation where we did not know where the price would end up, we did not know what our position was with respect to the CMA. So we could not then commit, and you see in, I think, paragraph 48, Dave Walters mentions quite significant sums, in the region of 2 to 4 million, to do a full validation and transfer changing API source, changing manufacturing site, conduct of new bioequivalent studies, new stability studies, and this is work that we intended to do, we were talking about doing this, in 2012, so this was fully six months before the investigation was born.

Q. Yes, and can I just ask you to turn then to your own statement at paragraph 26, please. This is where you discuss this issue also.

A. Paragraph 26?

Q. Paragraph 26.

THE PRESIDENT: Tab 5 in the bundle.

A. I am there, yes.

MR MCCARTHY: {XC1/1/11}.

You say this at 26:

"As discussed in Walters 1, the CMA has characterised Flynn as merely considering developing an alternative source of API but not incurring any investment costs. I am confident that Flynn would have continued exploring the development of an alternative source of API and/or finished product, had the OFT ... (and [subsequently] the CMA not continued) its investigations which have paralysed Flynn's attempts to develop an alternative source of API."

A. Yes, I read that.

Q. So essentially beyond the steps that Mr Walters has identified, you do not suggest there are any further steps taken by Flynn to source some alternative API?

A. We did not take further steps, as I said, because we were in effect paralysed by the investigation, although we continued to explore our alternatives, we continued to look at what alternate API suppliers are out there with the appropriate approval, which is a CEP or certificate of suitability and even secondary site manufacture, new manufacturing sites, because we are conscious one day that this product will not hit the

buffers, but it will be in trouble as the volumes continue to decline, and it would be prudent as we determined when we set out in 2012, to look at alternatives, to look at what our options are, but we are still in the midst of the investigation and the legal proceedings.

PROFESSOR WATERSON: Could I just check there, so you are looking for an alternative site.

A. Yes.

PROFESSOR WATERSON: But you said earlier that a potential problem with parallel imports was they might not be exactly equivalent.

A. Yes.

PROFESSOR WATERSON: If you were thinking about an alternative site obviously it would be a different manufacturer, presumably, than Pfizer, for sourcing this product?

A. Yes, it would, but we would take as our reference point, as our comparator, let us call it phenytoin Flynn, you may substitute the active with another source, and you may make the physical product at another site, and when -- on a licence when people see the term or use the term "manufacturer", it is not necessarily a reference to the physical site of manufacture. Quite often that is disguised on the product labelling. It is the

physical site or the address of the entity which places the product on to the market which releases it for sale.

So it is certainly possible for Flynn or another company to develop a product and secure regulatory approval from the MHRA for a product which is identical and interchangeable to the product we talk of as phenytoin Flynn, and that has happened as recently as October 2022 when Viatris secured their own authorisations for all four strengths.

MR DORAN: So Viatris does not manufacture at site?

A. They do not, but there is a sensitivity because obviously we entered into a deal with Pfizer but then I believe it is 2020 Pfizer span out its established products business and merged it with Mylan into a new entity called Viatris. Our manufacturing agreements were novated to Viatris, but then -- and you can imagine it was a surprise to us when we see in October 2022 that a Viatris entity, in this case Mylan, had been granted approvals for all four strengths, but they are different products and they are almost certainly made in a different site, and I believe that is a Mylan facility in Hungary, not Freiberg in Germany.

MR DORAN: So the guidance which requires the same manufacture and form actually goes to the name on the packet rather than the geographical location and the

plant that is doing the manufacturing?

A. In my view, yes, it does, sir.

THE PRESIDENT: Is that a function of what the contract between yourself and the manufacturer says?

A. Well, in a product regulation sense, if a company goes to the regulatory authority with sufficient data which establishes beyond reasonable doubt -- perhaps that is the wrong expression, but gives a very high degree of confidence that the new product, it could be new by virtue of a new API, it could be a modification to the manufacturing process, it could be a new manufacturing site, but if you generate the data to show that they are one and the same, then you will get your variation approved or your second site approved. For instance, it is possible for many pharmaceutical products that the licence names not one site but two sites for physical manufacture, or they might name not one but two sources of API.

THE PRESIDENT: But it is quite possible for the obligation to supply between, let us say, Flynn and Pfizer is more specific in terms of what needs to be provided, I mean, that is legally possible, but it is not in practice something that is stipulated?

A. I think because there are concerns about narrow therapeutic index you would proceed more cautiously,

produce more data, and in particular, I think with the bioequivalence study, which is something that you do a crossover study in healthy volunteers, you would use a larger number, and you would apply tighter confidence intervals to get a better level of confidence that A is indeed the same as B.

THE PRESIDENT: Thank you.

MR MCCARTHY: Dr Fakes, I want to turn now to the question of regulatory responsibilities. If I could ask you to turn back to your witness statement at paragraph 53, please. {XC1/1/23}. At 53 you say this:

"As an MA holder for phenytoin capsules, Flynn is subject to a multitude of responsibilities, as it is for any other product where Flynn is an MA holder."

And then in the subsequent paragraphs you describe some of those responsibilities.

To be clear, the responsibilities that you are describing there, and the activities which Flynn undertakes as part of that, are activities which you undertake in respect of all of the medicines in relation to which you are an MA holder? In other words, these are activities and regulatory responsibilities which are applicable across the board in respect of medicines for which you are an MA holder?

A. I think there is an important distinction. The

responsibilities, the legal compliance responsibilities that one has are far broader and more onerous where you are the MAH, the marketing authorisation holder, than if you were a distributer, for instance. We get back to this fudging of the difference between the activities --

Q. Sorry, Dr Fakes, just my specific question, though was that the activities that you are referring to and/or responsibilities, whichever you prefer, what you are describing in your statement are responsibilities and activities which concern all medicines for which you are the MA holder?

A. Yes.

Q. I want to just look at some of the specific individual responsibilities which you discuss, and I am not taking these in the order that they are set out in the statement, but just to deal with them sequentially. {XC1/1/27}.

At paragraph 60 you explain that as an MA holder Flynn is required in law to have a qualified person for pharmacovigilance and a deputy qualified person for pharmacovigilance. Is that not right?

A. Paragraph 60, yes?

Q. Yes.

A. Yes, that is right, yes.

Q. That is a statutory role, is it not? In other words, by

law the duties of a qualified person for pharmacovigilance are set out?

A. Yes, it is. I should add at the time of the relevant period, I think the QPPV was actually an internal employee, that was a Dr Hallwood, but currently and for some time it has been a responsibility, an activity I should say, that we contracted out.

Q. Just to be clear, are you saying that at the relevant time, 2012 to 2016, the qualified person and the deputy qualified person was in-house, is that what you are saying?

A. Sir, we need to be clear, we are talking in paragraph 60 about the QPPV which is the qualified person for pharmacovigilance?

Q. Exactly.

A. Which is a different entity, a different entity, to the QP.

Q. Right, sorry, speaking specifically about the qualified person for pharmacovigilance --

A. Yes.

Q. -- just looking at that person's responsibilities, that includes the following, does it not: maintaining a pharmacovigilance system?

A. Yes.

Q. Recording and reporting to relevant health authorities

suspected adverse reactions?

A. Yes.

Q. And providing pharmacovigilance information to health authorities where requested or required by law?

A. Yes, that is part of the responsibility, yes.

Q. Yes. In the administrative hearing before the CMA, I can take you to the transcript if it is helpful, but I think this point is non-controversial because it was your evidence, you confirmed that during the relevant period it was Pfizer which was the qualified person -- acted on Flynn's with behalf in relation to phenytoin as the qualified person for pharmacovigilance?

A. I am sorry, I disagree, counsel. We are confusing the role of QP for product release purposes with QPPV. These are quite different responsibilities. Now, the responsibility for the qualified person who is the approved person that places -- releases the product for sale on to a market, has always been contracted out to Pfizer. The QPPV responsibilities are a completely different animal and that has never been the responsibility of Pfizer under the ownership of the licences by Flynn.

Q. You say in your statement at 60 that the role of the qualified person for pharmacovigilance, that role has been -- is performed by ProPharma?

A. It is currently performed by ProPharma. At the time it was performed partly internally by Dr Phil Hallwood and partly with the support of a consultancy which was known as Diamond. Diamond was subsequently taken over by ProPharma which is an international organisation.

Q. So your evidence is that this role during the relevant period was part subcontracted and part performed in-house?

A. The QPPV --

Q. QPPV, yes.

A. -- responsibility, most of the activities were always contracted out, so if you go into the detail of what is involved, it would, for instance, require that you have weekly or fortnightly monitoring of the media and the scientific literature where you are trying to identify new information, new safety signals, which might teach you something about your product, and that is very hard to do for a company which has 20 people in an office and no organised literature-searching capabilities.

Q. Just to be clear, I think what you said a moment ago was that most of the responsibilities for the QPPV were contracted out?

A. Most of the activities were contracted out, not the responsibilities, yes.

Q. Most of the activities for the QPPV were contracted out.

A. Yes.
THE PRESIDENT: To just stick with your literature search example, there would be someone, a QPPV within Flynn, let us say, who would be responsible for ensuring that someone carried out a literature search for drugs that were within Flynn's responsibility and although the work in terms of the literature search was done outside, it was a responsibility to ensure that it was done within, in my example here, Flynn?
A. That is correct, yes, sir. They always retained that ultimate legal responsibility for the function.
THE PRESIDENT: Yes.
A. They help ensured they fulfilled that responsibility through audit and regular review, regular reporting. There is really a mass of detail behind what goes on in PV. Product safety in the real world is vitally important.
MR MCCARTHY: A second responsibility you identify is in relation to the submission of regulatory updates and variations to the MHRA, and you deal with that at paragraph 55. You also explain in your statement that that has also been contracted to a third party agency. Is that right?
A. That is right, yes, because they have the systems for -- basically an electronic interface with the regulatory

authority, they can do it more efficiently, but they do it under our direction and at our instigation. So we have a small regulatory department but we spend probably quite a lot more with the service provider who has a whole office full of experts in the area.

Q. Right, and then a third pharmacovigilance responsibility you identify at paragraph 58 {XC1/1/26} is the duty on Flynn to have in place arrangements to detect the emergence of side effects or adverse reactions to drugs, and that is a third responsibility that you identify.

A. Yes, I think there is two parts to that question. They look to identify emergence of side effects. Here you are really talking about safety signals, and you pick up safety signals by looking at all the reports coming in about usage of a particular product in all the patients from as wide a population as possible, and over time signals emerge, and that then develops or forms into a view that there may be a particular safety issue or precaution with a particular drug. So if you take phenytoin, for instance, we are seeing it with an emerging concern about hypothyroidism, which has been discussed at the MA and MHRA in the last two years, and that will probably lead to a change in the labelling, as will, I suspect, the concerns about congenital defects.

Q. So this responsibility that you are describing, what

this requires in practice is effectively screening, is that not right?

A. It is screening --

Q. Screening and recording of data?

A. -- a form of screening. They use complicated databases. In this case they used something called OSG which to be frank, I could not really describe what it does, but it is very large and expensive software which does a lot of the churning for you.

Q. Then you explain at paragraph 60 that presently Flynn subcontracts global pharmacovigilance screening and data recording to ProPharma?

A. That is correct, that is our current practice.

Q. But then at 62 you explain that during the relevant period, the period we are concerned with, it was Pfizer which maintained a global safety database for phenytoin, albeit with input from Flynn?

A. What I say in paragraph 62 is that Pfizer maintained the global safety database, so you have to keep in mind that Flynn purchased the MAs, the licences for the capsules and only the capsules in the UK, whereas Pfizer continued to market other presentations of phenytoin in the UK and various presentations of phenytoin outside the UK. Say if you are in a situation where you are honestly trying to look at product safety you look at

the biggest sample, the biggest population you can. Hence Pfizer retained and still retained and Viatris retain the responsibility for the global safety database.

It is Flynn's responsibility to carry out the updating in respect of the UK market with the MHRA, so it is Flynn that submits what is called the pharmacovigilance safety update report or PSUR. So what I am saying here is eminently sensible.

Q. Yes, you are explaining that insofar as Pfizer is carrying out it out, there is sensible reason for Pfizer to carry out and to have to carry out that screening exercise?

A. Yes.

Q. But ultimately I suppose the point I am putting to you is simply that it is Pfizer that during the relevant period, and from what I understand currently as well, runs that database, the global safety documents?

A. Yes, they do, because they have access to far more patient exposure data than we could possibly do, so as a patient, that is what I would want to happen.

Q. Then at paragraph 62, you also explain that again during the relevant period it was Pfizer which produced and submitted updates to the MHRA in respect of using data from its global database?

A. Do I say it was Pfizer that submitted it?
Q. At 62.
A. I say at 62:
"As an MA holder, Flynn is responsible for filing a [PSUR] periodic safety update report, when required with the MHRA..."
So I do not say that it is Pfizer, I say it was Flynn.
Q. I am sorry:
"... and during the relevant period this report was produced by Pfizer on Flynn's behalf using their database."
A. During the relevant period Pfizer supplied -- generated a global PSUR. Now, thinking back to the period, there was probably one -- I think there has probably only been two updates of PSUR since the beginning of the relevant period until to date.
Q. Right, so it doesn't involve a great deal of activity or homework in any event, is that the point?
A. If you look I think somewhere in the exhibits to my witness statement 1, I talk about the variations that were submitted, and I provide a list, I think, from memory of about 35, a great number of which are safety-related. So it may not seem like a big number, but if you are talking about a matter of safety or

addition of new language to a warning, these are very important things. They may not be labour-intensive, but they require constant vigilance.

Q. Standing back from the detail, then, and thinking about the various responsibilities and activities you have identified, so you agree that the role of a qualified person and the activities that go with that is one important pharmacovigilant responsibility that Flynn has?

A. Are you referring to a specific paragraph?

Q. I am just summarising the position and putting to you what I understand your evidence to be.

One important responsibility is that of a qualified person for pharmacovigilance?

A. Yes.

Q. That is a role that is subcontracted by Flynn.

A. Yes, it is, it is a role, again, we come back to the responsibility, stays with and rests on the shoulders of the MAH, of Flynn.

Q. Then we have the global screening of safety information which was a further pharmacovigilance responsibility and activity that you have identified?

A. That is a function -- if you have a drug company which markets a drug in many presentations in many markets, it goes back to the point that I made earlier that it is

eminently sensible to collect your safety information.

Q. Apologies, Dr Fakes, I am just putting to you the point that that is a second responsibility that you have identified: global screening of safety information?

A. Yes.

Q. That, during the relevant period, was carried out by Pfizer?

A. Yes, it was. I mean, there are other drugs for which we are MAH where we generate -- we, if you like, originate the PSUR.

Q. Yes, and then a further responsibility, pharmacovigilance responsibility you have identified is the maintenance of a global safety database to record safety information, so that is a further pharmacovigilance responsibility?

A. It is, and that is something which -- I should say it is probably Viatris legally now do, but Flynn has its own safety database which was maintained through ProPharma.

Q. But Pfizer did that during the relevant period on Flynn's behalf?

A. There is in place an SDEA which is a safety data exchange agreement, which will require Flynn to share and exchange product safety data with Viatris or prior to that with Pfizer. So if we are picking up adverse event reports or ASPRs, which is an acronym for

anonymised single patient reports, they are reports which come into the regulator about a safety event, we have a duty to relay them back to the global safety database.

Q. Yes, but, Dr Fakes, the point I am putting to you is just a straightforward one, that your evidence is that that is a responsibility, and that during the relevant period it was carried out by Pfizer. That is what you say at paragraph 62 of your statement. Do you agree? You say that:

"During the relevant period" --

A. I think we agree, if we are talking about it is Pfizer or Viatris' responsibility for the global safety database --

Q. Yes.

A. -- but in the UK market where we own the licences, it is our responsibility to engage with -- and keep the regulatory authority --

Q. (inaudible) to that. Then finally, the further responsibility that you identify is the identification of periodic safety updates to the MHRA?

A. Yes.

Q. That was carried out by Pfizer during the relevant period?

A. No, it would have been carried out by Flynn.

Q. At 62, I have read it out to you, but I can read it again, you say that:

"As an MA holder, Flynn is responsible for filing a periodic safety update report when required with the MHRA, and during the relevant period this report was produced by Pfizer on Flynn's behalf using their database."

So it was Pfizer that carried out that work during the relevant period?

A. Sorry, I thought, counsel, you said it was Pfizer that submitted the PSUR. The PSUR is, in effect, if you like, the summary update report from the global safety database. We have, if you like, the contractual right for a copy. It is our responsibility to file it with the MHRA, it is not Pfizer's responsibility.

Q. You file it, but Pfizer prepared it?

A. That is correct.

Q. Right?

A. And we contribute where we get patient safety reports, ASPRs and adverse events coming in from the UK market, because those reports come to us as the MAH.

Q. Then the final pharmacovigilance responsibility you identify is the submission of regulatory variations and updates.

A. Yes.

Q. You accept that is subcontracted by Flynn?
A. It is subcontracted to, again, the same company, ProPharma, so they handle our regulatory and our PV activities or large parts of them, yes.
Q. Just standing back and looking at the position, the reality is, is it not, that extensive pharmacovigilance activities are in fact carried out and were carried out during the relevant period on Flynn's behalf by others pursuant to subcontractual arrangements?
A. All or largely on Flynn's behalf but at Flynn's expense. I mean, these things are not supplied free. It is no different to if we do it under our own roof. It is probably more expensive.
Q. In relation to those costs, you had the opportunity, did you not, to submit those costs to the CMA in the course of its remittal investigation?
A. Yes, we did, but this comes back, I think, to a quite different point of how we recognised and dealt with the so-called common costs. We did not separate them out by product or by activity or functional discipline. It is simply not helpful, rightly or wrongly, to a business such as Flynn, but we have operational costs, and we know all of our sales must cover all of our costs, so those costs are within there.
Q. Insofar as the activities that we are concerned with

here, those pharmacovigilance subcontractual arrangements, all of those costs were submitted to the CMA?

A. All of those costs would have been built into the operational cost data that was supplied to the CMA throughout its investigation, yes.

MR MCCARTHY: Sir, I am not sure whether you want to take a morning break or continue?

THE PRESIDENT: I think we should.

MR MCCARTHY: I do not have -- I have some more material to put to Dr Fakes.

THE PRESIDENT: We are halfway through the morning, so if this is a convenient moment we will take it.

MR MCCARTHY: It is.

THE PRESIDENT: Just so that I understand, Dr Fakes, your involvement in the creation of the direct and indirect costs attributable to capsules, how great was your involvement, because we have transited in the course of your evidence just now from what Flynn did where obviously you do know exactly what is going on, to how the CMA incorporated those costs in the material that has been submitted to us as part of this appeal, and if you do not have much by way of direct evidence to give on that, then I will make sure that we do not ask anything further, on the other hand, if you --

A. I would say I am very familiar with the whole common cost debate and the number of packs by revenue, by activity and so on, so I can happily try and assist the Tribunal.

THE PRESIDENT: Thank you very much. We will rise. It is 11.45. We will rise until 11.55. Dr Fakes, I am sure you have been told this many times before, please do not talk to anyone about your evidence whilst you are in the witness box, and we will rise for 10 minutes.

A. I understand, thank you.

THE PRESIDENT: Thank you.

(11.44 am)

(A short break)

(11.58 am)

THE PRESIDENT: Mr McCarthy.

MR MCCARTHY: Dr Fakes, I want to turn to the supply agreement between Flynn and Pfizer, please.

If you could turn, please, to tab 17 of your bundle, and the Opus reference is {XG/132/1}. If you could turn, please, to internal page 17 of the agreement {XG/132/18}.

A. Yes, I have it.

Q. In your witness evidence you summarise your view of the effect of this agreement at paragraphs 34 to 37. I will come back to that in a moment, but just to sort of

position us in terms of the evidence on this. Looking at clause 18.1 {XG/132/16}, which is page 15, clause 18.1, it says this:

"Supplier shall indemnify Purchaser against all liabilities, costs, expenses, damages and losses (including any direct or indirect consequential losses, loss of profit, loss of reputation and all interest, penalties and legal and other reasonable professional costs and expenses) suffered or incurred by purchaser arising out of or in connection with ..."

A. Yes.

Q. Then if we look over the page at 18.1.2:

"Any claim made against [the] Purchaser arising as a result of or in connection with any failure of the Products [in this case the phenytoin products of course] to comply with the Manufacturing Authorisation, the Specifications or [the] applicable Laws."

A. Yes, I read that.

Q. Yes. So you agree looking at this clause that effectively Pfizer provides Flynn with an indemnification for non-conforming products, products which do not conform to specification or which do not conform to the requirements of the marketing authorisation?

A. Yes, that is what is in 18.1.2 specifically, yes.

Q. Now in your second statement, you deal with the question of this £2 million limitation of liability. This is at paragraph 36 --

A. Of the second witness statement?

Q. -- of your second witness statement, exactly. {XC1/2/13}.

A. Yes, I am there.

Q. I will just read out what you say there:

"As explained in ... Fakes 1, clause 18.1.2 [so this is referring to the indemnity] is very limited in scope as it only applies when Pfizer delivers capsules which are not compliant with the MA. It would not cover situations where, for example, the product is manufactured in accordance with the MA but ... causes [other] adverse reactions ..."

Then you say this:

"In addition, even where the capsules are not compliant with the MA, the value of the indemnity is limited to £2m."

You then make the point that:

"This cap is [very] small in comparison to the value of potential claims that could be brought against Flynn, as [an] MA holder."

A. Yes.

Q. I just wanted to look at this with you, please.

If you could look back to the supply agreement at clause 19.5 and that is on page 18 {XG/132/18}, this is where the £2 million limitation of liability is imposed. It says this:

"Supplier's Financial Liability. Without prejudice to clause 19.3 or clause 19.4, Supplier's total liability arising under or in connection with [the] Agreement, whether arising in contract, tort (including negligence) or restitution, or for breach of statutory duty or misrepresentation, or otherwise, shall in all circumstances be limited to £2 million."

You see that?

A. Yes, I see it.

Q. But do you see that it says that this is without prejudice to clauses 19.3 or 19.4?

A. Yes, which are the carve-out clauses.

Q. Yes. So if we go, then, to 19.4, which is just over the page on page 16 {XG/132/17}, it says this:

"Limitations on Exclusions. Nothing in this Agreement shall limit or exclude the liability of either party for ..."

Then various matters are mentioned but if we look down at 19.3.6:

"The indemnities ... in clause 18."

Do you see that?

A. Sorry, would you repeat the last bit?
Q. Of course, yes. We are looking at clause 19.3.
A. Yes.
Q. On page 16. It says:
"Limitations on Exclusions."
A. Yes.
Q. It says there:
"Nothing in this Agreement shall limit or exclude the liability of either party for ..."
Then looking down to 19.3.6:
"The indemnities contained in clause 18."
A. Yes.
Q. Do you see that on its face the agreement does not apply the £2 million financial limit to the indemnity included in clause 18?
A. First and foremost I am not a contracts lawyer, that is not my understanding.
Q. I appreciate that. Just on that point, just before you answer, I appreciate you are not a lawyer, and I just ask, because you commented in your evidence about commercial risk arising from this agreement.
A. Yes.
Q. So bearing in mind that you are not a lawyer but just looking at the agreement, I am just putting that point to you to see your reaction to it.

A. I can only say my understanding, my interpretation of the agreement is as set out in my witness statement, that there was a limitation on liability for Flynn in regard to Pfizer of 2 million, and vice versa in regard to the same sum subject to the carve-outs. I think what counsel is now putting to me is that that does not apply in your assessment.

Q. Yes, precisely.

A. I would need to ask a lawyer, and I think Pfizer would be concerned by this, if they thought they --

Q. Can I just put this point to you, which is not a legal point at all, but if I am right about this point, do you accept that in fact the commercial risk that arises from this agreement is materially less than for Flynn than you thought it was?

A. I think if I -- it is a complicated question, but if you are saying --

THE PRESIDENT: You are being asked to assume that you are wrong in your understanding, so on that assumption.

A. On the assumption, with which I do not agree, if your assessment of this clause is correct in that Pfizer is not insulated from in effect, if not unlimited, much larger liability then, yes, your assessment is correct.

MR MCCARTHY: So you are accepting that the level of risk faced by Flynn is materially less than that which you

thought it was?

THE PRESIDENT: No, he is not accepting that, and that is a question that I do not think you can put to this witness. It is a matter for us. The witness has quite clearly articulated what his understanding of the agreement is. That understanding may be right, it may be wrong, but it is his understanding, and I am not, with great respect to you, Dr Fakes, very interested in your contractual reading of what these documents say.

A. Thank you, sir.

MR MCCARTHY: Apologies, sir. My question perhaps wasn't clear. I was simply focusing on the question of commercial risk, but --

THE PRESIDENT: Yes, but commercial risk arises out of the understanding of the true construction of the agreement.

MR MCCARTHY: Sorry, I meant on the assumption that the point I was putting was correct.

THE PRESIDENT: Yes. Well, you have answered the question in terms of assuming your understanding is wrong. I have that evidence.

A. No, you explained it well, thank you.

MR MCCARTHY: There is just one other point in relation to this that I want to just briefly deal with.

In your witness statement, if I can just take you to paragraph 36 where you say this --

A. Sir, is this 1 or 2?
Q. Sorry, the second witness statement. You say in paragraph 36 that the indemnity in clause 18.1 also excludes a wide range of types of loss.

Now, if I can just go back to the clause 18.1, and it says this {XG/132/16}:

"Supplier shall indemnify Purchaser against all liabilities, costs, expenses, damages and losses ..."

And so forth and so on.

A. Yes.
Q. Now, again, I am not putting to you a legal proposition, understanding of course that you are not a lawyer, but you accept that on its face that is not excluding any important category of losses that Flynn might face?
A. There is firstly the legal point, but more fundamentally, there is something in my mind that a contract manufacturing organisation would -- and that is all that Pfizer is in this instance -- knowingly accept a liability beyond their responsibility to supply me with the product which complies with my specification? Now, I think counsel is saying they could well be in it for far worse.
Q. I am just asking you whether, from your perspective, on the face of this clause is there any important category of loss which Flynn might face which is being excluded?

A. I think in part to answer this one if you go to -- it will be in clause 19, the limitations. One important one might be a claim against us as the licence holder for a serious adverse event or a fatality caused when the product is used in accordance with its licence but nevertheless meets the specification in that licence.

I believe in 19.4 as well there is a limitation or a carve-out of loss of profits and loss of goodwill or loss of business. So in the situation where Pfizer, or now Viatris, was unable to supply us and we were out of the market, we would suffer all the consequences of that without recourse to them.

Q. Yes, again, I am not -- it is not a point I think we need to pursue much further, but to be clear the point I am putting to you is that if clause 18.1 does what it says it does on its face, it is not excluding, is it, any important category of loss that Flynn might face?

A. Again, we are back to the point on the assumption that you are right, it does not protect us, but that is not my understanding or my reading.

Q. Fine. Now can I ask you briefly to turn to clause 17.1 of the supply agreement, please {XG/132/16}?

A. Yes, I am here.

Q. There we can see that clause 17.1 requires Flynn to have in place product liability insurance with a limit of no

less than £2 million. Do you agree?

A. Yes, I agree. I see that.

Q. Prior to 2012 in supplying phenytoin capsules Flynn, acting responsibly, will have obtained appropriate insurance consistent with the requirements of the agreement?

A. I think any pharmaceutical licence holder or distributer will always maintain public liability insurance. In our case, it is actually for a total sum of £10 million, and in the course of -- and this is not something I am directly involved in, but in the course of renewing the policy, so to speak, you are expected to tell people about your product portfolio, your market reach, if there is any particular risks, but that is all quite standard, and 10 million is a big number in one sense, but not when it comes to liability claims about patient harm or death.

Q. Can I ask you, then, to turn to -- it is an email exchange, and the Opus reference is {XG/182.1}, and it is at tab 18 of your bundle.

A. Yes, I see it.

Q. In this exchange we see that Flynn's insurance broker at the time emails Martin Bain, Flynn's finance director, to explain that he had obtained product liability insurance.

A. Yes.
Q. Mr Bain responds:
"Good result."
A. Yes.
Q. So Mr Bain was satisfied, was he not, that Flynn had obtained an appropriate level of product insurance?
A. On the evidence the basis of he said "good result", yes, I had a lot of faith in Martin.
MR MCCARTHY: Yes, I am grateful.
Dr Fakes, those are my only questions.
A. Thank you.
THE PRESIDENT: Before, Ms Stratford, you rise, just a couple of points, Dr Fakes.
Questions by THE TRIBUNAL
THE PRESIDENT: Could you go in the bundle to tab 5 which is your first statement, and in that tab to paragraph 80 where you are discussing the pricing of products {XC/1/34}.
A. Paragraph 80 you say?
THE PRESIDENT: Paragraph 80, yes, it is external reference page 34.
A. I have found it.
THE PRESIDENT: Just cast your eye over 80 and the following paragraphs just so that you know what I am asking you about. I mean, I am sure you are familiar with it.

A. I do recognise this. (Pause) Yes, sir.

THE PRESIDENT: Looking at paragraph 81, you say that as regards the pricing of individual medicines:

"... Flynn generally adopts a market-based approach."

In your own words, could you just explain what you mean by that?

A. Yes, I can. It is probably simpler or it would have been simpler to say we look at, dare I say it, comparators, we look at reference points in the market, where there would be the same molecule, similar molecules in the same therapeutic class, because that is more often than not how your offering will be compared and measured, whether it be a brand or a generic or a branded generic even.

So you do not start from the bottom up trying to form a view of things such as willingness to pay. You look at what the market as it is -- we are not an innovative medicine.

THE PRESIDENT: So when you use the term "comparator" what relationship does comparator have with substitutability?

A. It does not have a direct relationship, but you could have a situation if we took a therapy area with two molecules A and B, they are clearly different molecules, and they will be used at different dosages with

different frequencies, but they can be used in, let us say, a therapeutically comparable way. So, for instance, if the cost of treatment for treatment A is £10 and I come along with treatment B, I would be mindful that if I start exceeding that £10 threshold I need to be making a stronger case offering value added, offering more, because the market and the purchasers, the formularies, will look at the cost of treatment A.

THE PRESIDENT: Let us, if you do not mind, test that. So I am thinking now about the products in issue here.

A. Yes.

THE PRESIDENT: So we have phenytoin capsules and we have phenytoin tablets, and I think it is accepted that -- indeed you have said so yourself -- the prescription written by the doctor will specify capsules or tablets or a combination.

A. Yes, I did, yes.

THE PRESIDENT: We know that patients are quite sensitive to a continuity of supply in that if they are on tablets or they are on capsules, they will want that regime to continue.

A. Yes, a great many that will be the case, yes. Most probably.

THE PRESIDENT: So knowing this, a doctor is unlikely,

absent good reason, to shift their prescription from, let us say, capsule to tablet or vice versa.

A. I would agree with that, yes, sir.

THE PRESIDENT: So my question then is that being the case, and therefore capsules and tablets not being substitutes, although they may be comparators, why do you consider yourself, if you do, constrained by the price of tablets?

A. Because they can be used in a therapeutically interchangeable way, and it is the same molecule. If I look, for instance, at the public assessment report, say, for a tablet, I see it has been licensed as being essentially similar, which has an important regulatory context, essentially similar and comparable or interchangeable with the capsule, and in fact, the most recent approval that I referred to earlier was the Mylan phenytoin capsules, and the public assessment report for that which was only published two weeks ago actually uses the words they can be -- they are interchangeable.

So it is an obvious -- it is a therapeutic comparator. People will look -- would naturally look at, be drawn to what am I paying for the treatment with the tablet, and you would have to have a very good case to go north of that, which is not something we did.

THE PRESIDENT: Just to be clear, you are in pricing by

reference, let us say, to tablet, looking at an implied value in the sense that you are saying that what is an appropriate price for a tablet ought to inform the price of the capsule, even though they are not, in the patient's eyes, substitutes?

A. No, I agree, there is an implicit assumption on our part perhaps that they are the same, they are equivalent, it is the same drug used at the same dosage for the same indication, with the same caveats, contraindications and warnings.

THE PRESIDENT: Do you apply any kind of commercial value judgment to the price that is being charged by other entities on the market for, let us say, tablets? In other words, what happens -- it may be you do not form this view, but what happens if you did form the view that the price of the tablet is either indefensibly low or indefensibly high? I mean, do you apply any kind of thought to that, or do you just take the price as it exists in the market?

A. In this particular situation, we took the price as is, but cognisant of the history, cognisant of what we believed had happened in 2007 and then cognisant of looking at the stability of the cat M price for four to five years, up to the point when we made our pricing decision for a generic, and it was a generic, so quite

clearly we were not looking to differentiate beyond one is a tablet, one is a capsule. It was a generic. So it would be, in our minds, priced in those terms, and our case, as the records show, priced at a discount, so the reference point which in our case we said was the drug tariff.

THE PRESIDENT: Let me be clear that this last question is a hypothetical one, but let us suppose that, for whatever reason -- and value is a very difficult thing to grasp, but for whatever reason, your view is that the price of the tablet is indefensibly high. Would Flynn nevertheless price to the level of the tablet because that is a market-based approach, or would you price lower than that because you considered on this hypothetical example the price of the tablet to be indefensibly high?

A. If I think -- hypothetically speaking of course -- if we took the view that the price was indefensibly high we would proceed with extreme caution, we may well never have gone down this road, but the reality of the situation in 2010, 2011, 2012 was we were looking at a multiyear history and the belief that there had been an intervention and a negotiated agreement. So whilst we might have been wrong, all the signals were telling us this was an acceptable price point and so if we came

in below that we did not, at the time, think there would be an issue in terms of pricing, or that issue.

It is not as if, if you look at the phenytoin tablet price I think leading up to the October 2007 meeting, I think it peaked at about £113. Now, I could perhaps be on less safe ground if I take that price as my start point, but we did not. When you see it come down and hold, there is an assumption that that was agreed, and there was if you like evidence that it was agreed, and it held for a long time, and then if we look again at the Scheme M arrangements, they tell us, they tell the industry participants that if the Scheme M price is not recalibrated in any particular quarter, or when it is there is an assumption that the recalibration -- if the average selling price changes up or down, let us say, by a pound, they will adjust the cat M price by the same sum in currency terms, not a percentage.

So we had every reason to believe that there was underlying stability in the ASP and therefore the cat M price, because that is what the scheme arrangements directed us towards.

THE PRESIDENT: I am grateful.

MR DORAN: Could I just ask you, Dr Fakes, about your second witness statement which I think is at {XC1/2} if I have it correct.

A. I have found it.

MR DORAN: You set out the risks faced by Flynn, and you mentioned a couple of them this morning. You mentioned the congenital abnormalities that more recently have come to light in respect of anti-epileptic drugs. How do you cover yourself against these risks because I noticed at paragraph 25 you say there is no contingent capital, so there is no contingent protection. How do you cover yourself against these risks?

A. It is a very good question. I think the answer is we can only do so up to a point, up to the limit of our liability insurance firstly, and then secondly, we are not so much protecting ourselves, it is protecting patients first and foremost, so we are alive to and alert to the literature and the evidence coming through on the risks, how the various regulatory authorities, not just in the UK but elsewhere, are addressing these matters, and we will play our full part in that collecting the data. So I think if for phenytoin in particular there is a lot more sensitivity whenever there is an adverse event reported to us, it is fed in, because it is such an important area of medicine, and this whole problem of congenital risk in epilepsy patients, and it applies to both male and female of course, not just women of childbearing potential.

MR DORAN: So it is a vigilance response?

A. It is, and you might say for this area of medicine given the history, there is some evidence on file about sodium valproate and the risk of that and what Dame Henrietta Hughes has said about that. More recently, we know that the MHRA is looking at topiramate which is another anti-seizure medicine, and it would not surprise me if they are drawn down the same path for phenytoin, because you have still got a situation where there is perhaps, let us say, 40,000 patients in the UK taking it, and you have the two or threefold higher risk of congenital abnormality now. If and when that happens, that is quite profound and quite serious in this day and age.

MR DORAN: But in terms of insurance or capital?

A. We do not have any contingent capital and in my working career, which started quite a long time ago, 1985, I have not been aware of any pharmaceutical company that I have worked in or with that has had the practice of putting in place contingent capital. My limited understanding was it is a practice more associated with the banking and financial institutions.

We, like most pharma, will have public liability insurance up to a point. Much larger companies are probably in a very different position, they can be more resilient, they can have access to much greater levels

of funding should something unpleasant happen, and I think in the evidence you have seen that when I talked about the risk to Glaxo arising from the nitrosamine issue in Ranitidine or in Zantac, there has already been several cases and settlements, and there will be more cases, but you can only do what you can realistically do, and I do not know how a company like Flynn, which is small and modest in reality, could put in place sufficient capital to cover a contingent risk of unknown probability or unknown magnitude.

MR DORAN: So it is a portfolio risk which is dealt with by means of your public liability insurance?

A. Yes, it is. So we insure the portfolio. You know the risks of some of the portfolio members are higher than others and they will change over time. You mitigate the risk through changing labelling or on some occasions by product withdrawal. There have been a number of product withdrawals in recent years to eliminate the risk.

MR DORAN: And you do not develop it in relation to particular products?

A. I would say not as a general rule. There may be some particular products. If I gave you one unrelated example, I think thalidomide is of course infamous for what happened in the 1960s but it still remains a licensed product and a very expensive one, I might

add, but it is covered by the most intense safety monitoring and controls on the patients. Now, I would imagine for such a product you might have particular insurances in place because of the history and the risks, but as a general rule I think you are quite right, sir, it will be a portfolio approach.

MR DORAN: Thank you very much.

THE PRESIDENT: Thank you.

Mr McCarthy, if you have any questions arising out of that, do feel free to ask them.

MR MCCARTHY: No, sir, thank you.

THE PRESIDENT: I am grateful.

Ms Stratford.

MS STRATFORD: No further questions from me, sir.

THE PRESIDENT: Well, in that case, Dr Fakes, thank you very much for your time and your evidence. You are released from the witness box.

THE WITNESS: Thank you, sir.

MR MCCARTHY: Sir, the CMA calls Andrew White, please.

MR ANDREW WHITE (affirmed)

Examination-in-chief by MR MCCARTHY

MR MCCARTHY: Mr White, you should have two witness statements in front of you.

A. Which tab are they in, sorry?

Q. I believe they are in a -- it should be in a small

bundle.

THE PRESIDENT: Perhaps we can assist the witness to make sure that he does not have Dr Fakes' bundle before him.

MR MCCARTHY: Yes.

THE PRESIDENT: By all means someone can approach to ensure that he has the right material.

A. This says "Flynn's factual evidence".

THE PRESIDENT: Right, I think we have the wrong files for you.

Mr McCarthy, do you want to proceed by using the screen?

MR MCCARTHY: I could do. I do not immediately have the references. Apologies. No, I do, actually, apologies.

If we could go to {XC1/3/1} -- sorry, {XC2/5}, please. If we could -- first of all, Mr White, could you look at that statement and confirm that that is in fact the statement you have provided in these proceedings?

A. It is, yes.

Q. If you could go to the signature page, please, on the statement {XC2/5/6}?

A. Yes.

Q. If you could look at that signature and confirm that that is your signature?

A. It is, yes.

Q. If we could go to the second statement which should be at {XC1/3/1}, if you could look at that statement and then go to the signature page on the statement, please {XC1/3/12}. I think it is just one back, actually {XC1/3/11}. If you could look at that signature and confirm that that is your signature?
A. It is, yes.
Q. Can you confirm that the facts set out in both statements are to the best of your knowledge and belief true?
A. Yes, I do that.
Q. Apologies, just to clarify, Mr White, I believe your bundle is just behind you on the shelf, if you could take a copy of your bundle with witness exhibits, please.
A. I think that is it.
Q. Does that have your two statements and exhibits to those statements?
A. I believe it does, yes.
MR MCCARTHY: I am grateful.

Cross-examination by MR BREALEY

MR BREALEY: Good afternoon.
A. Good afternoon.
Q. I am going to be going -- obviously you can go to the hard copies, I will be going also to the electronic

versions as well.

Could we go, first of all, to your second witness statement, and it is paragraph 1. We do not get this from the first witness statement, but I take it from your second witness statement that you are a pharmacist. Is that correct?

A. I am, yes, that is right.

Q. Did you practise as a pharmacist?

A. I am still on the register as a pharmacist, yes.

Q. But do you dispense?

A. Not for some years. Probably 2005 was the last time I did that.

Q. I got that. So obviously you have not prescribed any anti-seizure medicines either?

A. No, I have not.

Q. You say at paragraph 1, if you look at it:

"I am currently ICS Chief Pharmacist ..."

I will come on to that.

"I was formerly the head of Medicines Optimisation at NHS Greater Manchester Shared Service ..."

That was your role at the time of the launch as I understand it?

A. That is correct, yes.

Q. Can you just explain to the Tribunal exactly what that entailed, what did you do as head of medicines

optimisation?

A. So I led a small team, we looked after the prescribing decisions made for Greater Manchester which has a population of 2.8 million people. There were around 500 GP practices organised in 12 clinical commission groups. We had a formulary for the whole of Greater Manchester, shared care decision-making and gave advice to prescribers on the best products suitable for populations, and my team contributed towards the Greater Manchester Medicines Management Group which was a group constituting of CCGs, trusts, community pharmacy, essentially all stakeholders. I was on a decision-making body on behalf of the whole of Greater Manchester to come up with a consistent population -- so there was no postcode prescribing, there was a consistency across the whole population, so essentially raising standards, looking at quality, safety, as well as cost effectiveness and patient factors.

Q. So in other words, you were not actually part of the CCG, you were there to advise and support?

A. Technically employed by a CCG but on behalf of all 12, so I had a host employer, but effectively we were giving advice on behalf of all.

Q. You say now at paragraph 1:

"I am currently ICS Chief Pharmacist at Lancashire and South Cumbria Integrated Care."

Can you just explain what that entails? Are you now a part of the CCG, as it were? I know CCGs do not exist anymore, but --

A. CCGs have gone, we have integrated care boards which essentially commission all of the system. Integrated care system or ICS is the collection of all the various stakeholders and healthcare systems, so I have moved from Greater Manchester to a bit further north to Lancashire and South Cumbria doing similar to what I did previously, but also have a wider responsibility for being profession lead for that whole system.

Q. You are still advising, are you? Is that what you do now?

A. That is part of my job, yes.

Q. So can we go to page {XC1/3/4} of your witness statement. It may be at the bottom of page {XC1/3/3} so you can get the context.

Right at the bottom, paragraph 11. You see:

"CCGs were:

"Membership bodies ..."

And then over the page at page {XC1/3/4}, you say:

"Responsible for commissioning healthcare including mental health services, urgent and emergency care,

elective ..."

Could you just explain what these are, these commissioning healthcare services? What does that actually entail?

A. So essentially money is handed down from the Department of Health to --

Q. Can you just speak up a little bit?

A. My apologies, sorry. Money is handed down from Department of Health to NHS England and there are some nationally commissioned services which NHS England retain, and essentially all other healthcare services are commissioned or were commissioned by clinical commissioning groups until July 2022, from April 2013 until July 2022.

Q. We will park that for a moment. Go to paragraph 15, the first sentence. We will just try and drill down into this. You say at 15:

"Each functional area such as, for instance, hospital, primary care and prescribing, was assigned a budget from the allocated amount from NHS England."

So could you just explain what these functional areas are? So that is what I am trying to get your evidence on.

A. So macro levels, hospital, community, primary care, mental health services, you know, so dentists,

opticians, pharmacists as well as hospital care. Now, within that, there will be subcategories such as prescribing, so there will be a prescribing budget within hospitals, a prescribing budget within primary care, and effectively that is pooled together on the basis of your population, historic prescribing practices and the needs of your population.

Q. Okay, let us drill down even further, then. So you mention primary care. As I understand it, there are secondary care and tertiary care. Are you aware of those?

A. Yes.

Q. Can you just explain what they are: primary, secondary and tertiary?

A. So primary care would be the four pharmacists, general practitioners, dentists, optometrists. Acute care, so hospitals would contain both secondary and tertiary care, secondary care being in most district general hospitals, tertiary care generally being in large teaching hospitals of particular specialism, and in Greater Manchester we had a few university teaching hospitals who did things which were either national exemplars or one site for the whole of the population, so concentrating expertise in particular sites.

Q. So if someone has unfortunately an epileptic seizure,

what would be the healthcare services associated with that patient?

A. Diagnosis through neurology which would generally be in a secondary or tertiary hospital, ongoing --

Q. I beg your pardon, if someone has a seizure, do they go to A&E first or --

A. We aim to prevent that, but if somebody does have a seizure --

THE PRESIDENT: Are you talking about someone who has a seizure for the first time or someone who has been diagnosed with epilepsy who may have had seizures before, because it may be the response would be different?

MR BREALEY: It may be different but let us ask the question. I was not really asking for the first time, but if someone in the street has a seizure, what happens?

A. We would expect the ambulance to take them to the emergency department and a full assessment to be made, and that would look at their previous medical history which may include history of epilepsy or other conditions, it may be unrelated to epilepsy, some people have seizures for other reasons, and we would expect that to be fully investigated at a suitable site. It would not be something a general practitioner would do,

that would be something that a hospital with specialist input would --

Q. So a neurologist?

A. I would expect the neurologist to be involved. Maybe not in the immediate acute phase, but certainly in the investigations I would expect them to be involved, yes.

Q. So can you just take the Tribunal through the various stages, whether it is a new patient or -- let us take a new patient.

A. Okay.

Q. No, sorry, let us take an existing patient, so phenytoin has, essentially, legacy patients, so let us take an existing patient. They are not on phenytoin, they are on some other drug, or whatever, and they have a seizure. Could you take the Tribunal through the services that are provided to that patient? So they collapse in the street, for example, have a seizure.

A. So some people do and it is expected as part of their care and they have self-management plans which they and their family can manage. If that is unexpected, then an ambulance may be called, or if a member of the public is concerned an ambulance may be called, somebody may be taken to an emergency department, and an assessment made at that point.

Q. So an assessment is made and then they are seen by?

A. That would be down to the assessing clinician, whether it is something that the ED consultant can deal with or whether they need specialist input, it is not something I deal with day in, day out, so I am going on my limited knowledge of that current pathway, and that may vary in different places or for different -- two people with an epilepsy diagnosis may have different care plans, and you may follow that care plan depending on what is in place for them.

Q. We saw a moment ago that that bullet point at paragraph 11, community care. Would that be community care, social services?

A. There are epilepsy nurses very often, so you may find that somebody is not seen by a neurologist but seen by an epilepsy nurse who is a nurse specialist who looks after the long-term management of the patients, but that would be generally linked up to the neurology department.

Q. So in very broad terms, what would be the difference in healthcare services between a person who is seizure-free and who is not seizure-free? So what is the difference in healthcare services between someone who is seizure-free and not seizure-free, because there are a significant number who are not seizure-free as I understand it?

A. Yes, stable or not stable.
Q. Yes.
A. So somebody who -- we would aim to keep as many people stable as possible so that we can undergo the everyday parts of life, whether that be driving, holding down a job, participating in society, that would be the treatment aim for all long-term conditions, not just epilepsy. If somebody is unstable, then we would expect them to have reviews just as if you are cardiologically unstable, you would expect to have input from a specialist, although I would say that epilepsy is something which is not dealt with by GPs in the main, if there is instability, they would seek specialist input whether that be from a neurologist or a specialist epilepsy nurse. I am not aware of any GPs that would actively change anti-epileptic medication at all. They would refer that on to a specialist.
Q. Can I just ask the question again: what will be the difference in healthcare services that is provided to someone who is seizure-free and not seizure-free? So if someone is seizure-free, they are going to be less hospitalised, they will see the neurologist less often. That is what I am trying to get a feel for.
A. As you say, the only impact that it may have on somebody who is stable is collecting prescriptions from the GP or

from the pharmacy, and there will probably be an annual check, and that may be a shared check where the GP does it on behalf of the neurologist, or it may be something where there is a neurology review, that depends on how stable or otherwise somebody's condition is.

Q. So if you are seizure-free there will be fewer A&E visits?

A. Potentially.

Q. Less inpatient care?

A. Potentially.

Q. Less outpatient care?

A. Potentially.

Q. Potentially fewer social service visits?

A. Yes, although the population tends not to have social care input to a great extent.

Q. It follows, therefore, does it not, that anti-seizure medicines benefit the NHS because they save the NHS money?

A. The cost of the medicines is probably less than those emergency episodes you are referring to, yes.

Q. So the answer is "yes"?

A. A medicine is designed to prevent a bad thing from happening, so these anti-epileptic drugs, just as many other drugs for long-term conditions, are designed to prevent bad things from happening, yes.

Q. So if you are seizure-free, you are costing the NHS less because there are fewer -- potentially fewer A&E visits, less inpatient care, less outpatient care, correct?

A. Yes, and your quality of life would be better.

Q. And that is a social -- sorry.

THE PRESIDENT: I just wanted to understand exactly what you meant when you answered a series of counsel's questions by using the word "potentially". Now I of course accept that you are talking in generality terms rather than specifics.

A. Yes.

THE PRESIDENT: But if you have a patient who is diagnosed as suffering from epilepsy but is on a drug regimen that means that they are stable in the sense that they are not having seizures, then you would expect them really just to be picking up their repeat prescriptions, taking their medicine and not troubling the NHS further?

A. There would be a level of ongoing management, but not to the acute extent that was referred to, that is right, so much less input.

THE PRESIDENT: So the answer, when you were asked about less involvement of other forms of treatment, it was "yes", but of course there is always the exceptional case.

A. I will try and be clearer.

THE PRESIDENT: No, no, I just want to assess the quality of your --

A. There are many thousands of people who have the condition, and it is not a uniform condition, there are very different forms of epilepsy, they all come under, if you like an umbrella grouping, but there is lots of different types of epilepsy for which different treatments are chosen for their various properties.

THE PRESIDENT: Thank you very much.

MR BREALEY: As formerly the head of medicines optimisation, you are obviously aware of the scheme called the PPRS?

A. Yes, I am.

Q. In your own words, can you explain the purpose of the PPRS?

A. I am not an expert on this, this is something the Department of Health arranges with the ABPI, The Association of the British Pharmaceutical Industry, and it is an old scheme which has been superseded by a new one. Effectively, it a way of managing the branded drug cost for the NHS for the UK.

Q. You refer to it in the letter that you referred -- you wrote a letter on 10 October 2012.

A. Yes.

Q. We do not need to go to it at the moment, but you cite from it the PPRS.

A. Yes.
Q. I thought you had some experience in it.
A. I am a -- I have not been involved in negotiating it, but I am somebody who is the end user of it, yes.
THE PRESIDENT: Sorry, is it Mr or Dr White?
A. It is Mr.
THE PRESIDENT: You will, I am sure, be asked a number of questions about how various schemes operate. Can I just be clear that this is not intended to be either a memory test or a legal examination.
A. Indeed.
THE PRESIDENT: But it would I think assist when you are asked these questions if you were to give your sense of how they work, because you are obviously involved in the industry and therefore your answers are valuable, but equally, when you give those answers if you feel uncomfortable about the expertise that you are giving, that also would help if you gave it to us, but do not worry about being an expert in the regulations, I am much more interested in the sense that you are providing as a qualified pharmacist, amongst other things, to how the system works.
A. It is the application of it rather than the development of it would be my area of expertise.
THE PRESIDENT: Indeed, and we will take your answers in

that light, just so that you are both clear.

MR BREALEY: It is your area of understanding?

A. Yes.

Q. The fact that you cited from the PPRS in your letter I thought you did understand its components.

A. Indeed, yes.

Q. With that in mind, just before lunch, could we go to a document to see whether this resonates with your understanding. This is not in your bundle, I do not believe. It is {XG/20}.

Now, this is an Office of Fair Trading, which as you probably know is now the CMA; yes? You are nodding, but --

A. Sorry, yes.

Q. It is a market study, a CMA market study, the Pharmaceutical Price Regulation Scheme. It is dated 2007.

If we can go to page {XG/20/5}, please, this document is a good document because it describes the components of the PPRS --

THE PRESIDENT: Now, pausing there, first of all, Mr White, is this a document you have seen before?

A. I don't recall seeing it before.

THE PRESIDENT: No. You will be taken to parts of it, and I anticipate, it being a market study, it is quite

a long document. If at any point you want to see pages either side of where you are being asked, do say. The problem with these electronic documents is you cannot actually turn the pages yourself, so just ask counsel and the context will be provided.

A. Thank you, sir.

MR BREALEY: I can give the witness my copy.

THE PRESIDENT: Mr Brealey, it is simply I want to deal with the problem that one has with electronic documents that one cannot leaf through what there is, but I know you will do it fairly, it is just we need to make sure the witness knows that he can ask to see something more if he feels it appropriate.

MR BREALEY: I really do not mind the witness having a look at it over lunch. All I wanted to do was get a few -- get your evidence as to your understanding as to the workings of the PPRS which I thought that you were -- since you were head of optimisation, I thought you were well versed in it.

A. That is fine.

Q. You see on the --

THE PRESIDENT: The page has gone. I think we had better bring it up.

MR BREALEY: {XG/20/5}, you see on the first page, you have the executive summary, you have key recommendations and

the role of the PPRS, and then at the bottom, we will just have a look at these and then maybe we will close for lunch, you see:

"The workings of the scheme are complex, but at a broad level it comprises two main components:

"Profit controls, which set a maximum level for the profits that a company may earn from the supply of branded drugs to the NHS. Exceeding this level will require a repayment of excess profits to DH. The profit control also enables companies to increase prices if their profits fall below a given minimum."

Is that your area of understanding?

A. That is my understanding of PPRS.

Q. Do you think that is correct?

A. Yes, and it is an OFT official document, so, yes.

Q. If one goes over the page {XG/20/6}, then "price controls", so this is the second main component of the PPRS:

"... which give companies freedom to set the initial price of new active substances but impose restrictions on subsequent price increases. They also comprise price cuts, which are agreed at the time of scheme renegotiations. A seven per cent cut was imposed as part of the negotiation of the current PPRS scheme beginning in 2005. Companies are given some flexibility

in deciding which products to target in cutting prices, a system known as price modulation."

So does that accord with your understanding as well, the price controls?

A. Yes, across the basket of drugs that the companies produce, yes.

MR BREALEY: I see the time.

THE PRESIDENT: That is a convenient moment, is it, Mr Brealey?

Mr White, we are going to rise for a lunch break. We will resume at 2.00, so be back here a few minutes before 2.00. Please do not talk to anyone about your evidence, but if your legal team are going to get you a sandwich, then that is absolutely fine, you can ask them about that, but do not discuss your evidence. We will rise until 2.00.

(12.58 pm)

(The short adjournment)

(2.00 pm)

THE PRESIDENT: Mr Brealey, good afternoon.

MR BREALEY: Thank you.

So, Mr White, I do not know whether you have on screen there your last answer just before lunch, because I just want to remind you what you said, we were talking about the PPRS.

A. Of course, yes.
Q. And how it operates, and I do not know if it is on your screen, but you said -- when you were talking about the PPRS:

"Question: So does that accord with your understanding as well, the price controls?"

And you say:

"Answer: Yes, across the basket of drugs that the companies produce, yes."

A. Yes, I've just got somebody's transcripts in front of me at the moment.
Q. It is [draft] page 117, line 4. I just want to remind you of what you said. So page 117, line 4.
A. Yes.
Q. I was asking you about the PPRS, and you said:

"Answer: Yes, across the basket of drugs that the companies produce, yes."

So in other words the portfolio of drugs?

A. Indeed, yes.
Q. While we are on that, can we quickly go to the transcript {Day4LH1/62:25}.

Just so you know, this is Mr Holmes, who you have probably met, he is the CMA's counsel, and this is a transcript of what he was submitting, so clearly it is not evidence and I just want to find out from you

whether you agree with what he said.

A. Okay.

Q. At {Day4LH1/62:25}, this relates to what you just said about the portfolio, he said -- this is Mr Holmes speaking:

"Epanutin's profitability, the capsule's brand, was therefore limited, and to be clear, the profitability of the individual product cannot fairly be assessed in isolation because of the nature of the scheme."

The scheme is the PPRS.

A. Yes.

Q. So essentially he was saying there that the PPRS does not identify the profitability of the individual product. Do you accept that?

A. And there will be profitability and loss-making possibly across the portfolio is my understanding.

Q. Yes. If we go back to the document that we had, the market study, that is {XG/20/1} and see if you agree with what the CMA, the OFT, said in the document. If we go to page {XG/20/7}, maybe enlarge it a little bit, it is the bit in bold and the paragraph below it, and whether this accords with your experience of the PPRS. It reads:

"Profit and price controls do not reflect the value of drugs."

MR HOLMES: I hesitate to interrupt. I just want to make the observation, which I hope the Tribunal is well alive to, that this witness is not being tendered as an expert on the PPRS. The terms of the PPRS can be considered and understood as a matter of submission. This witness' evidence is about the adverse impact on CCGs of the price increases by Flynn and Pfizer.

Now, how Mr Brealey uses his time in cross-examination is obviously a matter for him, but I would just put down a marker that this witness does not mention the PPRS in either of his witness statements, does not give evidence about it, and I do find it somewhat troubling that he is being used to ask questions about something that he has not given evidence about at any stage during the course of these proceedings.

MR BREALEY: I do not accept that in the slightest. I think it is a very unwelcome intervention.

THE PRESIDENT: Well, just pausing there. Anyone is permitted to ask relevant questions of any witness whether it is addressed in their statement or not. Whether the witness is competent to deal with them is a matter which we will assess after the evidence has been given, but, Mr Brealey, if you want to explore the PPRS with the witness -- and if you do not know the

answer you will just say, Mr White -- then you must go ahead.

MR BREALEY: Thank you.

We will come on to that minute. I just want to be completely fair here. I think if one goes to {XD1/3/11}, that is on the screen, that is a page of the letter that you wrote to the Department of Health and the various bodies. Do you recognise that?

A. Correct, that is right, yes.

Q. You see there:

"Pharmaceutical Price Regulation Scheme (PPRS)."

So I just want to indicate to you that Mr Holmes is wrong when he says that is not mentioned in your evidence because that is an exhibit in your evidence.

A. I agree.

Q. Can I go back, then, to what I was doing which was the document at {XG/20/7}. Before the unnecessary interruption I was reading:

"Profit and price controls do not reflect the value of drugs."

This is the CMA/OFT speaking:

"However, we have an overriding concern with the scheme as it is currently designed: neither the profit cap nor the price cut helps secure prices that reflect the therapeutic value of the drugs companies are

supplying to the NHS."

My simple question is you can agree with the CMA/OFT or you can disagree. I am just asking within your area of understanding was that your experience at the time; did the PPRS reflect the value of drugs, individual drugs?

A. It is not something that we dealt with in CCGs. The prices were those which were in the national price list, and we paid the prices that were negotiated by the Department of Health with the industry. So we were recipients of the PPRS, aware of the overarching elements of the scheme but not involved in any of the detail of it.

Q. That is a fair answer. Essentially that was in the remit of the Department of Health, what prices they were prepared to pay and reimburse pharmacies?

A. Yes, that is the price. The value is something that NICE and other health technology appraisers would look at the value of that. We all know the costs of everything, the value of nothing sometimes. So others will help us with that.

Q. In your letter you do refer to the PPRS drug tariff reimbursement price of £2.83. Is that a figure you remember?

A. If it's in the -- if that is what is written in the

letter. That's page --

Q. Do you want to go to it?

A. -- {XD1/3/10}.

Q. So in the middle there you are referring to the reimbursement price for the capsule, the drug tariff price and then you are referring to the price increase; yes?

A. At the time, yes, that is right.

Q. And that is £2.83 for 84 capsules?

A. Yes.

Q. In these proceedings, if we can go back to your second -- your statement now {XC1/1/3}.

A. XC1/1/3 is not mine.

Q. {XC1/3/1}. Yes, thank you. And it is page {XC1/3/9}. I just want to ask you few questions about paragraph 32.

We saw there that you mention the drug tariff reimbursement price of £2.83. That is for 84 capsules, and just to -- you may know this, but in these proceedings we have recalculated this to represent a price for a pack of 28 capsules, so we have divided by 3. That is just the maths.

A. Okay.

Q. I hope I have this right, but it works out, if you take the reimbursement price, the PPRS reimbursement price equivalent for 28 capsules, it is 94 pence.

A. Yes.
Q. Yes. Now, in paragraph 32 of your second statement, you say:

"While phenytoin tablets were also expensive at the time this was a secondary concern, as tablets were prescribed to a much smaller number of patients; therefore the tablet price had a limited and predictable impact on recurrent budgets. The price of phenytoin tablets had gradually increased over time making it manageable, if undesirable [you say] (a markedly different situation to the higher patient numbers and the sudden, unpredictable increase of phenytoin capsules' price)."

Why do you refer to the price of the tablet there? It seems a bit out on a limb there. Why do you refer to the tablet price?

A. I think it is related to the paragraph above where it says the switch from phenytoin capsules to tablets would have been clinically inappropriate in the light of NICE and MHRA guidance and had the potential to cause harm. So on the face of it, although these two drugs have the same name, they are not clinically interchangeable, and we would not --
Q. Paragraph 32 does not really follow from that. You are talking in 31 about substitution, but then you go on at

32 to say the price of the tablets was a secondary concern. So why was the pricing of tablets a secondary concern?

A. So if you look at the overall volume and therefore our costs, it was a higher unit cost for the tablets but much smaller patient numbers and was relatively stable in terms of prices, whereas there was a -- I think it was -- was it a 24 times increase in cost in the capsules between the drug tariff price for Epanutin and then the Flynn prices, with much higher volumes of patients. Therefore the quantum of the cost increase in that individual year was utterly unpredictable compared to usual patterns.

Q. Were you aware of the drug tariff for the tablet at the time?

A. I looked it up certainly.

Q. Because you refer to this in the past tense. You say this was a secondary concern. So it gives the impression that you were aware of the drug tariff for the tablet at the relevant time.

A. We refer to the tablet prices of many drugs. You know, it is how we do business. The volumes prescribed are multiplied by the cost that is laid down by the national drug tariff, so we are -- and that can change on a monthly basis.

Q. But were you aware that the drug tariff price for the tablet was £30? Were you aware of that in 2012?
A. I became aware of it particularly when this price increased because we were looking at our options, clinically, as this price increased. It is not something I look at every single day. It is something which I looked at, at the time.
Q. You did not raise this in your letter, the price of the tablet?
A. The price of the tablets had not changed and had not changed from Pfizer to Flynn and had such a large price increase.
Q. But it was still a significant price differential. I will just remind you of the prices. It was £30 for the tablet and 94 pence for the capsule.
A. That is a large difference.
Q. But you did not draw the Department's attention to that?
A. No, because the tablets were working in a generic market and the Epanutin was in a branded market and you do not expect the branded prices to change when a drug is marketed by its original company. And a generic market is volatile, it is a market that is subject to supply and demand so therefore prices can rise and fall. However, with brand prices, unless by exception, prices tend to remain the same.

Q. But Flynn debranded and put the capsule into the generic market?
A. It is actually still a brand, albeit Flynn-branded generic with Epanutin still printed on the capsule, it is essentially the same product.
Q. Is it, or is it not, in the generic market?
A. You could call it a branded generic.
Q. Right.
A. But it is still branded in the sense that for safety reasons you would want that same continuity of supply and therefore you would not want just phenytoin capsules if another came to the market, you would want that specific product for your patients.
Q. You mention here the difference in the number of people taking tablets and capsules. Do you know what the difference in the numbers was, or do you need me to tell you?
A. I do not have that to hand at the moment.
Q. So capsules in broad terms were four times as much.
A. Okay.
Q. But you are not seriously suggesting that because the NHS buys more capsules than tablets, it should pay one thirtieth of the price for a capsule, are you?
A. It was less the comparator, it was the sudden increase of a consistent product that was used for many patients

for many years. The biggest concern we had was a price increase at that time, not a comparison with other products.

Q. So for you it was less the comparison, more the price increase at the time?

A. Absolutely, yes.

Q. At paragraph 25 of your second statement, that is {XC1/3/6}, you set out what you said in your first witness statement, and I just want to refer you to paragraph 11 of the first which you set out there, where, relating to what you have just said:

"The increase in the price of Phenytoin Capsules in September 2012 charged by Flynn occurred in the middle of the financial year and came without any warning."

A. Yes.

Q. I take it from that that the Department of Health did not warn you?

A. No, not to my recollection.

Q. Are you aware that the Department of Health were told of Flynn's intentions before it launched in September?

A. That did not filter down to me, to my memory.

Q. At paragraph 33 of your second statement, which is at {XC1/3/9}, you refer to a letter that you wrote on 10 October 2012; yes?

A. Yes.
Q. Complaining about the price increase?
A. Indeed.
Q. You do not mention in your statement whether you got a response. Did you get a response?
A. Some several months later, from -- I think it was one person from the Department of Health who is in the correspondence.
Q. You do not exhibit it?
A. I have not, no.
Q. Could we go to {XG/243/1}, please. Do you just want to refresh your memory about this response? This is dated 20 December 2012.
A. Okay. (Pause). I think I received something similar to this.
Q. Then go over the page when you have finished {XG/243/2}.
A. Yes.
Q. This is the Chief Pharmaceutical Officer, yes, who is responding, and your letter of complaint was -- he was one of the addressees of your letter?
A. He was not. I did not receive a response from Keith Ridge, it was a different person I received a response from.
Q. Who did you receive a response from?
A. It was somebody in the correspondence department of the

Department of Health, but it certainly was not Keith Ridge.

Q. If we go -- he says:

"I would be happy to meet with you to explore this further."

Could you just go to page {XG/243/1}, please. This is a letter from the Department of Health:

"... impact of change of marketing and distribution."

He says:

"Thank you for your letter of 19 October ... on behalf of NHS Clinical Commissioners about the recent increase in the price of phenytoin capsules~..."

So you may have written a letter on 10 October, you say you got a response but we have not necessarily seen that, or it is not exhibited in your statement.

A. I have a hard copy of it.

Q. This is a response essentially to the NHS Clinical Commissioners.

A. Yes.

Q. So this is a general response; would you accept that?

A. So the NHS Clinical Commissioners was a representative body of CCGs.

Q. Yes.

A. So I presume they wrote a similar letter to the one

I wrote.

Q. Do you remember seeing this?

A. I do not.

Q. Well, let us see if you can -- so this is the Department responding to the NHS Clinical Commissioners who, as you say, represent the CCGs. He says:

"I know that a number of your colleagues in Clinical Commissioning Groups have also written to the Department or to their local MPs and I can assure you that the Department fully understands the concerns in the NHS around this issue and its effect on NHS budgets.

"The new supplier of phenytoin capsules, Flynn Pharma ... is not marketing the product under the original brand name and, whilst the company is a member of the 2009 Pharmaceutical Price Regulation Scheme [the PPRS], this product is not covered by the scheme."

The Chief Pharmacist goes on:

"The Department is in discussion with the company about ensuring that the NHS is getting value for money when purchasing this product."

Then we get this:

"However, as I am sure you will appreciate, one of the Department's principal concerns has been to ensure continuity of supply to those patients currently being treated with phenytoin capsules -- in line with NICE

guidelines."

Then I would like you to focus on the next paragraph, please:

"The cost of any medicine has to be balanced with the potential additional costs to the NHS through adverse reactions and reduced patient outcomes if supply is interrupted."

I will continue, just to finish the letter off:

"Whilst any price increase is unwelcome, especially at a time of financial restraint such as this, systems are in place to ensure, in the main, the NHS obtains the best value from medicines. For example, we were able to move quickly, earlier this year to reduce the cost of atorvastatin to the NHS when it came off patent."

The paragraph I would like you to focus on, please, is:

"The cost of any medicine has to be balanced with the potential additional costs to the NHS through adverse reactions and reduced patient outcomes if supply is interrupted."

Did your response have a similar paragraph to that?

A. I cannot remember exactly, but I would imagine it was a very similar letter produced by the Department of Health to a number of respondents. I remember the atorvastatin paragraph at the bottom in the letter

I received, so it seems consistent, but I have not got it in front of me to compare directly.

Q. If you had seen this, what would you understand by that paragraph, that penultimate paragraph, beginning, "The cost~..."?

A. So there is a little bit of: look over here, not over there, particularly the last paragraph. The cost of any medicine, I agree, does have to be balanced with the additional costs. Essentially, if you have -- and I direct you to the paragraph above where, quite rightly, we want to ensure continuity of phenytoin capsules because they are absolutely required for a number of epileptic patients. So if the option was no supply or supply at a slightly higher cost, that would be advantageous. The big issue we had was this was an enormous increase in the cost for that supply compared to what we were currently paying.

Q. I am not interested at the moment with the enormous increase. I am interested in the concept, yes? And this letter clearly concerns phenytoin.

A. Mm-hmm.

Q. I suggest to you that the Department of Health is telling the CCGs here that the cost of phenytoin, the drug, needs to be balanced by the potential costs of patients who are not seizure free. So we looked before

lunch at the costs of people who are not seizure free.

A. Yes.

Q. What the Department is telling the CCGs here is that those potential costs have to be balanced with the price of the drug.

A. I would agree.

Q. Why do you not say that in your evidence, in your statement? Why do you not mention this balancing effect of the cost savings with the costs of the drug?

A. I believe I do absolutely refer to the need to maintain epileptics on a consistent treatment. Therefore we were left with no option but to absorb this huge increase for what was the identical product. Not a generic version, not something similar, the identical product from the same manufacturing unit. So that was what we strongly objected to, was the many times increase in cost for the identical product.

Q. But you do agree --

THE PRESIDENT: By "identical product" -- I am so sorry, by "identical product", what are the two products you are saying are identical?

A. So Epanutin when it was branded with Pfizer was made in the same factory as Flynn capsules and in fact the Flynn capsules even had Epanutin printed on them when they were in the Flynn packaging, and, as I understood it,

came out of exactly the same production line, which would be desirable for control of epilepsy.

THE PRESIDENT: Thank you.

A. Occasionally you will get different capsules from different production lines called the same things, but they may not have the same or identical therapeutic characteristics or release characteristics.

THE PRESIDENT: Mr Brealey, are you going to be asking the witness about paragraph 31 of his second statement? If not, then when you move on to another topic, could you let me know because I have some questions about it.

MR BREALEY: I was not. I was just going to ask a couple more questions and then I will let you, sir, ask the question on 31.

THE PRESIDENT: Thank you.

MR BREALEY: I was just trying to see what you said, but I think you do agree, you may quibble with the increase, but you agree that the cost of phenytoin must be balanced with the cost savings it affords to the NHS?

A. There is a cost to keeping people epilepsy free.

Q. A cost to the NHS, yes?

A. Yes, absolutely.

MR BREALEY: I have no further questions, sir.

Questions by THE TRIBUNAL

THE PRESIDENT: Thank you. If we could bring up {XC1/3/8},

and what you will see is if we can get the page straddled so we can see paragraph 31. Here we are comparing phenytoin tablets with phenytoin capsules.

A. Yes.

THE PRESIDENT: What you are saying is it would be clinically wrong for healthcare professionals, by which you mean essentially doctors --

A. Yes.

THE PRESIDENT: -- to prescribe to an epilepsy sufferer being treated with phenytoin tablets, capsules or vice versa?

A. Although they are the same drug at the same strength, they are not identically absorbed by the body. So therefore, because they are I think on a narrow therapeutic window; in other words there is quite a narrow -- the effect and the risks are quite close, so therefore you have to be maintained on the same product to maintain the benefits and avoid the side effects.

THE PRESIDENT: So you are here saying that the reason for the non-switching is not, as it were, a psychological desire in the patient to have continuity of supply, but it is in fact a medical reason that it would be clinically deleterious to the patient's health?

A. Entirely inappropriate to switch between the two.

THE PRESIDENT: I see. For non-psychological, for clinical

reasons?

A. Because of the risk of people having a relapse of their epileptic seizures, which we would not want to have through a switch of medications.

THE PRESIDENT: I see. Do you then issue any guidance as to how healthcare professionals are to proceed if one has a combination of tablets and capsules in the treatment, which we heard this morning is sometimes possible?

A. That would be a balanced amount of phenytoin that somebody was receiving through that combination. We certainly would not have considered switching or advising switching any patients between different products because of that fine balance. It would be far worse, as we described, for somebody to have an epileptic seizure as a result of a medication switch. We should do everything we can to avoid that, particularly if somebody is stable.

THE PRESIDENT: I see. Just to follow through on what you were saying about branded versus generic versus branded generic --

A. Indeed.

THE PRESIDENT: -- if one moves phenytoin from Pfizer phenytoin capsules to generic phenytoin capsules, does that affect the medical professional's, the healthcare professional's ability to specify a product in the

prescription? In other words, is one, as a healthcare professional, deprived of the ability to say: I want you, the dispensing pharmacist, to dispense Pfizer products?

A. If the Pfizer product is no longer available, as was the case here, from memory I do not think there was any other phenytoin capsule on the market but because the Flynn branded capsules were pharmacologically identical to the Pfizer ones, we wanted to maintain continuity of supply and I believe we did say: do not just write "phenytoin capsules", write "Flynn phenytoin capsules" on the prescription, to maintain that continuity of supply.

There are some medications where you would prescribe them as brand because of those therapeutic differences. There are some that it is okay to prescribe generically. In this circumstance, following the MHRA guidance, you would stay with the same product throughout.

THE PRESIDENT: So what you are saying is that in fact the shift in this case from branded to generic did, in prescribing in dispensing terms, absolutely nothing; it did not change anything?

A. It was not as you would expect a generic -- so normally when something goes from branded to generic you would expect a big price decrease, particularly if there is no

reason to swap between different brands. In this case, that was quite the opposite. You absolutely had to continue with the same product throughout to maintain epileptic control.

THE PRESIDENT: Thank you.

A. No problem.

THE PRESIDENT: Thank you very much, Mr Brealey.

MR BREALEY: I have no questions arising out of that, sir. Thank you very much, Mr White.

I think you are free to go, unless, sorry --

THE PRESIDENT: Sorry, I had not realised you were finished. There are a couple more questions, Mr White.

I think it follows logically from the answers you have given, but I will put it to you anyway, I am thinking now about not the impact of excess prices on CCGs, I am thinking about the way a pharmacy would think of things.

A. Okay.

THE PRESIDENT: Now, a pharmacy will be, in the case of a generic product, looking to the margin between the reimbursement rate and the price they obtain for the drug they buy in.

A. Indeed, yes.

THE PRESIDENT: They will be looking to maximise the gap between one and the other.

A. And it is part of the known reimbursement of pharmacies, that there is purchase profit as part of that arrangement. That is recognised and expected with the idea to keep the NHS's costs managed as well as possible.

THE PRESIDENT: So let us take a situation where one has generic capsules and we have, at least for certain periods of the relevant period, capsules provided by NRIM and capsules provided by Pfizer through Flynn, and let us suppose there is an open prescription that simply says: phenytoin capsules in a certain dosed amount.

A. Yes.

THE PRESIDENT: Now, first of all, that is a perfectly possible scenario?

A. Possible, but undesirable.

THE PRESIDENT: Well, leave the desirability apart.

A. Okay.

THE PRESIDENT: Possible?

A. Yes.

THE PRESIDENT: How possible?

A. We would advise GPs to write "as branded" for these sorts of products, but there are sometimes when people get confused and they just write the generic phenytoin on a prescription, but we would hope to minimise that as much as possible.

THE PRESIDENT: Okay, so there would be advice to GPs from yourself saying --

A. There is national MHRA guidance and we would expect that to be followed through. Sometimes we have to remind GPs to -- if we find things written generically where they should be written as branded.

THE PRESIDENT: You mentioned national guidance. You are not referring, are you, to the November 2013 document which says you should stick to the same manufactured supply?

A. The MHRA guidance, as I understand it, has run right before this case started and afterwards that for phenytoin you should not switch.

THE PRESIDENT: It would be helpful, I think, to see that, if we have not already seen it so that we understand what exactly that guidance says. But you are saying that the guidance says where you are intending that a particular sort of generic capsule be prescribed, you should say either NRIM or Flynn Pfizer --

A. Continuity of supply --

THE PRESIDENT: -- on the prescription?

A. -- whichever one that is. Yes, absolutely, because that way the pharmacy has to dispense what is requested by the prescriber.

THE PRESIDENT: Right, so even though these are both

generics, you get effectively closed, not open prescriptions?

A. And you would expect the pharmacist to check with the patient which -- (inaudible - overspeaking) --

THE PRESIDENT: No, let us take it in stages, Mr White, I do not want you rushing on ahead.

A. Of course.

THE PRESIDENT: Just answer the question I am putting to you and we will get on much better.

At the moment I am at the stage of the healthcare professional, not the dispensing pharmacist. Is it your evidence that in most cases -- and we are talking about two generic capsules -- in most cases the prescriptions issued by the healthcare professional will effectively be closed? Now, if you do not know the answer to that, do say.

A. Are you saying specifically with regards to phenytoin or in general?

THE PRESIDENT: I am talking specifically about phenytoin. The scenario I am postulating is that we have two generics, we have NRIM and we have the Flynn product.

A. Okay.

THE PRESIDENT: So differently manufactured products, but both generics.

A. Yes.

THE PRESIDENT: How many prescriptions out of 100 will say just phenytoin capsules and how many will say NRIM and/or Pfizer?

A. I do not know off the top of my head how many will say --

THE PRESIDENT: You do not know. But would you think that something had gone wrong if a prescription did not specify NRIM or Flynn Pfizer?

A. I would expect continuity of supply and the easiest way of doing that is to ensure the brand or manufacturer is specified on the prescription. So if somebody is initiated on one product I would expect that to continue until --

THE PRESIDENT: I understand that is your expectation.

A. Yes.

THE PRESIDENT: But you do not actually know. Is that the position?

A. I do not know. I would hope from a professional pharmacy perspective that would be asked and the continuity would happen, but I cannot 100% guarantee that would happen.

THE PRESIDENT: We are going to come to continuity, I promise you.

A. Yes.

THE PRESIDENT: I am interested at the moment in how far

a healthcare professional would close down what would otherwise be an open prescription.

A. I would expect it to be closed, but there may be exceptions.

THE PRESIDENT: Okay, so it will be the exceptional case, it would be very rare?

A. That would be my expectation.

THE PRESIDENT: I see. So that would mean that the pharmacy will have its hands tied?

A. Yes.

THE PRESIDENT: If you have the vast majority of prescriptions closed in this way, then there is no option, you have to go either down NRIM or Flynn Pharma?

A. Yes, absolutely.

THE PRESIDENT: Okay. So if you have, exceptionally on your evidence, an open prescription which just says "phenytoin capsules", what, in your view, ought the pharmacy to do?

A. To ask the patient what product they regularly receive and continue to supply the same product, and it may be they would contact the GP to ask that to be branded. That would not always happen, but I would expect the pharmacy to check which brand the patient always gets as a minimum.

THE PRESIDENT: So you have an element of -- can I put it

this way -- second-guessing of an open prescription?

A. Professional expectation.

THE PRESIDENT: That is not because continuity of supply is generally important but it is particularly important in this case?

A. Absolutely.

THE PRESIDENT: And a dispensing pharmacist would know that phenytoin capsules were in this special case?

A. They certainly should do, yes.

THE PRESIDENT: Okay. So let us hypothesise that there is a very material difference in the margin that one gets from NRIM and the margin that one gets from Flynn Pharma.

A. Okay.

THE PRESIDENT: Let us say it is £10 or £15 or £20 a packet.

A. Okay.

THE PRESIDENT: That is something which you should not as a pharmacist take into account. You should ask instead of the patient what is the previous dispensing product and you should make sure you prescribe the one rather than the other even though one is significantly more expensive to the pharmacy than the other?

A. There may be a profit motive, I agree, but professionally it would be, in my view, essential that the same product is continued, whether that is at an

adverse cost or an advantageous cost. So whatever the person had previously should continue.

THE PRESIDENT: I have asked this question already but I just want to ask it in a different way to close out this line. The reason one is sticking to continuity of supply is not because of a well-founded psychological desire in the patient to stick with that which has worked before, it is because of the clinical reasons that you articulated before?

A. The primary reason is a clinical reason, but you are right, there may be anxiety from patients about any switches which could change their life if they lost control of their epilepsy, but this is a pharmaceutical, pharmacological, not a psychological we are referring to here.

THE PRESIDENT: Thank you very much. Mr Brealey, if you have any questions, do ask?

MR BREALEY: Just to assist both the witness and the Tribunal, the prior stage as to the number of prescriptions, if we could go to {XA2/1/59}, and it is paragraph 3.88, one sees there:

> "... evidence submitted by Flynn and ... Pfizer indicates that over the period ... 2014 to ... 2015 [so that is after the guidelines] 91% of prescriptions for phenytoin sodium capsules were open."

And that is not just the Flynn/Pfizer.

If one goes to page {XA2/1/200} of this document and at the bottom of the page, if you can enlarge it, footnote 591 you see there:

"NHSBSA data shows that over the period ... 2014 to ... 2015, 91% of prescriptions for phenytoin sodium capsules were open ..."

Just to assist.

THE PRESIDENT: That is very helpful, Mr Brealey and thank you.

Mr White, you should feel free to comment on those. It is clearly at variance with what you think is going on.

A. Well, if there is only one phenytoin sodium capsule on the market people would receive that whether it was branded or it is a phenytoin sodium. If there is more than one available, then moving to branded would be advantageous.

If there was only Epanutin available, which became Flynn capsules, they would -- patients receive the same product throughout. If another one was on the market, that could cause that choice, and although I agree that is BSA data, that must be correct, I would hope with this that branded anti-epileptics for phenytoin should be the case. Unfortunately that is not what the

prescribing data bears out.

THE PRESIDENT: Thank you.

PROFESSOR WATERSON: We have been talking about the NRIM capsules but also at times there were parallel imports of the Pfizer product.

A. Okay.

PROFESSOR WATERSON: In your view, would they be considered identical to the Flynn capsules?

A. I think in my evidence statement I said I spoke to Dave Fakes who I think was on prior to me at the time and he said that the product was made in the same factory worldwide, so it had Epanutin on it. I would expect, wherever that came from in the country, it would have been identical products, whether they were parallel imported or as a UK pack, so therefore it should be bioequivalent.

PROFESSOR WATERSON: Okay, so from your point of view, you would be more concerned about the NRIM product than about the parallel imports?

A. Any change I would be concerned about.

PROFESSOR WATERSON: Right.

A. But if the parallel import market was there, that would indicate it was being sold cheaper in other markets than it was in the UK, so there was an advantage in buying even at the low prices that Epanutin were marketed for,

they were being sold for less in other markets and being imported for profit into the UK.

PROFESSOR WATERSON: Thank you.

MR DORAN: One little point of detail.

Earlier on I understood you to say that these tablets would be -- sorry, the capsules would be prescribed by and large by neurologists, or it would be a hospital-based prescription regime.

A. Initiated, certainly and then continued in primary care by the GP.

MR DORAN: The extent to which the GPs have the scope professionally to vary the prescription compared to a referral back to the neurologist?

A. For drugs like this where there is a narrow therapeutic index, I would not expect any changes to be made by a GP.

MR DORAN: Right.

A. There are other drugs in other categories of MHRA for example, Category 3 there is a drug called levetiracetam which is another anti-epileptic which came off patent in the last year and a half, and it is quite okay to switch people between those, and there is enormous windfall savings then to NHS on the basis of that and that it is perfectly safe to do that, which GPs can do, but for those of a narrow therapeutic index we would not expect

a GP to make any changes at all to the regime.

MR DORAN: I had understood the conversation you were having with the President and with Mr Brealey was about GPs changing prescriptions. Does this also apply to the neurologists in terms of scope to issue open, truly open, prescriptions?

A. I would -- I believe that a neurologist would probably say phenytoin capsules, the continuity would be what the GP and the pharmacy continue to supply for that person. No GP that I am aware of would make a change to an epileptic regime if somebody is unstable, they would expect that to be with a specialist, whether that be an epilepsy specialist, nurse or neurologist.

MR DORAN: I think you had said in your witness statement that the guidance recommended -- the NICE guidance from 2012 recommended consistent supply of a particular manufacturer's AED unless the prescriber considered this was not a concern so that in writing an open prescription it would be on the basis that the prescriber, in the case you are talking about the specialist, felt that it did not really matter?

A. The neurologist would start the prescription, the continuity would happen with the GP, so the most important thing while somebody is in stable phase is that the GP continues that supply.

MR DORAN: So it's the maintenance --
A. The maintenance by the GP would be what is written on that prescription and what is dispensed by the pharmacy, and if it is not overtly written on the prescription I would expect a conversation to be had with the patient to clarify what they are on and that supply to continue.
MR DORAN: So what you are saying about the need for consistent dispensing applies in relation to whether it is -- whether the specialist has written the prescription, you would expect in line with what you said that unless they specifically said it can be any phenytoin, you would expect it to be the phenytoin that they had been on before, initially identified?
A. Continue and should remain on that until or if there was a reason to change clinically.
MR DORAN: And then a discussion to be had with the consultant before any change?
A. Absolutely, yes.
MR DORAN: If the pharmacist happened to be stocked out at any stage so they had no stock of the normal, would that be a conversation back with the specialist before anything else was --
A. I would certainly expect that, but probably you would look to mutual aid first to see whether pharmacies locally or others within the chain could obtain the

supplies because it is so essential that patients remain on the same. So pharmacies would go out of their way to try to continue that supply, and in extremis if there was no supply at all, then I would expect a specialist to be involved in any decision after that.

MR O'DONOGHUE: Thank you very much indeed.

THE PRESIDENT: I will finish off and then Mr Brealey can have the last word in cross-examination or reply.

It is just to do with the branding of a generic and parallel imports.

A. Yes, okay.

THE PRESIDENT: Now, we have discussed the fact that the parallel imports are essentially the same product --

A. That is my understanding, yes.

THE PRESIDENT: -- and your concern of risk of shifting between, as it were, the Flynn generic and a parallel Pfizer import would be less concerning than a move from Flynn to an altogether different manufactured product?

A. Epanutin is still -- if Epanutin is still printed on the capsule my understanding is they still come out of the same factory, so --

THE PRESIDENT: So your concerns would be much less, if any?

A. But again, I would expect continuity of supply as an utmost concern.

THE PRESIDENT: That is why the branding of the generic is

important?

A. Absolutely.

THE PRESIDENT: Because you cannot be assured on a parallel import, unless you look at the whatever labelling it is in the fine detail?

A. Which may be under foil so you are unable to see that as the dispensing pharmacy.

THE PRESIDENT: So your evidence is that the branding of the generic is absolutely critical to the continuity of supply which is in itself important for clinical reasons?

A. Absolutely, yes.

THE PRESIDENT: I am very grateful.

Mr Brealey.

Further cross-examination by MR BREALEY

MR BREALEY: Thank you, sir.

Just for completeness, just so that -- you have been discussing about prescribers and dispensers. If we actually go to -- you mentioned the MHRA guidelines in your statement, but if we can just have a look at them at {XG/307} we have just seen the data that 91% of prescriptions are open.

A. Could you zoom that in, please?

Q. It is more at the bottom, if you can enlarge it at the bottom, so there we go:

"Additional advice for pharmacists."

We will read it and then you can give your evidence on it:

"Dispensing pharmacists should ensure the continuity of supply of a particular product when the prescription specifies it. If the prescribed product is unavailable, it may be necessary to dispense a product from a different manufacturer to maintain continuity of treatment of that AED. Such cases should be discussed and agreed with both the prescriber and patient (or carer)."

Then I would like just your comment on the next line, because we have just seen that 91% of prescriptions are open:

"Usual dispensing practice can be followed when a specific product is not stated."

So that is the advice to the pharmacists that I think Mr Doran referred to a few days ago. Do you want to comment on that?

A. Yes, and that is in the context of the three categories above that where, as I have said, Category 3 is not changeable whereas Category 1, which phenytoin is within, is not interchangeable, which is just off the top of the screen.

Q. So you read that as not relating to phenytoin?

A. Sorry, no, quite the opposite. Continuity of supply is even more important in the Category 1 products than it is on the Category 3 products.

Q. But when a prescription is open, the guidance, and that one line I have just read out, "usual dispensing practice can be followed when a specific product is not stated", if phenytoin -- if a specific product is not stated, if it does not say NRIM or Pfizer or Flynn, the pharmacist can adopt usual dispensing practice and dispense the cheapest?

A. You can. However, if you are talking about an epileptic supply, professional ethics would be such that you should be asking about that continuity of supply, as we have just discussed, so usual dispensing practice would include, as it says above, should be discussed with the patient and the prescriber.

Q. Well, we can debate that, but --

THE PRESIDENT: Well, we can, but I think if we could just move up a little bit to see Category 1. First of all you mention guidance. Is this the guidance that you were referring to in your evidence?

A. Yes.

THE PRESIDENT: We do not have to look at anything else?

A. No, this is the one, yes.

THE PRESIDENT: Thank you. If one looks at the Category 1:

"For these drugs, doctors are advised to ensure that their patient is maintained on a specific manufacturer's product."

So what you are there saying is that whether it is generic or branded, you should enable the dispensing pharmacy to work out who has manufactured it so that continuity can be maintained?

A. Yes, and to pick up the point of counsel's, I would class that as usual dispensing practice for the pharmacy to make that clarification, given it specifically says that patient should be maintained on a specific manufacturer's product.

THE PRESIDENT: If one looks just below that, do you see the heading:

"Advice for healthcare professionals"?

A. Yes, I can see that.

THE PRESIDENT: That is I think -- but do correct me if I am wrong -- referring to the distinction you have been drawing between a branded product, ie specifying a brand name, or by using the generic drug name and the name of the manufacturer?

A. Correct.

THE PRESIDENT: In other words, you are saying it should not make a difference whether the drug is generic or branded, you will be specific in terms of what should be

dispensed?

A. That particularly matters for phenytoin and the other ones in Category 1, but the drugs in Category 3 may be interchangeable between different manufacturers and different generics, but absolutely, Category 1 you should, wherever possible, stick to the same manufacturer throughout.

THE PRESIDENT: Again, you may not be able to answer this because the distinction between open and closed prescriptions may be a rather more nuanced one than one would like, but if I were a doctor prescribing a generic drug with the name of the manufacturer, would that prescription be closed or open in your classification?

A. That would be closed.

THE PRESIDENT: That would be closed, thank you.

Mr Brealey, your last chance?

MR BREALEY: No.

THE PRESIDENT: Any re-examination?

MR MCCARTHY: No, thank you.

THE PRESIDENT: Well, thank you very much, Mr White. We are very much obliged to you for your assistance. You are now released. Thank you.

THE WITNESS: Thank you very much.

MR MCCARTHY: Sir, the CMA will now call Shaun Green, please.

MR SHAUN GREEN (affirmed)

THE PRESIDENT: Mr Green, good afternoon. Do sit down, make yourself comfortable. I suspect that is the file you should put away, but there may be behind you, a file which has your witness statement in it. Why do you not see if you can find that. They are whispering it is the same bundle.

MR MCCARTHY: Yes.

THE PRESIDENT: Why do you not check if in that bundle you have your witness statements in there because you will be referred to them in a moment.

I will hand you over to Mr McCarthy who has some questions for you.

Examination-in-chief by MR MCCARTHY

MR MCCARTHY: Mr Green, can I just check that is the bundle with your two statements in it?

A. I am looking at A3 for my statement.

Q. Yes, and there should be two separate statements.

A. Yes, A4.

Q. And I will just give the Opus references for each of them if that assists. The first statement is {XC2/6}. If we could go to the signature page, please, on that statement, I think it is at page {XC2/6/6}.

Mr Green, could you look at that signature and confirm that that is in fact your signature?

A. Yes, that is correct.
Q. Can you also confirm that the facts you set out in your statement are to the best of your knowledge and belief, true?
A. That is correct.
Q. Thank you. Could you look at the second statement you have given as well, please? That is Opus reference {XC1/4}, and again if we could go to the signature page, please, on that statement {XC1/4/8}. Again, this is also your signature, is it?
A. That is correct, yes.
Q. Again, if you confirm that the facts set out in that statement are true to the best of your knowledge and belief, please?
A. They are, yes.
MR MCCARTHY: I am grateful. If you wait there, my learned friend might have some questions.

Cross-examination by MR BREALEY

MR BREALEY: Just a few.

Good afternoon, Mr Green. Shall we go to your second witness statement, please, which is on the Opus {XC1/4}, and you say at paragraph 1 you are the Deputy Director of Clinical Effectiveness and Medicines Management for the NHS Somerset, you have performed your current role for approximately 20 years, and then you

say that basically this role carries with it two responsibilities: production of prescribing guidance and efficient use of Somerset CCG's prescribing budget?

A. That is correct, yes.

Q. Can you briefly summarise what those roles entail, those two roles?

A. Yes, very much looking at optimising the patient benefit from medicines that are available, looking at new evidence that is produced when new drugs come to market, and where there is a choice of medicines, making sure that they are prescribed in the most cost-effective way, and importantly, making sure that patients are getting the best benefit when taking their medicines as well.

Q. I take it you are a pharmacist?

A. I am a pharmacist by background.

Q. You just did not say. So everybody seems to be a pharmacist.

Like before, have you dispensed any anti-seizure medicines or have you been employed in this role for many --

A. I have been a pharmacist for 35 years, and the first 15 years of my career I was working in a community pharmacy dispensing medicines, yes.

Q. So you know all about anti-seizure medicines and --

A. I do, yes. I know a lot about Epanutin. It was even

around when I first qualified.

Q. Sorry, I beg your pardon, I missed --

A. Epanutin was around when I first qualified.

Q. Right, I think it has been around for about 100 years.

THE PRESIDENT: I think that was a joke, Mr Brealey.

MR BREALEY: If you go to [paragraph] 10 of your statement, that is page {XC1/4/3}, you say correctly:

"CCGs no longer exist but historically held devolved budgets from NHS England and ultimately the Department of Health from which they needed to commission all health services including primary and secondary care which fell under their remit."

Just on the budget, can you just take the Tribunal to how the Department of Health essentially set the budget. I know it is based to a certain extent on historic, but how did the process work?

A. There is a formula that the Department of Health use, I do not know the exact details or what it is called anymore, but it is based upon your population's health, age, levels of deprivation, etc.

Q. How much control does the Department of Health exercise over that budget? Is it fairly tightly ring-fenced?

A. There are certain elements of the budgets that are devolved that are ring-fenced, for example, there was a requirement around mental health spend that that must

be met. The rest of the budget is not so tightly ring-fenced.

Q. I think we saw from Mr White that essentially the price of the drugs, the reimbursement prices are controlled by the Department of Health?

A. The drug tariff comes out every month and gives the reimbursement prices from a CCG budget perspective at the time between 10% and 15% of that overall budget would be a drug spend, would be the sort of range roughly.

Q. At paragraph 12, if you go to page {XC1/4/4}, can we just have a look at paragraph 12. You say:

"Part of the process of planning prescribing expenditure included assessment of new drugs coming to market, how beneficial that drug would be and estimates of the patient population who may require that new drug."

Something you have just been referring to.

"One of the savings CCGs relied upon each year, when estimating their prescribing budgets, was when branded drugs lost their patent exclusivity and generic equivalent drugs entered the market. Generic drugs would almost exclusively be less expensive than the originator brand and so CCGs would encourage and support prescribers and patients to switch to the generic

version."

How would you encourage them to switch?

A. We would take a number of different approaches: education, newsletters, annual meetings or regular meetings with the general practices, and then if need be, incentivising GPs to switch as well.

Q. You say in the second sentence that you are estimating the cost in the budgets. How would you do that when drugs are coming off on patent? How would you estimate the potential cost saving in the forthcoming budget?

A. So each year I would get a budget from my finance director for the 65 GP practices we probably had at the time, and then I would set a budget for them based upon their historical spend, their population, age of their population, and where we had prevalence of various disease stated within each practice.

So the cake that I would be given each year by the director of finance I would cut up 65 ways, delegate that down to the GP practices and work with them through the year to try to manage --

Q. When you are making this estimate, when it looks as if the drug is coming off patent, you will be estimating, what, the fall in the volume in the incumbent brand?

A. Yes.

Q. Then you will be estimating what you consider to be

a fall in price?

A. That is correct, yes.

Q. So when you are looking at the budget you take the higher price of the brand and the lower price of the generic and then you add these costs up for the forthcoming budget, do you?

A. So we would horizon-scan which is looking forward about what is coming and what drugs were going to lose patent, so you mention the Keith Ridge letter and he talked about atorvastatin losing its patent and that being a cost saving to the NHS. So the guidance that would come out nationally each year would be us forward-planning, seeing which drugs we thought were going to lose patent and whether that would bring a windfall or not to us, and we could take that into account.

Q. So the CMA in its Decision has helpfully given some examples of this. If you go to -- if we go to {XA1/1/369}, which is the Decision. Maybe blow it up a little bit. Do you know this product?

A. Yes.

Q. This is an anti-seizure medicine and you see here lamotrigine which is the generic, yes, and Lamictal, the brand, and these are tablets, and in the red, you have the brand, and then obviously in 2005 it came off

patent, and the generic takes over, it looks like half and half, and then the generic really takes off. Although we have an increase in the volume supplied, these are in millions. I am just trying to work out what you are doing when you are estimating the budget.

As you just said, you will be estimating the fall in volume, and you will be trying to work out what the decrease in price will be.

A. Yes, you would estimate if, for example, a drug had a cost of £50 as a brand, you would use your experience and whatever guidance was coming out, and you would probably expect that to drop by a certain per cent in year one and then by more as more competition came to market going forward into year two, etc.

Q. So in other words, for each budget you are estimating the overall cost to the NHS -- you are estimating the overall cost to the NHS of the generic and the brand?

A. Yes.

Q. In your statement, you refer -- I think it is at paragraph 26 at page {XC1/4/7}, that you were concerned about the price increase. Is that correct?

A. Very.

Q. You wrote to the Department of -- you wrote to the ministry, the Department of Health?

A. I wrote to, I think, the Chief Pharmaceutical Officer.

Q. The chief pharmaceutical --
A. And as a CCG, we wrote to a number of MPs, Department of Health, and then I think we even took it to the OFT. That is how concerned we were.
Q. If we can go to {XD1/4/27}, can we have a look at that? That is the response from the Department of Health. You fairly exhibit this to your witness statement, but you do not actually mention it. As I said, you do not kind of refer to the text, so I wanted to go to the text.
    The first paragraph of this is from the -- it is the Parliament Under Secretary of State who is the relevant minister in charge; yes?
A. I do not see who it is from because I --
Q. Sorry, go to page 2 {XD1/4/28}, but it is at the top of the page --
A. Earl Howe, yes.
Q. Yes. If you go back to page 1 on the top left, you see Parliamentary Under Secretary of State for quality. {XD1/4/27}
    This is referring to Somerset's clinical commissioning group of 30 October; yes?
A. That is correct, yes.
Q. He says, this is the first paragraph:
    "I am replying as the Minister responsible for medicines and pharmacy policy."

So as the minister responsible for medicines and pharmacy policy he has been charged with responding to your complaint; yes? He says:

"I note Dr ... concerns about the recent increase in the price of phenytoin ..."

He says:

"As [the person] is aware, the new supplier ... is not marketing the product under the original brand name of Epanutin."

Then I think you have been listening to the evidence given by Mr White, you will see here the penultimate and last paragraphs are very similar to the letter that we saw a few moments ago.

A. Very similar to Keith Ridge's letter, yes.

Q. So:

"The Department is in discussion with the company about ensuring that the NHS is getting value for money when purchasing this product."

Then:

"However ..."

Again, it is the same statement:

"... as I am sure you will appreciate, one of the Department's principal concerns has been to ensure the continuity of supply to those patients who are currently being treated with phenytoin."

I would like you to focus on the next sentence, please:

"The cost of any medicine [in other words, phenytoin here] has to be balanced against poorer patient outcomes and the potential additional costs to the NHS from adverse reactions if supply is interrupted."

Now, you obviously saw this at the time in 2012. Can you explain to the Tribunal what the additional cost to the NHS would be?

A. We all felt we were being fobbed off by this letter.

Q. No, I would like you to answer the specific question, not to repeat what is in your statement. Can you answer the question: what are the additional costs to the NHS?

A. From the increase in price or from patient outcomes?

Q. Patient outcome.

A. So if Epanutin had gone off the market, then there were risks to patient outcomes. As has previously been explained, the only option you would then have potentially would be to switch patients to phenytoin tablets.

Q. Right, let us just try and work this one out. If you look at that first sentence, last paragraph:

"... the potential additional costs to the NHS from adverse reactions if supply is interrupted."

What are the potential costs to the NHS if a patient

is no longer seizure-free?

A. So if supply was interrupted because Epanutin was no longer available, then there were risks around patients not being stable and having fits and, as you previously discussed, an ambulance journey, mortality to patients, patients being admitted. So everything we want to do round epilepsy medication is to stop any patient having a fit.

Q. Can we focus, please, on the question. What would be the additional cost to the NHS, not to the -- I am not looking at the patient now, I just would like you to give the evidence to the Tribunal from your experience, what would be the additional costs to the NHS?

A. If supply were interrupted and the patient did not remain stable, then the risk would be they would have more epileptic seizures, there would be a cost to the transport for the ambulance to get to them and there would be a cost if they were admitted into hospital because of that fit.

Q. Costs of hospitalisation, costs of neurologists?

A. Yes.

Q. Outpatients?

A. Nursing care.

Q. Nursing care?

A. Feeding the patient in the hospital ward, all sorts of

costs, yes.

Q. Can we please -- you say "all sorts of costs". Can you give me as many costs as you can, please?

A. Well, there are costs you could probably get around each hospital admission and what that would take, and depending on how many days they were in. You could get a patient who had a fit and ended up in intensive care, you could get a patient who had a fit and was discharged the same day because they recovered very quickly. So it would vary from patient to patient.

Q. Are they significant costs?

A. They are costs we want to avoid, yes.

Q. Are they significant?

A. The NHS's budget is very significant, and a lot of that goes on hospitals.

THE PRESIDENT: Mr Green, is there a sort of average cost of a visit to hospital?

A. There is, but I do not know what it is, sir.

THE PRESIDENT: Then I am sure it can be obtained as something to supplement your evidence, thank you.

MR BREALEY: You would accept, logically, that phenytoin as a drug produces benefits to the NHS because it avoids the costs we have just been talking about?

A. Yes, you educated me by saying it had been around 100 years, and as far as we were aware, it was doing

a very good job for most patients for that length of time it had been on the market.

Q. I take it that the answer -- you said "yes", is it does produce benefits to the NHS because the drug leads to the NHS not incurring the costs we have just been talking about?

A. Any drug that gets a licence in the UK has to satisfy the MHRA that it is producing benefits for patients and phenytoin is certainly amongst those drugs, yes.

MR BREALEY: Sir, I have no further questions.

Questions by THE TRIBUNAL

THE PRESIDENT: Thank you. Mr Green, you were in court when Mr White gave evidence.

A. I was, yes.

THE PRESIDENT: So I am going to keep my questions commendably short and just work out whether there are any differences of emphasis between you and him, it would not be surprising if there were, but there may not be.

So starting with the reason why in the case of phenytoin capsules, continuity of supply is important, do you agree with him that the primary reason is a clinical reason and there is a secondary reason for psychological patient comfort?

A. Yes, that is correct.

THE PRESIDENT: Do you have anything to add by way of --
A. From when I worked in community pharmacy to doing this role, my understanding was that even a generically written prescription would get dispensed as the Epanutin brand. I was not even aware there was another capsule on the market until this case arose. So I do not know if the panel, etc, has heard the volumes of the other capsule brand and how many were actually dispensed compared to Epanutin being dispensed, but my understanding was always 99% of capsules were dispensed as Epanutin whether it was prescribed as Epanutin or as the generic prescription.
THE PRESIDENT: Okay, so we have jumped a little bit to the --
A. Sorry.
THE PRESIDENT: No, no, that is fine -- to the dispensing side. Just to stick at the moment at the healthcare professional level, that of the doctor, you heard what Mr White said about the importance of closed prescriptions, and his evidence was that a doctor should either prescribe by reference to a brand -- Epanutin -- or by reference to a generic product but identify the manufacturer. The upshot is the same. You have continuity of supply. Is that again your evidence?
A. Yes, everyone in my position became aware of the MHRA

guidance that came out with the 1 to 3 categories, and so, yes, Category 1 we would very much recommend brand prescribing.

THE PRESIDENT: I take it, then, you would share surprise that I think was evinced by Mr White when he saw the 91% open prescriptions in the data?

A. Yes, except that Epanutin dominated the market. as I said earlier, I was not aware there was another capsule on the market, so my understanding were the vast majority would have been Epanutin dispensed whether it was --

THE PRESIDENT: So an explanation may be that in fact the difference between open and closed mattered far less because whether you said phenytoin or Epanutin, it meant the same thing?

A. Yes.

THE PRESIDENT: I see. Then finally if one is at the level of the pharmacy dispensing and one has a choice between two phenytoin capsules, what is best practice regarding the dispensing where there is a choice?

A. As both my colleagues said, very much you would want to stick with what the patient had had before. We have a code of ethics as pharmacists to put the patient first, and God forbid you gave a different capsule and the patient had an epileptic fit and did not survive,

you would have that taken against you, I would say, at a professional ...

THE PRESIDENT: So when assuming a choice and an open prescription you have a significant financial advantage in going for one rather than the other, your evidence is that you disregard the financial advantage and you stick with the continuity of supply as trumping?

A. I think you are taking a huge risk if you do not, yes.

THE PRESIDENT: Thank you.

Mr Brealey, do you have anything to say?

MR BREALEY: Just on the NRIM market shares, I have been referred to a document, so I am flying blind here, so {XJ/46}. I know from dealing with the case before NRIM got about 30% market share, I think, but there is a graph, if you go to page {XJ/46/2}, and you blow it up, you see there that Flynn is the blue, the NRIM is the orange, and those are the market shares. It is {XJ/46/2}.

PROFESSOR WATERSON: The table unfortunately does not have a vertical axis.

MR BREALEY: No. Over the next page, I am told {XJ/46/4}.

A. Can I just clarify was NRIM launched in April 2013?

Q. Around about then, yes.

A. Okay, yes. I was not aware of it when we were writing letters.

Q. No, it acquired quite a significant market share in a very short space of time. We see in 2013 Flynn had 92, and then --

A. So prior to Flynn launching, every generic prescription would have been dispensed as Epanutin.

MR BREALEY: Yes. There was no generic before the capsule. If you look at 2014, quarter 4, NRIM has acquired 26% of the market.

THE PRESIDENT: Again, these are not figures you are expected to know, and it is only fair if we ask you if you have any comment on this to comment.

A. No, just very much at the time we were writing about this case NRIM had not launched, so as a community pharmacist, if you had a generic prescription, would you dispense Epanutin.

MR BREALEY: Sir, I have no further questions.

THE PRESIDENT: Mr McCarthy, do you have any?

MR MCCARTHY: No re-examination, sir.

THE PRESIDENT: Thank you very much, Mr Green, we are very much obliged to you for your time. You are now released from the witness box, thank you.

MR BREALEY: We could rise now. I think I will be 10 minutes with the next witness, so I do not know whether you would prefer --

THE PRESIDENT: I think we will rise in any event and we

will resume in that case at 3.35.

MR BREALEY: Can I just ask, do you want Professor Walker to start? He is due for his teach-in, I think we did arrange for him to come if we finished in due time.

THE PRESIDENT: Well, I must say if he is here and given we have all budgeted at least to run until 4.30-5.00, it would be a shame not to, but that is a very marginal thing and if anyone has strong views about that then perhaps we will hear after --

MR BREALEY: He is a busy man. He has actually taken time out.

THE PRESIDENT: Well, in that case, first of all, we are very grateful to him, and secondly, what is more convenient to him.

MR BREALEY: Thank you.

THE PRESIDENT: We will rise for ten minutes, thank you.

(3.26 pm)

(A short break)

(3.40 pm)

MR MCCARTHY: Sir, the CMA will call Susan Smith, please.

THE PRESIDENT: Thank you very much.

MS SUSAN SMITH (sworn)

THE PRESIDENT: Good afternoon, Ms Smith. Do sit down and make yourself comfortable. I hope you have some water there.

A. Yes.
THE PRESIDENT: You should have, I hope, your witness statements before you.
A. I have got Shaun Green's in front of me.
THE PRESIDENT: Well, I hope counsel will take you through the necessary tab to find your evidence.
MR MCCARTHY: Your witness statement should be in the same bundle.
THE PRESIDENT: If you leaf through it.
A. Under which section? Yes, I have it.
THE PRESIDENT: Very good.
A. Okay.

Examination-in-chief by MR MCCARTHY

MR MCCARTHY: Just to give the Opus reference, it is {XC1/5}.

Now, Ms Smith, can you just look at your statement, familiarise yourself with it, and just to confirm that is in fact your statement, please.

A. Yes, it is.
Q. And if you look at the signature which should be on page {XC1/5/6} of the statement?
A. Yes, that is my signature.
Q. Can you confirm for the Tribunal the facts that you set out in the statement are true to the best of your knowledge and belief?

A. Yes, they are.

MR MCCARTHY: I am grateful. My learned friend might have some questions for you.

Cross-examination by MR BREALEY

MR BREALEY: The great thing about going last is you get fewer questions.

A. I am not complaining.

Q. So if we just quickly go to your witness statement just to get the relevant point in time, paragraph 1, this is at {XC1/5/1}, you are also a registered pharmacist and you have been since 1983.

A. Yes.

Q. If one goes over the page {XC1/5/2}, in the middle, the relevant period is from 2011 to 2016, you were Head of Prescribing and Medicines Management at NHS Nene and NHS Corby Clinical Commissioning Groups, so you were Nene and Corby?

A. That is correct.

Q. At paragraph 15 of your statement, that is at {XC1/5/5}, again, we have been through this with Mr White and Mr Green, you also refer to a letter of complaint that you helped draft to the Chief Pharmaceutical Officer, I think his name has been read out, but it is the doctor you see there.

A. Yes.

Q. Then you fairly in the penultimate sentence, on 5 November 2012, your colleague received a reply from the doctor:

"... which acknowledged the concerns regarding price but also stated that one of the Department of Health's principal concerns was to ensure continuity of supply for patients."

As I say, you fairly produce that letter at SS1/24.

Can we go to that, please? That is, for Opus, {XD1/5/24}.

It is a small point, but you just may want to correct it. You say in your statement you received a reply from Dr R, but actually it is from somebody else, the initials SS, Medicines, Pharmacy and Industry. It is from the Department of Health, but I do not know whether you know?

A. Yes, I do acknowledge that that is a different signature, yes. I think it was on behalf of Dr Ridge.

Q. I think -- I think his name has been read out -- Dr Keith Ridge asked this Simon person to reply; yes?

A. Yes.

Q. What would be the Medicines, Pharmacy and Industry? Is that the Medicines, Pharmacy, Industry department in the Department of Health, because this is a Department of Health reply? What is the Medicines, Pharmacy and

Industry?

A. That is a section within the Department of Health that would deal with this kind of matter and matters relating to medicines, pricing, procurement, etc.

Q. So they are in charge of the pricing?

A. I am not --

Q. Or they know about the pricing?

A. I am not 100% certain if they are in charge of it, but, yes, my understanding is they would know about the pricing.

Q. They would be aware of the policy concerns relating to any price, because they are the Department of Health?

A. I do not know.

Q. No, okay. Let us have a look at the letter, then. Did you see this letter?

A. Yes.

Q. It starts off:

"Thank you for your letter ..."

The Department of Health says:

"The Department fully understands your concerns."

This is almost a standard letter. It is very similar to the letters we have seen. The paragraph is:

"The new supplier [is] Flynn ..."

There is a paragraph:

"The Department is in discussion with [Flynn] ..."

Then as with Mr White and Mr Green I would like you please to focus in on the next paragraph where we have the same statement by the Department of Health to the CCGs:

"The cost of any medicine..."

That is phenytoin here, yes?

A. Yes.

Q. "... has to be balanced with the potential additional costs to the NHS through adverse reactions and reduced patient outcomes if supply is interrupted."

I would like to ask you the same question I asked to Mr White and Mr Green, and please focus on the question: in your evidence, what would be the additional cost to the NHS if someone was not seizure-free?

A. Do you want me to quantify that in terms of pounds? Is that what you mean?

Q. No, I want -- well, if you could?

A. No, I cannot, I cannot, but as my colleagues have said, if a patient's epilepsy became uncontrolled, they may well have a seizure, they may well be admitted to hospital, potentially by ambulance, they may well need a hospital stay and further neurology consultations. I mean, it probably would not be that this would necessarily happen to everybody.

Q. No.

A. Some people may well switch to a different anti-epileptic drug quite satisfactorily, but some people, yes, would be at risk of seizures and those consequences.

Q. This is for the purposes of the Tribunal because the Tribunal has to write its judgment and you are here to assist the Tribunal as well. Could you identify the potential cost to the NHS? We have looked at hospitalisation. Mr Green referred to the costs of feeding, ambulances, community care. Do you agree with all those?

A. I would agree with all of those, yes.

Q. Could you expand? You receive this and the Department is telling you, you have got to balance the additional costs for the NHS?

A. I cannot really think of anything further than what my colleagues have said: ambulance costs, hospital costs, community epilepsy nurse costs potentially. I cannot really think of anything additional.

Q. The secondary care?

A. Secondary care is hospitals, yes.

Q. Right. Also the consultants, it is secondary care if you visit a consultant, not in the hospital, but in their practice?

A. Yes.

Q. So it is not limited just to hospitals. Anything else you can --

A. There may be more GP appointments, there may be more GP follow-up appointments if somebody's medicine is changed subsequently, but I think my colleagues have covered all the likely scenarios, yes.

THE PRESIDENT: Ms Smith, it is something of an unfair question, but I will ask it anyway, and to be clear, I am only really getting -- wanting a ballpark answer, but if we define something as an avoidable seizure, in other words, where a seizure results because continuity of supply has been breached, so just assume that, there is a seizure in an epileptic that would not have happened but for the change to a different form of medicine, resulting in the typical having to go to hospital, see a consultant, all these things. What sort of cost are we talking about in a ballpark? £100, £1,000, £10,000, £100,000, that sort of figure?

A. I think we are talking several thousand pounds if somebody is admitted to hospital.

THE PRESIDENT: Yes.

A. But I would not want to quantify it closer than that.

THE PRESIDENT: Fair enough, but if we are talking my orders of magnitude, it is perhaps in the ballpark, in a bad case, will be more like 10,000 than 1,000, or

would you --

A. Again, there is such a spectrum of patients.

THE PRESIDENT: Of course.

A. It is really hard to be precise. I would not want to be drawn on that, but we are probably talking thousands of pounds, not hundreds of pounds.

THE PRESIDENT: That is very helpful.

MR BREALEY: Just to be clear, as the President just said, phenytoin is used not just when there is a breach of continuity of supply, it is when other drugs have failed as well, so phenytoin is the only effective drug because it kicks in when other drugs have failed. Are you aware of that?

A. I would not personally define it quite like that. It is a very old drug, as we have said. It would be very unusual for it to be used first-line in anybody because it has an adverse event profile that you would not particularly want. So --

Q. It is basically a third-line drug.

A. Yes.

Q. When other drugs have failed, patients are tried on phenytoin, and it can be very effective in those circumstances. Do you accept that?

A. Potentially. I am not a neurology expert, so I would not like to --

Q. No, we are going to have evidence from one in a minute.
A. Exactly. I would think it would be quite unusual for anybody to be initiated on phenytoin nowadays.
Q. Well, we will find out.
A. I am sure people much more knowledgeable than me will know that, but it is mainly prescribing that has been -- patients that have been on it for many, many years, in my experience.
THE PRESIDENT: But Ms Smith, just to be clear, leaving on one side continuity of supply and sticking with Mr Brealey's questions as to why one would prescribe phenytoin capsules for the first time, presumably that will be because first and second-line regimens were not working and one would do so in order to minimise or ideally eliminate seizures in the future?
A. As I say, there are so many anti-epileptic drugs available now I would be quite surprised if anyone was initiated on it or that many people were, but certainly many years ago when there were not many others available it certainly would be a good, important drug for many people to stop or reduce their seizures.
THE PRESIDENT: Fair enough, it may be that the options are increasing such that the need to prescribe for the first time phenytoin capsules is receding.
A. Yes.

THE PRESIDENT: But can you think of any other reason why one would prescribe phenytoin for the first time save to eliminate the risk of future seizures?

A. I am not sure I fully understand the question, I am sorry if I am missing the point.

THE PRESIDENT: That is all right, no, not at all. What I am asking is you very fairly made the point that drug regimens are evolving and that the need for prescribing phenytoin capsules for the first time is diminishing.

A. Yes.

THE PRESIDENT: If, however, a phenytoin capsule regime is commenced in a patient, then the only reason, I am suggesting to you, why one would do that is to minimise seizures which would otherwise occur if one tried something else.

A. Yes.

MR BREALEY: Thank you.

So for the cohort of legacy patients, the many thousands of them, I think you would accept that phenytoin remains an essential and effective drug?

A. Yes.

MR BREALEY: Thank you.

I have no further questions, sir.

Questions by THE TRIBUNAL

THE PRESIDENT: Ms Smith, you were in court I think when

Mr White and Mr Green gave evidence.

A. Yes, I was.

THE PRESIDENT: So like Mr Brealey, I am going to keep this as short as he has.

You heard my questions about the importance of continuity of supply, the consequent importance for closed prescriptions and even when one had open prescriptions, the importance of a dispensing agent to maintain continuity of supply.

Do you have anything to add to the answers that were given by your colleagues or anything to contradict?

A. I would completely agree with them.

THE PRESIDENT: Well, I am not going to force you to rehearse why you agree with them because they gave very full answers.

PROFESSOR WATERSON: I was just going to ask, so you talked about these people largely being legacy patients.

A. Largely.

PROFESSOR WATERSON: So do you know or can you estimate roughly would they typically have been on the product for many years?

A. I would say so, yes, by and large.

PROFESSOR WATERSON: So just to complete that, is it right to say that once someone is put on a drug and it appears to work for them, then they remain on that essentially

for the rest of their life?

A. Yes, if it is working for them, it would be very unlikely to be changed.

PROFESSOR WATERSON: Thank you.

THE PRESIDENT: Mr Brealey, any further questions?

MR BREALEY: No, I am grateful, and thank you very much indeed.

THE PRESIDENT: Any re-examination? No.

Ms Smith, thank you very much.

THE WITNESS: Thank you.

THE PRESIDENT: Very grateful for your time. You are released.

THE WITNESS: Thank you.

MR JOHNSTON: Sir, I have spoken to Professor Walker. We have a nice window of time now that could be sensible in using for his teach-in if that is convenient for the Tribunal.

THE PRESIDENT: Yes, we think the teach-in probably best from the witness box and probably best that he be sworn. I know we did not do that in other cases, but given his cross-examination will follow from the teach-in, we will do the swearing at the outset.

MR JOHNSTON: Just to be clear sir, the process that has been agreed, disregard it if you feel differently, is that Professor Walker would do his teach-in followed by

Professor Sander tomorrow morning, followed by Professor Walker's cross-examination.

THE PRESIDENT: I see.

MR JOHNSTON: That is what has been understood between the parties, but as I say, we are very much in your hands. There would be successive teach-ins, they would not be in purdah after the teach-in, if I can put it that way, but of course would be if they were (inaudible).

THE PRESIDENT: That is a very helpful clarification. It is not the order in the trial timetable I have got. That is none the worse --

MR JOHNSTON: No, indeed, that was rectified by counsel for the CMA over the weekend so (inaudible).

THE PRESIDENT: None the worse for that. Just to be absolutely clear, therefore, we will have teach-in from Walker and Sander, followed by cross-examination of each. We will swear them once, they will be released in terms of being able to speak to their legal teams after their teach-in is concluded, not in the middle of the teach-in if we have a break, and we will not be re-swearing them, they will be under oath continuously, but the purdah will operate in the attenuated manner that I have just described.

MR JOHNSTON: Sir, I am very grateful. That is a very helpful clarification. I would like to call Professor

Matthew Walker.

Sir, while Professor Walker is settling in in the box, there is one other point of practical detail as regards Professor Walker's evidence. He gave three expert reports at the previous trial, each of which were exhibited to his fourth report, so I am not proposing to ask him to affirm each of those statements which he has previously affirmed in 2016 but rather to affirm only his fourth and fifth reports.

THE PRESIDENT: Does anyone have any problem with that? That is absolutely fine.

MR JOHNSTON: I am very grateful.

He is going to be sworn now, is that right?

THE PRESIDENT: We will swear you now, yes, and then we will proceed. Thank you for waiting.

PROFESSOR MATTHEW WALKER (affirmed)

THE PRESIDENT: Professor, do sit down, make yourself comfortable. You have brought some materials into the witness box with you.

A. Yes, these are my witness statements. I am quite happy for them not to be here, but I just --

THE PRESIDENT: No, no, as long as that is all they are, you are very welcome to them, they are your work.

Teach-in by PROFESSOR WALKER

MR JOHNSTON: Professor Walker, that is very convenient,

because I am not sure that there is actually an expert bundle in the box at the moment, but I will work electronically and you also have them in front of you in terms of affirming the statements.

If you could turn to the first page of your fourth expert report, and that is at {XE4/4/1}, is that your fourth report?

A. Yes, fourth expert report in front of me.

Q. If you could turn to page {XE4/4/18}, is that your signature?

A. That is my signature, yes.

Q. Does that expert opinion reflect your opinion to the best of your knowledge and belief?

A. It does.

Q. Thank you. If you could turn --

THE PRESIDENT: Professor, you will have heard the exchange between counsel and myself. Your fourth report exhibits your first, second and third reports in the first round of these proceedings. We are taking it that you have nothing to change in respect of those?

A. No, sir, no. Those are my reports.

THE PRESIDENT: We will leave it there, then.

MR JOHNSTON: I am grateful.

Professor Walker, if you could turn to your fifth report --

A. Yes, thank you.
Q. -- to page 1, just confirm, it should pop up on the screen in a moment, it is at {XE4/5/1}. Is that your fifth expert report?
A. It is.
Q. If you could turn to page {XE4/5/22}, please, is that your signature?
A. That is my signature.
Q. Does that reflect your expert opinion to the best of your knowledge and belief?
A. It does.
Q. Now, sir, I suppose perhaps the final wrinkle as the guinea pig in this process, it is agreed that we are not affirming position papers, so I am not proposing to take Professor Walker to his position paper at this point.

Professor Walker, as you have heard from the exchange with the court, this is an opportunity for you to provide a teach-in to the court and, as we have discussed, I will ask you some questions, doubtless the Tribunal may have some questions as well, it is an opportunity to give some context and unpack your expert reports to help the Tribunal. So can I start by asking you what role phenytoin plays in your work as a neurologist?

A. Yes, certainly.

So it plays really three roles, so I have three specific times when I use phenytoin. The first are those people who are already prescribed phenytoin for their epilepsy and in whom there is no suitable alternative. The second group of people are people who have severe seizures, severe and prolonged seizures, when they come into hospital, and we use that initially intravenously, in through the vein to stop the seizures, because it is very effective at doing that, and then they will go on to oral phenytoin whilst in hospital and for some time afterwards, and then the third group of people in whom I use phenytoin is as a third-line treatment as outlined in the NICE guidance, so when people have failed on first and second-line treatments.

But I have to just add in something there as well, which is that whenever we have a patient in front of us, you know, every person is different, and the side effects of specific drugs may be unsuitable for that particular person, so, for example, valproate at the moment would not be used in women of childbearing age in focal epilepsy, and then you can take another drug, topiramate that I think was in 2012 used down as a second line drug, but people very often have problems with word-finding difficulties, there can be some cognitive problems with that that can be quite profound,

so in some instances I prefer phenytoin sometimes above that even though it is a third-line drug in the NICE guidance, so it is about taking the patient in front of you and trying to sort out what is the best sequence of drugs to use, and that is also when third-line means when other drugs have failed, so they have not controlled the epilepsy.

Q. Could you assist the Tribunal to understand how the role of phenytoin might have changed in the period since 2012?

A. Yes, so it has changed in a number of ways, one of which is, as you have heard, there are more anti-seizure medications available, so it is used probably less commonly as a third-line treatment as there are other treatments that may be used ahead of it in that respect.

Also we very much like to monitor the drug levels or at least get the phenytoin levels monitored especially when starting people on phenytoin, and over Covid, for example, it was quite difficult to do that, and so over Covid we did not or certainly I did not use phenytoin quite as much as I did prior to and subsequent to Covid, because it was just difficult to get people to their GPs to get their drug levels monitored.

Q. Thank you. Could you give some examples of patients that you treat or are treating at the moment who are on

phenytoin?

A. Yes, certainly. So I have given some examples. I can go over those examples, and also some additional examples.

So the examples I gave are of a woman who is in her 60s if I recall correctly who had had epilepsy since childhood, in fact she had a generalised epilepsy which is she had convulsions, and they were actually quite poorly controlled as a child and they came under control with phenytoin, and over the years, there had been attempts to try to change her on to other medications, she still had occasional convulsions, but it was not possible to change her, this was done mainly by other neurologists, and then when she came to me we added in another medication, levetiracetam, she became seizure-free, and then there was the idea of trying to withdraw her from phenytoin, but we were unable to do that, and so she required phenytoin and levetiracetam, and she remained seizure-free and has been seizure-free for 20 years or so.

The other person I can think of is a man who again was on phenytoin, prescribed in his 40s, and he was in his 70s when I saw him, and again, the reason he was referred to me was that people had tried to take him off his phenytoin and he had had a recurrence of seizures

and we established him on his phenytoin, and he became seizure-free. He is a writer, it had no impact on his quality of life, he had no adverse effects with phenytoin, was very happy with it and in fact there had been other neurologists who had been unhappy and wanted to try to convert him but without success.

I can give many examples. A third example, just as a contrast, was a 19-year-old boy who had very severe epilepsy, he was having many seizures every single day, and he had been tried on multiple anti-seizure medications. He was referred to me, in fact, he was transferred from one hospital to another, we put him on to phenytoin, that actually controlled his seizures pretty well. It did not stop the seizures altogether, but it controlled them to such an extent that he was able to walk, for example, which he had been unable to do because of the frequency of the seizures that he had had previously. So it had worked when other drugs had failed.

THE PRESIDENT: Professor, forgive my ignorance, but you have been mentioning the word "seizures" quite a lot and as I understand it, there are different sorts of seizures that confer(?) an epileptic event?

A. There are, yes.

THE PRESIDENT: Are the avoided seizures using phenytoin of

the same range as the avoided seizures using other drugs or is phenytoin used to avert particular types of -- type of seizure?

A. That is a very good question, sir. So we divide seizures into focal seizures and generalised seizures, and within the focal seizures, these are seizures that begin in one part of the brain and then spread, and then they can spread throughout the brain in which case the person has a convulsion. Phenytoin is used specifically in those types of seizures, as are most of the anti-seizure medications.

There are, then, generalised seizures and those come in a number of different forms. There are absent seizures that people can have with blank spells, and little jerks that people can suddenly get and those seizures do not respond to phenytoin, in fact, there are many anti-seizure medications they do not respond to and so we have a rather restricted range of drugs we can use in that type of epilepsy, and then as generalised seizures people also can have convulsions, sort of tonic-clonic seizures as we term them and they respond well to phenytoin, and indeed, there I have one instance that I can think of off the top of my head of somebody who has a mixture of absences and other seizures, and also the convulsions, who is now on phenytoin because

the other -- the major seizures have not responded to any medication.

THE PRESIDENT: So applying an extremely broad brush, phenytoin, when it is appropriate to prescribe as part of the regimen, targets a broad range but at the more serious end of the seizure range than the minor -- is that putting it too trivially?

A. Yes, it targets the most serious -- the ultimate seizure is a convulsion, I mean, that is the most serious form of seizure, and it targets that, but it also targets other smaller seizure types as well, but there are a range of seizures for whom we -- and seizure types where we would not use phenytoin, we would use other drugs ahead of that.

THE PRESIDENT: Thank you.

PROFESSOR WATERSON: You have obviously talked about cases that have been beneficially treated with phenytoin. Do you also find that some of the people that you put on phenytoin, it does not work for them?

A. Yes, a very good question as well. So when we get to third-line therapies, we are talking about probably only 5% of people becoming seizure-free regardless of what we try, so many of those patients will not respond to phenytoin, so they will go on to phenytoin for a short period of time. If it has been successful, they will

remain on it, if not, they will come off, and indeed, I have had that recently, somebody where we were trying different drugs, we tried phenytoin and indeed it did not have a big effect on the seizures and they came off that drug, so it is not invariably effective.

THE PRESIDENT: Just to understand the process, what sort of timeframe does it take to work out whether phenytoin -- let us use that as the example -- is working or is not, because presumably you have not merely the question of whether in principle this third-line treatment works, but also to get the dosage right and presumably there is an interaction between the two questions?

A. Yes, absolutely. So one of the advantages of phenytoin is that we can actually introduce it quite rapidly, and some of the drugs, for example, lamotrigine, which is a first-line therapy, it can take months before we get up to a dose where we think that is going to have a therapeutic effect. Phenytoin, if we are using it in hospital, we can get a therapeutic level almost immediately, so we can just load people up with an adequate dose. When we are doing that as outpatients we do not want to do that because if you give them too much they have side effects, so we start at a fixed dose, and I would say that usually within about a month we get on to a dose where we would expect that to have some

1 therapeutic effect.
2 Then obviously, judging whether it has had
3 a therapeutic effect depends on how frequently people
4 have seizures. If they have them every day, then we
5 know quite quickly, but if they have them every month or
6 so, we may have to wait a while before we know it has
7 been effective.
8 MR DORAN: You mentioned at the outset that you do blood
9 tests regularly and that is often dependent on people
10 going to GPs once they have gone out of hospital.
11 A. Yes.
12 MR DORAN: Those are done to make sure that you do not
13 over-medicate, if, say, the right effect can be had at
14 a lower dose. Is that the point?
15 A. Yes, so phenytoin has an almost unique -- what we term
16 pharmacokinetics, which is the way the body deals with
17 the drug amongst the anti-seizure medications, and it
18 shows something that we term saturation kinetics, so
19 that means that as we step up the dose, so the levels go
20 up, but once we get to a certain level, then small
21 increments in dose will lead to larger increases in
22 blood levels, and one of the usefulness of monitoring
23 the blood levels is to know whether you are within that
24 range. So, for example, if you are below that range,
25 take an example, I may start somebody on, say, 200mg and

I would be happy to increase it by 50mg, and once they get within that range I would only be increasing in increments of 25mg because of the risk of the levels shooting up.

MR DORAN: Just as a follow-up, you said pre-Covid you perhaps used more phenytoin and post-Covid it has changed your prescribing?

A. No, during Covid it changed. There has been difficulties more recently with patients accessing GPs, but during Covid it was particularly difficult, and so I was not so keen then when it was important to be able to monitor levels, but that is now reverting to the way things were, so now people can get access to having their bloods done.

MR DORAN: Your prescribing has reverted?

A. My prescribing has reverted, yes.

MR JOHNSTON: Professor Walker, do you know if other neurologists in the UK, including your colleagues, prescribe phenytoin to patients for the first time?

A. I do know that, and I know that from two sources, one of which is that I get referred patients from colleagues for third opinions, and I have been referred patients, in fact I was referred a patient recently who had been put on phenytoin as a third-line treatment, so I know very well from that experience.

I have to say that I read of course Professor Sander's report, I know Professor Sander very well, and I do respect Professor Sander, and so having read his report I was slightly taken aback about the view he had taken, and I wanted to know from my own point of view whether that was, you know, a view which was shared generally amongst colleagues.

So I have spoken to colleagues, I have spoken to a number of colleagues within my own department, and also outside, and asked them about their use of phenytoin, and I have found that it much more aligns with my use than it does with the complete abandonment of phenytoin as an anti-seizure medication.

So it is my experience, obviously it is a straw poll, it is not looking at all the neurologists within the UK, but it has certainly been my experience that the majority of the people I have spoken to seem to be using phenytoin as third-line.

Q. Thank you. Can you explain why in your opinion and understanding phenytoin was made a third-line treatment in 2012?

A. Yes, so phenytoin has always been a very effective anti-seizure medication, and when you look at it compared to some of the other anti-seizure medications, it is amongst the most effective medication, so it has

always been recognised that it is an effective medication.

It has side effects, so it is in a class of drug called sodium channel blockers, and there is a number of anti-seizure medications now in that class, and they have very similar side effects as the dose goes up, so if you get up to high doses people become unsteady, they get double vision, they feel sick. If you have very high doses they will go into coma, so as the dose goes up, you have those particular problems.

With phenytoin, because of its pharmacokinetics means it is more difficult to use than many of the others because you can get into that sort of therapeutic range, and then you find that as you go up, you can actually get toxicity more readily, sometimes more than you could do with the others. So the pharmacokinetics has really been there driving phenytoin down the order of drugs that we use because the other drugs, it is just much easier because you know that as you give a dose, when people have low levels, it is in effect the same dose when you give them and they have higher levels, whilst with phenytoin in effect it appears like a higher dose when you are using -- when the levels are high, if that -- if I have made that clear.

Then also phenytoin interacts with other

anti-seizure medications, and because of its interactions, it makes it more difficult to use when you have other medications, and you are adding it in, because of the possibility of interacting with those medications.

So that sort of -- those what we term pharmacokinetics characteristics of the drug have really driven the use of phenytoin down into third-line therapy.

Q. You have given plenty of evidence across all of your reports about the side effects of phenytoin and also various other drugs. Can you summarise for the Tribunal your views in relation to the side effects of phenytoin starting with the acute side effects of phenytoin and how in practical terms as a clinician you would manage those?

A. So I went over the acute side effects. The main acute side effects would be unsteadiness, double vision, nausea, and then at high dosages you get into coma, but those side effects are dose-related so as the levels of the phenytoin go up, so those side effects can appear, and that is something that is shared with many other anti-seizure medications because many of them fall into similar class of drugs, and the way that we address those acute side effects is to reduce the dose.

So what I would do is you would step up the dose, you warn the person about these acute side effects and then you say: if you start to get this problem, then reduce the dose by 25mg and then those side effects usually resolve.

THE PRESIDENT: So one of the attractions of, at least sodium phenytoin, is that once you have the regime right you do not need to adjust it, assuming no material change of circumstance in the patient?

A. Yes, so once you get on to a steady dose, then you can just leave the person on that dose. I have to qualify that, sir. So the -- you know, if people start to take other medications they could interfere with phenytoin so you would have to monitor them. Obviously pregnancy is another issue. Then sometimes as people get older, they handle -- their body handles drugs differently so you have to monitor the phenytoin levels then. But these are all things that are usually quite manageable, and people will have regular, perhaps yearly, phenytoin levels done to make sure that it is still in the same range, and if it looks like it is sort of creeping off, then you may adjust the dose or if they start to complain of side effects then you may adjust the dose.

THE PRESIDENT: But it is unlike -- again, do forgive my ignorance -- some painkillers you have to increase the

dosage as a matter of course to retain the same effect, and that is not the case with phenytoin?

A. No, you don't, you are right, so there is this thing where you can get tolerance to a drug and then you have to increase the dose and that is precisely what happens with some painkillers. There are also classes of anti-seizure medications where that happens as well, where you have to constantly increase the dose to get the effect that you would like, but phenytoin is not in that class, you are right, once you are on it, and indeed that is my experience, as I say, I have people who have been on it for 60-odd years, and they have stayed on almost the same dose they had 60 years ago.

MR JOHNSTON: Thank you. Could you assist the Tribunal to understand a bit about the idiosyncratic side effects of phenytoin and again, how they would be managed?

A. Yes. So the idiosyncratic side effects are almost like allergic reactions that happen to drugs, and this happens with many drugs, like penicillin, it happens with many of the anti-seizure medications. The main ones of concern with phenytoin would be a rash, which can occur, maybe in about 3% of people on phenytoin, and you would then just stop the medication. This is very common to all of the anti-seizure medications.

There are more serious idiosyncratic reactions and

I think a good example of that is something called Stevens-Johnson Syndrome, which is a very severe reaction which can result in death. That is very rare with phenytoin, it is probably less than 1 in 10,000. It is more common in probably drugs like lamotrigine which is a first-line therapy, so again, it is a side effect that is used by others, and the way that we try to avoid that is by warning people that if they develop any allergic reaction, develop fever or develop a rash, then they should -- they need to come off the medication, see their GP and be appropriately treated, and indeed, the new drugs, cenobamate which has just been licensed and has been used to a large degree because of its efficacy, again, has exactly the same sort of problems that we can see with these allergic reactions.

In fact the last one I saw was lamotrigine, so that was a young woman who ended up on intensive care and lost her vision, but lamotrigine started as a first-line therapy, so these are risks that we have to warn people about.

MR JOHNSTON: That is very helpful. Could you assist the Tribunal to understand a little bit about the chronic side effects of phenytoin and how they would be managed?

A. Yes. So chronic side effects, there is a sort of range

of definitions of how long you have to be on something for it to be chronic. I mean, for phenytoin, phenytoin has been around for 80 years, so we know people who have been on it for -- I am not sure if I know anybody who has been on it at the moment for 80 years, but certainly there has been people on it for 50, 60 years, and there has been a long experience of its use, and we know that over time you can see these chronic side effects, one of which, for example, is swelling of the gums, and that is something that, you know, I warn people about. There is good evidence that good dental hygiene can reduce the instance of that and that, if they are monitored by -- I will also make sure they are monitored by their dentist, and I have to say that although it was something that was considered a concerning side effect when I started in neurology, which was a few years back, it has become less so, and I think that may well be because of things like better dental hygiene.
I certainly do not see it as a big problem, but there has been an instance where I changed somebody's drug from phenytoin because of it.

Then there are other things that we consider, so there is something called coarsening of facial features, there was quite a lot made of that back in the 1980s, actually, and again, that is not something that I have

seen as a particularly concerning side effect long term in the patients whom I have on phenytoin. In fact, the majority of people who I have on long-term phenytoin do not complain of chronic side effects.

Then the last thing that we do get concerned about, and there has been growing evidence about this, is osteoporosis, and this is obviously a concern for us all as we get -- as we do not get any younger, but with drugs like phenytoin, which are enzyme-inducing drugs, there is a concern that they can speed up osteoporosis. The mechanisms by which they do that are not absolutely clear, but one of them may be by reducing vitamin D levels, so we now closely monitor vitamin D levels and make sure that people are on vitamin D who are on these drugs, but there may be other mechanisms because although reduction of vitamin D by enzyme inducers which are drugs that increase the breakdown of certain substances in the body, the thought has been that it was vitamin D that was the main culprit, but we now find that a number of these drugs that are not enzyme inducers are also associated with osteoporosis, one of the biggest examples is sodium valproate, but that is also something that we warn people about, we monitor their vitamin D, we make sure they are on vitamin D, certainly if they are deficient, or the default is

usually to put them on vitamin D and then also we monitor their bone health as they get older.

Q. Could you explain to the Tribunal a technical point that has arisen at various points: the difference between side effects and tolerability?

A. Yes. So side effects, I mean, they have a number of different names, but side effects is any unwanted, or indeed, sometimes you could say, even a wanted side effect to the drug, but it is an effect of the drug that the drug was not designed to have, so phenytoin is an anti-seizure medication. As a matter of interest, it has recently been shown, for example, that phenytoin decreased the instance of long Covid if you were on it, so that may be a positive side effect, but most side effects are negative. But they are just a list of anything that is an unwanted effect.

Tolerability, on the other hand, is the person's response to those side effects. So people will be quite happy to have some side effects from medication and again, I can take an example, topiramate which although it may cause word-finding difficulty, causes weight loss and some people would be very happy to accept that as a side effect. Other things like word difficulties with topiramate may be something that some people in society would be happy to contend with, whilst others, you know,

lawyers, for example, would not want that as a specific side effect of their medication.

So the tolerability of a medication depends really upon who you have in front of you, and also depends upon what they perceive as the benefit as well from the medication, so it is a perception.

Q. Thank you. Can I ask you -- and you have already touched on this briefly -- to explain to the Tribunal the difference between enzyme-inducing AEDs and non-enzyme inducing AEDs?

A. Yes. So the liver has enzymes in it that break down drugs, but they also break down other things in the normal body like hormones and they will also break down vitamins as well, so the liver acts there breaking down these things into other molecules that can then be easily excreted from the body, so this is something that we all have, and some of the anti-seizure medications have no effects on these enzymes at all. Some of them inhibit those enzymes so that the body will be less good at breaking down other drugs, or indeed, may be less good at breaking down other toxic compounds, and other drugs are what we term enzyme inducers, where they increase the activity of these enzymes, and enzyme-inducing drugs, because they increase the activity of those enzymes, they interact with other

drugs that are broken down by those enzymes, not only anti-seizure medications but things like the contraceptive pill, and then they will also reduce things like the vitamin D level, things that we can monitor, so they may have other effects as well.

So we tend to broadly divide the drugs into those two categories and the enzyme-inducing drugs tend to have more interactions, but phenytoin is not unique in this. I would think that almost the majority of anti-seizure medications we have are enzyme-inducing. Carbamazepine, which in 2012 is listed as a first-line therapy is a very potent enzyme inducer, in fact, there is evidence to suggest it is probably more potent than phenytoin. So this is a property shared by a number of the drugs.

MR JOHNSTON: Sir, I am conscious of the time. Does the Tribunal have another, probably ten minutes. I am going to touch on continuity of supply, and I am mindful that that may cause some questions from the Tribunal as well, but I think it would be useful to finish today if we can.

THE PRESIDENT: I think it would be useful to finish today. I see we have budgeted until 5.00 --

MR JOHNSTON: I am very grateful.

THE PRESIDENT: -- so we are very happy to continue until

then, Professor, if you are.

MR JOHNSTON: I am very grateful. I had one more question in relation to enzyme-inducing AEDs. How clear is the evidence or the boundary between enzyme-inducing AEDs and non-enzyme-inducing AEDs in terms of their chronic effects?

A. So I think the boundaries, the main chronic side effects, the chronic side effects that we are concerned with enzyme inducers, are osteoporosis, and the second one that over time has been there as something that has caused some concern as well is whether there is an increased risk of cardiovascular disease because they can have effects on cholesterol levels, amongst other things, and so if I take us back to 2012, it was thought that enzyme-inducing drugs were the main reason or the main drugs that increased osteoporosis, but even then we recognised that sodium valproate which is a non-enzyme inducer can also.

There has been mixed evidence about some of the other drugs. It is now thought that the effect on osteoporosis is not just reduction of things like vitamin D, but also it may be the way that they affect the cells in the bone, so we have these cells in the bone that eat bone and remodel bone and then lay down bone, and those cells themselves are affected by

anti-seizure medications and it is now realised that many of the medications that are not enzyme inducers may have effects on those as well, so this is still something that is under investigation.

The other concern was of increasing the risks of stroke and cardiovascular disease, and there had been a sort of theoretical risk that had been raised many years ago because of these concerns about raising cholesterol, and it has always been said that, you know, it is very important to maintain cholesterol, measure the cholesterol levels on those people on the anti-seizure medications, and the absolute risk, where there was a risk, was in 2012 was completely unknown, more recently in 2021, there have been two papers that have come to opposite conclusions. Both papers conclude that the risk of stroke and cardiovascular disease is higher in people with epilepsy and one concluded that enzyme-inducing drugs were worse than non-enzyme-inducing drugs and the other one concluded there was no difference.

So there is still controversy in this area, but it does mean that when people are on enzyme-inducing drugs we will monitor, in fact, I think now everybody has their cholesterol monitored in any case, but we will monitor more carefully things like cholesterol levels.

Q. Before we come to continuity of supply, can I ask you just to take a step back. There has been an incredibly helpful volume of detail there about all of these different issues and we have focused particularly on phenytoin, but I would like to try to put it into context alongside some of the other AEDs that the Tribunal is going to be hearing about over the next day or so, and particularly to start maybe by asking you about an opinion that Professor Sander has articulated where he says, and I perhaps may be not directly quoting him but very close, that phenytoin provides the worst package as an AED, taking into account everything, taking into account the side effects, chronic, acute, idiosyncratic, non-linear pharmacokinetics, all the things that you have been talking about, his evidence is that it is the worst package, or to put it another way, perhaps the worst product, the worst AED available at this moment.

Do you agree with that conclusion and can you try and put phenytoin into some kind of context alongside the other products that you or the other drugs that you prescribe?

A. Yes, so, I do not agree with that. I am going to start with the fact that there are greater evils, and there are, so a number of the anti-seizure medications,

vigabatrin, for example, a third of people will start to lose their vision on it, and that is now rarely used because of that.

There are drugs like topiramate, for example, where people can have quite marked cognitive problems, and then, when you start to compare and think about phenytoin compared to the other drugs, no matter how you look at it, phenytoin remains one of the most effective anti-seizure medications, and in fact, although it is not in my evidence, there was a paper last year indicating that it was effective in a form of epilepsy that many of the other drugs were ineffective in. So it has always remained a very effective medication.

Its side effect profile in terms of the acute side effects and tolerability are very similar to that of carbamazepine, and when it has been compared head to head against carbamazepine as monotherapy, the side effect profile and the tolerability to people staying on the drug was very similar.

Lamotrigine, it is probably less well tolerated than lamotrigine, and so that is why lamotrigine and levetiracetam we would now use as first-line therapies ahead of others.

So it remains something that is probably as well tolerated as carbamazepine, it remains a particularly

effective drug. In my experience, I think it is probably more effective than lamotrigine, that is not borne out by large studies, but most of the large studies, the efficacy overlaps from one drug to another, so it is very difficult to separate them out, but certainly in my practice phenytoin will work when lamotrigine has failed.

Its side effect tolerability is very similar to carbamazepine. The long-term side effects are not things that I have found to be particularly troublesome, and the things I find most troublesome with phenytoin is its pharmacokinetics and its interaction with other drugs.

Q. That is very helpful. Can I ask you --

THE PRESIDENT: Are you moving on to another topic?

MR JOHNSTON: Of course. I was going to move on to continuity of supply at that point, so it may be a good point for you, sir, to ask a question.

THE PRESIDENT: In that case, just a question to clarify, as it were, the question one is asking about the package that is phenytoin.

In a sense, the description of phenytoin as a package is postulating a freedom of choice which does not really exist, because what one is doing, as I understand it -- and do correct me if I am wrong -- is

one is identifying a malady, the epilepsy, there are various first and second-line drugs which are used to combat that, and if they cure the problem, well, then, that is fine.

You turn to phenytoin as one of a range of alternatives when the problem is not resolved by other means. So the benefit is the avoidance of the seizures, and if that does not work, well, then, the question of side effects does not arise, because you just do not use it.

So is not one asking a rather more nuanced question than: is the package worth the candle. One is asking: given that the package works in the sense that it is eliminating seizures that would otherwise occur, otherwise you would not be prescribing it, is it worthwhile doing that, and is that perhaps a more helpful way of framing the question as to why one might use phenytoin?

A. Yes, it is, sir, and that is a very good way of putting it, and, yes, I mean, it is like at what cost? So there are certain drugs which have been removed from the market, even though they may help some people stop seizures because their side effect profile is so severe that they are unacceptable and then when you put somebody on to phenytoin, the question is have you

removed their seizures with the side effects that are tolerable or with no side effects at all, and that occurs with phenytoin. So it remains a useful drug in those patients.

In others, as was brought up earlier, you find it does not control the seizures, and, as you push the dose up to try and get control of the seizures, people have side effects and they say: look, I cannot -- at the moment I am feeling so dizzy and sick I cannot put up the dose any further, it is not having an adequate effect to my seizures, I would rather come off. So in the end it is what patients prefer and what is the effect in any individual patient.

THE PRESIDENT: So looking at a patient who has been tried on various first- and second-line drugs and they have not worked, presumably there is a question of clinical judgment as to what one tries next, and would it be fair to say that different clinicians have different batting orders as to what they try by way of their third line approach?

A. Yes, they would, and indeed they have different batting orders and second -- first-line, I think it is very difficult to avoid that, and I will explain why. So for first-line therapy there is actually now quite good evidence, so there have been large studies comparing

drugs in newly diagnosed people with epilepsy and they have been randomised to different drugs, phenytoin was not included in this, and it was found, for example, lamotrigine was better tolerated than carbamazepine, it may not have worked quite as well, but it was better tolerated overall, so that is the drug we should be using as first line in focal epilepsy, and valproate, although its problems with women, was found to be the best tolerated and most effective in generalised epilepsy. So we now have that sort of evidence for first-line.

When you get beyond first-line, when you get to add-on therapies, there is very little comparative data, in fact, the comparative data is woeful, and this is because those studies, where you actually are trying to compare one against another, of things that are effective, to see a difference you have to use large numbers, vast numbers of people, and this is at great expense and the drug companies, for example, will not be interested in doing that because they could only lose if they are going to be doing that, they are not going to win, or would be very unlikely to win, and so these comparator studies have not taken place, or when they have taken place, they have been rather small and underpowered studies, so when you start to say: right,

what is the batting order for the drugs, we have to sit there and make that as a clinical judgment, and we do that based upon the knowledge that we have of the drugs and our experience of using them, and, as you rightly say, there is no right or wrong, and people will have different batting orders, and that is the way it is, that is the way treatment, epilepsy treatment is.

PROFESSOR WATERSON: Thank you. I would like to ask a couple of questions. You obviously have a great deal of experience in this area, I know you to have, so one very broad question would be, I do not know, but you will know, I think: what is the incidence of epilepsy amongst the population generally? Is it increasing in significance or decreasing?

A. Well, there two -- there is instance, so how many new cases we get per year, and there is the prevalence, prevalence being about 1%, about 1 in 20 people have a seizure in their lives, 1 in 30 people will develop epilepsy, 50 in 100,000 people will be developing epilepsy every year. So -- now, the question about whether it is increasing or decreasing, that is probably around about stable, it differs from -- these figures differ from the countries -- high economic countries to low economic performing countries, and that is because of the range of causes. So infection, for example, is

very prevalent, head injury is a cause in some of the low economic countries.

What is changing is not so much the prevalence or instance but the population. So we are moving more towards older people developing epilepsy and less at the younger end, and that is because there is better perinatal care over the years, and then at the older age it is because we are living longer and in the older age things like stroke, dementia, tumours, these are all things that can cause epilepsy.

PROFESSOR WATERSON: Things that I can look forward to?

A. Yes, that is right, unfortunately things that we can all look forward to, and those things are major causes of epilepsy, so we are looking at a slight shift in the demographics over time, but generally the instance, prevalence remains the same.

PROFESSOR WATERSON: I think you said at some point you start people on 200mg?

A. Yes, usually 200mg, yes.

PROFESSOR WATERSON: Yes, okay. Throughout your teach-in so far, you have always used the word "phenytoin", you have not distinguished between tablets and capsules.

A. No.

PROFESSOR WATERSON: So in your experience do you use both?

A. So this is a complicated factor, so if I were to

prescribe -- so generally I do not prescribe phenytoin, so the prescriptions, repeat prescriptions are mainly from GPs, and I usually initiate the phenytoin, I initiate it in hospital, and the phenytoin that people get will be whatever phenytoin our hospital stocks, and usually we stock the capsules, and that is because they come in the smaller dose of 25mg whilst the tablets do not, so that is probably what they would be started on.

When I look to my prescribing, so we now have electronic prescribing, there is no warning about maintaining the continuity of supply or manufacture, there is nothing there on it, which I can come to in a minute, and there is no real space to say exactly what you are to do, you have to put it down as a footnote, you know: I would like them to stay on the, you know, Accord or Flynn or something and you put it in. Most people I expect do not put it in.

Interestingly enough, again, you know, this whole case has brought this to my attention because I went and asked younger colleagues whether they even knew about the MHRA guidelines because it is not there on our prescribing, they do not and they just describe phenytoin, they do not say anything at all, and people would be started on whatever the pharmacy has at a hospital.

PROFESSOR WATERSON: Do you have a suggestion as to why roughly of the 100mg drug which is available both as tablets and as capsules, around four times as many people have capsules than tablets?

A. No, I mean, I do not prescribe -- so what -- I will start the prescription and then the prescription will be maintained in the community by the GP, and so I do not -- I have some insights into what happens, but I do not -- it is mainly anecdotal, I cannot tell you what the majority of GPs or pharmacists are doing, that is not my expertise. I see people, patients of mine, who are on a mixture of tablets and capsules, so I may have asked the GP to start on phenytoin and they start them on the tablets and then we have to increase the dose by 25mg, there is only the capsules, so they will be on a mixture of tablets and capsules, so I see that not infrequently, but, you know, the insights I have is that -- well, I do not know if you want to talk about continuity of supply, I am happy to talk about --

THE PRESIDENT: I think we will let counsel ask you the question and then follow up.

MR JOHNSTON: Thank you. I was just going to ask you if you could assist the Tribunal by briefly explaining the origins of the MHRA guidance on continuity of supply as a sort of first question, and then we will move on and

ask some more as we go.

A. Yes. So the idea of continuity of supply with epilepsy drugs was not a new thing, so we had all known about this as something that we would like to happen, and in 2004, the NICE guidelines actually said that people should be maintained on their brand of anti-seizure medication unless they discuss with their doctor to change the brand. That was not happening at all. So people were being prescribed whatever, and in fact earlier on the only difference that -- the only distinguishing thing you could do was to do brand or generic. It only later became possible to actually then say the manufacturer for the generics, so brand and generic.

So from my point of view, what happened in the 2000s, and this is -- I speak -- I was chair of something called the Joint Epilepsy Council at that time which was a body of all the epilepsy charities, patient-representative charities in the UK of which there are about 26, and there was quite a lot of concern because lamotrigine had come off patent, and so there was then a generic lamotrigine, and lamotrigine was being used to a greater extent, and people were -- a lot of patients get very attached to their drug, you know, they like the same colour drug, the same drug in the

same packaging, and if you are seizure-free and you are terrified of having seizures the worst thing is that that could then change.

So they were getting very concerned about this, there had been some surveys of patients who had said that they were very unhappy, and then levetiracetam came off patent in, I think, about 2011, I think if I am correct, I cannot -- but it is around about then, it was before the MHRA guidance. Levetiracetam, again, people started to get unhappy about the fact that this was being prescribed as generic when they wanted to be on Keppra, and so there was a great push from us towards the MHRA to try to make this guidance, you know, to have greater guidance, and this was really from lamotrigine and levetiracetam.

So the MHRA then produced its guidance for this which was guidance, and they stated that there are these groups, group 1 is where phenytoin is. Ironically, levetiracetam, which was causing quite a lot of concern at the time was group 3 which said you could change willy-nilly. Group 2 was where lamotrigine stood where you were supposed to discuss this with your doctor and get an agreement to change the prescription. So it came in specifically for that reason. In fact, we had a meeting with the MHRA shortly after or shortly just

after the guidance came out, because of the unhappiness about the patient groups that drugs were going to be swapped.

Since that time, it has not been particularly noticeable to me that these rules have been obeyed, so again, I cannot speak for all pharmacists and all GPs, and I cannot speak around the country, I can only speak from my experience of my own patients, but, for example, lamotrigine would be a good example. People have been quite happily converted from one brand of lamotrigine to another. Often the brand that they were on depends on where -- which one their local pharmacy has, and the GPs are certainly not prescribing, to my knowledge, by manufacturer.

With phenytoin, again, I have had patients who have changed from one manufacturer to another. Many of the patients I have on phenytoin would not even be able to tell you what manufacturer the phenytoin is. It is not something that they are particularly concerned or bothered with.

The MHRA guidance as well was important because there are concerns with those group 1 drugs that if you convert somebody from one to another that there could be either side effects or breakthrough seizures. Again, ironically, the MHRA -- so the MHRA, and in fact, at the

time the European -- the EMA, and the FDA as well, have very strict rules to try to make sure that you have the same amount of drug in every generic, in generic versus branded, and they have certain criteria that they use, and for drugs with narrow therapeutic index such as phenytoin, for example, those criteria are much stricter, so they are even stricter, and in fact there is not a lot of evidence that if you give a single dose of phenytoin that, whether it is a generic or branded or a different generic, that there is much difference in terms of the levels that you get in an individual person, and that is necessary for the generic to be licensed.

The thing with phenytoin that is different is that, because of this, slight differences in dose can make big differences, because people may be on it chronically, then there may be some indication that there may be some problems swapping from one to another. It has not been a big problem that I have encountered, and if people -- people who are on phenytoin, their blood levels tend to vary quite markedly anyway for a variety of reasons, one of which is for example that about 20 or 30% of drugs are not taken, people forget their drugs regularly. Also things like antacids can affect the levels, and the levels go up and down, and the effects of changing from

one brand to another I do not think are quite as severe or quite as desperate as people make out, but it certainly has been my experience that people have been changed since that guidance has come in.

MR JOHNSTON: Sir, I do not have any further questions in relation to continuity of supply, and you may do as the Tribunal.

THE PRESIDENT: Thank you.

So let us start with the hospital treatment where you are mainly involved where you have someone who is suffering from epilepsy, is not responding to first- and second-line treatments, and you are trying to stabilise them on phenytoin. So they are a first user as it were.

As I understand your evidence, you really do not mind whether it is tablets or capsules or who has manufactured them. You want the sodium phenytoin in whatever form, and you will stabilise the patients accordingly?

A. Yes.

THE PRESIDENT: You have a preference over capsules, not because they are capsules but because of the different dosages which gives you more flexibility as the physician in charge to manage dosage?

A. Yes, sir.

THE PRESIDENT: But that is the only magic in it?

A. That is the only magic in it, yes.

THE PRESIDENT: So -- and I am talking here about the very best practice. I do not want us to insert compromise. Let us just talk what would be the very best practice. You are, in the first prescriber situation, the new patient, indifferent as to manufacturer of capsule, assuming there is a range of manufacturers. You have a preference for capsule over tablet but only because it makes your life easier in getting the dosage right.

A. Yes, sir.

THE PRESIDENT: So let us postulate therefore that we have a patient who is stable on let us say capsules, and so you have a repeat prescription which hopefully is working going on.

We then get two elements. We get what is clinically appropriate for the patient going forward and what is, as it were, reflecting the psychological concerns of the patient because of course, if they are seizure-free, they will want to remain so and they will not want to have a worry that a regime change might cause that happy situation to alter. So one has these two factors in mind. Would that be fair?

A. That is absolutely correct, yes.

THE PRESIDENT: So let us start with the clinical question. If you were a -- well, it would be -- would it be the

general practitioner? Who would effect a change of supply for clinical reasons?

A. Right, so the -- again, I cannot speak for the GP prescribers or pharmacies. So GPs will prescribe phenytoin. Things have changed somewhat more recently because they do electronic prescribing, so when they do electronic prescribing, phenytoin will come up, they will be offered capsules or tablets, they will choose one or the other. I think they can even -- there may even be a space where they can put the manufacturer if they wish to.

So again I was interested to know what happened, so I cannot again speak for all GPs but I spoke to a GP friend of mine and just said, you know, so when you prescribe phenytoin what is it that happens, and what happens is that they get a warning triangle which is be careful about prescription in women of child-bearing age, that they are not pregnant or warn them about pregnancy, and then they get a sort of advisory note to say that the MHRA recommends that you maintain the same manufacturer, but it is an advisory note, it is not -- it is certainly not as strong as I want the MHRA advice to be followed, which is, back then, I wanted the MHRA advice to be strong that people were maintained on the same drug for both the clinical and psychological

reasons.

In terms of what the GPs do, I do not know what they do, but I expect that many of them will see this as an advisory note. They will do whatever they want. They do not know about the MHRA advice.

THE PRESIDENT: Now, the electronic system you just described, that presumably was not around at the time of the relevant period?

A. No, so for the majority -- so then they would have to put it on the prescription, and I cannot remember exactly when you could actually put manufacturers down as something that was necessary, but it was available at that time in 2012. I would expect that there would be nothing there that -- there was, sorry, notification in the BNF, if they'd looked it up in the BNF. If they hadn't and just thought, right, I am just going to prescribe phenytoin, they may not even have any knowledge of the MHRA guidance, and certainly the year after the guidance -- or colleagues of mine, consultants now, that I have spoken to, are not aware of the guidance, even though, as you say, the guidance is I think fairly clear.

THE PRESIDENT: Moving away from the position of the GP, if I may say, up a level of expertise to someone who is in your position who is very expert in the treatment

regimens for epilepsy including phenytoin, let us assume you have a patient that is stabilised on a regime, let us say capsules manufactured by Pfizer. Presumably inertia is a good thing. If it works, you do not really want to change unless there is a reason?

A. Absolutely, sir.

THE PRESIDENT: Could I try to quantify what might be a reason for changing? In other words, how concerned would you be if there was an immediate need for sodium phenytoin but you did not have any capsules to hand conveniently and therefore you had to shift to tablets? How great a problem would that be in terms of the patient's continued treatment and welfare looking purely at the clinical side of things and ignoring the psychological aspect?

A. So the problem is probably not as great as I think necessarily people make out. So it would cause me -- when anybody gets changed, certainly from phenytoin, that would cause me some concern that the levels could change. The evidence would be that it is not going to be an initial thing because the single dose evidence indicates that they are going to be equivalent. So it is more what would happen after a week or two weeks or longer, and so what I would do is get a blood level to make sure that what we have is similar to the levels

that have been measured previously, and we would adjust the dose if that were necessary. So that is what we would do.

One of the big things that happens -- this happens all the time, and patients contact me, not just about phenytoin, but about all the anti-seizure medications -- is that there will be supply shortages of one particular type or brand, that all the pharmacies in an area will not stock something, that it was impossible to get hold of this. I got contacted the other day about carbamazepine actually, about a brand of carbamazepine that they could not get hold of, which again is in that class 1 category.

So what patients receive depends upon what their GPs do, whether the pharmacies have access to that, and whether they are able to -- if they needed to get a specific manufacturer, whether they would pull that in from elsewhere, and I think people's medications changed quite a lot, much more than I as a clinician would like to happen.

THE PRESIDENT: I was asking you about a shift between capsules and tablets, but moving to a shift between capsules manufactured by manufacturer A and capsules manufactured by manufacturer B, how concerned would you be about a shift there?

A. I would not be so concerned, and I would -- but I would want levels to be monitored, so we can monitor the levels, and if people have side effects then we would suggest that the dose is reduced, or if they -- the idea would be that hopefully they are not going to have breakthrough seizures, and again it differs between those people who are seizure-free, where the risks of having a seizure are enormous, to those people who are having regular seizures where we are using phenytoin to try to control their epilepsy better, where if the seizures became a bit more frequent we can adjust the doses. So the risks in those two groups would be different, and the risks of having a seizure are great.

So having seizures, even if they are infrequent seizures, has an impact on your risk of mortality, on other morbidities, on injury, on employment. You cannot drive. I mean, it is just -- it is a really big effect having seizures, so we would -- if someone is seizure-free, you would try very hard to make sure that they did not have seizures.

THE PRESIDENT: Thank you.

Any questions, Mr Johnston?

MR JOHNSTON: None at all, sir. I am very, very grateful. I am conscious that the transcriber has been here from 10.00 until 5.00.

THE PRESIDENT: Well, indeed. We will draw the hot-tub session to a close, Professor. Thank you very much for your time. I am afraid you will be back tomorrow for cross-examination.

MR JOHNSTON: Yes.

THE PRESIDENT: I am afraid we will be taking up more of your time, but you can feel free -- do not feel obliged to, but you can feel free to speak to your legal team if you wish. You are, in other words, released from the purdah that I would normally impose on a witness, but I look forward to seeing you again tomorrow.

THE WITNESS: Thank you, sir.

THE PRESIDENT: We are resuming at 10.00 tomorrow, not because of timing issues, but because there is some form of building evacuation that is going on. I would get here for about 9.45, Professor, if I were you, otherwise you might be out in the rain. So until then, 10.00 tomorrow morning. Thank you.

(5.02 pm)

(The hearing adjourned until 10.00 am on Tuesday, 14 November 2023)