UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA
WEST PALM BEACH DIVISION

CASE NO. 20-md-02924-ROSENBERG

IN RE: ZANTAC (RANITIDINE) PRODUCTS LIABILITY LITIGATION.

West Palm Beach, FL
September 22, 2022

DAUBERT HEARING (in person and through Zoom)
BEFORE THE HONORABLE ROBIN L. ROSENBERG
UNITED STATES DISTRICT JUDGE

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THE COURT: Good morning, everyone. You came back.

Let's get all of our equipment on.

Let's start with this: The magnifying glass that we needed to review the chart that we discussed yesterday, but we were going to pick up with today.

So, for the record, we all know why we are here. We are here because we are continuing to discuss, in 20-md-02924, the Daubert motions and we have a few carryover questions from yesterday's epidemiology motion, and as I stated on the record last evening, we are going to go into the remaining experts motion.

We had cabined a little bit of time this morning, I don't intend to use the full hour before the remaining expert's motion begins.

So, I previewed my questions, so if you know the answers to them, Mr. Cheffo, I want to let you just respond.

MR. CHEFFO: Thank you, your Honor. My partner, Mr. Sachse, is going to address the issue if that is okay with the Court.

THE COURT: Sure. Did we have to fly him in for this?

MR. CHEFFO: No, he has been sitting here.

THE COURT: Do you need me to repeat anything or did you make note of the questions?

MR. SACHSE: No, your Honor, I did make note. Thank you. Will Sachse for GSK.

I thought what made sense is to start by putting this document in context and explaining the background and giving you the timeline.

So, this document was created in 2019, it was after the Valisure Citizen Petition first disclosed levels of NDMA in Ranitidine, and regulators around the world, including EMA, asked GSK and others to look into whether and why NDMA was forming.

This master data sheet is kind of like the rough draft work sheet that is to answer that question.

What happened was GSK, working with some outside labs, they went through and collected samples from around the world and tested those samples and collected the results on the master data sheet. Once that baseline testing was done, GSK essentially exported the data into what is known as the root cause analysis, or RCA.

That root cause analysis is a very lengthy document, about 150 pages, lots of figures, lots of tables, analysis designed to answer the questions of is there NDMA in this product; and if so, why?

That document ultimately gets shared with the regulators, with EMA and FDA, and in an extra step the GSK scientists who worked on the root cause analysis submitted the work they had done for peer review and that ended up getting published in 2020 in what is known as the King paper.

I am not sure, Judge, if anybody attached the King paper as an exhibit to any of our motions, but I know we have both cited it, and we have cited it in our brief, the Najafi brief. That's DE 5698, at page 49, and the Plaintiffs in their general cause challenge, that's DE 5841, footnote 83, page -- can't read my handwriting -- 58, maybe.

If your Honor does not have a copy, I actually have a copy that my colleague just ran over here. I would be happy to hand it up. It is useful to look at and to help put all of this in context.

THE COURT: What is the name of it?

MR. SACHSE: We call it King.

THE COURT: You say it is part of the record?

MR. SACHSE: It is part of the record, your Honor.

THE COURT: Do you have a copy for Plaintiffs as well?

MR. SACHSE: Sure do.

THE COURT: That would be helpful to get from you. Thank you. Great, thank you. Okay.

MR. SACHSE: So, with that background, maybe we can walk through the chart. I see you have your magnifying glass out.

THE COURT: You sure need it, it is so small. Maybe it is the way I printed it out.

MR. SACHSE: It is not you, your Honor. I will have to take my glasses off because I can't see it either.

The other thing -- do you have a color copy of this?

THE COURT: I don't. Do you have one?

MR. SACHSE: I do.

THE COURT: Do you have one for the Plaintiffs?

MS. LUHANA: I can see it on the screen.

THE COURT: Are you going to be putting it on the screen or working off the hard copy?

MR. SACHSE: Working off the hard copy.

THE COURT: You all are younger at that table, so you probably can see it. Okay.

MR. SACHSE: Okay. Hopefully, as we go through this, I will hit all of your questions, but I am sure you will let me know if we don't.

THE COURT: Okay.

MR. SACHSE: So, what I thought, just to orient you, this is the master data sheet, this is the raw data that is coming in when GSK and its outside research labs are testing the product. You asked the question, was this an effort to test API or finished product? The answer is both, and that is what is recorded here.

So, just kind of starting at the left hand, and a couple columns I want to focus on that are of particular importance, the first is the third column, which is the formulation, and that is what it says on the ten, was the product tested a syrup, a tablet, or injection.

The second column that I think is important is about halfway across, and that is the API manufacturer name.

You will see there are a number of different names here, Saraca, S-A-R-A-C-A, Orchev, O-R-C-H-E-V, SMS, and a few entries on the last page Jurong, J-U-R-O-N-G.

So what are these different API manufacturers?

To understand that we have to do a mini history lesson about how GSK made its product.

For the overwhelming majority of the time GSK was making and selling Zantac in the United States it made its own API, and it made its own API in the Jurong facility in Singapore. So, the Jurong facility would make the API and then it would get shipped to other markets, including the United States, where it would be made into finished product and then shipped out to markets in the U.S.

So, from 1983, '84 to about 2012, Jurong is the sole exclusive manufacturer of API that GSK is using.

Beginning in 2010, 2011, 2012, as this product is sort of aging in its life cycle GSK explores using other suppliers of API for the U.S. market, gets approval from the FDA in 2010 to use Dr. Reddy's.

Starting in 2012, GSK is using Dr. Reddy's and a little bit of Jurong's API to make its product for the United States market. Jurong stops making API in 2014, and from 2014 through 2017, in the U.S. GSK is using only Dr. Reddy's API.

Why did I go through all of that? Because if you look at this six, seven page master beta sheet you will see a whole lot of Dr. Reddy's, a whole lot of Saraca, some Orchev, some SMS, a smattering of Jurong, all on that last page and we submit that the Jurong API is what really matters, and the Jurong product is what really matters in this litigation.

If you think about that time period, 1983 to 2012, that is going to capture every -- or almost every Plaintiff in this litigation in terms of the product that they got, the API. Okay. So, that is why I wanted to highlight that column. I will come back to that in a little bit.

I also should mention Saraca, Orchev, SMS never came into the U.S. market. When you see Saraca results, it has nothing to do with any product that ever would have been in the U.S. market.

The next column that I think is important to highlight is date of API manufacture, and that is important because these products have expiration dates. One thing I learned in the course of this litigation that was a little bit surprising is that the expiration date can depend on which region you are in.

For the United States, and this is all done in connection with the FDA, the expiration date for API is two years and the expiration for a finished product is also two years.

So, this chart can be a little bit confusing in that

regard because when you look at, for example, the API expiration date, manufacturing date and expiration date, it suggests a five year expiry period, when in fact in the U.S. market the expiry is much shorter.

Now let's get to the testing. You see there is that blue column and then a pink column next to it.

THE COURT: The API NDMA content?

MR. SACHSE: You got it. And now I have to take my glasses off.

So, the API NDMA content and then the finished product NDMA content.

What the company did, they went and collected finished product to test, to do baseline testing. They also then, if there was API that was used to make that product, they tested the API, and the results are just tabulated here.

To interpret this, these numbers might be strange because it is recorded in micrograms per gram, which is not something that we are normally talking about in this litigation. Usually we are talking about nanograms or PPM, so the way I think of it is the translation essentially is micrograms per gram is the same thing as PPM.

If you remember, the FDA, when it talked about the 96 nanogram average daily intake threshold, that is equivalent to .32 PPM. So, when you are looking at micrograms, you can consider this column PPM, and if it is .32 or below, that is

below the average daily intake number, that 96 nanograms. If it above, it is above.

So, looking at the API column, those results for all of the API that they got from all of the different suppliers, including that handful of API they had from Jurong, they tested that and record the results here.

They also tested, as I said, the finished product. So you have results of finished product that don't line up with the results for the API. And I think one question you asked was, I am looking at this chart, and why is it that sometimes I see the API seems to be higher than the finished product? And I think -- there are a couple of answers.

One that I think scientists and lawyers don't like to give, which is nobody is really entirely sure. What we know, and what the scientists know from studying this, is that when API gets made into a finished product, it seems to slow down this degradation process.

So what is likely to have happened is, if you have API sitting on the shelf and you take some of that API and you turn it into product, then you have the API continuing to degrade at a certain rate, the finished product perhaps degrading at a slower rate, and that might explain the gap, but as I said, the scientists at GSK at least, when they looked at this, no clear conclusions.

The other thing to keep in mind, or two points to keep

in mind about this, is, one, there is no real consistent pattern. I can't say that I went through and did a really comprehensive analysis of this, but you can see just eyeballing it there are results all over the lot.

So, sometimes the API is lower -- the API result is lower than the finished product result, sometimes it is the other way around. There is no real consistent pattern.

The other important point to keep in mind is that no patient is buying API, patients are buying the finished product. So the finished product results are sort of what would be more apropos here.

So, that is kind of the chart.

What I would like to do is, if you flip to the last page of the chart, that is where the Jurong results are, and as I said, there are not that many. I did draw little arrows to guide you to the columns that -- or the rows that have Jurong.

THE COURT: Yes.

MR. SACHSE: The important take-away with Jurong here is that the -- I should say first of all, the rate of degradation for this product is very slow overall, but for Jurong, the rate of degradation is particularly slow.

So, when you look at the numbers, they are really, really low. In most instances they are below that .32, there are a couple that are a bit above, but we also need to keep in mind when this testing was done in 2019, that API was made in

2014, so this is expired API. This is expired product in the U.S. marked that is being tested, and that is very low compared to results that are definitely much, much higher, and we acknowledge that.

There are Dr. Reddy's and some Saraca that are much higher, but that Jurong product seems to test very, very low, and this is an interesting question for the scientists. They look at it and they say, what is different about Jurong?

It turns out that what seems to be different with Jurong is that GSK took an extra step when making the API at Jurong, and this extra step GSK scientists believe turned the crystals into a more stable morphology. If you look at the King paper, there are actually some pictures that show the difference.

I will say that this is disputed. I think Dr. Najafi, we'll hear about him later, he takes a couple of shots at it, but this is at least GSK's conclusion, that there does seem to be a difference in the structure, and GSK attributes that to this extra step that makes the API that GSK is making more stable than, for example, the Dr. Reddy's.

Another thing that I think is sort of very striking, if you look on page three of the King paper, in the bottom right-hand column there is a graph -- I will wait until you get there.

THE COURT: Yes.

MR. SACHSE: That shows -- this is a compilation of the results that GSK collected in its root cause analyses, and you see those green -- very, very low green dots. That is the Jurong stuff, and then you see these peaks and valleys and much higher results. That is the product made with other manufacturers' API. So, that is another important take-away from this root cause analysis.

Last piece on the root cause, the GSK scientists concluded that, as I mentioned, this is a slow degradation pathway, and for the Jurong product in particular, GSK calculated that the rate would be about .04 micrograms per gram, PPM, per year, so very, very slow degradation to NDMA.

So this is all baseline testing, meaning you take the product off the shelf, you test it immediately, that is the results you get, and before I forget, you asked the question about the strike throughs.

THE COURT: Right.

MR. SACHSE: The strike throughs are, whoever was taking this information from the data sheet and exporting it to the root cause analysis framework, when they exported it, they crossed it through to say, okay, now I have exported data value one, data value two, et cetera. So that is why you see those strike throughs. That is all it means.

THE COURT: Okay. Unless there is any factual description, because I have a couple more questions, and we can

always revisit it at the end of the day of the day, does that cover all of the answers?

MR. SACHSE: I think it does, yes.

THE COURT: Did the Plaintiffs have a question or comment or anything?

MS. LUHANA: I do want to respond to what Mr. Sachse has addressed after he is done.

THE COURT: Are we done with the chart?

MR. SACHSE: Yes, your Honor, unless you have any other questions.

THE COURT: Not at this time.

Response.

MS. LUHANA: Good morning, your Honor.

THE COURT: Good morning. For the record, your name.

MS. LUHANA: Roopal Luhana for the Plaintiffs.

A couple of things to know about the master data spreadsheet. While it was a working draft, that ultimately was attached to the root cause analysis that was submitted to the FDA. A couple of things to note about the testing that was done.

What you see is that the API in tablets both degrade. It seems once a tablet forms it adds more stability and possibly less NDMA may be generated, but once those tablets are exposed to heat and humidity, you see far more NDMA being generated.

So, the root cause analysis is in the record. If you look at Table 39, it is page 80, you will see the Jurong samples, when they are exposed to heat and humidity there are thousands of nanograms of NDMA being formed.

So, even though Defendants have made this argument that it is this morphology that makes it more stable, the first thing is, for root cause analysis of Jurong there were only a handful of samples that were tested, so we have limited information on that.

In addition to that, once it is tablet and it is exposed to heat and humidity far more NDMA is generated. Judge, this is also all new argument. None of this was discussed in the Daubert papers and it is not part of the record.

The other thing I wanted to note is the King paper, if you take a look at it, I believe it is page -- so the King paper is what was published by GSK noting the results of the root cause analysis. If you look at page D with Table 1, they report the values that they found in the root cause analysis, which is the drug substance and the tablets; however, you will see the master data spreadsheet has far more values above these numbers than what was published in the King paper.

Judge, if you take a look at some of the values you see dozens of samples that are above 435 nanograms in the finished dose. If you look at the API, the highest value

reported is 21.4 micrograms per gram, so that comes out to over 12,420 nanograms.

In terms of the API in tablets, what is important to note is when you take the API at whatever time you are taking it and you are making a tablet from it, the NDMA that is in the API is going to be reflected in the tablet.

The only reason you are seeing differences is because the API was made in, let's say, 2015, and the tablets are made, let's say, six months later, so that is the NDMA levels reflected at that time; however, as the API is degrading more NDMA is formed there, but once you are making tablets from the API, it is indicative of the NDMA that is going to be there.

I think Mr. Nigh has some additional comments to add.

THE COURT: Okay. I do want to be mindful of time. We can also save some of the argument for the final arguments. I want to give you a chance to respond because I realize there was a factual explanation, so I wanted you to have an opportunity.

Can we hold it?

MR. NIGH: It is about two minutes and the Defendants just interjected all sorts of arguments, so I would ask if I could briefly do it in about two minutes.

THE COURT: Two minutes. I am not going to hear back from Defense, so save your points so that you can wrap it up when we have final argument at the end. I didn't want to get

into this much of an argument as much as just an explanation of the chart.

MR. NIGH: I understand. We just want to use our closing for other issues. It is two minutes.

What I wanted to point out is the King study, they want to say that that shows variability based on the API. Those results are only to the API itself. When you look at the root cause analysis, Table 39, and you compare GSK Jurong compared to Saraca of a drug tablet, what you see is that they both act similarly. They both break down due to humidity.

I highlight humidity because the heat is a small factor, the majority of it is humidity, and you see that they both break down due to humidity similarly. The numbers for the GSK Jurong at 50 degrees Celsius, 65 percent relative humidity, 27,000 nanograms of NDMA. So I wanted to highlight that.

THE COURT: All right. Let me move on, if I may. Thank you all for that. If I have any followup questions after I digest everything on one of the breaks, I might come back. If you feel something really needed to be said you could take a minute or two from your final arguments. I want to make sure we get through all of our questions.

So let me straddle -- let me see where my other question was. Let's see.

Plaintiffs, you were going to get back to me on citing to me any part of the expert report that Dr. -- that says that

Dr. McTiernan used adjusted non-crude numbers. As I indicated, from my review she references both numbers when discussing the study and does not verify which number was the one she used for her analysis.

If you have an answer to that, can you cite it and read it into the record?

MR. RONCA: I can read it into the record.

THE COURT: State your name for the record.

MR. RONCA: Jim Ronca for Plaintiffs. I can read it and I also have it typed up. All the references are in the typed up part.

THE COURT: How long is that there?

MR. RONCA: It is a whole page. I have copies.

THE COURT: Did you provide a copy to the Defendants as well?

So you have the citation?

MR. RONCA: Page and number from the deposition and pages from the reports. It is a little chopped up because, if you recall, or maybe you don't recall -- I presume you reviewed everything. The Adami paper was published with an error, the first figure was wrong, so the initial report didn't pick that up, picked up the stuff that was in the published version. The peer reviewers, nobody picked it up.

Then there was an addendum report and then there was an additional deposition where that was covered. The

explanation is actually in the deposition.

THE COURT: Okay. If it is one page, read it slowly into the record.

MR. RONCA: Sure. I won't read that explanation, I just said it. For Norgaard, bladder crude and adjusted results. There are three different types of adjusted results.

THE COURT: Page and line.

MR. RONCA: I'm sorry. Page 184 and 318, page 16 of the rebuttal report for Adami. Report of crude estimates are pages 208 and 332, and there is a smaller subset of continuous prescription adjusted numbers on page 208.

For liver, the crude estimates are reported on 226 and 341, and the adjusted for continuous prescription subset is on 226. For pancreas, the crude estimates are on 240 and 249, and the subset for continuous prescriptions, 240. For stomach, the crude estimates are on pages 259 and 362, and the adjusted smaller subset of continuous prescriptions on 259.

The trimming is discussed in pages 103 and 127. These are all in the first report. You should also look at the addendum that was dated May 28, 2022, that discusses the changes in the article from the first published to the corrected published.

THE COURT: Are the quotes from the depo on that paper you are reading from, too?

MR. RONCA: Yes. Page 730, line 3, to 731, line one;

page 731, line 23 to 732, line one; and page 733, line 11 to page 735, line 11.

THE COURT: Okay. If I could have a copy of that, the same what you gave to Defendants. You put the page and cites in the record now, and you have the quotes there. Okay, thank you.

A couple more questions. So, for the Plaintiffs, putting aside legal argument, the legal question about the state of the law with respect to identifying or not having to identify a threshold, the number, I want to know what the Plaintiffs' position is factually, factually in the record evidence as to when does Ranitidine ingestion become toxic.

So, again, I know what the legal positions are, but as a matter of record evidence, what is the Plaintiffs' position on that? You know, for example, referring back to your motion at 5868, page 67, there was reference to the statement the Plaintiffs' general causation theory in this litigation is for long term use of Ranitidine. The claim is not that Ranitidine causes cancer after one dose or even a year's worth, but over many years of regular use.

Tell me what the Plaintiffs' position is factually in the record as to that question.

MR. NIGH: Your Honor, we know that it is toxic at least at those cumulative threshold levels.

THE COURT: Be precise. When you say cumulative

threshold level, can you give me numbers?

MR. NIGH: Daniel Nigh for the Plaintiffs.

Your Honor, we know at the levels calculated on that chart by Dr. Salmon that it causes a statistical significant increased risk as seen in those dietary studies.

THE COURT: Just be very precise, because there are a lot of numbers we looked at.

MR. NIGH: Page 233 from the Salmon report.

THE COURT: What numbers? Give me an example of what you are talking about.

MR. NIGH: On the very right side it discusses -- I don't have the table in front of me.

THE COURT: The Emery average after consumer storage?

MR. NIGH: Yes. So we know that for gastric cancer, 1.42 years; esophageal cancer, 1.81 years; bladder cancer, 3.86 years; pancreatic cancer, 3.86 years; liver cancer, 6.65 years.

THE COURT: That is the Plaintiffs' position as to when Ranitidine ingestion becomes toxic for those cancers, at those time periods?

MR. NIGH: We know that it is at least causal at those time periods.

THE COURT: What about the amounts?

MR. NIGH: I say at least causal because those relate to very high statistically significant increased risk, higher magnitudes of effect. At lower amounts there could still be

lower magnitudes of effect.

THE COURT: What lower amounts? Where would I look to know what you mean by lower amounts?

MR. NIGH: For example, liver cancer, on the chart on page 221, liver cancer has an OR of 1.96 at those levels demonstrated in the Hidajat study. That means a 96 percent increased risk that is statistically significant.

We can see the confidence intervals go from 1.16 to 3.29, so at levels lower than what was demonstrated in Hidajat it could still cause cancers, and Dr. Salmon did detailed dose response slopes to demonstrate that.

THE COURT: Do we have a number associated with that lower number?

MR. NIGH: The slopes are earlier in the report, but depending on the amount of cumulative NDMA would let you know the amount of increase of the risk, because the risks in Hidajat are linear for liver cancer. So you can actually track -- between those quartiles, you can track all the way through them and see what would your increased risk be at lower levels.

THE COURT: Are you able to say the levels?

MR. NIGH: I can. It would take some time. We would be doing a calculation for every level on down and seeing what the increased risk would be.

THE COURT: Do you want to defer answering the

question and maybe include that in your final remarks and think about it and how best to explain it to the Court in a way that the Court can understand?

MR. NIGH: Yes, your Honor.

THE COURT: Amounts, dosage, and amount of time.

Again, you are not waiving any legal positions you have taken. I am trying to understand what the record evidence is trying to tell the Court, what you are trying to tell the Court through the record evidence.

MR. NIGH: I should just clarify, we know that it is statistically significant at least at those levels.

THE COURT: You keep saying those levels, I just want to know what are the levels.

MR. NIGH: Page 233, again that chart.

THE COURT: But you say, but they are also statistically significant at lower levels. You said these --

MR. NIGH: Statistical significance is a function of the design of the study, so, no. But in terms of linearity along the chart you can see what the increased risk would be at lower levels.

THE COURT: I want to know what are the Plaintiffs relying upon. It may be the numbers are not statistically significant, maybe they are. What are the numbers the Plaintiffs are relying upon for the proposition of ingestion of Ranitidine, when it becomes toxic, the dosage, the duration of

time.

MR. NIGH: Sure. For general causation, in the right column, these levels let us know. When I say these levels, the right column of page 223, Emery, after consumer storage. These tell us the amount of years that it would take to reach those statistically significant increased levels. So we know that it is carcinogenic at those levels and total dosage is the cumulative amount on the left side, which shows gastric, esophageal, bladder, pancreas, liver. That is under study cumulative milligrams.

THE COURT: It is at least that, but it also could be less than that?

MR. NIGH: For general causation, we know that it causes cancer at those levels.

THE COURT: Do we know that it causes cancer at any other levels for general causation per the Plaintiffs' position?

MR. NIGH: I think the Plaintiffs' position is, we don't have to answer that question.

THE COURT: I know your legal position, so I am not trying to argue with you about the legal position. I want to know whether there is something in the record that tells me other numbers and periods of time other than we know at this level.

MR. NIGH: I do need more time where we can piece

together what the slope would tell you the increased risk would be at lower levels.

THE COURT: Okay. That is what why I brought it up this morning. It is not a gotcha question. I wanted to give you the time to think about it and understand it. If you can't answer it, not that you don't want to answer it, just tell the Court you can't, but if you can, even though I understand you feel you don't have to legally, I appreciate that.

MR. NIGH: I understand. Thank you, your Honor.

THE COURT: Okay. And then for both parties, Plaintiffs first, I guess, a hypothetical question. I am going to ask the flip side, so no one panic.

For the Plaintiffs, do you agree that if I were to grant the Defendants' motion in its entirety as to Drs. McTiernan and Moorman for all of the reasons that have been set forth in their motion and argued here, that Dr. Salmon, Dr. Michaels, and Dr. Le should be stricken, or would be stricken for the same reasons that Dr. McTiernan and Dr. Moorman were stricken?

And in fairness, I am going to be asking the Defendants, do you agree that if I were to deny the Defendants' motion in its entirety as to Drs. McTiernan and Moorman, that the motion should also be denied as to Drs. Salmon, Michaels, and Le?

Plaintiffs first. If that is a question you need to

think about and you want to answer at the end of the day, that is fine, too. Or do you want to answer it now?

Come to the podium, because that is the only way that our Zoom attendees can see you clearly.

MR. HEINZ: Noah Heinz for the Plaintiffs.

I think the answer is no, and that is because the Defendants have provided a number of different reasons to exclude Drs. Moorman and McTiernan, some of which are particular to Drs. Moorman or McTiernan, depending on particular things that they said in their reports. So, if those reasons do not apply to the other experts then that would be no reason to exclude them.

There are some overarching arguments, as an example, saying that the active comparator for Ranitidine studies are definitive and one could not come up with a reliable opinion in light of what those say, if that sort of broad brush argument is the one that carries the day, then it likely would apply to the other experts down the line.

That is not the only argument that the Defendants presented, so we'd say you have to look argument by argument based on what they actually said and how it applies to each expert.

THE COURT: Okay. If there is anything that you want to elaborate on and have specific examples, you can save that for the final presentation, that would be fine, drawing any of

those distinctions as to arguments made as to some and not the others.

And from the Defendants.

MR. HOLIAN: Thank you, your Honor, Matt Holian.

The answer to your question is, you should also exclude Drs. Salmon, Le, and Michaels even if you don't exclude Drs. Moorman and McTiernan for the additional reasons that we discussed in our briefs and at argument yesterday. We rested on the papers for Drs. Le and Michaels, so I am happy to discuss that if the Court would like to hear it, but they had additional flaws.

But if you grant the motion on Drs. Moorman and McTiernan, you should grant it on the other three for the reasons that we set forth, because they can't show a statistical association free of the bias and confounding that the active comparator studies address. They have offered opinions that are not generally accepted anywhere in the medical community.

They haven't offered, other than Dr. Salmon who we have talked about extensively, a threshold dose at which anything is observed.

So, you would have to disagree with us on all three of those in order not to exclude Drs. Le and Michaels and Dr. Salmon for the reasons we have identified. Even if you let Drs. Moorman and McTiernan get past that, there are

additional flaws that we identified in our papers.

THE COURT: Thank you. Same for Plaintiffs, if you think of other things that you want to say on that issue for the final arguments, that would be fine as well.

Thank you so much.

Let's move on now to the remaining expert's motion at Docket Entry 5696, which has also been fully briefed and we have speakers lined up. The group that was coming up -- or maybe one speaker for the Defense, Ms. Rydstrom, who was going to speak at 10:00, but we are starting a little early. It looks like you wanted 15 minutes?

MS. RYDSTROM: Yes, your Honor. Good morning, your Honor, it's Jessica Rydstrom.

The good news, your Honor, is that, given the discussions that we had yesterday about epidemiology, we actually don't think the Court needs to go any further and to reach this particular motion because, as Mr. Holian just explained, if there is no association under the epidemiology, if Plaintiffs' experts, as we believe, can't reliably provide or opine about an association in that epi, then it is the end of the road because Plaintiffs' experts can't bootstrap using what they told you yesterday are these secondary methodologies, they can't use those to fill in holes in the epidemiology that just aren't there.

What I am actually going to talk about is why we don't

see in the epidemiology that association between Ranitidine and the five designated cancers, because the theories that Plaintiffs' experts have articulated, these unreliable endogenous formation and extrapolation from animal studies, actually help explain why we don't see that in the epidemiology, why it is not working that way in the human body.

Next slide, please.

These remaining opinions fall into three broad buckets, and I am going to spend my time on the first one, which is the endogenous formation theory.

The question here, your Honor, is the one that the Court posed to us, which I will attempt to answer as I am going through this presentation, and that is really why the well-designed studies that we see that have come out recently, what they don't show.

What they don't show is what Plaintiffs want to advance here, that NDMA forms endogenously from Ranitidine under real world conditions. That is the focus here, that real world condition.

And the reason that is important, your Honor, is, in part, because under real world conditions that we actually see in the human body, if Ranitidine were forming NDMA endogenously under those conditions, well, that would be baked into the epidemiological studies that we talked about for so long yesterday. We would actually see the results of that theory if

it were true, but it is not.

That real world, real people is actually a nice segue to the second bucket theory that I am going to talk about, and that is Plaintiffs' experts attempts to really stretch these animal theories beyond where they ought fairly to go.

We have to be careful about that here because there are very, very real differences between the way that animals behave in studies and the way that NDMA or Ranitidine behaves in the human body. We have problems with dose extrapolation. We have problems taking one species and translating it to another species, and we even have problems, as we see here, your Honor, with there being different tumor sites where we are seeing effects in animals that you don't see in people.

Finally, and very, very briefly, I want to talk about that threshold issue. Specifically, not with respect to the discussion that we had yesterday, but to the fact that Plaintiffs' experts here really are trying to advance that theory that any amount of NDMA is essentially too much, and we know under the law that that is not true.

Next slide, please.

So the endogenous theory. Any discussion of this theory, your Honor, has to start with these guys, Dr. Florian and Dr. Gao. We have heard about them over the course of the year since this paper came out. They are researchers at the FDA who designed, in 2021, studies to answer precisely this

question: Is NDMA forming endogenously from Ranitidine in real world conditions? As we can see, both of them answered that question in the negative.

I don't actually think, your Honor, that there is a real dispute that this is the starting point for any discussion of the endogenous formation theory. What does it say about Florian?

Next slide, please.

To be clear, there is no question that the aim of this study was to answer the question that Plaintiffs' experts are sort of fighting against, and that is: Is there an increase in NDMA from Ranitidine inside the body under these real world conditions?

What Dr. Florian found when he studied these volunteers was, the answer is no. He found that Ranitidine didn't have a significant increase, a significant affect on the levels of NDMA that were found in the human body, in the urine of these volunteers.

I expect that when Ms. Luhana gets up she is going to tell you that there was a near doubling of NDMA in the plasma levels. Your Honor, when you look at the paper, you see that is actually not a statistically significant result.

But Dr. Florian did find a statistically significant increase, it is just not the one that Plaintiffs' experts want to focus on here, because what they found was that the thing

that actually does increase the amount of NDMA that is formed endogenously in the body is whether or not you have a cured meats diet, high in nitrites and all that bad stuff, or whether you have a non-cured meats diet. That is the statistically significant difference that they found.

Next slide, please.

The criticism that Plaintiffs' experts lodge here, your Honor, is that it is very hard to find NDMA in urine. I gather that they want to sort of say that it is like catching lightening in a bottle. But Dr. Florian and his colleagues did find NDMA in the urine of the volunteers that they tested and they did find that statistically significant increase that I just mentioned.

Again, it wasn't the one that Plaintiffs' experts want to the talk about here. They want to suggest that there is an increase between Ranitidine and placebo. Dr. Florian found that there was not. He found that the thing that statistically significantly increases the amount of NDMA in the urine is going to be that cured meats versus non-cured meats diet.

The basis, I gather, for the concern about finding NDMA in urine is this 1982 paper by Spiegelhalder, setting aside that 1982, long time ago, methods have advanced since then, the Florian paper and its findings directly refute that criticism.

Next slide.

There is a very small amount of criticism, your Honor, that the Florian researchers did their testing on -- gave the Ranitidine on fasting conditions. They did that because one thing that Plaintiffs' experts do get right is, in the litany of studies that they cite about the endogenous formation of NDMA not from Ranitidine, right, how NDMA can generally form endogenously in the body, what those studies find is that you need a very low pH. You need a highly acidic environment.

Dr. Florian and his colleagues said, how can we best create that? We should create it with our volunteers on fasted conditions. That is why they did that.

Next slide, please.

Briefly, your Honor, there are two studies that are cited by the Plaintiffs' experts with respect to the findings of NDMA in urine and Ranitidine. The first one, the Matsuda paper, we can dismiss pretty easily because that paper is actually a study not just of Ranitidine, but of a host of different H2 blockers. It's essentially the class, Cimetidine, Floxatidine, Famotidine, and Ranitidine, and what the Matsuda researchers concluded is actually there was no difference as between those four.

The reason I think that is important, your Honor, is because for the two years of this litigation the Plaintiffs and their experts have tried to suggest that there is something uniquely villanous or dangerous about the Ranitidine molecule,

that it is special and ripe for nitrosation. What the Matsuda paper shows is that is not true. What we see here is an increase in this paper across those various forms of medicines within the class.

Next slide, please.

The Krawczynski paper is the other paper dealing with NDMA in urine that Plaintiffs' experts talk about. This was a study in which the researchers took two groups of children, one that had H. pylori infections and one that didn't, and they gave them, importantly, your Honor, not just Ranitidine, but they gave them also two different kinds of antibiotics, the treatment group.

They gave them these antibiotics for a period of time and then they stopped the treatment and they waited four to six weeks. So, four to six weeks after that treatment was concluded, not after it started, but after it was concluded, those researchers measured the levels of nitrosamines and found they had increased.

Now, which nitrosamines? We don't know because they don't provide us that specific data in the paper, but we do know that whatever it was and whatever caused that increase, it could not have been the treatment that folks hadn't had for four to six weeks before that.

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So, I would like to move on to the in vitro, and this

is the Gao paper, this is the other of the two big pillars, right, answering this question recently. The main criticism that Plaintiffs' experts have lodged about the Gao paper is the one that Dr. Panigraphy says here, because we asked him, what is physiological? Do you agree that this particular study, the Braunstein study, didn't include any physiological conditions?

He says yes, but what he then goes on to say is basically, well, physiological, you have to consider a whole bunch of different things. You have to consider other factors, food, disease, pH, bacteria, but the Gao researchers knew that.

Next slide, please.

The very first thing that they did when they were doing and concluding their experiment, is they went out and they scoured the medical literature. They looked at studies of endogenous formation that had been done in fasted and non-fasted groups, sick people, healthy people, and when they synthesized all that information what they said was, look, overall these studies provided conservative cover bound.

So, what are we likely to see for gastric fluid nitrite amounts? Less than a hundred micromolars per liter. They weren't trying to answer the question, what are the ideal conditions under which you can force the endogenous formation of NDMA. They were asking the real world question, which is, what do we see in people when we go out and look at all these various studies that have been done?

Just for the record, 100 micromolar is .1 millimolar, and that is important because when we move to the next slide what we see is that what the Gao researchers found is entirely consistent with what all the other studies of endogenous formation from NDMA have found, including that Tanner study.

And that is, at physiological levels, at levels that the Gao researchers found are within what you are likely to see in a human body, there is going to be no increase, no endogenous formation of NDMA from Ranitidine. It is not until you get to those super -- those academic can we force this reaction levels that you start to see those increases.

Next slide, please.

Before I move to the animal studies, just a word about a study that I believe that Plaintiffs showed yesterday, the Helstrand study. You will remember there were pictures of the lungs, and I think, if I remember correctly, we were told we ought to all just look at the pictures. I think we should look at the article, too, because in that the article what the researchers attempted to do was inject the mice with cancer.

So, they injected them with melanoma cells and then studied to see what happened and whether particular types of cells metastasized. What they found was, importantly, Ranitidine and another H2 blocker had the same effect.

So, when the Court looks at the study, we have to look at the starting point, which is, they were attempting to give

cancer cells to these particular mice.

On the animal studies, very briefly, your Honor, I want to talk about the Peto study because I know that is something about which the Court had asked a question.

This study, your Honor, gives us both the problems with tumor sites from animal studies, and also the problem with dose, because what we saw in this study is that the rats were given enormous, enormous amounts of NDMA, and even with those large, large amounts of NDMA, what we saw -- we only saw increases in tumors in the liver, not anywhere else in the body.

That makes sense because the enzyme that metabolizes NDMA, which is not dangerous when it is just sort of bouncing around in the body, right, the enzyme that turns NDMA into something that could cause DNA damage is found predominantly in the liver. So it is not surprising in the Peto paper that that is the only site in the rats that they found that particular damage.

Briefly, your Honor, the Gombar paper, which is another one about which the Court had asked us to pay particular attention.

Next slide, please.

The Gombar paper answers two smaller questions, and the first one is: Can we do the calculation that I have up here on the screen? Can we take one mg per kg, and what does

that tell us about what that would translate to dosage-wise in a human? What the Gombar paper said is, you actually can do that calculation. That is not strange to say that if you gave a mouse one mg per kg that would translate to -- here we have 70 million nanograms of NDMA in a 155 pound or 70 kilogram adult.

The other question that the Gombar paper couldn't answer is how the bioavailability of NDMA scales up for animals, because what Plaintiffs' experts suggest is that small animals have a tiny, tiny amount of bioavailability. That is the amount of NDMA that gets past the liver and can circulate in the body.

Big animals, they say, dot, dot, dot, and also people have bigger amounts of bioavailability. That is precisely the opposite of what the Gombar paper concluded. They said there is no uniformly predictable relationship between those two things and it is a difficult relationship, in fact, for them to be able to explain.

What all this tells us, your Honor, is that Courts are right to be cautious about extrapolating from animal studies to human studies in the way that Plaintiffs' experts have suggested that we do here.

THE COURT: You're at 15 minutes.

MS. RYDSTROM: Thank you very much. If I may, one last slide on Dr. Panigraphy and his threshold testimony.

We asked Dr. Panigraphy point blank, are you going to come in here and say FDA regulatory limits are reliable evidence of real world cancer? And he said yes. That is directly contradictory not just to what the FDA says about how we should look at those ADI limits, your Honor, but also how the Eleventh Circuit tells us that we should think about them as well.

Thank you.

THE COURT: Thank you. That was slightly over 15, close to 16, so Plaintiffs can have the same.

Let's hear now from -- is it Ms. Luhana who is going to argue the Plaintiffs' position? Okay.

MS. LUHANA: Roopal Luhana for the Plaintiffs.

Judge, I am going to use my phone to track time. Is that okay?

THE COURT: Okay.

MS. LUHANA: Judge, I am going to address Plaintiffs' opposition to the Defendants' motion to exclude Plaintiffs' remaining general causation expert opinions.

Can we go to the next slide.

So, Daubert and Rule 702 require the Court to undertake a three-part inquiry for expert admissibility. Here, with this motion Defendants have only raised that Plaintiffs have not met the reliability prong. This is simply false.

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The Supreme Court has stated that the reliability prong requires Courts to consider four factors, is the scientific method -- can it be tested, is it subject to peer review, does it have a knowledgable rate of error, is it generally accepted in the relevant community.

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So, Defendants invite this Court to impermissibly weigh the evidence. As we will discuss, Plaintiffs' experts have cited to literally hundreds of peer reviewed studies which allow our experts to conclude, and reliably conclude, the following:

That Ranitidine endogenously to form NDMA; that there are over 175 animal studies that not only confirm the carcinogenicity of NDMA, but that NDMA forms tumors in all five sites, including the esophagus, stomach, pancreas, bladder, and liver.

Judge, we are not extrapolating doses that these animals are exposed to. We are using the animal studies to prove the carcinogenicity of NDMA, which is known and established around the world. This is why NDMA has been banned in this country from commercial use since the 2000's, and lastly, that every regulatory body has concluded that genotoxins like NDMA don't have a threshold.

This has been repeatedly declared by every regulatory and authoritative body, so Plaintiffs agree with that position.

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Defendants challenge the endogenous formation opinions of the following Plaintiffs' experts: Drs. Panigraphy, Michaels, Marletta, Le, and Najafi.

What is telling is Defendants haven't moved to exclude Dr. Zeiger, who also has provided endogenous formation opinions.

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So, Plaintiffs' experts have reviewed the relevant evidence. These are just some of the studies that our experts have reviewed to conclude not only that nitrosation happens endogenously with Ranitidine, but also that NDMA is formed endogenously in Ranitidine.

Next slide.

The studies Plaintiffs' experts have reviewed are similar to exactly what GSK identified as relevant when regulators asked GSK to discuss endogenous formation of NDMA from Ranitidine.

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Defendants' experts don't argue that NDMA can't form endogenously from Ranitidine. Tanner, in 1982, confirmed that it does. Instead, Defendants argue what physiologically relevant nitrite levels are, but Defendants' experts focus only on one factor, nitrite levels, which are involved in the endogenous formation process. Plaintiffs' experts rely on the

corpus of studies showing that endogenous formation results from the interplay of a multitude of factors.

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Judge, as you can see, there are numerous factors that impact the gastric environment and how much NDMA is produced, as Plaintiffs' experts opined. If you have ulcers and GERD, like Ranitidine users, you are more prone to nitrosation. You will have lower acidity that results in higher pH, and that results in more bacterial overgrowth, and that is a perfect recipe for endogenous formation of NDMA.

This has been written and studied and extensively discussed by our experts. Your diet is going to play a critical role, your thiocyanate levels are going to play a role. Your pH will play a huge role, as Gao discusses, and I will get to that, as well as your stomach volume, as our experts know. You can't just focus on one factor, all these factors contribute to the endogenous formation of NDMA.

Next slide.

So the Gao study in 2021 was done to assess Ranitidine in varying levels of sodium nitrite, pH, and gastric fluid volume to assess how much NDMA would form.

Our experts note that the critical limitation of Gao, which is acknowledged by the authors, is that it didn't include gastric conditions in the presence of a meal.

So this is important because the gastric environment

impacts NDMA formation. Gao confirmed some of this.

Lastly, even though Gao collected over 20 studies which reported nitrite levels, the majority of those studies were fasting, and only one study referenced Ranitidine, and unfortunately that study, when they measured the nitrite levels, those samples were Ranitidine free, which was problematic.

Next slide, please.

So Plaintiffs' experts, in assessing Gao, similarly raised it is not just one factor, there are multiple factors in the dynamic gastric environment that are necessary to assess NDMA formation.

Next slide, please.

So, this is a chart from the Gao study, and as you can see, the pH is on the bottom, the NDMA is on the Y axis, and if you look at the factors, it is 50 milliliters of simulated gastric fluid with 10 millimoles of nitrite. If you change the pH, if it is 5, it is only 200 something nanograms of NDMA generated. However, if you go to a pH of 1.2, that is 11,000 nanograms. This tells you pH plays a huge part in the formation of NDMA.

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Judge, the same thing here, if you look at 50 milliliters versus 250 milliliters, it is double the amount of NDMA when you increase the volume in the stomach. So the

fasting stomach, you have very little fluid; however, if you have a fed stomach, you have a lot more fluid and it will generate a lot more NDMA.

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So, the objective of the Florian study was clear. The Florian study's purpose was to redo Zeng and Mitch. They simply state that was the objective.

Florian's objective as designed wasn't to assess endogenous formation of NDMA from Ranitidine. If that was the purpose they would have tested the GI tract for NDMA. However, the authors noted specifically that the purpose was to assess the NDMA in the urine.

Defendants, however, impermissibly try to stretch Florian beyond its objective to conclude that endogenous formation does not occur in Ranitidine users, even though the study authors provided that the limitation of the study is that it only included healthy participants, and didn't exclude formation of NDMA from the GI tract.

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Plaintiffs' experts opine that the gastric environment of those who suffer from GERD or ulcers, like Ranitidine users, is very different than someone who is a healthy individual.

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So, let's see what Florian really showed.

This is a small -- our experts opine it is a small

study. It is only 17 healthy participants who don't resemble the Ranitidine population or their gastric environment. They one 150-milligram pill with only ten nanograms of NDMA, and they were given -- that was with and without a cured meat diet, and then they tested the urine, which showed very little NDMA.

Our experts state that this has been known for decades that you don't look at the urine for NDMA, it is a bad gauge for it, and this has been studied and discussed, and what our experts refer to and rely on to say it is a bad tracker of NDMA.

In fact, in terms of the samples of NDMA in the urine, 73 percent of those samples were below detection, and even if you looked at the cured meat participants in this study, if you calculate the amount of nitrites they were consuming, it was about 325,000 nanograms of nitrites that they were being exposed to; however, that was not even showing up in the urine.

The highest level that you saw in the Florian study was 150 nanograms in the urine, so clearly it is not a good gauge of NDMA.

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Even Defendants' toxicologist, Dr. Guengerich, agrees that NDMA is metabolized quickly and it is difficult to measure, and that a low fraction of NDMA would be present in the plasma or urine.

Next slide.

And our experts highlight that the FDA knew this, of course, as well. The FDA, in the March 2021 working group on nitrosamines, said that NDMA metabolizes quickly and is difficult to measure, noting only rough estimates are available in the literature on endogenous formation of NDMA based on its detection in blood and urine. Because of its rapid metabolism, only a small fraction is excreted in urine.

The only purpose of Florian was simply to redo Zeng and Mitch and contest those results or confirm those results. It was to test the urine for NDMA and that is it.

Next slide. This is the right slide.

Our experts highlight, including Dr. Le, that despite Florian's limitations the NDMA plasma levels in the Ranitidine in cured meats groups were doubled compared to the placebo and compared to the cured meats groups.

This was 17 participants, this study wasn't designed to check for statistical significance of plasma levels. That is why it wasn't found. Dr. Le testified it wasn't powered to find this because it was designed as a urine study, but even despite that, with all the issues with Florian, it is double the amount of NDMA with the Ranitidine in the cured meats group.

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So, Plaintiffs' experts at length discuss and explain why the results of Florian and Gao don't answer some of these

critical questions; however, scientists outside of the litigation have published similar concerns and criticisms of Florian and Gao, among them recognizing that Florian only used a healthy population, which we discussed is very different than the Ranitidine population, and that in addition to that, Gao didn't include the numerous variables that exist in the human stomach.

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We talked about Matsuda. Matsuda tested 72 healthy subjects and 279 patients with gastric ulcers before and after Ranitidine treatment. So, Ranitidine users there had 41.2 percent NDMA detected in their gastric after Ranitidine use. These are fasted samples without any nitrite.

If you look at the 6.7 nanograms it equates to, with 250 milliliters, close to -- it's 1,975 nanograms of NDMA. And so while the Defendants say look at all the other H2RAs, they are producing NDMA as well, and that is a problem with this population of people, they are more prone to NDMA formation, however, these other two H2RAs don't have the issues that Ranitidine has. You are not getting the amount of NDMA baseline because it is not degrading to form NDMA.

Also, these other H2RAs tertiary means that when they come into contact with nitrite form NDMA. Ranitidine is a three-time assassin in that regard.

Next slide, please.

Of course, our Plaintiffs have assessed Matsuda and discussed this at length.

Next slide.

Krawczynski, in 2002, 30 kids were treated with Ranitidine for 28 days with chronic gastritis and H. pylori infections, and they had statistically significant levels of nitrosamines, including NDMA specifically. They didn't quantify the NDMA, that was found in this population.

What is important to note with Krawczynski and Matsuda is the chronicity and the type of population that they are measuring. So, Ranitidine users are using Ranitidine for a long time.

Florian, you had a short study with a healthy population. In terms of Matsuda and Krawczynski, it is the right people, it is people who are suffering from GERD and ulcers, they are more prone for NDMA to be generated in their stomach.

This is very telling when you are seeing statistically significant results with this population. Guess what? They are measuring the right metric. In Matsuda they measured gastric fluid. In Krawczynski they measured gastric fluid. You know why? Because those are better indicators of the NDMA in your body than urine.

Next slide.

So, similarly, our Plaintiffs' experts have assessed

Krawczynski and it has gone to the weight of the evidence to support endogenous formation.

Next slide.

So, the Ozon study is from 2003 and it tested 28 drugs based on their chemical structure to see if they would nitrosate under simulated gastric conditions.

THE COURT: Your time is about up.

MS. LUHANA: Just one more minute. Ranitidine was incubated with .13 millimoles of sodium nitrite, so that is a level that Defendants are saying is physiologically relevant. The tests confirm that the nitrosated Ranitidine was genotoxic, it led to DNA damage and activated the DNA repair mechanisms. Ranitidine, in fact, in this study had one of the greatest responses to DNA repair mechanisms going into effect compared to other drugs.

For this reason, Judge, we believe you should deny Defendants' motion.

Thank you.

THE COURT: Okay, thank you very much.

So I think what we will do is shift the schedule a little bit. We will take a break now. It is 10:15, and we will take a break until 10:30, and we will come back and I will ask some questions, and depending on how long those take, I want to be fair to the group addressing Najafi, it is possible we might hear on the Najafi/Davis motion before lunch,

depending on how long we go on the questions for the remaining experts.

I wanted you to be prepared for that. We might take a lunch break and then hear from the Plaintiffs. If the questions go longer, we may keep with the schedule where you are presenting after lunch. So, be flexible on that.

Okay, we will take a 15-minute break and be back at 10:30 for some questions on that motion.

Thank you.

(Thereupon, a short recess was taken.)

THE COURT: Okay, you may be seated.

Apparently the last comment I made before we broke my mike was off. I said we were going to take a 15-minute break, which we just did, and have questions now on the motion that was just argued. Depending on how long those questions take we may or may not get into the first part of the next presentation on Najafi/Davis, which was otherwise scheduled for after lunch.

For those of you who didn't hear me, that is what I said. Sorry about that.

So, questions, let's see.

This is a question for Plaintiffs and it relates to Florian, so if the person or persons who want to answer the Florian questions want to come up to the podium, that would be great, and others can come to help if need be.

So, as I understand the Plaintiffs' position, through

their experts, that Dr. Najafi has criticized Florian 2021, in part because the study, quote, "missed an extremely critical aspect of NDMA production from Ranitidine interaction with food." That is Najafi's report at page 105.

Do your experts explain how long after beginning a meal or finishing a meal the participants in Florian 2021 would have needed to have taken Ranitidine in order to satisfy the requirement that Florian 2021 accounts for Ranitidine interaction with food?

Do your experts explain generally when participants in any study of Ranitidine would need to eat food in relation to the time they took Ranitidine in order to account for Ranitidine's interaction with food?

If there are specific places in your expert reports or depo transcripts that you can point me to, that would be helpful.

MS. LUHANA: Sure. Roopal Luhana for the Plaintiffs, Judge.

Dr. Najafi had done a number of experiments, including experiments with simulated gastric fluid with food to measure the amount of nitrite there. He had done ham, sausage, hotdogs, and one other food group, and measured how much nitrite -- we'll direct you to that chart that was going to be part of my endogenous formation presentation yesterday, so I would highlight that.

In addition to that, he did testing -- this was all done per the protocols that were established from Gao and Braunstein. Then, the other testing he had done was mixing Ranitidine with food in simulated gastric fluid, and the he measured the amount of NDMA at different times intervals.

If we take a look at that chart -- I'm also phoning a friend, my colleague, Rosemary Bogdan, who can discuss it further.

THE COURT: Can you give me the timeframe that you are saying?

MS. LUHANA: He started at zero hours and went several hours forward. You see with ham and then Zantac, and Zantac and then ham, at the 1.5 hour interval there is a significant amount of NDMA being generated. I want to pull up the report and direct you to the specific charts.

Can I quickly grab my PowerPoint?

THE COURT: Yes.

MS. LUHANA: Okay.

THE COURT: And I guess in the question, when does somebody need to eat? What is the position -- what is the Plaintiffs' position on that?

MS. BOGDAN: Rosemary Bogdan on behalf of the Plaintiffs.

THE COURT: When would the participants in Florian have needed to eat in relation to when Ranitidine was

administered?

MS. BOGDAN: To answer the Court's larger question here, you have multiple things going on. You have Ranitidine being taken, okay. Ranitidine is absorbed after oral administration and it reaches its peak plasma concentration in about two to three hours, but Ranitidine is unique because it has two peak plasma concentrations. The first one is at two to three hours and the second one is at three to six.

There is phenomenon called entropic hepatic circulation, so basically Ranitidine is available in the system for up to six hours because of the way that Ranitidine is metabolized.

THE COURT: In the Florian study, what is the Plaintiffs' position with respect to when the participants would have needed to eat in relation to when the Ranitidine was administered?

MS. BOGDAN: How I would first respond to that, your Honor, is I would point to Florian's limitations, and what Florian says, the authors themselves, is that this study only includes healthy participants, which you heard and you have seen in our briefing, and it did not exclude formation of NDMA in the gastrointestinal tract that was not absorbed and detected in plasma or urine.

THE COURT: I am aware of the limitations. I am wondering if there is an answer to the question, when would

they have needed to eat relative to when they took the Ranitidine.

MS. BOGDAN: They would need to eat so that they would be in that window, which is from when the Ranitidine was taken to six hours --

THE COURT: Any time from when the Ranitidine was taken to six hours they would eat?

MS. BOGDAN: They would eat, and the food would be there with the Ranitidine.

The issue in Florian is that they are measuring these values in plasma, and when NDMA forms in the gastrointestinal tract and is metabolized in the gastrointestinal tract, it never reaches the plasma to be measured, and that is what they are stating in the limitations in Florian.

They also stated in the limitations in Gao that they are not assessing some physiological conditions and they don't include an evaluation of gastric conditions in the presence of a meal, aside from substituting in nitrite which is different than the food.

What Emery did was actually do the Gao experiment, but with food, and in the Table GG in their report they explain the nitrite levels that are reached with the food and the simulated gastric fluid.

THE COURT: Thank you. Going back to Florian, researchers administer the Ranitidine just one minute before

study participants started eating breakfast. That is Florian 2021 at page 241.

Do your experts explain why this timing does not account for the factor of interaction with food; and if so, where?

MS. BOGDAN: They explain that the way that Florian is measuring the NDMA is problematic.

THE COURT: So it is not the timing?

MS. BOGDAN: It is not the timing of when the drug necessarily is being given with the food, because they are what I would call on board at the same time. If you take the Ranitidine right before you eat, they are both in the gastric compartment at the same time. That is common sense.

The issue that they are taking were with it is that NDMA can be generated endogenously in the stomach, in the gastrointestinal tract, and when you are measuring plasma, that is not an indication of whether NDMA was formed, and the total amount of NDMA that is being formed because the NDMA, if it is metabolized before it gets to the plasma, it doesn't get counted.

Also, NDMA has a very, very short half life, so if you are -- like in the Florian study when you are measuring NDMA in half hour intervals in the plasma, which much of it doesn't reach the plasma to begin with, and you are measuring it, it is disappearing because its half life is shorter than the time

that they are measuring.

These issues are discussed in both Dr. Le's and Dr. Panigraphy's report. It is poor metric to study endogenous formation of NDMA, because the Florian authors state right in their study that it did not exclude formation of NDMA in the gastrointestinal track.

My colleague, Ms. Luhana, was explaining about how Ranitidine can nitrosate in the intestinal track to form NDMA, and the Florian study does not address that issue. It is not the timing specifically, although that can be an issue with regard to someone that chronically takes Ranitidine and they have a baseline level in their system. That is something that is also a factor out there.

But if you ask me, the real issue here is that the Florian study, designed as a urine study -- understand that these investigators were really trying to just see if the Mitch paper was -- that was the whole purpose of it.

THE COURT: Well, I guess to go back to what I started with, Najafi, at 105, says the study missed an extremely critical aspect of NDMA production from Ranitidine interaction with food.

MS. BOGDAN: That is absolutely correct because the studies show that when you do the experiment with food a tremendous amount of NDMA forms, and we have a slide --

THE COURT: But Florian, I thought, gave food one

minute before -- gave the Ranitidine one minute before eating breakfast.

MS. BOGDAN: Yes, but Florian is only determining if NDMA has formed by measuring the blood, and what happens to NDMA is that it is rapidly metabolized by the human body and it never reaches the plasma.

THE COURT: Okay.

MS. BOGDAN: Once it is metabolized into the metolazonian ion, it is not available to be measured. What Emery Pharma did is they took the food and they were able to calculate how much NDMA forms in the vessel, right, and that is indicative of what would be forming in the stomach.

THE COURT: Okay, I need to move on. Was there an elaboration on that point?

MS. LUHANA: I wanted to bring up the slide and walk you through the process.

THE COURT: There it is. Is that it?

MS. LUHANA: Yes. If you can go to slide 7. The slide before, actually. Perfect.

So, Judge, as Ms. Bogdan was explaining, Emery did test actual food in simulated gastric fluid, and they didn't add sodium nitrite into the mix, so the first example you see they gave Zantac and then sausage, and then they measured the NDMA content in the simulated gastric fluid.

You see at the two hour mark there, there is 27.4

nanograms, and that has to be multiplied by 250 millimeters, because that is the concentration in the fluid. If you look at that, that would be approximately over 6,000 nanograms of NDMA, 6,850.

If you look below in terms of when the food is given versus the Zantac, the second chart there, you see Zantac then ham, you see NDMA being generated at the 1.5 hour mark, at 29.5 nanograms. The same calculation has to be done, multiply it, and then you see later on, in terms of mixing it up and doing the ham first and then the Zantac --

THE COURT: Just to focus the question, it really had to do with timing, when to take Ranitidine in relation to the food intake.

MS. LUHANA: This is showing you it does impact it some. The makers of Zantac direct people to take it soon after a meal or before bedtime. So, that would have been the appropriate time for Florian to do the testing, however, Florian wouldn't be able to measure NDMA because they weren't using the appropriate gauge. It was urine and plasma as well, which are not appropriate. You should be testing the gastric fluid or other metrics to assess NDMA because it metabolizes so quickly.

THE COURT: I am assuming some of this is going to be discussed in the Najafi presentation. We can reserve additional argument on this to the end, so if there is anything

further you wanted to say, just hold that thought, if you would. I have several more questions.

Earlier today, for Plaintiffs, you explained that the nitrite level is one of many factors that affect NDMA formation. Can you explain how that level affects NDMA formation? Can you also provide a range of nitrate levels that would be realistic to find in the human stomach?

If you have expert reports or any other sources you can point the Court to. If you could tell the Court, because I have your presentation. Direct me to what to look at.

MS. LUHANA: It's Table GG. Importantly, as I raised during my argument, the nitrite concentrations that have been measured have been largely in fasting stomachs. Unfortunately, that is not going to give you a true gauge of nitrite. There is always that one factor and Gao confirmed that.

You change the volume of simulated gastric fluid, there is a lot more NDMA generated, double in Gao between 50 milliliters and 250 milliliters. If you change the pH, there is a lot more NDMA generated. Those factors play a critical role.

However, if you look at Table GG, I believe it's page 100 of Dr. Najafi's report, what it does --

THE COURT: I'm sorry, what page?

MS. BOGDAN: Page 100.

MS. LUHANA: He has -- instead of adding sodium

nitrite and mixing it with Ranitidine and seeing how much NDMA is generated or how much -- what the nitrite content is, he put them in foods and put them in simulated gastric fluid, and as I said before, it was per the protocols established by Braunstein and Gao.

If you look at the sausage, 46 grams is a normal serving size, if you take sausage and put it in simulated gastric fluid, you have 19,100 micromolars being generated. So that is 19.1 micromolars of nitrite. Similarly, if you look at the bacon, that bacon is 13 grams, that is a slice of bacon. You put it in simulated gastric fluid, you have 7,400 micromolars being generated. That is 7.4 millimolars of nitrite --

THE COURT: Is there a level of sodium nitrite that would be toxic to humans that has been established by anyone, per the Plaintiffs' position?

MS. LUHANA: I don't believe we have discussed the toxicity of nitrite; however, what you see here is Ranitidine is a tertiary mean and it comes contact every single day because it is taken after a meal, and after a meal these are the levels that you are seeing of nitrite in the stomach.

It is a recipe of things, as I discussed. It is the pH and the volume of the stomach. You can't isolate it, but here you are seeing that there is enough nitrite clearly being generated once you have a meal, and these are single serving

sizes.

THE COURT: You might not want to talk about food too much because that is going to get everybody hungry, which segue-ways into my next question which does have to do with food, bacon in particular. I am not sure if anyone had bacon this morning.

Back in the hearing on June 3, 2021, the Defendants had represented that mathematically the amount of bacon that someone would need to take to have 15 millimoles of sodium nitrate in their stomach was 33 pounds. That is at Docket Entry 960, at 38.

At that time I had asked Ms. Meeder, do you disagree with what the Defendants presented at the Science Day, or at that particular presentation, that is their presentation as to how they translated 50 millimoles.

Ms. Meeder responded, your Honor, sitting here today, I don't have an opinion on that one way or the other. I would need to refresh my recollection from an expert. That was from the transcript of the oral argument June 23, 2021, pages 216 to 217.

Are the Plaintiffs in a position today to answer the question, that is, do you agree that the Defendants' calculation that a person would have to eat 33 pounds of bacon in order to have 50 millimoles of sodium nitrite in their stomach is accurate? If you don't agree, do you have anything

in the record that informs me of the Plaintiffs' position of approximately how many pounds of bacon a person would need to eat to have 50 millimoles of sodium nitrite in their stomach?

MS. BOGDAN: Yes. Yes, there is something in the record, and yes, I will be happy to explain. Actually, the Court is very intuitive because this dovetails right into Table GG which we were just discussing, which tells us the level of nitrite generated by the food itself.

Could you hear me?

THE COURT: Yes, but talk into the mic.

MS. BOGDAN: This dovetails right back into Table GG, which is the measurement of the nitrite that is generated from the food in the SGF. If we look at Table GG we can see -- and we are focused on bacon here, so that one serving, which is 13 grams of bacon, results in 7,400 micromoles of nitrite concentration.

So, essentially, if you have four servings of bacon, right -- excuse me, if you have seven servings of bacon, that would result in 51,800 micromoles of nitrite concentration, which puts you at that 50, which is what you are asking about, 50 millimoles. So, essentially 91 grams of bacon is 0.2 poinds.

So, simply, just so you just -- literally, you take the amount of bacon that is in Table GG, which is --

THE COURT: Do you want to put the table back up? Was

that the one that was just up?

MS. BOGDAN: It was. You take the 7,400, which is you know the amount of nitrite generated by that, if you multiply the 7,400 by seven, which is seven servings, you get to over 50,000, which is 50 millimoles. So you would multiply the serving size of 13 grams by seven, and when you convert the 91 grams a pound you get .2 pounds.

That is the power of actually using the food, because it is the nitrite that is available, it is on board directly from the nitrited foods and able to interact. The nitrite in the food, not resting in simulated gastric fluid, it is the interaction of the food with the gastric fluid. It is there in the food, it is in the matrix, and that is what is missing in Gao, and that is also what is missing because of the way they choose to measure NDMA in Florian.

THE COURT: Let me see if the Defendants want to respond. I will see if the Defendants have any response on that. Do you want to come to the podium?

MS. RYDSTROM: Sure. Jessica Rydstrom, your Honor.

I can tell you that I have had this exact nightmare where I have to stand up before a group of people and walk through a mathematical calculation, so thank you for this experience.

THE COURT: You will remember it fondly.

MS. RYDSTROM: I will. Thank you.

I can explain to the Court how it is that we reached the 33 pounds back when we did. First, the Court is absolutely right to focus on the nitrite level. That is exactly what we see in Florian and Gao and what the papers teach us. That is what forces the NDMA reaction.

To answer the Court's question from before, the reason, of course, that Florian times the study the way that they did is because an empty stomach is most acidic. So, as soon as you start eating the acid levels in your stomach go down, so you would expect to see that NDMA formation decreasing that rate, as the stomach becomes less acidic.

At a very high level, your Honor, I could walk you through the calculation we made. I think that it starts with the Valisure study, Table 2 of that study. In that study you will recall, and with all the attendant problems with Valisure that we won't repeat, there was a 25 millimolar level of sodium nitrite that was reported in those studies.

That is what Valisure did and that was the starting point for this calculation. That is how we calculated it. I think it was calculated based on the 25, which was the first level at which you saw the increase, and not the 50, although the 50 gets you an even more eye-popping number.

What you do is you convert the millimoles there, the 25 millimole calculation, and you have to go from moles to grams, and in order to do that you have to take the molecular

weight of sodium and of nitrite, which we have calculated very recently, I assume it has not changed, at 46.006 grams per mole of nitrite. And then you have to go from the grams per liter, because you are dealing with a volume concentration, and we were trying to get to an actual concentration in grams of how much bacon.

So when you convert that from grams per liter to milligrams per liter, you end up with 1,150 milligrams of nitrite per one liter.

When we calculated the amount, your Honor, from a Grisenbeck (phon) paper, which I don't believe is in the record -- this was all long before expert discovery. This particular calculation wasn't a subject of expert discovery. I am happy to provide the Court with a copy of that paper, but it came up with an amount of .467 milligrams of nitrite in two slices of bacon.

So, what that gives you is, to achieve that concentration, that 25 millimole concentration of sodium nitrite, you would have to have 4,925 slices of bacon in one liter of stomach, but of course our stomachs are not that big.

So to go to slices in a pound -- I apologize, your Honor, I am trying to slowly both for Ms. Stipes' benefit and for the Court's.

You would assume for purposes, as we did at this time, that there are 16 slices of bacon in a pound. I actually think

at the time we did the calculation, the estimates we found online was there were 18 to 20 slices, so the fact that the numbers are off means there are different assumptions that we put in.

To go from one liter of simulated gastric fluid to one millimeter of gastric fluid, you end up with .0378 of weight per milliliter, and to figure out that volume of the human stomach we took someone who had consumed that amount of bacon and drunk half a glass of water, which we calculated at 121 milliliters. When you multiply that .0378 per milliliter by 121 milliliters, we assume someone would not just eat bacon, they would drink water, we ended up with 37.25.

THE COURT: The Defendants come up with 37.25, and the Plaintiffs, you say .2. Is that the Plaintiffs' number?

MS. BOGDAN: That is correct.

THE COURT: Let me ask the Defense and then I will ask the Plaintiffs after Defense, can you surmise why your number is so much higher than the Plaintiffs' number.

MS. RYDSTROM: I imagine, your Honor, it has something to do with what we'll hear in a bit about Dr. Najafi and the testing that he did.

One thing that I would say is that we have heard a lot about simulated gastric fluid. That is one of the variables that Dr. Gao considered. They looked at simulated gastric fluid when they were determining what those physiological

amounts of nitrites is. So, whether it is 37 pounds of bacon, or 20 pounds of bacon, the point is that in order to juice that NDMA formation from Ranitidine, it is very clear that you need those extra high levels of nitrite.

THE COURT: Thank you. From the Plaintiffs, any sense, unless you think it will be further explained in the Najafi presentation, why your number is so much lower than the Defendants' number on the topic of bacon?

MS. BOGDAN: Your Honor, it is because our number is based on the actual measurement of nitrite in simulated gastric fluid that is generated from bacon. The Defendants are taking numbers that are just whole and doing these concentration calculations, but they are numbers being taking and converted to mass. It is a calculation that the lawyers have done, I haven't seen this done by any of their experts.

What I am presenting to the Court is in Dr. Najafi's report as far as the actual nitrite concentrations that are generated in simulated gastric fluid from bacon, and that is the best evidence to figure out how you reach 50 millimoles.

THE COURT: Thank you. Leaving bacon for the moment, moving on to Krawczynski and Matsuda. Question for the Plaintiffs.

Defendants argue in their remaining opinions motion that your experts' reliance on in vivo studies of endogenous formation is unreliable. That's at Docket Entry 5696-7. In

response, you assert that your experts relied on studies that "consistently demonstrated that NDMA forms endogenously, naming Krawczynski and Matsuda as examples. That's at Docket Entry 5913 at pages 6 to 7. And you also discussed Matsuda and Krawczynski today during your presentation.

Can you explain to the Court what arguments you made in your response to show that Krawczynski and Matsuda are reliable? In other words, are you able to direct the Court to pages in your brief where you actually make the argument, other than just referring to Krawczynski and Matsuda, that Matsuda and Krawczynski are reliable?

I want to make sure I found the right place in your opposition where you are saying that.

MS. LUHANA: Roopal Luhana for the Plaintiffs.

Judge, they are reliable peer reviewed studies and they have also been accepted in the medical and scientific communities. The only ones that are saying peer reviewed studies are not reliable is the Defendants.

THE COURT: Do you know offhand where in the response you say that?

MS. LUHANA: I will have to pull up my response and I am happy to provide that cite to you.

In Krawczynski I will note the Defendants are raising this four to six week measurement after treatment. It was a Polish publication and it was translated into English, and

there are 6 or 7 other places in the publication where they note that the testing was done before treatment and Ranitidine was given for at least four weeks and then after treatment.

So, interestingly enough, when GSK submitted Krawczynski to regulators -- to the EMA, as well as to the Japanese regulators, they never mention the fact about this four to six week time period. They simply stated -- they didn't state how much NDMA there was a statistically significant increase of in the gastric fluid. They never raised that argument.

This is lawyers raising these arguments for litigation. However, I provide to you that these are peer reviewed studies with a rate of error and they are established an accepted in the medical community. The only ones that are calling them unreliable are the Defendants.

THE COURT: That is fine. I want to make sure I found that in your opposition so that I can match what you are saying here in court with what I was reading.

MS. LUHANA: I can provide that for you.

THE COURT: I will say you will get back on that. While I ask other questions maybe you will have the answer. If not, maybe you can give that to me at the end.

Same question on Krawczynski -- another question. Am I correct that the researchers in Krawczynski utilized GCMS to measure the nitrosamines in children's urine? If that is

correct, given that the FDA previously determined that GCMS is unreliable because the method itself creates NDMA, can you explain to the Court how a reliable methodology could include reliance on studies that use that instrument, the GCMS.

MS. LUHANA: Judge, it is not that GCMS unreliable, it is just that Ranitidine degrades with exposure to heat. If you keep Ranitidine in excessive temperatures NDMA forms, and so the GCMS is calculating the amount of NDMA. The only difference is, you can't tell how much of that is baseline versus how much is created with the heat.

It is not that it is an improper methodology, and specifically for Krawczynski, the differences not only -- it measured urine, however it measured gastric fluid and it was measuring the gastric fluid after these kids had eaten, so it is sometime after, when the Ranitidine is digested, so it is the NDMA that is measuring with the GCMS, and not the Ranitidine.

THE COURT: So, is GCMS, in the Plaintiffs' view, reliable or not reliable?

MS. LUHANA: GCMS is reliable for measurements of NDMA alone. GCMS is not reliable for measurements of Ranitidine because you can't tell how much is created when you are exposing it to heat versus how much is already in the tablets at baseline.

THE COURT: Doesn't GCMS apply heat that creates the

NDMA?

MS. LUHANA: With Ranitidine, yes, not with NDMA on its own.

That is the concern, right, because if you expose Ranitidine to heat -- and so this is the difference, for example, if you look at Tanner, it was GCMS injection versus Valisure where they exposed it to heated temperatures and kept it there for 15 minutes. GSK scientists internally discussed this, and they said the difference in why Tanner was reliable is because it was injection and it was immediately volatilized and the NDMA measured, versus with Valisure where they maintained high temperatures for 15 minutes, and they discussed internally those high temperatures for 15 minutes are what created the extra NDMA, and then you couldn't differentiate what was created with the heat versus how much was already in the pill at baseline.

THE COURT: Does GCMS make nitrates create NDMA?

MS. LUHANA: I'm sorry, I don't quite understand.

THE COURT: Does GCMS cause nitrosamines to create NDMA?

MS. LUHANA: GCMS is a method where you use heat, and it is a very sensitive method, it's an accepted method to test drugs for nitrosamines.

The difference with Ranitidine is it is activated by heat and humidity and generates a lot more NDMA. That is why

it is an unstable molecule and that is why it is no longer on the market. The FDA lost confidence in the ability for Ranitidine to maintain below the ADI because with heat and humidity, it creates a lot of NDMA.

That is a specific problem with the Ranitidine molecule, not with all these other drugs.

THE COURT: Okay. During yesterday's hearing Plaintiffs explained that studies combining results for Nizatidine and Ranitidine were discounted by Plaintiffs' experts because of the adverse effects of Nizatidine was not the question there. However, the Court understands that, if I am correct, Krawczynski put together findings for different nitrosamines and did not analyze data for NDMA alone.

Am I correct in that statement; and if so, can you explain to the Court how the Plaintiffs would reconcile their experts discounting the findings with Nizatidine with their reasoning for relying on Krawczynski and other studies that lump together findings of different nitrosamines.

MS. LUHANA: Those are two very different points, Judge. With the epidemiological study, if they are trying to assess for exposure to Ranitidine is causing an increased risk of cancer, it is important to look at only the people taking ranitidine. When you are combining Ranitidine with Nizatidine, that will not be able to assess and tell you whether Ranitidine use is leading to an increase of cancer. That is why that is

problematic.

With Krawczynski, they measured a number of other nitrosamines where there was a statistically significant increased risk -- not risk, statistically significant levels of NDMA that were found in Ranitidine, however, they found other levels as well. They also excluded -- what lead me to believe that they measured the amount of NDMA from the gastric fluid is, they excluded all these other nitrosamines that were not measured there. I can point you to that reference in the study as well.

THE COURT: Okay, you will make a note of that?

MS. LUHANA: Yes. The fact of the matter is that Krawczynski found increased levels of NDMA in the gastric fluid, importantly, of kids who used it for a longer period of time, and kids who have gastritis.

THE COURT: I will wait for you to give me the cite on that.

Circling back to the GCMS and Krawczynski and the study, the researchers gave children Ranitidine, as I understand it, and then measured the nitrosamines. So, how is GCMS reliable if it creates NDMA from Ranitidine?

MS. LUHANA: Because when they measuring the gastric fluid it is absorbed already. They are not doing it when people are taking Ranitidine at the same time. It would be an aspiration risk. When they are doing the samples they provide

the methods when they are pulling the samples. By then the Ranitidine is absorbed in the system and they are measuring the actual NDMA.

THE COURT: Is that explained in the report?

MS. LUHANA: In the methods I believe it is discussed, yes.

THE COURT: Would you make a note to point out where that is as well?

MS. LUHANA: Sure. Again, Judge, we are going behind peer reviewed literature and studies that aren't contested. It went through the peer review process, and that means something.

THE COURT: These are just questions, I am not suggesting anything other than that, just trying to understand everything to the best I can.

Okay. I will move on to the topic of metabolization and bioavailability of NDMA.

The Court wants to understand the Plaintiffs' position regarding metabolization and bioavailability of NDMA. I want to take it one point at a time.

The Plaintiffs state in their response to the Defendants' remaining opinions motion, now I'm quoting, "the level of NDMA in the blood following oral administration is primarily controlled by the amount metabolized in the liver." That is Docket Entry 5913.

The Plaintiffs then provide data from animal

studies to assert that rats have an 8 percent bioavailability of NDMA, whereas monkeys have 49 percent bioavailability, pigs have 67 percent bio availability, and dogs have 93 percent bioavailability of NDMA. That is at Docket Entry 5913, at pages 13 through 14.

Good so far? Am I citing it correctly?

MS. LUHANA: I think so.

THE COURT: I will take that as a yes. There is a smile, so I will say yes, that is right.

So, now I want to make sure I understand, does that statement mean, for example, that 92 percent of NDMA is metabolized in the livers of rats, whereas 51 percent is metabolized in the livers of monkeys, and 33 percent of NDMA is metabolized in the livers of pigs?

MS. BOGDAN: Yes.

THE COURT: Okay. So, you also state that "because NDMA's bioavailability is higher in larger experimental animals compared to rodents, NDMA's carcinogenic activity can be more aggressive and result in many more tumor types in humans as opposed to rodents." That is at Docket Entry 5913 at 14.

Do you agree that -- or is this statement stating that humans are similar to larger animals, and therefore their bioavailability of NDMA is higher than rat bioavailability?

MS. BOGDAN: Absolutely, your Honor.

THE COURT: During yesterday's hearing explaining

Hidajat's conversion of inhalation exposure to oral exposure, it was argued that Hidajat calculated over 90 percent bioavailability of inhaled NDMA in humans which, you stated, confirmed the reliability of her extrapolation because it is a similar bioavailability to oral exposure.

What is the Plaintiffs' position as to the specific percentage of bioavailability of NDMA in humans?

MS. BOGDAN: All of the bioavailability studies, because NDMA is such a potent known genotoxic molecule, have to be done in animals. You cannot deliver a large dose to a human to measure the bioavailability.

What the scientists need to do is go to the best evidence we have of bioavailability, which would be the larger animals, which consistently -- the monkey, obviously, the swine and the dogs all exhibit much higher bioavailability of NDMA, which means that it bypasses the liver and is available in the systemic circulation.

Again, a rapidly metabolized molecule, etc., but it is bioavailable in the human body, and the reason that is important is that if you focus just on a rat study and you're looking at tumors only in the liver, if 90 percent of NDMA goes into a rat's liver, then that is where you are going to look for the tumors, as they did in the Peto study primarily.

But and with larger animals, the bioavailability is so much greater that it ends up in the systemic circulation.

THE COURT: So the human bioavailability is analogous to the 49 percent for monkeys, 67 percent for pigs, and 93 percent for dogs.

MS. BOGDAN: Right, and those are the three peer reviewed studies where they have actually given doses of NDMA to the animals to be able to study that.

THE COURT: Is there a particular percentage? I just named three.

MR. NIGH: Your Honor, if I may, Dr. Le specifically calculated this in her report and she demonstrated that it is greater than 90 percent.

THE COURT: Do you have the cite there?

MR. NIGH: I don't have the actual cite, I just know that it is an unchallenged opinion from the Defendants.

THE COURT: If you could make a note of it.

The Plaintiffs also seem to say in their briefing "It is generally accepted that NDMA is metabolized similarly in human tissue and rodent tissue." Docket Entry 5913 at 12. But in your response, as a reminder, you say rodents have a bioavailability of 8 percent.

I want to understand the statement that NDMA is metabolized similarly in human tissue and rodent tissue and the 8 percent bioavailability that rodents have.

MS. BOGDAN: When we are speaking about the act of metabolism we are talking about the cytochrome P 450 enzymes

and the way that it is metabolized is the same, but the sites of the metabolism are different.

The way that the actual cells in the tissues metabolize NDMA in the rat liver is similar to how the human liver metabolizes NDMA, but because the bioavailability is different, the human body has the opportunity to metabolize the NDMA at all the these different sites which have these very important cytochrome P 450 enzymes that metabolize NDMA.

It is not the mechanism of how the tissues metabolize that is different, it is the fact that the sites are different because of the NDMA reaching those sites in much larger proportions because it bypasses the liver and thus more developed in larger animals.

MS. LUHANA: Just to add to that, Judge, with rats it is being metabolized largely by the liver, 80 to 90 percent, whereas the human body, it is being metabolized by many other organs. In fact, the Hikura studies, which Dr. Salmon and many of our other experts cite to, specifically talk about how humans are more sensitive to NDMA in rats, seven times more.

In addition to that, in terms of the metabolism in the DNA forming, that similarity is discussed by WHO, and other organizations as well. We could provide those cites for you also.

THE COURT: Are they in the record already?

MS. LUHANA: Yes.

THE COURT: Okay. Okay. Do different sites matter, then, in terms of where the cancer can form? Am I understanding that is what you are saying?

MS. BOGDAN: Yes, because the NDMA needs to be metabolized in order to do the damage that it does and disrupt the DNA.

So, it is the metabolism of the NDMA at these different sites, one is bioavailability, bypasses the liver, is available in the systemic circulation, and then it is the ability of these different parts of the body to actually metabolize the NDMA, because the cytochrome P 450's are available in all of these sites.

Our expert, Dr. Panigraphy, goes through in depth each of the sites and explains how the tissue and the cellular studies show the NDMA can be metabolized in those five designated cancer areas.

THE COURT: Okay, thanks.

Let's move on to -- let me move on to the animal studies, so Gombar.

Can you just briefly explain how the Plaintiffs' experts relied upon Gombar 1990, in other words, which experts relied on the study and what proposition did these experts rely upon that study to show? Very succinctly.

MS. BOGDAN: The Gombar studies, and there are three of them, are the studies that support the bioavailability of

NDMA in large mammals.

THE COURT: So that is the proposition?

MS. BOGDAN: That is the proposition. It also supports the metabolism of NDMA with the short half life that I referred to earlier when I was speaking with regard to the endogenous in Florian of between seven and 21 minutes, which goes to the rapid metabolism.

The Gombar studies are cited by our experts with regard to bio availability as well as metabolism of NDMA.

THE COURT: Offhand do you know which experts relied on that for those propositions?

MS. BOGDAN: I believe Dr. Panigraphy, I believe they were mentioned by -- I don't want to misstate, I don't want to over state or leave someone out because many experts relied on those. Dr. Le definitely speaks to them. Dr. Panigraphy definitely speaks to them. Salmon definitely speaks to them. But there may be others that have who referenced them as well. I would like to be complete for the Court.

THE COURT: That is something you might want to make a note if you want to supplement on that.

So subject matter extrapolation.

For the Plaintiffs, do you agree that in order to meet the helpfulness prong of Daubert one must show that expert opinions and studies they relied upon are a "fit" to the general causation question in the litigation?

MS. LUHANA: Can you repeat the question, Judge?

THE COURT: You see discussed in the case law, the fit to general causation. Do you think that that is part of the helpfulness prong of Daubert?

MS. BOGDAN: The animal studies in this particular situation, especially when you can't do randomized control trials with humans because it is a known genotoxic carcinogen are very informative and they are one piece of the puzzle, especially when you cannot -- and all the experts have agreed that you could never run a randomized control trial with people so --

THE COURT: Right. I am trying conceptually, to make sure I am thinking about it the same way you are, that when you think of the issue of fit to general causation, whether it is animal studies have a fit to general causation to humans, or any other type of study, but in this case we have been talking about animal studies that fits -- goes within the helpfulness prong of Daubert.

MS. BOGDAN: It is one of the helpfulness prong, it is also one of the Bradford-Hill criteria with regard to plausibility. As the Court so aptly asked about the metabolism being the same between animal tissues and cells in humans, the qualitative part of that, not where it happens, that is very instructive.

Certainly, as far as the carcinogenicity studies that

show that NDMA causes cancer in every animal that has been subjected to it are very important and part of the general causation totality of the evidence.

So, yes, they are important. I think they have to be considered, especially in light of the situation where we are talking about a genotoxin like NDMA.

THE COURT: Okay. Let me followup on that question.

So fit is part of the helpfulness prong, among others, so, in doing that, do -- does that therefore mean that experts need to explain how they extrapolate from animals to humans? I am taking it one step at a time.

I know you discussed animal studies being used to show the carcinogenicity of NDMA. Are you in agreement that whatever you are learning and your experts are putting forward with respect to the animal studies, they must explain how that is extrapolated to humans, or are you not using the animal studies for that purpose?

MS. BOGDAN: We have the human epidemiology --

THE COURT: Are you using animal studies to fit humans to extrapolate from or --

MS. BOGDAN: Extrapolation is the applicability to them, so the animal studies show us what organs and tissues -- and they reinforce what we also know from the human epidemiology. It is a combination of all of this full body of evidence. So the animal studies allow the investigators to

actually administer NDMA, which you cannot do to humans.

THE COURT: Did the experts anywhere explain how they extrapolated on the basis of a species or on the bases of a dose, or are they not setting out to do that?

I can't tell whether you are saying the experts don't need to do that because the animal studies were not used for that purpose, or they did do that and I haven't found that.

MS. BOGDAN: If you are speaking of dose, the human epidemiology studies were used.

THE COURT: Not the animal studies.

MS. BOGDAN: We don't need to use animal studies for dose because we have human epidemiological studies for dose.

THE COURT: Very clearly state what the animal studies are being used for.

MS. BOGDAN: The animal studies are being used to show the carcinogenic nature of NDMA. They are also being used to show how NDMA is metabolized in the body. They are also being used to show where NDMA can cause harm in the body, because we have rat studies, but we also have a plethora of studies that are mentioned in Dr. Panigraphy's report.

There are animal cell and tissue studies, but also human cellular and tissue studies that show the harm that NDMA does to both, which allows there to be this comparison with he similar metabolism as far as how the tissues deal -- before that are formed, et cetera.

THE COURT: So, are there parts of the brief that explain how the experts have taken the information from the animal studies and applied them to humans? I am calling it extrapolation or fit, but we can call it whatever makes sense.

MS. BOGDAN: I would let one of my colleagues answer to the briefing. I can tell you the expert reports discuss the use of animal studies in this fashion.

THE COURT: Right. Maybe you can make a note of that and we can circle back. I want to know where the experts have relied upon, if they have, and the Plaintiffs have argued that to rely upon the animals both for how and why they were able to draw inferences about humans based on what they observed in animals.

MS. LUHANA: Judge, we will take a look at those cites for you, but it is a body of evidence, the totality of evidence. So, when IARC is reviewing NDMA and its carcinogenicity, it is reviewing the animal studies, it's looking at the mechanistic studies, and it's looking at the epidemiology. So it is one piece of the puzzle that is supporting it and --

THE COURT: Right. I understand that is the Plaintiffs' position, but I am taking it piece by piece. I want to focus on this piece.

MS. LUHANA: IARC, who says qualitatively you can use this data for humans because it is being metabolized similarly,

and those are the conclusions of scientists all around the world about NDMA, but we'll look at the cites during a break and provide them to you.

THE COURT: And one followup from the Defendants, if you want to say anything, because it was one of the arguments you made that the animal studies are not a fit, and that the Plaintiffs did not extrapolate on the basis of dose or species. I am paraphrasing one of the arguments the Defendants made in that regard.

Is there anything that you, in light of what the Plaintiffs have said, that you want to be heard on that issue? If you don't, that is fine.

MS. RYDSTROM: Yes, very briefly.

MS. BOGDAN: Your Honor, if I may, I might have had a little bit of tunnel vision when you asked me a question earlier with regard to timing of Ranitidine and food, and I was answering it in a mechanistic way with regard to the half life and the P plasma concentration.

I don't want the Court to take my comments to undermine some of the criticisms in our experts' reports with regard to the fact that if the food was already on board and already was in the process of digestion and the nitrate was readily available when Ranitidine was taken, then it would result in more formation of NDMA as opposed to taken on the fasting stomach, which has a low nitrite level, and then the

food ends up getting put on top of it.

That is a different order that is articulated in our reports, and that is something different than what I was answering.

So, if you were asking about that, because of my tunnel vision on, I tend to go right to, you know, half life and P plasma concentration and all the things that make this case so fun, but if you are asking about that, then there is an issue with regard to whether Ranitidine hits a fasting stomach or whether Ranitidine hits a full stomach that already has food that is in the digestive process and nitrite available from that.

I wanted to make that clarification. Maybe I did answer what you were asking, bit in the event I did not, I want to make sure I clarified that.

THE COURT: Thank you, I appreciate that.

Maybe before Defense speaks, I am going to go back to the extrapolation question for whomever can answer it.

During their presentation earlier today, I thought I heard Plaintiffs' counsel state that the experts did not extrapolate from animal studies. I guess I should premise the question with, did I hear that correctly? Can you confirm whether that is in fact the position of the Plaintiffs?

And if your experts did extrapolate, that is where I wanted to know, you know, the pages in the briefing where you

argue the experts conducted the dose extrapolation, but it came from what I thought I heard, a comment earlier today that the experts did not extrapolate from animal studies.

What is the Plaintiffs' position.

MS. BOGDAN: With regard to dose, the Plaintiffs did no extrapolation from animals for the doses that would increase the risk of cancer in humans. We have human studies for that. It was done off the dietary studies, the Hidajat study. We did not extrapolate from animal studies because we have human information.

With regard to using the animal studies as part of the totality of the evidence, for the reasons that I previously stated, biomechanism, bioplausability, carcinogenicity of NDMA, and an analysis of how the metabolisms are the same, the rate of metabolism of NDMA, the animal studies are very instructive on those issues. If you are asking about dose, that is all being done off of human studies.

THE COURT: Dose response, dose extrapolation.

MS. BOGDAN: Human studies.

THE COURT: Did the Defendants want to make a point on that?

MS. RYDSTROM: Very briefly, your Honor. Jessica Rydstrom, your Honor.

If the question is, in the face of what we know about humans, what does this tell us, what do these animal studies

tell us, I think Ms. Bogdan and I might be in heated agreement because the answer is not much.

We know, in the face of the human epidemiology that we discussed yesterday, that that can't be overcome by these animal studies. The reason for that are those three -- the fit problem arises with those three arrows that I had on the slide about species to species, amount, and the site of tumors, and to take one example, your Honor, it is the bioavailability question that you asked before.

I guess I would say this, that on the one hand the Plaintiffs' experts criticize Florian because they say the plasma levels -- wasn't able to detect NDMA in the plasma levels, and on the other hand they tell us that the bioavailability in humans is expected to be 90 percent, and that is a tension that I think is difficult to resolve.

One thing about the bioavailability, in the animal studies what we see is these massive doses, not a dose response question, but massive doses that are being given to animals, and what happens when that occurs is that the liver is actually swamped in its ability to metabolize the NDMA, so you would expect that when you are giving massive doses of NDMA to animals, that more -- that is exactly what you would see, that more is available in the blood stream because the liver's ability to metabolize it is basically overcome.

There are big differences, your Honor, between the way

that species -- perhaps not the mechanism by which the NDMA is metabolized, but the availability and amount of that enzyme that metabolizes NDMA is different between humans and mice.

So, that is one reason -- that is one thing that potentially explains that finding in the Gombar paper that it is not just a matter of saying small body, low bioavailability; big body, big bioavailability. That is one of the reasons why you have hit on this fit question, making it difficult to make the leap there from animals to humans.

I would say the last thing is, we do have some human data from Ranitidine about bioavailability, and that is from the Florian plasma levels. They measured the amount of NDMA after folks had taken Ranitidine that got into the bloodstream and what they found was that there was not a statistically significant increase as between Ranitidine and placebo, your Honor.

THE COURT: Okay. Thank you very much.

Since it is only 20 to 12:00, that maybe what we could do is have Mr. Bayman present, on your schedule, for 25 minutes. That would bring us to five minutes after 12:00, then we could break for lunch before we hear from Plaintiffs and then Defense rebuttal on the Najafi/Davis motion.

It is the brand Defendants' motion to exclude opinions and testimony of Plaintiffs' experts, Ramin Najafi, Ph.D. and Charles Davis, Ph.D. and other experts who rely on their

opinions. So you may proceed.

MR. BAYMAN: May it please the Court, Andy Bayman on behalf of Boehringer Ingelheim and the brand Defendants.

Your Honor, it is odd that the history major would get an analytical testing motion to argue, but I do have Mr. Bosso, our new member of the LDC, who has a Master's in pharmacy, available to answer any of the Court's technical questions, but when you look at this motion, your Honor -- next slide -- you don't have to be a history major to know that it really boils down to three simple take-aways.

Emery never produced its data in a form that would enable us to ask Dr. Najafi questions at his depositions in order to verify the reliability of his data. Emery rejected its own pre-litigation testing methods, and NDMA levels for Zantac. And finally, after being retained for litigation, Emery and Dr. Najafi used testing methods that no one else uses and reported significantly higher levels of NDMA than anybody else.

As my colleagues explained yesterday, your Honor, there is a huge body of scientific evidence that answers the question of whether ingestion of Ranitidine can cause cancer in humans. The FDA and peer reviewed authors have established reliable data on the levels of NDMA in Ranitidine drug products.

Plaintiffs, however, weren't satisfied with that, and

they hired Dr. Najafi to redo testing with a unique methodology that he developed for this litigation to report significantly elevated levels of NDMA.

Moreover, Dr. Najafi ignores or rejects all data other than his own, including the validated publicly available results from the FDA and other peer reviewed authors, and this is the most classic example of impermissible and inadmissible cherry picking and it is the exact type of opinion that the Court, in its role as gatekeeper, should not allow the jury to consider.

Next slide.

Even though the science at issue in this motion centers on analytical chemistry, I want to start with a concept that might save the Court some time and energy. Emery's analytical data is not sufficient to establish general causation. In fact, Dr. Najafi is not providing an opinion that Ranitidine can cause cancer.

Plaintiffs' counsel candidly acknowledged this fact in the statement from Dr. Najafi's deposition, but if the Plaintiffs can't come forward with sufficient evidence demonstrating that Ranitidine causes any of the five cancer types, there is no need for the Court to even consider this analytical data.

Next slide.

Your Honor, one of the topics you asked the parties to

discuss is the standards and controls used during Emery Pharma's studies. Now, the Plaintiffs would have the Court believe that any work done by Emery, because it is a lab, is necessarily valid.

In their opposition they quote the reference manual statement that, quote, "when analytical work is performed in certified highly experienced laboratories there is a reasonably high likelihood that analytical results are reliable."

Dr. Najafi himself admits and Defendants' expert, Dr. Olsen explains in his report, Emery did not follow any generally accepted laboratory standards when it conducted the litigation testing that Dr. Najafi relies on.

The manual provides, as you can see, that the lab should have developed standard operating procedures and quality control procedures, and it warns that it is very difficult to confirm reliability when analytical work is done in laboratories or by individuals who cannot provide evidence of certification or longstanding quality control procedures.

These procedures are necessary to make sure there are no problems or flaws that could cause the results to be invalid or unreliable and so they can be identified and corrected.

Dr. Najafi and Emery did not follow any such well-recognized standards, arguing those aren't necessary when you are doing research.

Next slide.

Here is what Dr. Najafi says about the standards: "The work that we have done for the Plaintiffs were not done under GLP and GMP."

There are well-recognized and generally accepted standards that apply to analytical chemistry laboratories and these are some of them. There is no dispute that standards exist, your Honor, but Dr. Najafi claimed that the standards at his lab are not written down anywhere, and he could not identify them, and he testified that he did not follow these kinds of standards in his litigation testing.

Next slide.

"As a result, there were no SOP's provided to us by anybody or by the Government or by ourselves."

So he didn't follow any SOP's. He claims in his report that Emery Lab is a current good manufacturing practice, and good laboratory practice, compliant laboratory, but he admitted that none of the work that Emery did for the Plaintiffs in this litigation complied with those standards.

In fact, he uses phrases like we adhere to the highest standards. Those are exactly the kind of phrases that the Eleventh Circuit rejected in the McClain opinion. The expert, O'Donnell, in that case said he followed, quote, "broad principles of pharmacology" and the Eleventh Circuit said those kind of sweeping broad statements like that without anything to back them up are of little value.

Next slide.

Emery's lack of compliance with any generally accepted standards is evident in his testing. As the Court knows, the Plaintiffs bear the burden of proving that each step in Dr. Najafi's testing, analysis, and opinions is reliable.

So, the threshold question is whether the Plaintiffs can prove by a preponderance of the evidence that a measurement itself is accurate. That requires proof that the analytical method was reliable or all analyses and conclusions drawn from the faulty test results would be unreliable. If the answer to that question is no, there is no need to continue.

Next slide.

So, the first step is, when looking at analytical testing and trying to determine whether it is reliable, have they proven that the analytical method is reliable? If the answer to that question is yes, that doesn't end the inquiry.

The next question is whether the measurements are the results of a properly designed peer reviewed methodology that uses standard scientific principles, such as randomization or proper sample selection. Again, if the answer to that question is no, the Plaintiffs fail to meet their burden.

Finally, even if the first two elements are met, the third step is whether the inferences the experts have drawn from the study are reliable or, as the Supreme Court warned in the Joiner case, is there too great an analytical gap between

the opinions and the data and the facts. In other words, can an expert reliably apply the experimental findings to a real world scenario.

For purposes of this argument, we will show how Dr. Najafi's opinions are unreliable at each step.

Next slide.

The first issue I want to discuss is whether the Plaintiffs have failed to produce sufficient data to provide the reliability of Emery's data. They have not done that, and as a result, the Defendants were not able to ask Dr. Najafi any questions about the reliability of his data.

In particular, your Honor, Dr. Najafi has not produced any chromatograms that he will authenticate. Your Honor has heard a lot in this case about the importance of chromatograms. Chromatography is a method by which scientists measure the presence of or amount of a substance present in a sample.

During testing, through an instrument, each compound is separated and measured. These measurements appear as peaks on a chromatogram. A chromatogram then gets processed or integrated, providing final results.

This processing can be done impartially by the machine itself or it can be manually processed by the analyst who replaces the machine's judgment with his or her own judgment, bur being able to review a process chromatogram is necessary to evaluate the reliability of the reported results.

Certain types of processing can lead to artificial over estimation of the amount of NDMA, so having access to the chromatograms is critical for determining the reliability of a measurement.

Next slide.

Defendants assert the Plaintiffs have not even provided any necessary support for Dr. Najafi's opinion and there is no way for them to meet their burden proving that his testing and his opinions are reliable, as required under Daubert and Rule 702.

To this day, he has not produced -- Dr. Najafi has not produced any processed chromatograms that he will authenticate. The Plaintiffs don't dispute that, but the argument is very simple, your Honor. 702 requires that the experts' testimony be based on sufficient facts and data and it is critically important that the underlying facts and data be available for review so the parties can understand the methodology and so other experts can review the same information and offer opinions about the data's reliability.

Next slide.

Now, Plaintiffs could have met their obligations under the rules and produced Dr. Najafi's chromatograms in any of these three formats, in pdf, raw data on a hard drive, or Plaintiffs could have allowed Defendants and their consultants to visit Emery, as Dr. Najafi offered, to view the data on

Emery's computer.

Next slide.

First, pdf's. Plaintiffs and Dr. Najafi repeatedly said pdf's were not an option, but their arguments as to why they were not an option are undermined by the evidence.

First Dr. Najafi claimed the chromatograms couldn't be printed or exported due to the sheer size of the file. There are two things wrong with that. First, outside of the litigation, Dr. Najafi and Emery have no issue in providing process chromatograms.

Through third-party discovery we found that Emery was able to and did export chromatograms to pdf for non-litigation clients. In fact, it did so in a report of its initial Ranitidine testing for Valisure that you can see up on the screen, your Honor.

Second, the Defendants accomplished what Dr. Najafi said was impossible. We filed a declaration of Dr. Mark Benotti who generated pdf reports from Dr. Najafi's raw data, and he said these took one to two minutes to generate and quite literally amounted to pressing a button in the master proprietary software.

Your Honor, more importantly, chromatograms can be printed to pdf, and Emery's own 30(b)(6) designee, Dr. Najafi's daughter, says Emery does this in the course of its business. Yet, today, your Honor, standing here we still have seen no

paper chromatograms produced by Dr. Najafi.

I don't know, after having looked at their slides, whether they intend to offer some of those as part of their presentation, and I will address that in the rebuttal, but as of right now we have received no paper processed chromatograms.

Secondly, your Honor -- next slide -- Emery could have produced the data in raw -- native format on its hard drive.

In early May, after repeated requests by the Defense, Plaintiffs finally produced a hard drive in the proprietary software mass center, but Dr. Najafi claimed that the data he produced might have been corrupted or manipulated, and maybe was not even his data.

So, despite seeing the data exactly as it was produced and exactly as it would appear on Emery's computer, Dr. Najafi refused to answer any questions about that data.

This is despite the fact that the Defendants showed him the pdf's of the chromatograms that were produced by our consultant off Emery's hard drive. When he saw those, he claimed he couldn't recognize them.

The Defendants then actually plugged in his hard drive and showed him the exact data as it appears on a computer within the proprietary software, but again, he refused to acknowledge that it was his data.

Instead, Dr. Najafi specifically said the data had to be viewed on his computer at Emery Pharma, and let's listen to

what he said.

"The first question on that is, the way I understand what you are saying, is that we would be required to look at the results on your computer to be able to see how the chromatograms really look; is that right?

"Objection to the form.

"That is exactly what I meant."

In fact, Dr. Najafi issued an invitation not once, but three times for the Defendants to visit Emery and look at the information on his computer.

Next slide.

"And I went one step further and invited, you know, the Defense experts to come to our lab and spend a day in front of our computer and be able to actually walk through all of our files, and if they had any question our team would be able to answer them. So we even suggested that. I don't know if you got the word, but --

"Objection.

"I will represent to you that I have not heard of this invitation, but thank you."

"So if he sees something other than what we see, then obviously I would send him a ticket -- buy him a ticket to come here and just look at our computer directly from here. That is the bottom line. That is what I originally had suggested, that we have the expert, Olsen, whoever, wanted to come out here and

spend a day just going through our computer. We would be happy to host them, but by me -- by us sending you some raw data, and then you guys opening it into your own system and potentially manipulating it and potentially, you know, essentially, you know, changing it, then obviously it won't work, but that is what I have been saying. If you go back to the records you will see that I have said that three times at least.

"Okay. Motion to strike, as not responsive, and I will represent to you there have been no changes made to these files that were sent -- copied and sent by Emery Pharma to us.

"Now, as to the invitation, we would gladly accept it, and we can be there next week with Dr. Benotti and other folks, and go through the data so that we can obtain an accurate set of data. We will definitely take you up on your invitation and we will talk with counsel about getting that on schedule. We appreciate that.

"It would be my pleasure.

"Wait, stop."

Plaintiffs' counsel put a stop to Dr. Najafi's invitation.

Next slide, please.

And subsequently in an email rejected the invitation by Dr. Najafi, or withdrew the invitation by Dr. Najafi to visit Emery's facility.

So, to date, the Plaintiffs have refused to

authenticate Dr. Najafi's data in any useable format, not in pdf, not in hard drive, not even in an on-site inspection, and we were unable to ask Dr. Najafi any meaningful questions, to evaluate the reliability of his data.

In fact, the Plaintiffs have not even offered an expert who can testify about the reliability of Emery's chromatograms. Therefore, the Plaintiffs cannot meet their burden of demonstrating the reliability of the data under Rule 702, and not a single expert can testify to this.

In fact, Dr. Najafi -- go ahead.

"What do you mean some or -- some and all? Did you review all the chromatograms or some of them?

"No, I did not review all of them. I reviewed some of them.

"Have you reviewed the chromatograms that underlie these values?

"I have reviewed some of them. I don't primarily rely on chromatogram, I rely on the data that my team provides to me, and I don't go to the underlying data. Like this morning, they provide me tables and those tables I rely on."

Next slide.

So, Dr. Najafi didn't evaluate the underlying data behind his chromatograms, but our experts looked at what was printed off in pdf format by Dr. Benotti from the hard drive and they found the data was unreliable, and specifically Dr.

Bumpus, who is now chief scientist at FDA, said the chromatograms were so poor that they have no scientific value.

Next slide.

So, without the underlying data the Plaintiffs can't prove the reliability of Dr. Najafi's result and they cannot get past the first prong of their burden, and the Court need consider nothing further.

Moving on to the second question, Dr. Najafi repeatedly rejected established generally accepted methodology, and instead used methods that were designed by his team which drove up the levels of NDMA.

Next slide.

This slide shows some of the ways Dr. Najafi deviated from generally accepted methodologies. Notably, instead of using one of two validated methods for the baseline testing that FDA designed and made available to scientists in September and October, that is the Reverse-Phase, liquid chromatography mass spectrometry, Dr. Najafi used his own HILIC method for this particular analysis. No one else has done that, your Honor.

He also designed consumer experience testing purporting to show how Ranitidine tablets could degrade with simulated tests that no one else, no other researcher or regulator has ever used.

So at each of these steps Dr. Najafi has deviated from

generally accepted methods and selected his own methods, which drove up the levels of NDMA. His methods are not reliable, they're not generally accepted, and the render his opinions inadmissible.

I want to talk for a minute, because your Honor asked a question about the HILIC method.

Next slide.

As you will see, Emery used HILIC for its litigation testing, but each of these other researchers, whether it be Government agencies like the FDA, like Health Canada, like the Australian agencies or other researchers use the Reverse-Phase. In fact, Emery itself used the Reverse-Phase in the testing it did on Ranitidine for NDMA as part of its Citizens Petition before it was retained in this litigation.

Next slide.

That begs the question then, your Honor, if the pre-litigation Citizens Petition is the result of a reliable method, why, then, after being retained in litigation did Emery use a different method?

Next slide.

Not surprisingly, as you will see here, your Honor, Emery's HILIC method generated much higher levels of NDMA than those reported by any other researcher.

This demonstrates just some of the significant differences with HILIC as compared to the generally accepted

peer reviewed method used by the FDA and others.

At the time that Emery did it pre-litigation testing, yo will see -- using the reverse method, you will see the results there, and then when it switched to HILIC for no apparent reasons the results are significantly higher, and he relies in his report only on his litigation testing and, in fact, ignores and rejects his pre-litigation testing.

Next slide.

This figure really shows how far afield Emery's results were from all the other researchers who looked at this question, and it is not the fact that he used a methodology that is not generally accepted, but it is also that he ignores or rejects all other discrepant data in arriving at his opinions, and that is the type of opinion that should not be considered by a jury.

Next.

Your Honor, we heard a little bit about his simulations. His simulations also drive up the amount of NDMA. Here on the left is Emery testing of product that was stored under real world room temperature conditions, for nearly four years and it experienced less than one nanogram per week of NDMA formation on average, but for the same product under Emery's room temperature simulation the rate of NDMA rose to 72 nanograms per week.

In other words, the same product and purportedly under

the same conditions, the simulation that no one else has done and has not been peer reviewed results in a significantly higher rate of NDMA formation compared to what actually occurred in the real world.

Similarly, your Honor, Dr. Najafi's incubated meat simulations are also significantly flawed and not accepted in the scientific community. They do not take into account, for example, the effect of stomach contents emptying over time, and Dr. Najafi assumes that there is the same amount of stomach contents over a four-hour period. It is a result oriented approach.

The testing was did designed to say -- or to look at what food, when it comes into contact with Ranitidine, creates NDMA. They didn't cook the meats. The meats were precooked, so they were not in a condition that most consumers would experience when they consumed the meat, and they didn't account for some of the things that other models that are generally accepted for simulating digestive fluids contains.

So, simply, this is Dr. Najafi's own methodology that has not been peer reviewed, that has not been adequately documented and should be inadmissible.

Your Honor, this is significant because Daubert warns that when experts reach a conclusion that other experts in the field would not reach the trial Court should be suspicious about the principles and methods and that they may not have

been faithfully applied.

Next slide.

THE COURT: You are just about at 25 minutes.

MR. BAYMAN: Okay. Your Honor, again, we are going -- have other examples of where Dr. Najafi's testing simply is not generally accepted, it is his own unique methodology, and he finds inconsistent results.

Lastly, your Honor, and very briefly, the Court asked us to address why Dr. Najafi's -- why the confidentiality order in this Court would prevent Dr. Najafi from producing something in the peer reviewed literature and, your Honor, the answer to that is very simple, there is nothing about the confidentiality order in this case that would prevent him from submitting to a peer reviewed journal.

In fact, he said in communications with the FDA that in fact -- go ahead to the last slide. Right there.

He said that he had an ongoing study and he hoped to publish it in peer reviewed literature, and then he said later that his research is not published in a peer reviewed journal and that is because it was not of publishable quality.

So, there is nothing that would have prevented him from publishing it if it were of publishable quality.

Thank you, your Honor.

THE COURT: Okay, thank you very much.

We will take our lunch break. It is 12:08, and I

think we allotted an hour, so we will come back at 1:08, and we will pick up with the Plaintiffs' response to the Najafi/Davis motion and then the rebuttal, and then we will probably go into some questions then, unless I want to take a break before the questions, before we move into the motion for summary judgment.

So, we will be in recess for one hour, until 1:08. The courtroom will remain open, and we will everybody back then.

(Thereupon, a luncheon recess was taken.)

THE COURT: All right. Thank you, you may be seated.

Okay, the Plaintiffs on the Najafi/Davis 5698 motion.

MR. NIGH: Your Honor, I am going to use a stopwatch on my phone if that's all right.

THE COURT: Yes, I have a backup here, too.

MR. NIGH: Good morning, your Honor, Daniel Nigh for the Plaintiffs.

THE COURT: Good -- well, actually, it is afternoon.

MR. NIGH: Good afternoon. Defendants chucked a lot of spaghetti at the wall hoping to see what sticks, but I am going to jump around the slides to be more responsive to Defendants' arguments.

First, I wanted to just take note that the Defendants' videos, those excerpts they had of Najafi's testimony are completely taken out of context, and even cut him off mid-sentences, where he provides more detailed responses in

other parts of his deposition. It is just a complete disservice.

I want to address Defendants' allegation that Emery Pharma never produced its data in a form that would enable us to ask Dr. Najafi questions at deposition.

This is utterly false. We produced an over 200-page expert report with very detailed information and this was a pdf. When Anna Najafi was asked how reports are typically kept, and she answered, we have a Word doc in a pdf format of reports, she is referring to reports, like the 200-page report Najafi produced, and for this litigation, it was produced as a pdf, just like for all their reports.

What Defendants are asking about are all the native underlying data. Emery Pharma does not store those underlying data as pdf's, and Dr. Najafi does not review those data as pdf's. Defendants created their own problems with reviewing this underlying data, and I would refer to our response to the motion to strike and Dr. Steffy's report that explains this thoroughly.

Defendants' reliance and insistence on printing an 8700-page pdf of this underlying data is precisely why they couldn't adequately question Dr. Najafi about it. That is not how he reviews the data.

To explain this briefly by analogy, it is like taking a Microsoft Excel spreadsheet with a thousand columns and

printing this on paper. That data would be printed on over a hundred pages, that would be nonsense, but rather than even attempt to tape the order of the columns together from one to a thousand, they are put together entirely out of order by the Defendants in their pdf.

That is how Defendants printed out their 8700 pages of pdf's for the underlying data, and even worse, Defendants then at deposition only show a few pages, of this Excel of columns 500 to 510, and showed only that to Najafi at deposition and asked detailed questions. Najafi says, I need to see columns 1 to 100 to even understand these columns at 500 to 510. I review this data together, and without that I wouldn't be able to know if the data at columns 500 to 510 are corrupted.

At deposition, Defendants can't show him columns 1 to 100, but rather say you are free to take a look at our jumbled up 100-page Excel that is completely out of order, good luck.

Defendants' problems at deposition were created by their own actions, possibly intentionally or through their own experts' nescience. Defendants admitted that none of their experts hired to criticize Najafi had ever even used Agilent or mass software, which is what Najafi and Emery Pharma use, and many analytical chemists across the country, they use this to conduct and analyze data from LC-MS/MS.

Now, Defendants argue that we never produced this material in a meaningful way. That is completely false, and

explained thoroughly in our response to the motion to strike, and Dr. Stefanis' report. We produced this data and made a format how it should be produced, just like how Excel spreadsheets should be produced and are produced in this litigation.

We purchased two hard drives with all the files in native format that Defendants could have used and still could use currently, but decided not to do so in an adequate way.

Defendants claim that Emery Pharma never produced chromatograms that he could authenticates. That is completely false. We produced them in a format he could have authenticated if they showed it to him in a format that he was used to using.

Now, let's take a look at slide 51.

These are screen shots of the video we sent to Defendants how Emery Pharma and Najafi view and analyze the data. We offered to record a video of the desktop view for how Emery Pharma views all of their results from Agilent MassHunter on the computer, and we sent this specific detailed video showing Emery Pharma's view for the validation testing and numerous tests it samples. The video scroll, it scrolls all the way down, and shows all the testing of these various samples with the validation.

This would have had the information -- slide 55 -- but the Defendants rejected this offer, rejected by Luke Bosso,

Defense counsel. This would have had all of the information in the order Najafi requested to view these chromatograms. We gave them a video that was eight minutes long and showed all the information of the testing in this run, with all the validation steps and Defendants rejected any further videos.

Defendants also didn't even prepare their pdf's in an order consistent with how this video demonstrates Najafi viewed results. Even today with the native data Defendants have, they could load up on an Agilent MassHunter system and view all the information the same way Najafi views it, but they insist on relying on an 8,700 page pdf.

Defendants created their own issues with viewing the underlying data either intentionally or through their experts' nescience.

Now, as Steffy states in his declaration, an Agilent MassHunter, the original native data generated from the LS-MS/MS analysis is preserved and remains unchanged. The data may be reviewed and processed, but the original unaltered data is always intact, paragraph 9.

When MassHunter is used to properly process that data, the software will always generate the same native data chromatogram and results, paragraph 9. Steffy confirmed this with the Emery data produced to Defendants which always generated the same chromatogram and values to 15 significant figures, paragraph 15.

With that original native data, it is possible for any trained analyst to generate the chromatogram and other numerical results and determine the amount of an analyte like NDMA in a given sample. The analyst, by using the original native data, can evaluate and interpret the chromatogram and data to arrive at the result. That is Steffy's detailed affidavit submitted in the motion to strike.

Your Honor, keep in mind that Defendants will not do their own testing to see if Emery's testing data is accurate or to support their baseless accusations. They could have done this.

Well, I should correct myself, they may have done this testing with undisclosed consulting experts, but that evidence is not presented here today.

Emery Pharma presented all their detailed protocols as to how they ran each of their experiments. Defendants had ever ability to try and replicate this, and they didn't, or they did so with the undisclosed experts and consultants.

Defendants had every ability to run their own testing that simulated real world experiences, especially what happens when a consumer breaks the seal on the bottle and the medication is susceptible to humidity, but they have never done this extremely relevant testing.

Next, I am going to discuss Defendants' claims that Plaintiffs have not demonstrated that the analytical method is

reliable, we have.

Slide 21, please.

Emery Pharma used the method FDA approved, LC-MS/MS.

Next slide.

In October, of 2019, the FDA announced this accepted method. Here is what it looks like.

Next.

Now, this is a diagram of the LC-MS/MS. The UPLC on the left feeds into the LC-MS/MS. The ESI ionizes the compounds in less than 20 milliseconds, and the QQQ process separates the compounds to make sure only NDMA is detected. This LC-MS/MS method has been utilized and validated by thousands of publications, and accepted by FDA testing for testing and detecting NDMA.

Next slide.

Now, Defendants argue that Emery's use of a HILIC column somehow inflated results, yet they don't provide one shred of evidence of this allegation, no evidence to suggest that the HILIC column could somehow inflate results, none. Only that it is a different column than FDA's initial method in October of 2019.

Next slide, and next one after that.

To understand why Emery chose a HILIC column, it is important to understand that NDMA is a polar hydrophilic compound. That is not disputed. It is in multiple studies,

it's everywhere.

Next slide.

As discussed by Waters, HILIC compounds have been used since 2003, as you can see in the highlight there, to separate extremely polar compounds like NDMA. Defendants' assertion that Emery choosing a different column than FDA's initial 2019 method is somehow using an unreliable methodology is flawed.

Next.

Every investigator testing NDMA since FDA's initial 2019 method has used a different column. FDA's 2019 method proposed the Ace Excel column. GSK used the Phetametic Synergy column. Other authors used the Shipmac column and Kinetex column, and even the FDA researchers in Florian used a different column, the Kinetex Biphenyl column. Defendants' arguments about the column are a red herring without any basis.

Next slide.

Now, Defendants' assertion that Emery Pharma did not follow approved methods is baseless and they conflate ideas. They try to argue that not following CGMP or GLP standards or the SOPs based on those standards makes Emery Pharma's methodology unreliable, but this, too is a baseless accusation.

First off, it is important to understand that Najafi's testimony about SOPs is taken out of context. SOPs, that statement, to the analytical chemist, in the pharmaceutical industry is a term of art that to them and Najafi means CGMP

SOPs. These standards apply to pharmaceutical development to gain approval to sell a drug or to manufacture a drug that is approved.

Emery Pharma follows these guidelines when they are applicable for their pharmaceutical work. You see, unlike Defendants, who chose all seasoned defense expert veterans, Plaintiffs chose an expert whose majority of work, even currently, is for pharmaceutical manufacturers, similar to the Defendants in this litigation who are pharmaceutical manufacturers.

The standards that are applicable to Emery Pharma's testing are published in the Analytical Procedures and Methods Validation for Drugs and Biologics, an FDA guidance document. Specifically, this FDA guidance document requires analytical method validation for specificity, linearity, accuracy, and precision.

Next.

The ICH also suggests these guidelines as well.

Next.

Now, I will go through these very quickly, but they followed all of these protocols. First, Emery Pharma's validation showed specificity, like seen on the screen.

Next.

Also, Emery Pharma's validation shows linearity and range, like seen on the screen.

Next.

Also, Emery Pharma's validation shows accuracy, like seen on the screen.

Next.

Emery Pharma's validation shows precision.

Next.

Emery Pharma's validation shows sensitivity.

Next.

And finally, Emery Pharma's method shows n matrix accuracy.

Now, most importantly, if Defendants' theories were true about Emery Pharma's method causing artifactually more NDMA created, then n matrix accuracy would have failed, but it didn't, so it shows them that it is not creating artifactual NDMA.

Next, next.

Now, Emery's extensive validation done in accordance with FDA, ICH, and USP guidelines proves the Emery LC-MS/MS method is accurate, precise, linear, and specific for NDMA. The passage of all these criteria through objective testing proves that the Emery LC-MS/MS method is valid. In short, it is suitable for its intended purposes.

I am going to skip a couple of slides here for time purposes. Skip, skip, skip, and skip.

Now, Defendants -- I will address this again,

Defendants' allegations are baseless. Defendants' assertion that NDMA forms at the MS source is baseless, as none of the sources cited report any observation of an in-source conversion of Ranitidine to NDMA. It doesn't happen because that small time that it has to ionize is less than 20 milliseconds, in an LC-MS/MS. That is why the FDA approves this method.

Next, and next, we'll skip that.

Now, Emery Pharma followed extensive quantification protocols as well, they are all stated here. You can see this for quantification of NDMA for Ranitidine by LC-MS/MS for Ranitidine syrups, injectables, and effervescent tablets.

Next.

Extensive quantification protocols for the stability assessment of Ranitidine towards NDMA formation by LC-MS/MS in simulated gastric fluid again. Again, these are all the protocols the Defendants could have analyzed and done the testing themselves, or if they had issues with how it was done, this is where they could have looked at it.

Next.

Nitrosation assay procedure, the NAP, and related procedures to evaluate NDMA production from baseline.

Next.

And Emery Pharma's consumer experience testing is grounded in published literature and established guidelines. These are the studies supporting the conditions used for their

vehicle conditions testing. They are all in our papers.

Next.

This is the published literature supporting the conditions for bathroom testing. It is in our published papers.

Next.

These are the established ICH guidelines for climatic zones that Emery Pharma's zone testing is grounded in, and the zone testing that Dr. Salmon relies upon.

Next.

This is the published literature that is the basis of Emery Pharma's SGF testing.

Next.

Along with Braunstein and Gao, this is the published literature that supports Emery's SGF study with food.

Next.

Now I want to skip to slide 58, and we are going to discuss the Defendants' allegations about confidentiality order.

Defendants' arguments that Emery Pharma should have published their literature are disingenuous. First, products liability testing is admitted as evidence all the time in courts where they weren't peer reviewed. That is not the standard.

Most importantly, Defendants insisted on

confidentiality that handcuffed publishing these results. First, Defendants insisted that Emery Pharma sign this document that would potentially put Emery Pharma at sanctions if they violated it.

Next.

Judge Reinhart's order that accompanied the production of Defendants' products to Emery Pharma demonstrates that Emery Pharma was directed to use this product testing, and you can see it there highlighted, the second part, for litigation related purposes only. And this document was drafted by the Defense counsel.

Next.

We can see more orders that show the same thing, they are all based on the same language.

Next.

There's BIPI, we have Patheon, there are numerous of these.

Now I want to go ahead and skip to slide 7.

Now, Defendants claim that Emery Pharma's testing are inconsistent with all other testing is false. They are just not showing you the testing that is consistent. Defendants want to focus only on Defendants' and FDA's baseline testing of pristine product. You can see that here in the upper left-hand corner. That is baseline Defendant, FDA, that's the pristine product.

What they don't show you is that other baseline testing has shown results that are actually very similar to Emery Pharma. One of them is Braunstein, another one, TGA, that is the counterpart to the FDA, and another one is actually Sanofi's own testing, which is another data point.

When you asked if we could -- FDA max, Sanofi considered those pieces of Sanofi testing -- Dr. Salmon considered those pieces of Sanofi's testing in forming his conclusions.

Next.

Now, to put this into context, before April of 2020, the FDA was only doing baseline testing and allowing Ranitidine with less than or equal to 96 nanograms to continue to be on the market. At some point before the recall they did do some stability testing, but that is not their testing published initially. That is not the testing Defendants are showing to your Honor.

The testing they are showing you is only the baseline testing.

Next, next.

Now, Defendants argue that Emery Pharma's results were somehow different for the petition that they filed -- that they filed compared to their litigation results, but that is because specifically Emery Pharma didn't know to test for humidity back then, they only tested for heat.

We have learned now that humidity is much more the driving factor and plays an even larger role than heat, in showing how much NDMA breaks down.

This is the petition they filed, they filed on heat alone, and heat alone was enough to show that Ranitidine was unsafe.

In 2020, the FDA granted Emery Pharma's request, in January, 2020, to recall all Ranitidine in the United States. Emery Pharma isn't some maverick, this shows instant credibility.

Defendants also argue that Najafi didn't publish this January 2020 Emery Pharma petition. That is what they closed with, but this was well explained, because Najafi -- what Defendants didn't tell you is that Najafi stated that he didn't need to publish these results. The FDA responded to this petition and recalled all Ranitidine in the United States. That is much more of a scientific impact than a publication.

Next.

Somehow Defendants dispute -- next.

Somehow Defendants dispute that Emery Pharma wasn't responsible for this recall, or at least in part, but even their own expert admits to this.

Go ahead and play the video, please. There, might be a delay.

Well, if you go back to that prior video, you can see

the deposition transcript of Dr. Wang at page 134, line 21, to 135, line 3, where he admits that Emery Pharma is responsible, at least in part, for FDA's decision to recall all Ranitidine in the United States.

Next.

Now, your Honor asked if there was some other data that was relied upon, for Salmon's FDA max number. Yes. Sanofi's own testing that they didn't include in their 19 results that they showed your Honor shows this.

You see, they tested only two batches that would simulate real world experience of what a consumer, our Plaintiffs, would have purchased before opening the bottle and then additional NDMA forming.

They presented these results that NDMA formed because the regulators required them. As you can see here, it says, in the meantime, comparison of this result of 5.24 PPM to the one obtained on the retained samples of the same batch, their retained sample, that would be their baseline testing that they want to rely on, their retained sample is only .73 PPM.

So we can already see a sevenfold increase just with the passage of time, let alone opening up the bottle. These aren't extreme conditions. 24 degrees Celsius, that is 77 degrees Fahrenheit.

To suggest that storage conditions has an influence on NDMA content in the drug product, and when you average just

these two results, they are right there, it exceeds Salmon's FDA max number. He explains this as support for his FDA max number.

Now, in addition, I want to go to slide 18 and --

THE COURT: Can I ask real quick, this screen 12, is that part of -- in the record?

MR. NIGH: Yes.

THE COURT: Where does that come from?

MR. NIGH: I couldn't tell you precisely, but we can get you that answer.

THE COURT: Okay. So screen 12. Thanks.

MR. NIGH: Yes.

Next, Braunstein, their testing demonstrates 824 nanograms to 1440 nanograms per 150 milligrams of NDMA at baseline. The Defendants' own expert admits that these testing results would be their baseline testing results. That is Dr. Bumpus. She admits that because she is citing the language from the Gow study that says this would have been their baseline results. These results are actually higher than Emery Pharma's results.

Next.

And as you can see, I want to go to -- if we can go back to the GSK document, I don't have the slide number, but it's a few slides before this, it shows GSK testing.

I only have a few more points, but I want to show

this, too, because GSK's root cause analysis of accelerated testing demonstrates that at 50 degrees Celsius, 65 percent relative humidity, there are 26,730 nanograms in a 150 milligram tablet.

I am sure the Defendants will come up here, and they will say, well, 50 degrees Celsius, that is not a real world condition, but the point on this that you can see is, when you look at 70 degrees, and you look at 60 degrees, those results aren't that much different than at 50 degrees. What is the driving factor? The humidity.

So, that is the question that needs to be answered, how much forms in real world conditions after you open up the pill bottle and suscept the pills to humidity. Some of these pill bottles have 150 pills in them. Our consumers, our Plaintiffs, they don't open up the bottle and down all 150, it is over time, after the seal is broken, and they place these in common spots, like the medicine cabinet, or in the car, in the sun and the shade.

I also want to show, for Saraca -- there was this argument that somehow Saraca with a different crystallization might show different levels of NDMA. That is for the API because the root cause analysis does not demonstrate that. You can look at the Saraca, and you can see at 50 degrees Celsius -- no, before that, don't change that. Thank you.

At 50 degrees Celsius, 65 relative humidity, you are

seeing similar results. It's not any different. When you apply humidity to the pill it breaks the liner and you see more NDMA coming, or it slowly degrades the liner and you see the NDMA.

Next, and next. I have one last slide.

Now, this begs the question how much NDMA forms in the real world? And the FDA -- the Defendants keep wanting to rest on the FDA as if their baseline testing that they published in October, and November, 2019 was their ultimate answer. It was not.

After that, they did stability testing and they showed -- they weren't confident that any Ranitidine wouldn't have excessive amounts of NDMA, so everything was recalled in April, 2020.

Fast forward even further to that, the FDA convened a panel of experts, and on March 29, 2021, these exact questions were being raised by these experts who posed the following: "Yeah, I mean I think there is a big focus on, you know, real world conditions, right, you know, the hot mailbox, the glove box in the car, you know, the human bathroom."

Emery Pharma didn't come up with this stuff themselves. "You know, I mean, if you think about those things, you know, what does it experience in the truck in the middle of the summer in the southern U.S., you know, so before it gets to the shelf."

Emery Pharma's testing --

THE COURT: It's time.

MR. NIGH: This is my last thing. Emery Pharma's testing answered this important question, asked by the FDA panel. The testing results are accurate and reliable and grounded in the validation and the guidelines established by the FDA, ICH, and USP.

Thank you, your Honor.

THE COURT: Thank you.

Okay. So now we have the rebuttal of five minutes. Plaintiff went over by about 51 seconds. If you need a little more time, 51 seconds or so, but otherwise five minutes.

You may go.

MR. BAYMAN: Thank you, Judge, just briefly. You know, Mr. Nigh spent a long time talking about that we rejected their offer to provide videotapes. What they offered to do was to do a series of screen shots and videotape those screen shots, so there is no way to toggle back and forth.

What he didn't say is that not -- Dr. Najafi said the only way to do it would be on Emery's computer, there, and he invited us to come three times, and they rejected that invitation. He said that is the only way to see the chromatograms, and even though they can produce reports, none of their reports contain any chromatograms.

And, so, that is why the offer of video was rejected.

With respect to the confidentiality, your Honor, in the quote from Judge Reinhart's order that it is not to be used for commercial purposes, that means -- that is for Customs reasons. That means they couldn't take the product and sell the product. It did not mean they could not publish the results of their testing. And in fact, Dr. Najafi intended to publish the results of his testing and he testified it was not of publishable quality.

Mr. Nigh mentioned matrix accuracy. They have no experts to support that at all. They have no expert who has actually demonstrated that the HILIC method achieves better separation. There is simply no support. This is just -- and the Daubert cases warn of this.

They are asking you to rely on what Dr. Najafi says without any proof of what standards he followed. He says, oh, yeah, we follow standards, but he doesn't provide the standards. He doesn't say what the standards are, that he follows, just that we follow standards. That is what the Eleventh Circuit in McClain found fatal with Dr. O'Donnell's opinions.

The explanation about heat is really a red herring because what you need to do is compare apples to apples to compare the baseline testing, and there was other testing done, including the GSK testing, Mr. Nigh mentioned, but that is in no way intended to simulate real world conditions, which is

what this litigation is about, what do consumers in the real world -- what levels of NDMA did they find, not some super heated samples to test to degradation. It is a different experiment.

Dr. (sic) Nigh mentioned Emery's data with respect to the FDA recall, and that it was a basis of the recall. Dr. Najafi testified that -- was asked if he was aware that the FDA relied solely on their own testing when requesting a recall of Ranitidine, and he said, I believe so. Dr. Najafi's testing was not the basis for the FDA's request that the product be removed from the market.

Again, it is important to point out that the results that were shown of the testing and how Emery's testing pre-litigation and post-litigation differed from the others. Those were all baseline testing, that was apples to apples. And, so, that is what -- that is the important measurements.

Mr. Nigh said a few times that Emery's levels are consistent with levels that are provided by others, or supportive of the levels that are provided by others, in other people's testing. Well, if that is the case, the Plaintiffs don't need Emery, they have that other testing data to rely on.

At the end of the day, your Honor, it still gets back to the fact that you are being asked to find this -- they have the burden of proving that his data is reliable, and you are being asked to find that it is reliable and allow a jury to

consider it when they have provided no standards.

They have provided nothing more than Dr. Najafi's statements saying broadly, we follow standards, but I can't show them to you and I can't tell you where they are written down.

They are relying on his testing, which has never been peer reviewed, and the Daubert cases say how important peer review is a factor to be considered. Never been peer reviewed, never been done by anybody else, and these simulations that are intended to mimic real world conditions do not.

He did not test Ranitidine by putting it in a glove box, that was a simulated test, not in a glove box of the car.

So, your Honor, for those reasons and others that are detailed thoroughly in our brief, we would ask that you grant the motion and exclude Dr. Najafi under Rule 702 and the Daubert case law.

Thank you.

THE COURT: Thank you. Okay, just a few questions. So, this is for both sides. Maybe I will start with the Plaintiffs.

Can you explain -- I know you touched on it, but what your record -- you know, what you have put forth -- in other words, I don't want anything outside the record, but distill it down for me what you have put forth in the record about what the hydrophilic interaction liquid chromatography, the HILIC,

is, how it works, how it is, or is not different than normal phase and Reverse-Phase chromatography.

Break it down like you are explaining it to a lay person and then, if the Defendants have a point of view about that, since I know you have challenged it, again, anything from the record, you can present that as well.

And I guess, you know, for background, let me fill it out for the Plaintiffs.

So, I want to understand -- if you want to make notes so you have kind of a list, you may want to incorporate it into one answer.

You got the first question. So, my followup questions are going to be along these lines if you want to make notes. They kind of all go together. For which studies did Emery Pharma use HILIC as part of its method of chromatography, and for which studies did Emery Pharma use a different method, such as normal or Reverse-Phase chromatography?

The Plaintiffs state in their response that different columns were used for different studies. That is at Docket Entry 5914, page 17.

The validation summaries attached to Dr. Najafi's report in Appendix A, that is at Docket Entry 5698-10, at page 167 to 71, indicate that the chromatography method was Reverse-Phase, and that's at HPLC.

The Court understands from Dr. Najafi's rebuttal

report that with respect to at least some of the studies that is a typo. And that is at Docket Entry 5698-11, page 13.

One last part, and if you need me to repeat anything, that is fine. During Dr. Najafi's deposition, he was asked about whether Emery Pharma's method of chromatography could have artificially generated NDMA.

This is kind of a different question, but I will ask it and I can repeat it. He stated that there was a published note indicating that this does not happen. That is in his deposition at page 520, lines 3 to 16.

So that question is going to go to, do you know what he was referring to, and has it been or can it be made available to the Court?

So, I kind of mixed the note part in with the chromatography, but that is kind of the long and short of what I am interested in.

MR. SELIGNAN: I am Matthew Selignan for the Plaintiffs, S-E-L-I-G-N-A-N. This is my first time appearing.

To answer your three questions, first, the HILIC column. So, our discussion of the HILIC column in our response to their motion to exclude is the first time we talked about it, and the reason is, as Mr. Nigh pointed out, every single test uses different columns. So there was never any reason to think that it was important for Dr. Najafi to talk about the specifics of the HILIC column, why it was a justifiable

methodology in the LC-MS/MS process until the Defendants raised that issue.

So, once the Defendants raised that issue, we responded to that in our brief, and that is on page 38 of our response.

In that response we cited to publically available information, reports by Waters Corporation, which is the manufacturer of HILIC columns, and other publically available studies explaining the nature of the NDMA molecule, that HILIC columns are particularly well suited to cause greater separation in the chromatograph, the liquid chromatography, than other columns for specific types of molecules that are highly polar and hydrophilic, namely NDMA.

So, that is the explanation for why Dr. Najafi used the HILIC column, and those are the sources that we relied on in explaining that.

And again, it wasn't in the report because nobody thinks that the column is actually a big -- makes a difference, which again is why all of the studies use different --

THE COURT: Did he use it pre-litigation or just post-litigation?

MR. SELIGNAN: Post litigation.

THE COURT: Do you know why he changed?

MR. SELIGNAN: The reason for the change is that the pre-litigation, pre petition testing served a different

purpose. What it was intended to do at that point is to demonstrate not precision -- or not accuracy of finding out exactly how much NDMA, but showing the proposition that heat could cause an increase in NDMA.

So, the non-HILIC column was adequate for that purpose, it was adequate for the purpose of what the petition was for.

When it comes time to do the litigation testing, where it is extremely important to show precisely how much NDMA is formed in different circumstances, in the baseline testing, in the consumer experience testing, then the more accurate HILIC column was better suited for that purpose.

Okay. Then your second related question is, which studies that Dr. Najafi performed used the HILIC column and which didn't. The answer to that is, he used them for all of the studies except for those that used liquid, the SGF in particular.

The reason for that is the HILIC column -- because there is a liquid matrix involved, the HILIC column isn't going to perform as well when you are using a liquid matrix as opposed to a tablet, which is the baseline testing. I believe the distinction there is the HILIC column is used except when the liquid matrix would have made it unsuitable in the SGF testing.

THE COURT: Is that made clear, in your opinion, in

his report?

MR. SELIGNAN: I think your Honor made reference to the fact that there might be some typos. I will go back and check that and confirm that the report accurately reflects what the actual column used for each of the experiments.

THE COURT: Could you define polar and hydrophilic?

MR. SELIGNAN: Yes. Hydrophilic means attracted to water, and a polar compound is one where the electrical charge between the different parts of the molecules is different. So, water is H, and then two O's, and as a result of that triangular structure, it is polar, part of the molecule has a positive charge and part of the molecule has a negative charge.

As a result of that, it is retained by different substrates in a column differently than a nonpolar column -- a nonpolar substance would be. As a result of that, different types of columns, so in a non-HILIC column, you would have something like silica packed in there, that type of substance. It wouldn't be as good at retaining these differentially charged molecules, where the positive charge of the molecule and the negative charge of the molecule are located at different physical ends of the molecule.

As a result of that, for a non-polar molecule, a silica, ordinary Reverse-Phase column would be appropriate; however, there is better separation in the -- as you put the sample through the chromatograph for a polar substance it is

going to be retained better when the column, HILIC, is suited to retaining these polar hydrophilic compounds.

Now what that means is, as you put the sample through the column, because the column is hydrophilic, and you have a polar compound, NDMA, NDMA is going to be attracted to the substance inside the column to a greater degree than otherwise and so it is going to travel through the column more slowly, and that is going to provide greater separation and therefore greater accuracy in the ultimate test.

THE COURT: Okay. And the note?

MR. SELIGNAN: So, a substantive response, Mr. Nigh responded to this a little bit, there is absolutely no basis to think that there is artifactual creation of NDMA in the MS process.

So, just by the way of contrast, the Valisure pre-petition testing showed astronomical amounts of NDMA, and Emery Pharma determined that a lot of that was artifactual and the reason was because it used gas chromatography rather than liquid chromatography, which involves heating the sample for several minutes to well over 100 degrees Celsius.

So, that testing procedure and gas chromatography can create artifactual NDMA. That is exactly why the FDA recommended using liquid chromatography, and in particular LC-MS/MS. In the MS process there is no indication, no reason to believe that in the 20 milliseconds that the sample is

passing by the ionization diode that it would create artifactual NDMA.

You mentioned there is a published note. I don't have that citation with me right now, but we can get that to you.

THE COURT: Right. Dr. Najafi said that there was a published note, and you can check his deposition at page 520, lines 3 to 16. So I want to know, what is the note?

Apparently Dr. Guengerich tried to find it on a website, he believed he found it, and he said at Docket Entry 5698-8, 9 to 10, he thought maybe Dr. Najafi was relying on figure 10, in the Waters note, but that applies to a different ionization technique, APCI.

So I just want to know what he is talking about.

MR. SELIGNAN: We will track that down for you. Just for some greater context here, the LC-MS method is the method that was recommended by the FDA. It begs belief to think that they would recommend a method that would create artifactual NDMA.

THE COURT: Okay. Did the Defendants want to address the HILIC --

MR. SELIGNAN: Thank you, your Honor.

THE COURT: Thank you very much.

-- column, since you raised it as a challenge, one of a number of challenges to the Plaintiffs' methodology? Plaintiffs point out that different techniques are used.

You might need to come to the podium.

MR. BAYMAN: Your Honor, I was just going to say I think you have hit the nail on the head. Emery is the only entity to use HILIC to test for NDMA and Ranitidine, and they did it only after they were retained in litigation. We think that speaks volumes. I am going to let my colleague, Mr. Bosso, answer the more technical parts of your question.

THE COURT: Hello, Mr. Bosso. Maybe take into account Plaintiffs' response that they showed the one screen where different studies were being conducted by different -- using different technology, different columns all the time, and just because it is different, what is the problem?

MR. BOSSO: Yes. So, one piece of context to be directly responsive to that, is that all the columns they showed you were Reverse-Phase columns.

THE COURT: All the columns they showed on their screen?

MR. BOSSO: Right, all the ones they are comparing it to, when they are saying different people are using different columns, those ultimately result in Reverse-Phase LC-MS method. The only person who is using a column that is a HILIC method is Emery. So let me explain to --

THE COURT: How do you know that all the other ones were Reverse-Phase? Is that in the record?

MR. BOSSO: Well, Dr. Olsen's report goes through the

various published literature, and notes that everyone else before has used Reverse-Phase, and that is in his report.

THE COURT: So some variation, but it is a Reverse-Phase. This is not Reverse-Phase.

MR. BOSSO: Right. The exact column, being used is a complete red herring.

THE COURT: So, it is not the column, it is that Reverse-Phase was not used, that is your challenge?

MR. BOSSO: Right. When you use -- so, let me give you some context about this.

When FDA validated its method, if you pull up those FDA validations, which are part of the record, you can actually see that FDA demonstrated that when Ranitidine and NDMA come out of that column and are exposed to that high heat during volatilization, that they exit separately so that the test isn't going to be confounded.

The true thing you have to remember is that the particles have to be separated from each other. That is literally the definition of chromatography.

So FDA, when they validated their method, they demonstrated that Ranitidine elutes separately from NDMA. Now, all those published literature that we have talked about, they take into account the Reverse-Phase method that ensures they elute separately. What HILIC does -- in Reverse-Phase, I believe NDMA comes first and Ranitidine comes second. HILIC

reverses the order, where Ranitidine will come first and NDMA comes second.

What ends up happening is, when you change that method, you have to ensure that you are getting proper separation, and the only justification in the record that Plaintiffs or Dr. Najafi have ever made for why HILIC was the better method than FDA's method or better than their Citizen Petition method was because they say it should account for better separation, but there is not one bit of proof that there is actually better separation.

In fact, Dr. Olsen, in his rebuttal report, addresses this, because he looked at the data that was given on the hard drive, although there is an open question that Dr. Najafi claims it was corrupted, but assuming it is not corrupted, he looked at it and said they are not separating NDMA from Ranitidine, so they are eluting at the same time, which means they are going to enter the detector at around the same time, and during that transition, it is 300 degrees Celsius, higher than what Valisure used.

Now, their claim is it is only 20 milliseconds, so it is so short that they have zero data to support the fact that 20 milliseconds isn't enough. In fact, Dr. Olsen considered this, and there is an Alshuri (phon) paper, Alshuri 2020, that he cites in his supplemental report that uses liquid injection, GCMS, which is a little bit different than what Valisure used,

but essentially it is also an instantaneous fraction of a second heat applied to the Ranitidine molecule, and he found that even a very short period of time can artifactually separate NDMA from Ranitidine.

So the issue is that NDMA and Ranitidine are coming out at about the same time from Emery's chromatograms and that high heat is applied.

Now, when researchers validate their methods, validation has to take into account all sorts of different parameters. It is an affirmative obligation of the researcher to demonstrate that their methods are accurate.

Now, if you have the potential that you have not ruled out the fact that you might be artifactually increasing NDMA you cannot claim your method has been validated.

There is a second point that goes along with this. Dr. Najafi, in his deposition, it was not a trick question, we asked him, if you are not using GOP, if you are not using GMP, can you tell me what standards you are relying on? He said, we are not relying on anything, it is not written anywhere, it is just general principles.

THE COURT: I think some of my questions are going to get into that. Anything more you wanted to say on --

MR. BOSSO: Well, for the validation, now there is a claim that -- today, now they are claiming that FDA, USP, all these different organizations have a validation standard that

they followed.

Part of that validation standard, if you bring it up -- which might be part of the record, we will have to check -- it actually requires investigators that if you have an FDA approved method that you want to depart from, you have to take the same samples and test it under both methods and make sure you are getting the same result.

Emery could have taken the same tablet sample and tested it under the Reverse-Phase method, recommended by FDA, tested it and confirmed these results are the same.

THE COURT: Your position is this is a departure from the FDA method, and as such, it would have had to have been validated?

MR. BOSSO: And it was not properly validated.

THE COURT: Let's hear a response from the Plaintiffs on that point.

MR. NIGH: Yes, your Honor. I have a quick response, and some others might want to respond on the technical issues.

THE COURT: I am sorry. Just on that FDA policy that you were just referring to, is that what you said, Defense, you weren't sure if it was in the record?

Can you all check that and maybe in our concluding comments let me know. If it is not, for some reason, can you check with the Plaintiffs to see if there is any objection to it being made part of the record? I think since it is probably

a public document there shouldn't be a problem, but I would like to close the loop on that.

MR. NIGH: Thank you, your Honor.

Your Honor, first off, the method that they are speaking about in those guidelines using two different samples, one from this method, one from the other, the method is LC-MS/MS. That is not applicable.

THE COURT: Did Emery use Reverse-Phase chromatography, yes or no?

MR. NIGH: I would refer to my others on this issue. That is not a method. Reverse-Phase or non Reverse-Phase is not a method spoken to by the guidelines. The method is LC-MS/MS.

THE COURT: I just want to understand, was Emery using Reverse-Phase or not?

MR. SELIGNAN: The answer is yes, but only for certain tests, the SGF tests, the ones that use liquid, and they used HILIC column for the baseline testing and consumer experience testing.

There is a distinction, between HILIC --

THE COURT: Do you believe his study makes that clear, his report makes it clear?

MR. SELIGNAN: I think it does. We can offer further clarification.

THE COURT: If you could look at that report and tell

us if he makes it clear and where he distinguishes that. To the extent that Reverse-Phase was not used, do you agree with the position taken by the Defendants that that would constitute a departure from FDA policy such that it would need to be validated?

MR. SELIGNAN: No. Even if it were a new methodology, Emery Pharma did everything that could be done to ensure the accuracy using the HILIC column.

First, for some context, if there was some difference in the methodology that made a difference in the accuracy of the results, for example, potentially because of artifactual creation of NDMA, then why is GSK's baseline testing almost identical in its result to Emery Pharma's baseline testing?

If the HILIC column is not -- the HILIC column is used for baseline testing by Emery, so if HILIC -- the HILIC column is an invalid method an inaccurate method, and as speculated for the first time today by Defendants, somehow elutes in the wrong direction, such that there can be the creation of artifactual NDMA in the MS part of the process, that can't explain why the baseline testing is virtually identical when you use a Reverse-Phase column as GSK did.

Now, beyond that, what Emery Pharma itself did to confirm that there is no artifactual generation of NDMA using the HILIC column is they validated it. Among other things, what they did, is they used the exact experimental setup, put

in a known amount of NDMA, and then tested how much came out the other end. So, that data is in the report, and we presented it again here today in our Power Point presentation.

THE COURT: Right. My next set of questions actually goes to the validation summary tables.

MR. NIGH: Your Honor, I have one more response, to the Defendants' suggestion, and that was this response of the Alshuri paper, liquid injection in GCMS, that is not support at all, for that there might be some NDMA artifactual creation in less that 20 milliseconds in an LC-MS/MS situation.

Those criteria, those data are not apples to apples. Now the Defendants are trying to use some other methodology to say somehow this would have created additional amounts of NDMA.

If they really wanted to raise that argument with any basis, and we are moving to exclude that argument, because there is no basis at all from Dr. Olsen for that argument, if they wanted to do so, Dr. Olsen is an analytical chemist. Analytical chemists don't just surmise, make guesses, assumptions, they test. He had every ability to test that assumption, that if he wanted to see if the HILIC column actually generates additional amounts of NDMA, as he surmises or guesses, he could have tested it.

He never did, therefore that opinion should be inadmissible.

THE COURT: Okay. Okay, thank you. Moving on to the

topic of validation summary tables, Dr. Najafi and the Plaintiffs point to the validation summary tables in Appendix A to Dr. Najafi's report at Docket Entry 5698-10, at page 167 to 71, to demonstrate that Emery Pharma's chromatography methods were validated.

What do these validation summaries demonstrate, and what don't they demonstrate? In other words, what is the Court to glean from the summaries?

So, I have the summaries, and we can take one of them, and I don't know whether we want to have Plaintiffs answer first, and then if Defense wants an opportunity to respond -- some of the followup questions I have, like for the Plaintiffs, for example, are the validation summary tables in Appendix A to Dr. Najafi's report all of the validation summaries for all of the testing that Emery Pharma conducted for this litigation?

So, for example, is the summary table labeled Validation Summary Table for NDMA Quantitation in Ranitidine in SGF, that is Docket Entry 5698-10, at 168, a summary both of the simulated gastric fluid, SGF study, with food, and for SGF testing without food. The summary doesn't mention anything about food, or more specifically meat.

That is kind of a subset, but if you want to take -- I am looking at -- I don't know if you have one in front of you.

MR. SELIGNAN: One moment, your Honor.

THE COURT: 5698-10, it's on page 167, of 214.

MS. BOGDAN: We are trying to pull those up, your Honor, and I don't have them right in front of me, but there are validation summary tables for each of the type of testing that Emery Pharma performed.

There is one for -- in the matrix of the SGF, there is another one for in pills, there is another one for the syrups.

THE COURT: Right. I wanted somebody to walk me through one of them to explain it, because there are similar descriptions for each.

MS. BOGDAN: If I could have it up on my screen so I could walk you -- we could take the walk together, so to speak.

THE COURT: What about the ELMO, does somebody have access to the ELMO there?

Why don't you look at that and we can come back to that question.

MS. BOGDAN: I have one of them up, I have the MAP study one up.

THE COURT: MAP is fine, I also wanted 5698-10, page 167 of 214.

Do you want to walk me through that one?

MS. BOGDAN: Sure. It has a short description of the method, it talks about the matrix, and to further elaborate with regard to the difference between the HILIC method and the Reverse-Phase method, the Reverse-Phase method was used for all the matrixes that were of a liquid nature, the SGF studies, the

syrups, the injectables, while the HILIC was used for the tablets.

That is because when you are running these things through you have different solvents that you are using to run these through the columns. So, when you are dealing with a slurry and a syrup -- this is me explaining it, but all of this is accomplished by them going through their protocols and their validations, and really why we need experts in cases, to explain things, with that caveat.

So, the SGF was used for all of those types of matrixes, because you are using a solvent that is compatible with the SGF, the meat that is in there. The syrup, it has different excipients, it is goopy, as opposed to the HILIC when they were just taking a solid, which is all tablet testing, and the stability testing and consumer experience testing was tablet based.

They used it for the API, again a solid, and that is really the difference, and it was because they were optimizing methods to be the best method to detect depending on what they were looking for.

Then it talks about the analyte, which is the target, that is what you are trying to find, then the internal standard. That is a -- basically a check and a balance that they put in NDMA in every single sample that they tested.

They put in the NDMA D6, which is similar to NDMA, but

it isn't NDMA, so that they can quantify that on the back end. They are telling you the calibration concentrations, that is sort of the sensitivity. They can detect as low as five nanograms and up to 1,000.

They then go through their QC concentrations, which is quality control. That is when they are testing to see when they have a known amount of NDMA, that is the amount that is coming out on the other side. So they are getting accuracy and precision because they know what they are putting into the system and they are detecting it on the back end. They are talking about the lower limit of quantification on this, which is that five nanograms.

Linearity is when you put in .5 NDMA, you get out .5, put in 10 NDMA, you get 10, put in a hundred of NDMA, you get a hundred, when you put in 500, you get 500.

And the response, and I think Daniel clicked through that, but that linearity, you saw that line, it was perfect. You can always make a line through two dots, but to make a perfect line through eight, is showing a high degree of accuracy of detecting the compound.

Then, with regard to the QC accuracy, that is giving you those percentages with regard to how close it is to what they know was put in, and then the QC percent, that is actually calculated off of a hundred, so with a hundred, they were within 1.23 percent.

That is the summaries. There were also validation protocols that spelled out everything they did, and importantly, in the hard drive that we provided to the Defendants, all of the validation data for all the validations they did on every single method for every study they conducted were in and the raw data was available as well.

THE COURT: Okay, thank you.

MS. BOGDAN: You're welcome.

THE COURT: Anything that Defense wanted to briefly respond to as it relates to the question regarding the validation summary tables?

MS. BOGDAN: I just had one other point to make, and I don't think it was made, but with regard to the artifactual formation of NDMA, when Emery did their testing, there were samples that tested that had very low levels of NDMA in the samples. If you look at their data sheet that is attached to their report, you will see certain lots, certain batches with low levels of NDMA.

If NDMA was being created by the method, you would have no low levels. There are levels under a hundred, there are levels that are under 20, there are levels that are under 15, there are -- this is the same method being used to test all these batches. If the ionization source was creating NDMA you would not have those values.

You know, that is like a common sense explanation, and

it is also rooted in the chemistry, but it is really easy to understand. If there is a problem with the process, it would be a problem with the process.

THE COURT: Okay, thank you.

Any brief response from the Defense?

MR. BOSSO: I wanted to quickly clarify that when they talk about some of the parameters, like perfect lines and being able to see when you put in this much NDMA you get this much NDMA out, all of those samples do not contain Ranitidine.

So, the big problem that has been raised with the HILIC method relates to whether the Ranitidine molecule is going to confound the results. So, pointing to this data does not answer that question.

And Plaintiffs counsel specifically said analytical chemists do not surmise, make assumptions, or guess, but they are surmising, making assumptions, and guessing that their method offers better separation although it has never been demonstrated.

That is it.

THE COURT: Okay, thank you. Okay.

MS. BOGDAN: May I respond quickly? The n matrix accuracy test that my colleague, Daniel Nigh, spoke to about originally is actually putting NDMA, a known amount, in with Ranitidine and it is seeing if that known amount comes out the other side.

THE COURT: Okay, thanks. Okay, this is one more question for the Defendants.

The validation summary table for NDMA quantitation in Ranitidine in SGF 5698-10, I believe that the Defendants have argued that this is insufficient to show the method of validation. You contend that in your motion at Docket Entry 5698, at pages 42 to 43.

You start off by saying: Despite the need to specifically validate the method within each meat matrix, Dr. Najafi did not validate his method for any of the meat matrixes, and then you have several citations and you go on to quote from the Bumpus report and things of that nature.

So, can you explain to the Court what should the summary have included to show method validation for the SGF study with food?

MR. BOSSO: Yes. So, the issue here is that, again that FDA guidance that we're were going to check about having been put in the record specifically notes you have to test -- validate within each matrix.

Now, Plaintiffs have made the claim, which is clearly unsupported, that simply validating SGF alone is the same as SGF plus all these various meats. As you noted, people like Dr. Bumpus and Dr. Guengerich looked at this and said there needs to be a validation of SGF ham matrix, there needs to be a validation of SGF bacon matrix, but there is no validations

whatsoever that have those. The only validation is SGF alone, and that is the issue.

Do you have any questions about that?

THE COURT: No. I probably should have asked the Plaintiffs first, the question I had, so you could tell me if it changes your answer. So, let's hear from the Plaintiffs on this question.

Are the validation summary tables in Appendix A to Dr. Najafi's report all of the summaries for all of the testing that Emery Pharma conducted for this litigation? For example, the summary table labeled Validation Summary Table for NDMA Quantitation in Ranitidine in SGF, Docket Entry 5698-10, at 168, a summary both for the simulated gastric fluid study with food and for SGF testing without food?

The summary doesn't mention that, so Plaintiffs, are you able to answer that question?

MS. BOGDAN: The simulation --

THE COURT: Both for simulated gastric fluids study with food and for SGF testing without food.

MS. BOGDAN: It is the validation protocol for the SGF testing, and it is our position that the validation done for the SGF study, as far as measuring accurately in SGF, is that validation covers the SGF studies.

THE COURT: With food and without food?

MS. BOGDAN: With food and without food, yes. And

importantly, within each SGF study they also did a control of meat alone, as well as Zantac alone, to be able to check as to whether or not either of those things in the SGF would generate NDMA, so it is n test or n matrix validation that is done. Dr. Najafi speaks to that during his testimony.

So, you know, Defense is sort of giving you an apple, when we are dealing with a whole fruit basket, and again, outside of, you know, what -- if the Court would like, I can explain all the different controls -- it is all in Dr. Najafi's report why these things were done within the food studies themselves.

You know analytical chemistry is certainly an experimental science, and they did all of these things as they went through every one of their studies, rooted in methodology, in the peer reviewed studies, and then they did many checks and balances to verify their results, and there is an n matrix validation done for the SGF studies, and it looks to -- and if you want to go through the report, you can see the controls that they did, and those controls are to make sure that NDMA is not being generated simply from the meat alone, and that is part of that validation process.

THE COURT: Okay. Thank you.

Are Defendants taking the position that there should have been a separate validation done for SGF study with food and a separate one for without food when you say the summary is

insufficient?

MR. BOSSO: Yes, it actually needs to be a separate validation for each food type. So it is not just with food or without food, it is actually -- if they want to measure in bacon, it is bacon.

A matrix by definition is all the molecules within the sample, so if you are changing the matrix by adding food, you can you not longer rely on the same validation, because it is outside the matrix.

THE COURT: Is that in the same policy statement you referred to earlier?

MR. BOSSO: The policy statement says that you have to test within each matrix. The definition of a matrix, I am not sure if it would clarify it, in the document, but our expert reports do cover this issue.

THE COURT: Okay. All right. Manual integration, this is for the Plaintiffs, have a complete set of chromatograms that you would acknowledge accurately depict Emery Pharma's data been filed anywhere in the record?

The Court understands that there was disagreement during Dr. Najafi's deposition over whether the chromatograms being shown to him accurately depicted the laboratory's data.

The Court is asking because it would like to have some understanding of the extent of Emery Pharma's manual integration, when processing its chromatography results,

whether manual integration was conducted more frequently during some studies than others, because the Defendants have contended on page 41 of their motion, that, "many of the Emery Pharma integrations were manual," and I didn't see where the Plaintiffs responded concerning the extent of manual integration.

So, could you address that first part of the question?

MS. BOGDAN: By its very nature of LC-MS/MS, your Honor, it is electronic data, it is generated, there are millions and millions of data points. So, the chromatograms that are generated from the LC-MS/MS data, as my colleague, Mr. Nigh, explained, they are set, they are preserved data. It is locked down by the program, so the chromatograms that are generated from that data out of MassHunter are the native chromatograms.

THE COURT: So, is the complete set part of the Court record?

MS. BOGDAN: Pardon me?

THE COURT: Is a complete set of the chromatograms part of the record?

MS. BOGDAN: We were not able to give the Court the raw data, it looks like gobbledygook, symbols and that type of thing. It has to be put through a widely available and well utilized system, which is Agilent, which is one of the main sellers and makers of LC-MS/MS systems, as well as software.

MassHunter is just Agilent, it is their proprietary software system.

So, I could not give the Court the raw data, it would looks like it looks, as far as when you put it in a Word document, you can't look at it that way.

What is important to understand here is that the native data and all the data that we provided to the Defendants actually creates the chromatograms, and they can be looked at. So, there are issues with the pdf's and their production, and Dr. Najafi cannot verify someone else's production.

THE COURT: How would the Court ascertain the frequency or lack of frequency of manual integration performed by Emery Pharma?

MS. BOGDAN: Manual integration, that is a matter of interpretation. It is something that experts do. The fact that the system gives you an auto integration, meaning it draws a line for you, but then it is actually imperative, and as Dr. Najafi explained during his testimony, for an analyst, a trained and skilled analyst to look at that line.

It is also by described by Mr. Steffy in his declaration, and then that is the judgment of the expert as to where that line is drawn.

The information is fully available in the LC-MS/MS MassHunter system, but the idea that more manual integration is bad, auto integration is good, that is completely something

that is up to and in the province of an expert to be able to explain, because if the computer, for example, is -- you are running an SGF meat matrix, right, it is not necessarily used for that.

So, the analyst has to make that call, you know --

THE COURT: I have to have you wrap up the answer. I have a lot more questions.

MS. BOGDAN: If the Court would like the data, we can provide the data, and we provided it to everybody, and it is absolutely something that any skilled chemist can analyze and look at, and quite frankly, the Defendants do not disagree that the native data can be processed. They can look at it.

Every one of their experts could have taken this data and done their analysis on it and done a comparison with the results that Emery has, they just haven't done it.

THE COURT: Okay. For the Plaintiffs, the Defendants contend in their motion that Dr. Najafi "has not produced any audit trails," which the Court understands would be trails that shows sequences of integrations that were made to chromatography data.

The Court understands that Plaintiffs argue that the software program Emery Pharma uses called the MassHunter automatically saves the original unaltered data, but in terms of the original -- in terms of a trail showing how the quantities that Dr. Najafi includes in his expert report would

derive from the original data, did Emery Pharma maintain such trails; and if so, have they been filed in the record so the Court would have a sense of what they look like?

MS. BOGDAN: What the Defense is referring to would be a CGMP or GLP type of audit trail, I am assuming, which obviously this was not CGMP or GLP work. Those standards are specifically for a drug or manufacturing of a drug that is for sale for people. Research and development is done with the protocols and with all of the checks and the balances and all the protocols and everything we provided to the Court following accepted practices, which were outlined in the peer reviewed studies, et cetera.

With regard to your question, I don't want to -- the printouts of the pdf's that Benotti created, while they don't accurately reflect the data that was given, as explained by Dr. Steffy, it is not for me to explain, but there are little asterisks on those where you can see what he printed, if there are manual integration, but the audit that you are talking about, there is nothing in the native data that shows that.

However, if you take the computer-generated chromatogram from the native data, and you see where the line is drawn, and you take that line, which is a matter of expert judgment -- this is, you know, outside of the locked down data, this is interpretation, which we talked about in our papers, different. They have experts, a lot of them, they could all do

their own interpretation, they are choosing not to.

But you could take that line on the chromatogram and move it, and when you move it, it shows you the quants, how meaning how much NDMA is in the sample.

THE COURT: I understand.

MS. BOGDAN: So, if it is showing the quant that Emery reported, it is the auto generated one, you just move the line.

THE COURT: That is pretty much what the Court would look to.

MS. BOGDAN: Yes.

THE COURT: Got it. From the Defendants, other than the quote from the Rule 30(b)(6) deposition that you included on slide 13 of your presentation, is there evidence that is in the court record that Emery Pharma has generated and produced chromatograms in pdf format for other clients or in other litigation?

MS. LUHANA: I am sorry, Judge, could I raise one point?

THE COURT: I want them to answer. I am just worried about time. In answering another question you can supplement it.

With the Defendants answer to the question, I just asked, if you have a brief response to any of the argument from Plaintiffs regarding integration.

MR. BOSSO: For the first question, the evidence we

gave you, is all the evidence we have. We got that through discovery and it was limited to just Ranitidine testing.

Those were the only reports we had, so it is not that many reports, but a hundred percent of the reports had chromatograms.

The other big issue I would point out is that Dr. Najafi and Plaintiffs here say they don't have to follow GLP, GMP. They claim that they followed this arbitrary research and development standard. If you actually pull up those pdf's, they are titled Research and Development. So, in their traditional work, research and development, this is the type of report they would generate. We didn't get that here.

In terms of your second question, about the manual integrations, there are a few things. It is important for this Court to understand manual integration is an opportunity for the analyst to make manipulations to the data, and so we should be able to review that data and be able to ensure its reliability.

Now, there was a comment made about expert judgment. The experts on the Plaintiffs' side who did this are not put forth as experts in this litigation. The only experts in this litigation who can talk about the reliability of Emery's processing are Defendants.

Now, Plaintiffs carry the burden of proving that Dr. Najafi's opinions are reliable, including that they are on the

basis of reliable facts.

If they have not put forth any expert who can actually come to this Court or on cross-examination explain why is their chromatography reliable, there is no way for them to meet their burden.

THE COURT: Thank you.

MS. LUHANA: Judge, may I raise one point about CGMP?

Defendants routinely do studies where they don't -- and experiments where they don't follow CGMP. In fact, I, myself, deposed Dr. Guengerich and Dr. Lindsey. They continue to raise CGMP as an issue. They have research labs where they work for pharmaceutical companies 90 percent of the time, and I asked them how often do they follow CGMP, and they said never.

They never do testing per CGMP. That is a red herring. All the experiments Dr. Najafi did are research and development experiments, not for drug manufacturing, and that is what CGMP is for.

THE COURT: Okay. I know there has been a lot of mention of that, and I want to make sure I have -- if this is contained in the FDA documents. To the extent any FDA documents were referenced during the question and answer part of this session, I want to make sure that there can be an agreement that you can get them together and give them to me. That would be helpful.

So, on the topic of internal standards, Plaintiffs,

can you provide the Court with an explanation of internal standards as they are used as part of chromatography? The Court is interested in what internal standards can show about the accuracy and validity of chromatography results and what they do not show.

For example, can internal standards show whether the method of chromatography is sufficiently separating an analyte, or show whether the method might be causing NDMA to form, or show anything about the accuracy of manual integration?

Brief answer from Plaintiffs, brief answer from Defendants.

MR. SELIGNAN: Sure. The internal standard is when a sample is spiked with NDMA 6, which is a chemical isotope of NDMA. So, it reacts identically to the testing apparatus, and so you can measure in the exact same sample how much NDMA 6 is put in, and how much NDMA 6 comes out.

Now, importantly, NDMA 6 is not naturally occurring, so as a result of that, in the exact same sample you can take a pill of Ranitidine, spike it with NDMA 6, and then confirm that the known spiked amount of the isotope that is put into the sample also comes out, and that prevents any possibility of mismeasurement of artifactual generation.

THE COURT: Okay. Defendants.

MR. BOSSO: An internal standard is like putting stickers at the end of the NDMA molecule so that you can

identify the one that has stickers versus the NDMA molecule that does not have stickers.

Ranitidine, if you just have a standard Ranitidine molecule that artifactually generates NDMA, it is only ever going to generate the naturally occurring NDMA. It is never going to create the stickered version of NDMA. There is no way that an internal standard could ever prove -- there is no way for an internal standard to ever disprove that artifactual NDMA formation is occurring. It is just not a possibility.

THE COURT: Okay. As long as you are up, I will ask you this question, then I will go back to Plaintiffs.

Some of the internal standard chromatograms entered as exhibits during Dr. Najafi's deposition show an asterisk, which the Court understands from Dr. Najafi's testimony indicates that manual integration was performed.

Why would a test and internal standard be manually integrated? If a laboratory analyst is manually adjusting the results, are the results still useful as a standard?

MR. BOSSO: So, why did Dr. Najafi have to manually integrate his internal standard is the question, so this is best answered by looking at one of the documents that we have. This is part of the Court record, and I believe we mentioned it in our briefing.

It is actually the actual SOP guidelines that Dr. Najafi at one point had said we would reference those for

integration. Those guidelines say that if you constantly have to manually integrate, it means that there is something wrong with the method.

So, if Dr. Najafi's analysts are having to manually integrate an internal standard, that is further evidence that there is something wrong with the method, because they cannot just have a computer get the correct value.

THE COURT: Thank you. Brief response from Plaintiffs.

MR. SELIGNAN: So, the use of manual integration is a standard practice in analytical chemistry and it would need to be done regardless of the context of the testing, including using an internal standard. The reason is because the algorithm in the MassHunter software draws a line underneath the curve automatically to calculate the area under the curve, but the artificial intelligence doesn't yet match human scientific expert judgment.

That issue is going to arise about the insufficiency of the algorithm whether you are testing a blank, whether you are testing SGF, whether you are testing a Ranitidine pill, whether you are testing an internal standard. That is -- the issue of integration comes up just whenever you are testing anything by chromatography and mass spectrometry.

Now, the Defendants have suggested numerous times that there is something improper about manual integration, and there

is not. So, manual integration is necessary precisely because the artificial intelligence of the algorithms are not yet perfect, and so I will quote from Dr. Steffy's declaration that was attached to the opposition to the motion to strike.

It is a little bit of a long --

THE COURT: Just give me the Docket Entry and number.

MR. SELIGNAN: I don't have the docket number, but it is paragraph 11. I will say one sentence then.

"An analyst reviews" --

THE COURT: Read the one sentence slowly.

MR. SELIGNAN: Sure. I apologize. I am new here.

THE COURT: You will learn quickly.

MR. SELIGNAN: Thank you your Honor, my apologies.

This is in paragraph 11 of Dr. Steffy's declaration, and I will get you the docket entry.

"An analyst's review and interpretation of the native data chromatography is a necessary and well accepted practice in the field of analytical chemistry."

So, that is in the record, this is a standard practice. There is nothing improper.

THE COURT: If you want to tack that on to the final remarks, that would be fine. I need kind of succinct answers to my questions.

Plaintiffs, we are talking about study controls now, Dr. Najafi states in his rebuttal report that no study protocol

was necessary for Emery Pharma's long-term refrigeration stability study because "the study was performed as a control." That is at Docket Entry 5698-11 at 24.

Is there authority for a proposition that a study intended to be a control does not need a protocol, yes or no? Are you able to answer yes or no? This is what you all do to deponents all the time.

MS. BOGDAN: I want you to understand the stability study was taking the product and putting it in a refrigerator at 4 degrees. That is the stability study, to verify GSK was correct, that if you put the product at 4 degrees it will stop NDMA formation.

THE COURT: I'm sorry. So, a study intended to be a control does or does not need a protocol?

MS. BOGDAN: It depends on the study.

THE COURT: Did the study in this case need it?

MS. BOGDAN: No. It involved taking the product and putting it in a refrigerator at 4 degrees.

THE COURT: So, no for that reason.

MS. BOGDAN: Yes. Yes and no, see I said both.

THE COURT: I am trying to think what the most efficient way to do this is.

Let me ask a followup question. What other study was the long-term refrigeration stability study a control for, or what does it otherwise mean to say that the refrigeration

stability study was a control?

MS. BOGDAN: The product, when it was received, was immediately put into the refrigerator. The stability study was done simply to check, as GSK had represented in its root cause analysis, that that would stop NDMA formation, so that the time period that took place between when they received the sample and when they were actually able to test the sample, that the samples would have the amount of NDMA in them as of the date that they were received.

They did it as a precaution instead of just leaving it in ambient temperature, which, by the way, would be the way the product was said to be stored, but they put it in the refrigerator because they wanted to arrest any NDMA formation that took place once they received it.

THE COURT: Okay. I will keep asking you, and then I will ask the same questions of the Defendants. I think it's easier since you are at the podium.

Turning to the SGF study that Emery Pharma conducted with food, the Plaintiffs argue that the tests with Ranitidine alone, NGSGF, and with meat alone, NSGF, both of which did not detect any NDMA, were controls that demonstrate the validity of the testing methods. That is at Docket Entry 5914, at 22 and 31.

Can you explain to the Court how these controls demonstrate method validity?

MS. BOGDAN: You are doing the study in a matrix, which is SGF, so you want to make sure that it is the combination of the meat and the drug that is causing the NDMA formation. So, by doing meat alone, you make sure it is not just the meat in the SGF fluid.

By doing the Ranitidine alone, you make sure that if there was any NDMA, you would know what it is, but those are controls that are done as part of the study to make sure when you are contributing NDMA formation to the condition of meat and Ranitidine in SGF, that it is a result of the interaction between the two.

THE COURT: Do the controls -- don't the controls for the SGF study with food demonstrate Emery Pharma's limit of detection was too high, given that Dr. Najafi does not report any test results where no NDMA was found in Ranitidine, and given that meats such as the ones Emery Pharma used for the study have been shown to contain NDMA?

In other words, how were the controls helpful when they did not measure the NDMA that logically would have been present in the Ranitidine and the meats?

MS. BOGDAN: They used Ranitidine with a known amount of NDMA and I would have -- I don't have the protocols up here in front of me, but I have a pretty good memory, but that was at known, and I believe they used Ranitidine with lower values.

With regard to the meat itself, they tested it in the

SGF and showed that there was no NDMA formed, and then they measured the nitrate concentration in the meat, which matched FDA values.

THE COURT: Najafi states in his rebuttal report when talking about the tablet bottles that he used during the studies and the impact it may or may not have on NDMA formation that, "in fact, the design of its experiments, DOE, analysis conducted in GSK's root cause analysis, RCA, confirmed that the nature of the container closure system head space issue is irrelevant." Docket Entry 5698-11 at 6.

What GSK analysis was he referring to? Was it contained in a document; and if so, where can the Court find it?

MS. BOGDAN: That I would have to have the root cause analysis in front of me to be able to direct the Court appropriately. It is a very lengthy document.

THE COURT: It is, and I will ask you not only the page, but where it is.

MS. BOGDAN: I will be happy to do that, but I can't do it on the fly.

THE COURT: No problem. Okay. Defendants, same questions. Do you want me to repeat them or do you get the gist of what I was asking?

MR. BOSSO: What was the first question?

THE COURT: The first one was that Dr. Najafi states

in his rebuttal report that no study protocol was necessary. I was asking the authority for the proposition that a study intended to be a control does not need a protocol, and then what other study was the long-term refrigeration stability study a control for? What does it otherwise mean to say the refrigeration stability study was a control, and then I went on from there with the SGF study.

Really, less kind of a question, and more, did you have any response to the Plaintiffs? You don't have to have a response.

MR. BOSSO: Just that protocols are the basic fundamental part of the scientific method, so every study needs a protocol.

THE COURT: Let's move on to the topic of peer review.

For the Plaintiffs, you and Dr. Najafi have contended that orders, and I know this was part of your presentation, entered in this litigation preclude Emery Pharma's work from being peer reviewed, Docket Entry 5914, at pages 29 to 30. The Defendants -- and you had some presentation here today.

Defendants, in turn, maintain that it is not clear what must be kept confidential for this litigation that would prevent peer review. That is at Docket Entry 5956, at 17.

I want to make sure the Court is abundantly clear, precisely what information and pursuant to what orders or agreements do the Plaintiffs maintain must be confidential now

that precludes peer review of Emery Pharma's work product, and did Plaintiffs ever make any request to me or Judge Reinhart to lift any restriction imposed by court order, if one exists, to enable peer review of Emery Pharma's work?

MR. McGLAMRY: Your Honor, I can do this one.

THE COURT: Okay. Start with introducing your name for the record.

MR. McGLAMRY: Mike McGlamry for Plaintiffs.

THE COURT: Did anyone make any request of either Judge Reinhart or of me to lift any restriction? Then tell me precisely what the restriction is, but was any request made?

MR. McGLAMRY: No.

THE COURT: Were there any restrictions other than -- any purported restrictions other than those which you have put on the screen? If you want to get those -- I don't know if you were looking for copies of those. I am trying to understand the Plaintiffs' argument on this.

MR. McGLAMRY: Sure. Like anything that you have heard today, it is not as simple as just this.

THE COURT: We have to keep it simple.

MR. McGLAMRY: I am going to go not too fast.

THE COURT: Simple, but not too fast.

MR. McGLAMRY: We went through this process, to get the product. You know it took a long time.

THE COURT: Yes.

MR. McGLAMRY: There were several components to that. One are these inventory lists the Defendants provide of their material.

THE COURT: Right. I am sorry to cut you off, but it is 3:00, and we have summary judgment. I know all of that. I just want to understand, just tell me what has kept the Plaintiffs from being able to try to peer review.

Maybe Najafi didn't want to, and that is fine. I am not saying he had to, but it seems like there is an argument he couldn't. He wanted to, but he couldn't have. Just in a nutshell.

MR. McGLAMRY: From our perspective, we didn't believe he could, because the orders say you can't, in our opinion, and it was an order prepared by the Defense that we worked with the special master to put together. It says it can only be used for litigation purposes, so it is not just a we had an order. We did have a confidentiality order, as was referenced before, and somebody could have said, well, we want to make a change to that.

Ultimately, when it came down to the product being produced to us, part of that process, it was determined that we couldn't use it except in litigation, and the Court ordered that.

It is not like, okay, now we come back and ask, can we use it, and, so, in our opinion, it is very clear in the

context of the orders, and that is how we interpreted it when we were asked to agree to it.

THE COURT: Okay. All right. And I know the screens did present the different orders. Did the Defendants want to be heard briefly on that issue before I move to my final -- I actually have one more topic.

MR. BAYMAN: On a nontechnical one, I can handle this.

THE COURT: The history major.

MR. BAYMAN: That's right. As the Court may recall, we moved the Court to unseal the Plaintiffs' expert reports, including Dr. Najafi's, and the Court granted that. So, the results of his testing, to the extent they are in his report, they are in the public domain already, they have been unsealed. And as I mentioned earlier, this can't be used for any commercial purposes was because of -- for Customs reasons.

The product was being sent in from Mexico to -- from Mexico BI to California, and we had to make it clear for purposes of Customs that the Plaintiffs couldn't resell the product. That is what commercial purposes means.

There is nothing preventing Dr. Najafi from publishing the results of his testing if the -- the documents from the batch records were marked as confidential, the lot numbers, things like that. That doesn't prevent him from producing the results of the testing and often in peer reviewed publications the authors say product one, product two, product three without

any further description. The only thing that prevents him from producing it is, it is not publishable quality, and he admitted that.

MR. McGLAMRY: Your Honor, may I say one sentence?

THE COURT: You can save it. We are using the end of the day as the catchall. I hope you are keeping a list of everything that you wanted to say, but couldn't say, but we need to get to the end of the day. Between this and that are a few more questions.

Plaintiffs, between pages 15 and 17 of Dr. Najafi's rebuttal report he cites studies by Braunstein, Aizawa, and Yoku to substantiate the temperatures and levels of humidity that Emery Pharma applied to Ranitidine during its simulated consumer experience testing, Docket Entry 5698-11, at 17 to 19.

Were any of those three studies peer reviewed? That is a yes or no.

MS. BOGDAN: Your Honor --

THE COURT: Or if you need to look at it and get back to me.

MS. BOGDAN: I need to look at them. There is one of the studies that I know was publically published and not peer reviewed, but I would want to give the Court very accurate information. I would prefer to be able to take the time at the break and come back and tell you exactly --

THE COURT: Perfect.

MS. BOGDAN: It was a difficult thing to find published information on, because we are talking about temperatures in vehicles, etc. They were from Government authorities and things like that.

THE COURT: Okay. So, for the Plaintiffs, page 13 of the Defendants' motion and page 41 of Dr. Olsen's report indicate that the maximum level of NDMA that the FDA found in a 150 milligram dose of Ranitidine is around 445 or 465 nanograms. That is coming from Docket Entry 5698 at 16.

Would you agree that is the maximum level of NDMA that the FDA has discovered in a 150-milligram dose of Ranitidine, yes or no?

MR. NIGH: I'm sorry, did you say that question was for the Plaintiffs?

THE COURT: Yes.

MR. NIGH: I missed the beginning, your Honor.

THE COURT: Page 13 of the Defendants' motion and page 14 of Dr. Olsen's report indicate that the maximum level of NDMA that the FDA found in a 150-milligram dose of Ranitidine is around 445 or 465 nanograms.

Would you agree that is the maximum level NDMA that the FDA has discovered in a 150-milligram dose of Ranitidine?

MR. NIGH: Other than the fact that the FDA has notice of Sanofi's testing, the result that I put up there on the screen earlier, that was 869 nanograms of NDMA, yes, I believe

that is accurate.

THE COURT: Okay. And then for the Plaintiffs, Dr. Najafi responds on page 22 of his rebuttal report to a criticism that Emery Pharma's testing of active pharmaceutical ingredient, API, for NDMA is irrelevant to this litigation because consumers do not ingest API. He states, "we have further demonstrated that the drug product making process does not influence NDMA levels," at Docket Entry 5698-11, at 24.

Can you tell me where in any of Dr. Najafi's reports he makes this demonstration, that we have further demonstrated that the drug-making process does not influence NDMA levels? So he says he has demonstrated that.

I don't know what he meant by that or where it was.

MR. SELIGNAN: Your Honor, I will have to get back to you with the exact citation of the place in Dr. Najafi's main report.

So, Emery Pharma actually used API and then made their own tablets, and they tested on both ends of that to see whether the process of putting the API into a finished tablet created NDMA, and through that comparison they determined that the -- that is the drug-making process that he is referring to in his rebuttal report. It is really the tablet making process.

We will get that citation to you.

THE COURT: Plaintiffs and Defense have been keeping a

list of anything that you were going to get back to me on? Okay. I have been pretty distracted up here so I have not kept one.

So, what I would like is in your closing to give me the answer -- kind of reference the question I asked that you weren't able to answer and answer it. If you can't answer it, just tell me that and then I can make a decision whether I want anything further to be supplemented on the record. I won't know that unless you tell me, you looked and you don't have the answer, which is fine. I'd rather you tell me you don't have the answer than something inaccurate.

Two more questions and then we are going to take a break.

MR. SELIGNAN: Your Honor, I can quickly tell you right now, it's paragraphs 262 to 264 of Dr. Najafi's main report.

THE COURT: 262 to 264 of his main report?

MR. SELIGNAN: That is correct.

THE COURT: Thank you. This goes back to questions that might have even been before lunch, so we have to remember -- those who were talking about extrapolation and -- species extrapolation and dose extrapolation, can we have that team back up here from the Plaintiffs.

Earlier today I asked you about whether you argued how and why your experts conducted a species extrapolation and a

dose extrapolation from their animal studies. I want to clarify what I was asking when I asked that question so there is no confusion. This is the Court speaking.

There is a difference between dose response relationship and a dose extrapolation as it relates to your experts' reliance on animal studies. Just listen to my definition here, of dose response relationship, dose extrapolation, and species extrapolation and answer my questions based on my definition. Hopefully they are not woefully inadequate or incorrect. I am doing this so that we are all thinking about the same thing when you are answering the question.

Dose response relationship describes how changes in the amount or duration of exposure to Ranitidine affects the risk of disease, either by increasing or decreasing that risk. That is not what I am asking about here.

Rather, dose extrapolation, which is what I am asking about, is an inference that researchers make when drawing from human beings based on the doses that were administered to the animals in your experts' animal studies. In other words, the question of dose extrapolation is a question of whether you explained how and why your experts could draw conclusions about human beings given the doses that were administered to animals in those studies.

So, please tell me whether you explained how and why

your experts were able to extrapolate by dose from animal studies to humans based on these definitions. So, when you were answering before, tell me whether you explained how and why your experts were able to extrapolate by dose from animal studies to humans based on these definitions.

If you don't think you provided such an explanation -- or if you did provide such an explanation, just tell me where you did that.

MS. LUHANA: Roopal Luhana for the Plaintiffs. Judge, I believe that there is a fairly simple answer to your question. Our experts do not do dose extrapolation from animal data to human data.

I will note, though, PETO, which is the most robust carcinogenicity study, is what is utilized by the FDA to set an ADI for NDMA. Our experts look at the animal studies for biological plausibility because they are animal studies and applying it for the totality of the evidence using the Bradford-Hill criteria. Our experts are not doing dose extrapolation.

THE COURT: Okay. Similarly, species extrapolation is an inference that researchers make when drawing conclusions about humans based on different species. In other words, the question of species extrapolation is a question of whether you explained how and why your experts were able to draw conclusions about human beings based on data derived from

different species of animals accounting for differences and similarities between species.

Can you tell me whether you explained how and why your experts were able to extrapolate by dose from animal species to humans based on these definitions?

MS. LUHANA: Once again, Your Honor, I don't think our experts extrapolate from animals to apply it to humans, although the IARC does note qualitatively NDMA acts the same in animals and humans. However, the metabolism in animals and humans is very different and we rely on the Gombar studies to look at the viability, of NDMA, but we are not extrapolating and taking those numbers to apply them to humans. We are relying on human epidemiological data and doses to come up with our dose response calculations.

THE COURT: Thank you.

This is one lingering question on the GCMS and the Matsuda, Krawczynski. So, the Defendants made the argument in their remaining opinions motion that studies that use GCMS are not reliable, or at least they are not reliable when they are testing Ranitidine. That argument appears at Docket Entry 5696, at page 8.

That argument is premised upon the FDA's conclusion that GCMS is not a reliable method to test Ranitidine for NDMA. This morning, I think you conceded that GCMS is not a reliable method to test Ranitidine for NDMA.

The Defendants have argued that the Plaintiffs have not identified any reliable studies for their endogenous formation argument, that is page 11 of their motion.

In response, the Plaintiffs have identified Matsuda and Krawczynski. Those studies use GCMS. This morning when I questioned Plaintiffs about GCMS and Krawczynski, the response from Plaintiffs was that Krawczynski was not testing Ranitidine pills, they were testing, for example, stomach fluid, and since that study was testing stomach fluid, not Ranitidine pills, the concerns about the reliability of GCMS did not apply.

What I am trying to understand is when researchers in studies such as Krawczynski tested the stomach fluid, why wasn't Ranitidine present in the stomach fluid, and therefore in the GCMS test?

For example, from Dr. Le's report, at page 8, she says there is "significant variability in oral bioavailability, a wide range, of 39 percent, to 88 percent of Ranitidine." My understanding is that she is saying that some amount of Ranitidine is not metabolized prior to reaching the bloodstream, so using the most conservative of her numbers, as much as 61 percent, say, of Ranitidine would pass from the stomach eventually into the bloodstream.

So, I wanted you to explain, if you could, your position that the stomach fluid in these studies that use GCMS, would not contain Ranitidine, meaning the GCMS was not

measuring Ranitidine, and reconciling your answer with your expert's opinion that Ranitidine is available in the blood.

MS. LUHANA: Judge, while our experts rely on Matsuda and Krawczynski, there is a bevy of scientific literature that shows endogenous formation and NDMA is resulting from Ranitidine, and this goes back to Mervish, Singer, Gallot. If you look at those studies, that is the reason why GSK did the Tanner study in 1982. In fact, the introduction of the Tanner study starts out with: Ranitidine contains a dimethylamine. There is concern that a dimethylamine with nitrite can form NDMA.

THE COURT: I am going to get to the Tanner study. I am sorry to interrupt. Are you able, though, to answer the question that the stomach fluid, does it contain the Ranitidine or not?

MS. LUHANA: With Matsuda, there were fasting samples and they didn't have Ranitidine in them and they didn't have the other H2RAs. That was when the NDMA was detected there.

In terms of Krawczynski, we are finding an answer for you, however, if there was Ranitidine in those samples, because they did those fluid tests at the end of treatment, if there was Ranitidine in those samples, you would have seen a spike in every single child that was tested, and there were some samples that had no NDMA and there were others that had some and there were others that had a lot.

THE COURT: But weren't the measurements taken after the Ranitidine was added?

MS. LUHANA: No, no, it was after treatment completely. So they were treated with Ranitidine for four weeks, in Krawczynski, and at the end of it they tested their gastric fluid to see if they found nitrosamines, and they found a statistically significant increase of several nitrosamines and they report that. That was at the end of treatment that it was reported.

My point to you is, if GCMS was causing these, it would cause a significant elevated spike in every single child's gastric fluid samples, but that wasn't seen. There were some kids that had no nitrosamines, others that had some, which is indicating the testing is working to detect NDMA accurately.

MR. NIGH: Your Honor, if I may, too, that 61 percent from the stomach to the bloodstream for Ranitidine, that is coming from Dr. Le's report, that doesn't speak to the timing of how long it takes to go from the stomach to the bloodstream and then empty from the bloodstream out the body.

The question is: Stomach to the bloodstream, would there still be some retained in the stomach? I don't think that that statistic from Dr. Le answers that question.

THE COURT: Do we know what is the timing from the stomach to the bloodstream? Do you have record evidence of

that from any of the experts?

MS. FINKEN: Your Honor, Tracy Finken on behalf of Plaintiffs. The evidence is two to three hours when Ranitidine is out of the stomach, so it would not be present after treatment when they took the gastric fluid samples from all of the children to measure whether there were nitrosamines in the stomach. I will get you a citation in the record on the two to three hour range.

MR. NIGH: The other part of it was, as Rosemary Bogdan stated earlier, there is a double -- I forget the name of the wording -- heteroptic loop, which it comes back into the stomach and that would be -- oh, that's for NDMA, never mind.

THE COURT: What about the timing of the NDMA in the stomach?

MR. NIGH: I didn't mean to interrupt. I apologize. That was for Ranitidine, it comes back into the stomach five to six hours later.

THE COURT: How long does it stay in the stomach?

MR. NIGH: That is the peak, and I don't know the half life thereafter. Generally when you peak, it is a couple of hours thereafter that it goes back out.

THE COURT: So, Tanner -- studies such as Tanner, which the Plaintiffs rely upon and which the Plaintiffs say stands for the proposition that as much as 3 percent of Ranitidine can transform into NDMA, does that mean, then, that

97 percent of Ranitidine would not transform and as much as 61 percent of that Ranitidine would not be absorbed into the body?

So, it goes back to the question of why wouldn't there be Ranitidine present in the stomach fluid at the time of testing, and studies such as Krawczynski? So it is following up.

MS. LUHANA: With the Tanner study, there was a 3.1 yield, of NDMA that was generated, 232 micrograms, so that is 232,000 nanograms. I recall there was only 62 percent that was recovered of NDMA, so there was still a lot of NDMA that wasn't recovered from that test. It was greater than 232 micrograms.

Your question was specifically? I apologize.

THE COURT: Going back to the question, of why wouldn't there be Ranitidine present in the stomach fluid at the time of testing in Krawczynski.

MR. NIGH: Your Honor, I can address this, as well. Dr. Le's figures are going to help to address this. We are talking about hours for Ranitidine, how long it is in the stomach. Krawczynski is four to six weeks later. It's not even close.

THE COURT: Did Matsuda test four to six weeks later, too?

MS. LUHANA: Matsuda tested over a period of two months to three years.

THE COURT: After?

MS. LUHANA: No. It was during duration and after treatment as well. We can get those specifics for you, but that is why those studies are so critical, because it is chronicity. You need it for a long period of time, and you need to test the right population, and then you see a lot of NDMA being generated there.

THE COURT: Okay. Okay, good, now we can take our break. We are just a little off schedule. Why don't we take a break for 15 minutes. We'll be back at 3:35, and we will start our summary judgment. We will be in recess.

(Thereupon, a brief recess was taken.)

THE COURT: Okay, you may be seated. Thank you.

Okay, we have now the motions for summary judgment at Docket Entry 5697. Each side had asked for 15 minutes. Starting with the Defense.

MS. RYDSTROM: Thank you, your Honor, Jessica Rydstrom. I am hoping to atone for going over in time this morning by coming in under time, on this particular argument. So much so, that if I keep that promise, with the Court's indulgence, perhaps I might have a few minutes to respond to what Mr. Gilbert has to say.

This motion, your Honor, is a bit of a palate cleanser, because, in our view, it is pretty straightforward. I don't think the following is ultimately disputed, that if the

Plaintiffs do not have expert testimony to support their general causation opinion, then they cannot prove general causation.

If they cannot produce general causation, then summary judgment is, of course, appropriate on one or all of the cancers for which Plaintiffs are articulating their claims.

Now, those summary judgments, are, of, course, dependent on the Daubert rulings, that we are going to receive from the Court. On this voluminous record, we submit that, as you have heard over the course of the past two days, Plaintiffs' experts simply do not have reliable testimony and reliable opinions that are the product of those scientific methodologies that Daubert and the cases tells us they have to have.

They don't have that, your Honor, because they have not shown an association between Ranitidine on the one hand and an increased risk of the five designated cancers on the other hand that is free from chance, bias, and confounding, and that is what the Eleventh Circuit, of course, requires.

We know that they can't bootstrap their way into general causation with any of those secondary methodologies that we talked about this morning and that were the subject of the Court's questions throughout this part of the day.

So, if the epidemiology is out, in other words, as the Court knows, if it grants Defendants' motion to exclude the

epidemiological experts, then summary judgment is appropriate.

We don't know that, of course, until we receive the Court's rulings, but what do we know, today? We know tas of July 18th, because Plaintiffs put it in their papers to the Court, that Plaintiffs' general causation theory in this litigation is for long term use of Ranitidine. The claim is not that Ranitidine causes cancer after one dose or even a year's worth, but over many years of regular use.

We saw that quote in the introductions, your Honor. You asked the Plaintiffs about it yesterday, can I hold you to this statement, does this still hold true, and they told you, your Honor, that it does.

Now, that doesn't meet the standard, right? Many years of regular use is not a dose, it is not a duration, it is not an amount. As Mr. Petrosinelli said yesterday, that is a description.

Now, presumably Plaintiffs are going to stand up in their closing and answer the question that the Court posed for them today and that the Defendants have been asking since the beginning of this litigation, and that is, how much is too much, right? The how much is too much is the question that McClain tells us Plaintiffs have to answer in this litigation.

We are going to respond to that. We will respond to whatever it is that Plaintiffs put forth, and I suspect that we are going to disagree with whatever it is that the Plaintiffs

say that they are able to present by way of expert testimony on that question.

The Court is going to decide whether or not that is the product of reliable scientific methodologies and whether it is consistent with what they are telling the Court. We think the answers to those questions are going to be no.

We think that the Court doesn't have to reach them, of course, if it is with us on the subject of day one, that epidemiological evidence, without an association that is free of the risk of chance, bias, or confounding, your Honor, Plaintiffs simply cannot sustain their claims, and summary judgment would be appropriate.

Thank you.

THE COURT: You did come under, that was 4, 19.

And from the Plaintiffs.

MR. GILBERT: May it please the Court, Robert Gilbert, co-lead counsel for the Plaintiffs. Good afternoon, your Honor.

THE COURT: Good afternoon.

MR. GILBERT: The good news is I will be even briefer than my colleague, Ms. Rydstrom.

At the time the Court established the Daubert briefing process, your Honor also gave the parties the opportunity to file a proforma summary judgment motion on the issue of general causation. You had a specific reason in mind. We discussed

that at a meeting with you and the co-leads from the other side.

Defendants indeed filed a proforma motion for summary judgment as part of their road map Daubert brief, arguing that Plaintiffs are unable to establish general causation because all of our general causation experts must be excluded under Rule 702.

As you know from our papers, Defendants' motion did not comply with the Local Rule, 56(a)(1), which requires that a statement of undisputed material facts be submitted with the motion itself, and this alone is grounds for denying the motion.

More importantly on the merits, your Honor, Defendants' motion must be denied because Plaintiffs' general causation experts, through their reports and sworn testimony and other admissible evidence in the record, a lot of which you have heard about today, but all of which you have read about over the course of the summer, demonstrate conclusively that Plaintiffs have satisfied our burden of showing there is admissible evidence supporting claims that NDMA in Ranitidine is capable of causing the five designated cancers at exposure levels users might have reasonably experienced.

There is yet another reason for denying summary judgment. As noted earlier, Defendants did not challenge one of Plaintiffs' general causation experts, Dr. Errol Zeiger.

Like our other experts, Dr. Zeiger has unassailable qualifications. He performed and directed genetic toxicology testing, data analysis, and research at the FDA for seven years, as well as for 24 years at the National Institute of Environmental Health Sciences, an arm of NIH.

He served as an expert panelist during the FDA's expert 2021 workshop on nitrosamines as impurities in drugs. Dr. Zeiger offered multiple opinions regarding the genotoxicity and carcinogenicity of NDMA which are directly applicable to NDMA and Ranitidine.

Dr. Zeiger's opinions are unchallenged, and they demonstrate that Defendants' Daubert motions should be analyzed under the McClain one standard because the scientific and medical community generally recognizes the toxicity of NDMA to cause cancer in humans.

Moreover, even if the Court does not analyze this Daubert challenge under the relaxed McClain one standard, Dr. Zeiger's unchallenged opinions create a genuine issue of material fact further supporting the denial of summary judgment.

To be clear, this case is very different, in a very different posture, your Honor, than Chapman, where the Plaintiffs sought to designate new experts after the Court had already ruled on Daubert.

Here, Plaintiffs designated Dr. Zeiger as one of our

general causation experts at the same time as all of our other general causation experts. We provided Dr. Zeiger's expert report and he was deposed by the Defendants.

Defendants consciously chose not to challenge Dr. Zeiger under Rule 702, and therefore they forfeited this evidentiary objection to his testimony at trial. Therefore, Dr. Zeiger is entitled to testify in support of general causation at trial.

For all of these reasons, as well as the record before you, Defendants' motion for summary judgment must be denied.

Thank you.

THE COURT: Thank you. I do have questions. I know you wanted a rebuttal, but maybe when you answer the question, you can include any comments that you want. Let me know you are doing it at that time. That goes for both sides, now that you have had the benefit of each other's argument.

These may or may not relate to summary judgment, but I needed a place to cabin them, so this is where the questions arise. If you need to call a friend -- if you need to call an LDC member to help you answer the question, you can do that.

This is for both parties. As you know, I asked you to be prepared to discuss Chapman, and In Re: Abilify. Abilify being at 299 F.Supp.3d 1291, Northern District of Florida, 2018, in which the Eleventh Circuit has drawn a distinction between primary and secondary evidence.

So, why don't we -- let me start with the Defendant, why don't you come up. I guess you need to hear the question. It is about Chapman, these are Chapman related, legal questions about Chapman. Whoever feels --

MS. RYDSTROM: I am calling not an LDC member, but I am calling up the chain, your Honor.

THE COURT: Question number one, and state your name for the record, do you agree -- again, these should be yes or no, and if you need to explain, let me know you need to explain.

Do you agree that the Eleventh Circuit in Chapman has deemed epidemiology, dose response relationship, and background risk of disease as three primary methodologies?

MR. PETROSINELLI: This is Joe Petrosinelli, your Honor. I do.

THE COURT: Do you agree that the Eleventh Circuit in Chapman has deemed animal studies and mechanistic evidence as secondary methodologies?

MR. PETROSINELLI: Yes, I do.

THE COURT: And that the Court in In Re: Abilify has also deemed in vitro studies secondary methodologies?

MR. PETROSINELLI: Correct. Yes.

THE COURT: This is like the perfect cross-examination.

Do you agree that the Eleventh Circuit in Chapman has

held that an expert opinion that is unsupported by primary evidence cannot withstand Daubert scrutiny?

MR. PETROSINELLI: I do, yes.

THE COURT: Do you agree that if I deny all three motions in limine, that as a result of the denial, Defendants' motion for summary judgment should be denied as well?

MR. PETROSINELLI: Correct. If they have admissible general causation testimony, then our motion saying they don't should be denied.

THE COURT: Do you agree that if I grant all three motions in limine, that as a result of the granting, Defendants' motion for summary judgment should also be granted?

MR. PETROSINELLI: Yes.

THE COURT: Do the Plaintiffs have any different answers to those questions? I am happy to go through them one by one if you want me to.

MR. GILBERT: No, I will join my colleague, Mr. Petrosinelli here. Plaintiffs agree with all of -- the same answers to all of the questions except with respect to Dr. Zeiger.

MR. PETROSINELLI: That I don't agree with because Dr. Zeiger did not offer a general causation opinion as to Ranitidine. That is why we didn't move as to him. If his testimony is admissible, that does not get them past general causation of Ranitidine.

THE COURT: He is mechanistic, isn't he?

MR. PETROSINELLI: Correct.

THE COURT: Do Plaintiffs agree he is not a general causation expert?

MR. GILBERT: Our position is that he is a general causation expert.

THE COURT: How?

MR. GILBERT: With regard to the genotoxic effect of NDMA and would -- would, together with specific causation experts at trial, be able to establish general causation.

THE COURT: Does he say or does not say in his report that he is giving a general causation opinion? I know many of the experts have made it clear that they are or are not.

MR. GILBERT: I am going to phone a friend.

MS. LUHANA: Roopal Luhana for the Plaintiffs.

Judge, Dr. Zeiger gives the opinion that NDMA is a known carcinogen and would fall -- and NDMA is in Ranitidine, and we would fall under claim one, where we would go to specific causation.

THE COURT: Okay. Walk me through the steps precisely as to why you think Dr. Zeiger -- his primary evidence, that his report, his testimony, his evidence is -- falls into -- first of all, which primary evidence, epidemiology, dose, response, or background?

MS. LUHANA: He is a toxicologist.

THE COURT: So, which one?

MS. LUHANA: He is talking some about dose, and he has mechanistic evidence as well, biological plausibility.

THE COURT: That is secondary.

MS. LUHANA: I mean, well, Abilify has said specifically, I don't think you need epidemiological studies, you can still get past general causation.

THE COURT: The Plaintiffs adopted the answers that I asked of the Defendants. The second question I asked was, do you agree the Eleventh Circuit in Chapman has deemed animal studies and mechanistic evidence as secondary methodologies?

Defendants said yes and the Plaintiffs agreed with that, so if I am working from that premise that mechanistic evidence is secondary methodology, is Dr. Zeiger giving mechanistic evidence testimony, opinions; and if so, wouldn't that be secondary evidence?

MS. LUHANA: Plaintiffs are proffering if we fall into McClain one where it is established that NDMA is a toxin at issue and it is generally recognized in the medical and scientific community that it can cause cancer, then we would get to specific causation.

THE COURT: If you are not in category one, what happens?

MS. LUHANA: If we are not in category one, I would have to confer with my colleagues to see if we can get past --

pass muster with Dr. Zeiger's opinions.

THE COURT: Well, maybe that is something you can discuss and it can be addressed in closing.

MR. PETROSINELLI: Can I phone another friend? They have like three now.

MR. NIGH: It's a very quick answer. If Zeiger's testimony doesn't meet McClain one in your opinion, then, no, we don't get -- in other words --

THE COURT: If this is not a category one -- McClain one case, Zeiger doesn't get you over the summary judgment hump.

MR. NIGH: Zeiger alone.

THE COURT: Okay. Now, this is a question for the Defendants. In addition to the categorization of primary and secondary forms of evidence in Chapman, the Eleventh Circuit has explicitly stated that an expert need not rely upon epidemiology in order to pass Daubert scrutiny.

In Rider they said "it is well settled that while epidemiological studies may be powerful, evidence of causation, the lack thereof is not fatal to a Plaintiff's case." Rider versus Sandoz Pharmaceutical Corporation, 295 F.3d, 1194, at 1198, Eleventh Circuit, 2002.

Given the Eleventh Circuit's jurisprudence regarding primary evidence and epidemiology, I want to understand the Defendants' position that -- I think I heard it a number of

times -- that if Plaintiffs' epidemiology is found inadmissible, that their experts must be stricken.

In your motion for summary judgment the Defendants state, "to the extent the Court grants Defendants' epidemiology motion, it need not go further because Plaintiffs cannot proceed without reliable and admissible expert testimony that Ranitidine causes the cancers they allege." Docket Entry 5697 at 6.

How do you reconcile this statement in your summary judgment motion with the Eleventh Circuit case law outlined in Chapman, Rider, and Abilify?

What I mean by that is, three forms of primary evidence, epidemiology, dose response relationship, and background risk, I am reading the motion thinking you are arguing if epidemiology is gone, the case is over for the Plaintiffs. I want to understand that.

MR. PETROSINELLI: The reason is, because the epidemiology is what they are using to try to meet the Daubert standard and the epidemiology is what they are using to try to establish, in one expert's case, that is Dr. Salmon, a dose response relationship.

THE COURT: You are the Plaintiffs' position, as articulated through everything they have presented, including their response, that the only primary evidence they are relying upon is epidemiology and not background risk and not dose

response relationship?

MR. PETROSINELLI: They are relying on epidemiology to prove -- that is why they have two epidemiologists as their main experts, but their other experts, like Dr. Salmon, who is not an epidemiologist, in trying to calculate a dose response relationship, he is relying on epidemiology, which we will talk about in closing when we get to it.

So, whether you look at it as proceeding under epidemiology via their main experts, or trying to establish a dose response relationship through epidemiology, if the epidemiology fails, then everything fails.

THE COURT: Okay. My next question for the Plaintiffs might help clear this up. This one is for the Plaintiffs.

So, yesterday in your slides you provided a checklist of primary evidence, which included epidemiology, background risk of disease, and dose response relationship. It appeared on slide 31 of slide deck named intro deck one, 9/20/22.

On the slide you stated that your experts relied on all three forms of primary evidence, epidemiological studies, dose response relationship, background risk of disease.

I guess, what I would like you to do is respond to what the Defendants just said about your dose response relationship as far as primary evidence, and maybe you agree that the way the Plaintiffs are trying to get to dose response is through your epidemiological, so maybe that are one in the

same.

I would like you to explain that to me, but in any event, where, if at all, you have relied upon background risk of disease as one form of primary evidence. I don't think I saw that anywhere in your papers, but you have it checked off on slide 31.

MR. NIGH: I am going to address the first part of that, not the second part. Maybe my colleagues will address the second part. The first part, I have a clear answer, and that is, no, those wagons are not tied together, dose response and epidemiology are not -- the Eleventh Circuit makes it clear that it is any one of those.

Our way that we attempted that question did not tie those wagons together. To say that an expert relies on epidemiology to do a dose response is not the same thing in terms of challenges of reliable epidemiology opinions. Those are two different things.

THE COURT: I suppose if a dose response relationship expert relies on his or her -- on an epidemiology study that has been stricken, hypothetically, and that is the input or the data or basis on which the expert -- the dose response relationship, maybe the toxicologist expert forms his or her opinion, that might be a different scenario.

MR. NIGH: That could be a different scenario.

THE COURT: But you are not talking about that

scenario.

MR. NIGH: Right. That would depend on the logistics of why the epidemiology study was stricken for the purpose of the dose response, but that is a different statement than if the epidemiology as a whole opinion is reliable compared to the dose response opinion. That is all.

THE COURT: Okay. And the background risk question.

MR. HEINZ: Noah Heinz for the Plaintiff. I think a useful thing to think about as far as what background risk means and how it can be contradistinguished from epidemiology is to read the descriptions of background risk in Chapman and McClain. I don't have the exact quotations in front of me, but it talks about the increased risks for people exposed versus the general population.

A useful context to think about that is the use versus nonuse studies, so if the Court were to conclude, for example, that looking at epidemiology by itself, maybe the active comparator studies are better epidemiology, for example, we would submit that you could still look at the use versus nonuse epidemiology for purposes of the background risk primary --

THE COURT: Did you make that argument in your papers?

MR. HEINZ: We may have mentioned it briefly in the context of describing background risk, but I don't think we articulated it in this fashion.

THE COURT: I would need to know where you think you

mentioned it as a form of primary evidence that you are relying upon to put forth your general causation theory.

I know you spoke at length about why use versus nonuse studies have certain relevance and why comparators at times don't, but you are making a very specific statement. You are making an argument that I don' think I saw. I want to know whether I missed it or whether that is a new argument.

I don't remember seeing background risk anywhere, so I want to be sure.

MR. NIGH: Your Honor, background risk, there is a whole section in Dr. McTiernan's expert report. We do have arguments in the briefing, to rely on that we have background risk. It has never been opposed by the Defendants, but we have put in our motions that we have background risk.

THE COURT: In your motions or in your response?

MR. NIGH: In our response to their motion.

THE COURT: Can you let me know where, if you could take a moment to look, so I know what you are relying upon so I can go back and look at that.

MR. NIGH: We will get you where it is in McTiernan's expert report, which in and of itself, we believe would be enough for the record, but we will also look for it in the motion.

THE COURT: Yes.

MR. NIGH: We may need to give that to you after the

break.

THE COURT: From the Defendant, any response, on -- you seem to take issue with how they characterized dose response, that it is a separate wagon, and then also the background risk issue.

MR. PETROSINELLI: I will hit the background risk first. They never argued this. In their opposition brief they argued that epidemiology is what they were relying on to defeat our Daubert, motion. There is nowhere in their opposition where they say we are proceeding under the background risk prong of Chapman and McClain and so on. So, I think your Honor is absolutely correct about that.

Secondly, in terms of the dose response, your Honor hit the nail on the head. We just heard from them in connection with the argument about animal studies, they said, I think it was Ms. Luhana, we are not relying on animal studies for our dose response. We are relying on the epidemiology.

We will get to this, but Dr. Salmon is relying on the Hidajat study and the NDMA dietary studies, epidemiology, NMA epidemiology, which is the problem. Your Honor is absolutely right, if you find that it is unreliable to rely on those studies, his whole dose response opinion falls apart.

Rider, which your Honor cited about, which says you don't need epidemiology, but when you have epidemiology, right, in all the other cases that is what the Plaintiffs rely on and

that is what the Plaintiffs did here.

THE COURT: Okay. To help Plaintiffs out, we did a word search of background and we didn't find it in the motion -- in the response other than factual background, the word background. And then we seem to -- we could be wrong. We looked at it in the expert reports, too. I do need clarification on that.

Okay. So, maybe some of these are repetitive, because we have been talking about dose response, but let's go through these questions that I have here.

This is now on dose response for Plaintiffs. Yesterday -- let me make sure I haven't already asked it. Let me read it, and then we'll see.

Yesterday, during the hearing when you were here you stated that some of your experts specifically looked at studies with the intent to analyze dose response, but those study authors stated that their study did not have data on dose response. You states that your experts' consideration of dose response in those studies, even though the studies turned out not to have any data on dose response, was sufficient to satisfy the primary methodology of dose response.

Can you confirm whether my understanding of what you said yesterday is correct? And if not, then can you correct me? But if it is, can you give me any support for that?

Looking at studies with the intent -- that your

experts looked at studies with the intent to analyze dose response, but that the study authors stated that their study did not have data on dose response.

MR. HEINZ: I am sorry, would you please repeat the question one more time?

THE COURT: Yesterday, during the hearing -- and I don't have access to the transcript, it's the best I could to write it down. I thought it was stated that some of your experts specifically looked at studies with the intent to analyze dose response, but that those study authors stated that their study did not have data on dose response.

You stated that your experts' consideration of dose response in those studies was sufficient, even though the studies turned out not to have any data on dose response.

Did I hear it correctly? And are you -- if I did, are you saying that is sufficient to satisfy primary methodology of dose response when an expert relies upon a study to analyze a dose response, but the authors of the study say they don't have data on dose response?

MR. HEINZ: The answer to would be no, that would not be sufficient. I believe, if I remember correctly, the point that I or Mr. Ronca was trying to make is that the Defendants said that a number of the Ranitidine studies disproved the notion of dose response.

For example, in the Norgaard study comparing two

prescriptions to ten prescriptions, there was a chart that said the does response actually went down. The point was mainly to say that sub analyses on dose response were not informative, largely because the doses were so low that the change within them would not be expected to identify a dose response effect.

The methodology of dose response that does satisfy the burden, were instead based on different studies that did show an effect. For example, for bladder cancer, that would be the Cardwell study which did find a dose response effect, and a number of dietary studies for each cancer, then the Hidajat occupational study for a number of cancers.

That would be the basis of the dose response, primary methodology and those studies are appropriately cited in the respective sections of each expert's report.

I also do have the background risk, answer if your Honor would like that.

This ran together a bit in my head, and you are correct that the background risk citation does not appear in the opposition. My colleague tells me that it does appear in the Moorman report at pages 12, and 13, and in the McTiernan report at pages 28, 32, 64, 161, 213, and 219.

The thing I was thinking of is in the quotation from McClain, for example, on what background risk is, is actually in our reply in support to our motion to exclude the Defendants' experts which has a section addressing this. I

believe it is on page 11, but it has a block quote, and makes the same type of inference that I stated earlier.

You are correct, that it does not appear in the response in opposition.

THE COURT: What were the pages, in Moorman and McTiernan again? State them slowly.

MR. HEINZ: In the Moorman report it is on pages 12 and 13. Then in the McTiernan report on pages 28, 32, 64, 161, 213, and 219. And Mr. Gilbert reminds me, they did not raise the point in their affirmative motion regarding background risk, and that is one reason we did not oppose on that specific basis.

THE COURT: Okay. Yesterday, during the hearing Plaintiffs stated that an opinion that exposure to one Ranitidine pill is not sufficient to get over what you described as the general causation hump for minimum dose, and Plaintiffs characterized exposure to one pill of Ranitidine as something like a one in one billion likelihood of developing cancer, which you stated would not be sufficient to meet the preponderance of the evidence standard.

Can you explain to the Court what exposure is enough to get over the general causation hump for dose?

MR. HEINZ: If I can ask a clarifying question. Is the question what particular doses of Ranitidine or sort of a more conceptual legal question of what number if it is, not one

in a billion?

THE COURT: I am just picking up on a comment the Plaintiffs made, exposure to one Ranitidine pill. You all were talking about Ranitidine and Ranitidine pill, and the general causation hump.

I wanted to know what exposure of Ranitidine pills is enough to get over the general causation hump.

MR. HEINZ: I think the conceptual answer -- and I will get to the practical answer quickly -- has to be something that would be sufficient for a jury to find by a preponderance of the evidence that it could be a cause under the relevant state law causation standards. That might be substantial contributing factor, for example.

In the context of Ranitidine, there are a number of estimates for what that dose might be. Your Honor has heard that Plaintiffs' position is that we do not need to specify a minimum dose, but if you disagree, the places to look for that would be especially the Salmon report, which does calculate cumulative amounts, the Panigraphy report which also calculates an amount.

We would also say, even though it is not precisely quantified, that the Moorman and McTiernan reports sufficiently do say that a dose would be sufficient, maybe something like three years, especially for bladder cancer, for example, stated in the dose response sections on that.

Those would be the answers.

THE COURT: Okay. Let's see what else you said yesterday. Also yesterday, during the hearing, Plaintiffs stated that they were required to show that a realistic dose can cause cancer. These are words the Plaintiffs used, counsel used, and then you explain that a realistic dose is a dose that a person can get from taking Zantac.

Can you clarify whether a realistic dose referred to a realistic dose of Ranitidine or a realistic dose of NDMA?

MR. HEINZ: I suppose it would be a realistic dose of NDMA in Ranitidine, so that would have to be a realistic number of pills and at an at least possible or plausible testing amount of the NDMA within the pills as well.

THE COURT: When you refer to realistic dose, what does that term generally mean and what does doses of -- what doses of Ranitidine and NDMA constitute realistic doses? Is there an approximate number, a range of numbers of what doses of Ranitidine and NDMA are considered realistic doses?

MR. HEINZ: I believe when I said that, and said something like, well, a thousand doses would be ridiculous, something like that, conceptually that way we would say the question should work is think about the highest plausible dose that one -- a Plaintiff in the pool could take. That's the way Judge Chhabria framed the question in In Re: Roundup.

So, we would say a realistic number could be two pills

a day for 30 or more years, something like that, is at least a realistic dose as far as the Plaintiffs in this litigation.

THE COURT: Where does that come from, two pills a day for 30 years?

MR. HEINZ: I suppose it comes from, you know, comes from -- part of it comes from what people have said in the registry as far as -- we did say in our papers that I think 60 percent of Plaintiffs used it for at least ten years, and there are indications for Ranitidine maintenance use, for example, in which that amount is permitted, one pill a day, two pills a day, higher for some conditions, and it is just not an outlandish number.

MR. NIGH: I wanted to add, Daniel Nigh, 37 years is the time that Ranitidine was approved and sold in the market in the United States. In addition to that, even some users could have had Ranitidine as part of a clinical trial before it was approved in the U.S. Clinical trials started, I believe, five years before approval, so it could be up to 42 years.

The second question is, what is the highest dose the Plaintiffs could have? Dr. Le answers that question in her -- she gives information on the prescribing and what people would take these doses for. For most, it is 300 milligrams a day, up to 300 milligrams. There are certain conditions, and I forget the names of some of the conditions, but some it is 600 milligrams a day, and so that is actually four times

150-milligram pills.

There are actually some conditions that are fairly rare, but they could be prescribed and they have been approved for prescription purposes to have up to 6 grams a day, so that would be much more Ranitidine, so those people could actually have a lot more dose.

THE COURT: Okay. Any response on any of those issues from the Defense?

MR. PETROSINELLI: Yes, your Honor, Joe Petrosinelli. This is the legal questioning we flagged in the opening, which is, what is the standard in the Eleventh Circuit as to what has to be proven at the general causation stage on dose? What you just heard again, which is the highest possible dose that any Plaintiff in the MDL could experience, is completely and utterly inconsistent with Eleventh Circuit precedent.

The Eleventh Circuit, in McClain, in Chapman, in all the District Court cases on products MDLs afterwards, Judge Altonaga in the Fixodent case, Judge Moody in Accutane, Judge Rodgers, in Deepwater Horizon, they all say -- I'll quote McClain and Chapman, to provide a reliable general causation opinion in a toxic tort case you have to prove the dose that can be hazardous to humans generally, by which they mean the threshold dose, what we have been calling.

The cases say it over and over again. I know Judge Chhabria said something different, and he interpreted Ninth

Circuit law as being different. That is not the Eleventh Circuit, it is the complete opposite of what you just heard.

They have to have reliable -- we're on Daubert, they have to have reliable expert evidence in considering -- in giving a causation opinion of the threshold dose. To quote McClain, the dose at which the compound, whatever it is, can be hazardous or cause the effect, here cancer, five cancers, in humans generally. That means the dose at which the person who could be a Plaintiff realistically had the lowest dose.

That only makes sense at the general causation stage because if they have that dose, whatever it is -- I still haven't heard what it is, which is a huge problem, but whatever it is, then it is specific causation. The Plaintiff has to prove I had more than that dose, and then they have proven general causation, and then the jury has to decide whether there is specific causation, and all the things that would go into specific causation.

That is the law and that is the fundamental defect in their -- whether you view it as them proceeding under the dose response relationship primary method or epidemiology which informs the dose response relationship primary method, they can't meet it. They haven't met it, either because -- for all of their experts but for -- all their experts who offer a general causation opinion, but for Dr. Salmon, explicitly say we can't say.

Dr. Salmon attempts to say it, and you have heard the motion on Dr. Salmon, and I have some more comments about him the appropriate time. That is the reason they can't pursue it.

THE COURT: I think this would be a good time, we can proceed into final statements. It looks like each side has asked for a half hour. I don't know if you need a break, first or whether we should go into them and take a break. I do want to get -- the lingering questions that I have put out there, I would like for you to put on the record what the answer is, if you found it, or if you haven't found it, that you haven't found it, so we know if there should be any followup post hearing. I do want to get everything on the record.

Are you okay to proceed?

MR. CHEFFO: We are, but if we are going to take a break, it makes sense to take a break now.

THE COURT: When did we come in? Are you okay, Pauline?

THE COURT REPORTER: I am okay.

THE COURT: We can proceed.

MR. CHEFFO: Thank you, your Honor. I am going to divide this with Mr. Petrosinelli.

At the outset, it is kind of unclear whether the Plaintiffs are going to offer any calculations. If they do, we would like an opportunity after this to come back. You will be the judge of that, obviously, your Honor.

First let me thank the Court again for the time and effort. A lot of words and documents have been put at your Honor.

I think there is a few themes throughout the last day and a half. The first, is that the Plaintiff -- this may have been lost in the way this has been presented, but the Plaintiffs have the burden of proof here, right, and they spend virtually all of their time trying to essentially poke holes at the peer reviewed Ranitidine data.

The second theme is that Plaintiffs have still and continue to fail to provide answers to dose and dose response, notwithstanding your Honor's multiple questions, and I think the time for that, frankly, was not even today, that was at the time when the expert reports were due.

The third is that there has really has been no dispute that no one other than the Plaintiffs' experts and their counsel have held these positions here on general causation, literally no one else.

The fourth is Plaintiffs are essentially asking the Court to speculate about what science might be or could be, if we just waited a little more time, or saw a curve, a change or looked at things, law lagging science.

And the final thing, is, you have heard a number of full-throated arguments, frankly, from day one of this litigation when the Plaintiffs basically said that there were

dozens of cancers, and hundreds of thousands of people who filed claims based on those. We now went to ten, and then there's eight, and now there is five. The reality is, the same studies, the same epidemiological studies that address the cancers were conceded govern the five.

It would be unprecedented, your Honor, respectfully, to allow Plaintiffs' experts to testify about a product causing cancer when literally the world's scientific community has a different view.

Next slide, please.

As your Honor may recall, the world kind of best and brightest looked at this issue and they spoke to this issue, and they spoke loudly.

Next slide.

And, you know, we heard, and I agree, Ms. Luhana said earlier today that we shouldn't look behind what the authors say, right, that would be inappropriate, yet, what we have only seen are data points from some of these studies, kind of we say cherry picking situational science. There hasn't been a lot of this what the authors actually said.

We went through that, so I am not going to do that, but you have read these studies, and you know not one of these authors say that you should read our data points as finding an association or causation. No one has said that, and both the case law, and what we have heard is that following what the

authors say in these peer reviewed studies is the appropriate methodology.

Next slide.

Okay. Again, you could search and study and you will not find anyone -- if this was so prolific, that literally millions of people over 30 years were subjected to this genotoxin, as the Plaintiffs say, could it be that it wouldn't be picked up in the evidence? That is just not the way science works.

Next slide.

Widespread acceptance is a critical factor. That is why we spent a fair amount of time talking about it. What is generally accepted is not just the conclusions of the authors, which is generally accepted, we have seen that from the EMA and the FDA, we haven't have seen anything new about that.

It is also the fact that the way these studies were conducted and the way they went about them, so using an active comparator, that is generally accepted. That is the way the scientific community addressed this.

Looking at Ranitidine data, not occupational data, not dietary data, that is generally accepted. No one else has done that, no one, except a few of the Plaintiffs' experts. Looking at statistically significant findings in order to make conclusions, that is what the world's community has done, so that is generally accepted. Looking at world use, and relying

on what the authors say, those are all generally accepted.

The Plaintiffs essentially have two main attacks on why your Honor should disregard or minimize the importance. They first talk about statistical significance.

Next slide.

You don't really need to look at the significance., maybe the Defendants spent too much time talking about it. We can look at trends, but as your Honor may recall from the presentation on Dr. McTiernan, that is not the way she has approached kind of her life's work outside of this courtroom. When she looks at the same data points in this litigation, it is increased risk, but everywhere else she says it is no association. That is the epitome of situational science.

Next slide, please.

Some of the Plaintiffs' briefs, Defendants argue that if the confidence interval study includes one, there no statistical association between the exposure and the disease. This flawed but repeated view is pseudoscience. Well, their basically expert says when the confidence interval includes one, you interpret the finding as no statistical association.

It is not the point of whether it is of statistical significance or not, the pint here is saying there is no association if it includes one. I don't think that is pseudoscience, and I don't think Dr. Le in this regard is practicing pseudoscience.

Next slide.

You have seen the slides about Dr. Salmon. He also recognizes the importance of statistical significance outside this litigation.

Next slide.

The next issue is followup time. The Plaintiffs basically say, well, a lot of these studies, you can't really rely on them because they don't capture -- cancer takes a long time. I heard that a lot before this hearing.

We put up yesterday a slide saying, well, what Dr. McTiernan is doing here is different than what she has done outside the courtroom. The Plaintiff said, well, wait a minute, there's 400 studies, you can't really rely on it. We are cherry pecking, so here is what we did.

Next slide.

We went back and looked at those 400 studies, and there are actually 20 studies that deal with medication and cancer, two of them are case controls, which would not have a followup, but of the cohorts, all of the cohorts studies, you can see many of them are less than the one -- the examples we used, but they are all less than the followup that we have seen has occurred in connection with the Ranitidine data, the epi data.

So, when the Plaintiffs say, oh my gosh, that is not reliable, their own expert, in connection with her own science

outside the courtroom, relies on followup that is substantially less than the peer reviewed literature we have been talking about, that is situational science and cherry picking.

Similarly, Dr. Panigraphy says you see a measurable effect within a period of four years. Again, we dispute that, but to the extent that is true, then that is squarely within the followup times of most of the studies that we have put forward and the world's scientific community has put forward as the reliable epidemiological data. Plaintiffs can't have it both ways here.

Next slide, please.

And this also highlights the point. Mr Petrosinelli is going to talk a little bit about this, maybe at some length, but if we take this as true, right, and it is accurate, at least as I understand, this, the Plaintiffs are saying the column on the right is the real world use, this is what happens in the real world, and people who have gastric cancer, they can experience cancer diagnosis at a year and a half, esophagus, 1.8, bladder almost 4, pancreas, liver.

Putting aside the fact that we don't think these are methodologically sound, you can't have it both ways. You can't say the reasons why I am disregarding epidemiological peer reviewed data is because of statistical significance when your experts rely on -- use statistical significance in different ways, you can't also say, well, gosh, those are not long enough

studies when your own data is saying we would expect to see cancers within this period of time based on it.

You can't have it both ways, so this is kind of the epitome of situational science, and I think what this highlights -- and I will turn it over to Mr. Petrosinelli -- is that when you look at the totality of the world's literature, when you look at what the EPA, the EMA, and all the scientists outside this courtroom have found, there is no support for general causation, and that is a methodology issue.

Thank you, your Honor.

THE COURT: Thank you.

MR. PETROSINELLI: Joe Petrosinelli here, you Honor. I will try to bring this home for us.

Next slide, please.

This is one more piece of situational science that Mr. Cheffo was talking about with Dr. McTiernan where she gave less weight to relative risks that were not greater than one, more weight to risks that were greater than one, which she does not do in her peer review publications.

Next slide, please.

You remember Mr. Brown showed this slide about Dr. Moorman, and I won't go through explaining it, here, but again, she set forth criteria, which you are supposed to do under Daubert if you are going to perform a Bradford-Hill analysis, she set forth criteria as to how she weighed the studies. That

is okay.

But as I said in my opening and as the case law shows, then the way that you do it has to have some reliable method. It has to be based on principles of science, and when you look at the studies that she gave little weight to versus strong weight to on the criteria that she herself said she was applying, it doesn't make any sense. It is completely random.

Next slide, please. Next slide.

Again, we made this point that the Plaintiffs in their briefing are relying on the Habel study, and their own experts say don't rely on the Habel study.

Next slide, please. Next slide. Skip that one.

Okay. So this gets to my piece on dose. You have saved me some time, your Honor, because I was going to do the McClain and Chapman cases that we just talked about.

Next slide, please.

One of the things I would say is, Judge Rodgers' opinion in Deepwater Horizon, super critical on this point. The chemical at issue in Deepwater Horizon was arsenic. They sprayed the oil dispersants in the air containing, among other things, arsenic, and the residents claimed that it floated onto shore and caused them injury.

Arsenic is a Class I carcinogen, human carcinogen under the IARC classification system, so much more than NDMA. The Plaintiffs said it is a Class I carcinogen, what is the

problem with general causation? Judge Rodgers said, no, it is about dose the eleventh Circuit case law tells us to get past general causation you have to have reliable evidence of dose, meaning exposure level and duration.

One of the reasons why she excluded a very highly qualified -- she says almost wistfully at the end of the opinion, I feel bad doing this, because I am not saying this person didn't honestly believe this, but in the Eleventh Circuit, you can't come in and say, oh, it is a known carcinogen and so it must be general causation, and that was the biggest problem in Deepwater Horizon.

The same thing here, except you don't actually have a Class I human carcinogen, you have a lesser under the classification system.

Next slide.

This is the quote that we have been talking about that we are still waiting for an answer. The Plaintiffs agree that, as a general causation matter, they are not claiming a year's worth of use could cause an increased risk of cancer. Many years of regular use does not satisfy the Eleventh Circuit standard.

So where does that leave us? Where I would say is sort of what I just alluded to, which is, if you think about the experts on the Plaintiffs' side who have offered general causation opinions on Ranitidine, you have Drs. McTiernan,

Moorman, Le, and Michaels, the four of them don't offer any opinion on threshold dose, what it is. They say they are not going to do it, and they don't have an opinion on it, and they offer no opinion on what is the dose response relationship, if there is one, between Ranitidine use and any of the five cancers.

You would have to provide it for each of the five. One would think, with different target organs, you couldn't can't have the same threshold dose and the response relationship for with five entirely different cancers. They haven't done it for any of them.

Their methodologies, which in the Eleventh Circuit it says if you are going to give a general causation opinion it must have a reliable analysis of threshold dose and dose response, they don't have it, they are excluded.

Dr. Salmon is the only one who offers a general causation opinion as to Ranitidine, not Dr. Panigraphy or Dr. Zeiger. They don't offer general causation opinions as to Ranitidine. He is the only one, and these are the charts that the Plaintiffs have presented.

I am not going to repeat. You heard from Mr. Holian yesterday all the methodological flaws in these two charts if you remember, these are the charts on pages 221 and 223 of his report.

So, starting at the top where he gets the dose, look

at what he relied on. For bladder, pancreatic and liver cancer to calculate the threshold dose of an increased risk, he relied on the Hidajat study, an occupational rubber, worker inhalation of chemicals study, completely, totally unwarranted to any scientific method.

Esophageal, cancer, you might remember the Keszei study. That dose that he put in there and the relative risk he calculates, it is for males only, not females, and squamous cell esophageal cancer, not adenoma carcinoma esophageal cancer, which, by the way, is the more common one, the definition of cherry picking, pick one gender and not the other, and pick one sub type of the cancer and not the other, those are unreliable.

Of course, the other, De Stefani, is an NDMA dietary study, and you know our position on relying on that. That is chart number one.

Then, to get to chart number two, the duration, right, you carry down the numbers. You see those milligrams of NDMA in the first column of the chart at the top, they are now in the first column of the chart at the bottom. This assumes that someone is taking a 300-milligram dose every single day for these number of years and that every single dose has the same level of NDMA in it, which is totally contrary to Plaintiffs' theory that there are variations in levels because it is about heat and humidity.

It is just completely untethered to any science or even their theory of the case. As Mr. Cheffo pointed out, I am still not sure what column they are relying on to say what the dose is. I think Mr. Nigh said today the right-hand column, because of course those have the fewest number of years, but that runs into two problems.

That is dependent on the admissibility of the Emery test, because those numbers are based on the levels found by Emery in their tests. So, if those are inadmissible, they can't rely on that column, nor can they rely on that other column that says Emery overall average. That is one problem.

The second problem, is what Mr. Cheffo identified. If these were methodologically sound and that is the number of years in which you would see an increased risk of cancer, then they run headlong into the Ranitidine epidemiological studies, all of which have a longer followup period than anything that is there.

It is a Daubert mess. There is no possible way they can rely -- Dr. Salmon can reliably offer opinions about these numbers to support a general causation opinion.

Next slide, please.

Finally -- click it one more time. Thank you.

Finally, I just want to mention one thing that was mentioned yesterday by the Plaintiffs. We have this all star lineup of MDL judges who have handled these pharmaceutical

MDLs, all of whom have excluded opinions under Daubert with qualified experts who offered Bradford-Hill analyses. The Plaintiffs haven't disputed that that was the holding in these cases and these three things are indeed features of these cases.

What they said was, if you look at the Eleventh Circuit cases, like McClain and Chapman, the experts there didn't offer any epidemiology, it just wasn't a close call for the Court. It is true that in those cases the experts didn't offer epidemiology, or very little epidemiology, although in other Eleventh Circuit cases like Allison they did.

If you look at these decisions, and I was involved in some of these cases, the experts were qualified epidemiologists who presented an abundance of human epidemiological studies, of varying significance and the whole fight in those cases is the exact same fight that we have here.

In the Viagra, Cialis litigation, in the Zoloft litigation that Judge Rufe handled, Plaintiffs had statistically significant multiple -- like a dozen epidemiologic studies showing an association between the drug itself, the studies were of the drug, and the outcome in question, and for various reasons -- in the cases, the judges carefully went through it and said that is -- the fact that there are some statistically significant studies showing increased risk doesn't get you past Daubert and it doesn't get

you into a Bradford-Hill analysis, or if it does, you have to do it reliably, and those Courts excluded those opinions.

It is not like this is some unique situation where Drs. Moorman and McTiernan have found things that no other epidemiologists have found in these other cases. These cases had evidence that was much more powerful, on its face at least, than what Dr. Moorman and Dr. McTiernan present here.

Next slide, please.

We talked about Abilify. If you want to know what a case looks like in the Eleventh Circuit, a pharmaceutical case where someone can get past Daubert on general causation, look at Abilify for the reasons we talked about in my opening. There was only one epidemiologic study and uncontradicted in the literature, and look at the statistically significant increased risk, massive.

Nothing like that, in this case and the broad scientific consensus in the regulatory and scientific community, which I need hardly say is not this case. It is just the opposite in this case.

Next slide.

Finally, Judge, to pick up on Mr. Cheffo's statement about law lagging science, if you look at the Eleventh Circuit cases, one thing you find in these pharmaceutical cases that have excluded expert -- or products cases I should say, Allison is a silicone implant case. In these toxic tort cases, there

is this theme that runs through it, which is that -- as you see in Allison and Rider, which is that, look, maybe some day in the future, when there is longer -- to the Plaintiffs saying there is longer followup in Ranitidine studies, or there is other data, maybe the Plaintiffs' opinions will be proven to be true, but the quote in Rider, says it all, you have to judge the science as it is today.

The Plaintiffs brought these lawsuits, they have to go with the science as it is today. As Judge Seibel said, I showed this in opening, it is not that anyone is saying these experts are insincere, or they don't honestly believe in their own minds that they have concluded this, but that doesn't get you past Daubert.

When the entire scientific community, having studied the question, is against you, the law can't wait until -- as we have heard from the Plaintiffs, well, what if the studies had a longer followup period, or what if higher dose, what if this or that, what if this abstract that they showed from May, 2022, that is not in record, for reasons we have talked about, what if that gets published and there is better data.

That is not how we deal with our motions, and these Eleventh Circuit cases, and in almost every one of the MDLs I showed, on the prior slide, that is what the judges said, that as we sit here today, based on the science, based on the consensus in the scientific community, these opinions are not

accepted, and they are not based on reliable methodology, and that fundamentally is what we have in this case and why we seek exclusion here.

Thank you, your Honor.

THE COURT: Okay, thank you very much.

Okay, from the Plaintiffs, closing.

MR. GILBERT: Your Honor, would you give me a warning at five minutes and at one minute?

THE COURT: For the full 30 minutes?

MR. GILBERT: Please.

THE COURT: Okay.

MR. GILBERT: May it please the Court, Robert Gilbert on behalf of the Plaintiffs.

Before I begin, on behalf of our entire Plaintiffs team, I, too, would like to thank the Court, your staff, and especially Ms. Stipes for your critical roles in connection with our Daubert proceedings it has been going on for quite awhile, there have been a lot of hearings related to it, culminating in the past two days, and we appreciate everybody's support and cooperation.

Let's start with the basics. After four decades, Zantac was pulled from the market. That was because there is no dispute that it degrades into NDMA, particularly when subjected to heat and humidity. And it is also undisputed that NDMA is a known carcinogen.

With those undisputed facts in mind, I am going to discuss three topics, the general causation question, the Court's role in deciding Daubert motions, and third, I will discuss each of our experts who have been challenged.

First, on the general causation question, I ask the Court to imagine a Plaintiff, like many of those in the registry, who took a 300-milligram Zantac tablet every day for two decades and stored that Zantac in her medicine cabinet subject to daily heat and humidity and developed one of the five cancers. If the Court grants Defendants' Daubert motions, that Plaintiff will never try her case to a jury. That can't be right, and as I will discuss over the next few minutes, that isn't right.

The reason it isn't right is because it violates the fundamental principles of Daubert.

We have heard a lot of talk by my esteemed colleagues on the other side about Judge Chhabria's decisions in Roundup, and as Judge Chhabria explained in that case, it is black letter law that a Court's 702 inquiry focuses on expert methodology -- methodologies, not conclusions.

As applied to the question of general causation here, Judge Chhabria's opinion framed the relevant inquiry this way: Whether Plaintiffs' experts utilized accepted methods to conclude that NDMA exposure from Ranitidine can cause any of the designated cancers for any Plaintiff based on the highest

dose a Plaintiff might have experienced.

Once again, that is our Plaintiff who consumed 300-milligram Zantac tablets every day for two decades.

The Defendants run from this legal standard in the hopes that your Honor will reach your own scientific conclusions. My colleague, Mr. Petrosinelli, tried to tell the Court that Judge Chhabria's decision wouldn't be good law in this circuit. He went on to say in his opening that if Judge Chhabria were here he would tell you that, too. I am confident that if Judge Chhabria were here, he would prove Mr. Petrosinelli wrong.

We don't have to speculate about this. Judge Chhabria's Daubert decision was appealed to Monsanto to the Ninth Circuit and the Ninth Circuit affirmed that decision and expressly rejected Judge Chhabria's assumption that the Daubert standard differs between the Eleventh and Ninth Circuits.

This is precisely what the Ninth Circuit said: "To the extent the District Court relied on In Re: Zoloft and McClain" -- and I am omitting the cites -- "those cases do not reveal a more flexible Daubert in this circuit," meaning the Ninth Circuit.

The Court went on: "Despite its incorrect assumption that this Court is more permissive than others in admitting Daubert testimony, the District Court still employed the correct legal standard for reliability when it

admitted Hardeman's expert testimony."

Judge Chhabria framed the general causation question properly for us, too, whether NDMA exposure from Ranitidine can cause any of the five designated cancers for any Plaintiff based on the highest dose a Plaintiff might have experienced.

That framing is consistent with McClain, which defines general causation as the, quote, "general question of whether the drug or chemical can cause the harm Plaintiff alleges," unquote. That is McClain, at page 1239.

A drug can cause a given harm, if it could possibly cause it for any Plaintiff. Judge Chhabria's formulation follows directly from that basic definition in any MDL with thousands of Plaintiffs all with different usage facts. Even though the Ninth Circuit made it clear that the standard is the same under both Eleventh and Ninth Circuit law, my colleague, Mr. Petrosinelli, continued to try to reshape the law of this circuit to fit Defendants' preferred outcome.

You heard him claim multiple times that Plaintiffs must identify the minimum, in fact he did it today again, Plaintiffs must identify the minimum threshold dose or we lose on general causation. Not a single case says Plaintiffs must identify the minimum threshold dose, not precisely, not in a range, not at all.

The closest the Eleventh Circuit cases come simply restate what Plaintiffs -- what we already agree with, dose

response is important to analyze. Defendants say this about McClain, quote, "As the Eleventh Circuit has explained, an opinion that exposure to a toxin at any level is too much conflicts with the importance of individual responses to toxins." That is found at DE 5696, at pages, 20 and 21.

Plaintiffs, of course, agree with that. We do not argue that any Plaintiff can prevail by saying he or she took Zantac a single time and then developed cancer. But nothing in that quote from McClain ever says that Plaintiffs' experts get excluded if they don't identify the minimum threshold dose after they have shown that many Plaintiffs exceed any realistic threshold.

Of course, this makes perfect sense. There is a world of difference between saying causation cannot be shown if no Plaintiff has enough of a drug to cause harm, versus saying causation cannot be shown even though many are above any plausible threshold, which is not precisely stated.

Defendants also try to include Mr. Petrosinelli's rewrite of the law in a footnote to the reply to the epidemiology motion, Docket Entry 5958, at footnote 48. Footnote 48 claims that Chapman says satisfies, and I quote, "To carry the burden in a toxic tort case a Plaintiff must demonstrate the levels of exposure that are hazardous to human beings generally, as well as the Plaintiff's actual level of exposure to the Defendants' toxic substance before he or she

may recover," unquote.

Your Honor, that quote does not appear in Chapman, nowhere. It is not off by a little bit, it is not in the Eleventh Circuit's opinion. It is instead a quote from McClain taken out of context noting a case where Plaintiffs did not offer any opinion about the specific Plaintiff's exposure. There is no authority, none, none, none, that converts the importance of identifying a dose response relationship into a requirement to identify a minimum threshold dose.

Defendants are pushing the boundaries of zealous advocacy to claim that the law in the Eleventh Circuit embraces the role they advocated yesterday and again just now.

As we will show your Honor, and have shown through our evidence, forfeiture aside, misstatements aside, our experts do identify thresholds that create increased risk.

Specifically, Plaintiffs' experts provide three proposed answers. From Dr. Salmon, cumulative lifetime doses, as stated in the chart on page 233 of his report.

From Dr. Panigraphy, 7.5 years of daily use for stomach, bladder, esophageal and pancreatic cancer, and 14.3 years of daily use for liver cancer.

From Drs. McTiernan and Moorman, a more qualitative dose of approximately three years, as I will explain in a moment.

Next, let's remind ourselves of this Court's role

under Daubert. It is, as I know you know, a limited gatekeeping role.

Shaky and strong evidence alike pass through. Only a wholly unreliable -- only wholly unreliable evidence can be excluded.

THE COURT: Can I have you repeat what you said a minute ago about the three sources. Can you say that again?

MR. GILBERT: Sure. Dr. Salmon, cumulative lifetime doses, as stated in the chart on page 233 of his report.

From Panigraphy, 7.5 years of daily use for stomach, bladder, esophageal, and pancreatic cancer, and 14.3 years of daily use for liver cancer.

From Drs. McTiernan and Moorman, a more qualitative dose of approximately three years.

Second, to remind ourselves of the Court's role under Daubert, a limited gatekeeping role. Both shaky and strong evidence alike passes through. Only wholly unreliable evidence is excluded.

That is what Abilify explains, and I quote, "This weight of the evidence approach to analyzing causation can be considered reliable provided the expert considers all available evidence carefully and explains how the relative weight of the various pieces of evidence led to his conclusion." That is Abilify at page 1311.

Here is what Schultz from the Seventh Circuit says,

quote, "Rule 702 did not require or even permit the District Court to choose between those two studies at the gatekeeping stage. Both experts were entitled to present their views and the merits and demerits of each study can be explored at trial," Schultz at 433.

Your Honor, for the gatekeeping role to be limited. It really has to mean something, that Daubert is about methodology, not conclusions. It has to mean something, that the Court is not permitted to assess an expert's credibility or a particular study's persuasiveness.

Focusing on methods, Plaintiffs' experts' methodologies are beyond reproach. Our experts opine that Zantac can cause cancer using the Bradford-Hill criteria and a weight of all of the evidence approach. That, as the Court knows, is a widely accepted methodology that scientists routinely employ. For that reason, the weight of the evidence approach is routinely viewed as reliable, noted in Abilify, Bear Hugger, Milward, and even in the Reference Manual on Scientific Evidence.

Plaintiffs' experts reviewed and weighed Ranitidine specific epidemiology, dose response relationship for NDMA, and the background risk of disease. As Judge Rodgers noted in Abilify, echoing the Eleventh Circuit, any one of those souces of evidence suffices to show general causation.

We did and urge the Court to do a control F of the

Defendants' motions, as the Court indicated earlier with regard to our opposition. Should the Court do that, the Court will confirm that the Defendants never moved to exclude the opinions of Drs. Moorman and McTiernan on background risk, so, of course, we don't oppose in our opposition an unraised argument.

Their background risk opinions are unchallenged, and that alone means that we prevail.

Defendants know that they have a problem. There is ample evidence in the peer reviewed literature that Ranitidine is associated with each of the five designated cancers, that NDMA is associated with cancer, and that Ranitidine degrades into NDMA.

That is more than enough for a qualified expert, applying reliable methodologies, to conclude that Zantac causes certain cancers. It is far, far more evidence that the Plaintiffs had in Roundup where Judge Chhabria, applying the same standard, permitted Plaintiffs' experts to testify.

So, how did Defendants attempt to overcome this problem? They go to the familiar playbook when the Plaintiffs' evidence is this strong, they invite this Court to go beyond the limited inquiry into whether Plaintiff's experts used reliable methods.

While they pay lip service to that standard, it is obvious that what they really want you to do is pick and choose which studies are better and which are less credible.

You could be perfectly sure that is what the Defendants really want because they don't even try to say that Plaintiffs' experts did not carefully review all the relevant scientific literature.

They don't even try to argue that the factors Plaintiffs' experts identified as strengths, such as long followup periods, really are strengths, and factors identified as weaknesses, such as not accounting for cancer risk factors, really are weaknesses. They skip right over them and debate the merits of each study, telling you why the ones they like are probative and the ones they don't are irrelevant.

That is fundamentally a disagreement with the experts' conclusions, not their methods.

So, Mr. Cheffo told you yesterday that the conclusions are so out of whack that they are akin to opining that two plus two equals five. They threw that Hail Mary because Defendants know full well that Courts cannot focus on conclusions unless they are utterly divorced from a valid scientific method, and that is their only way to try to get the Court to accept only the studies that are good for Defendants, tempting your Honor to agree with them that those studies represent the scientific consensus.

They will quote, as Mr. Cheffo called it, the loud chorus from the respectable science that Ranitidine is safe according to Defendants.

Mr. Cheffo put his ask to the Court on full display when he discussed the Ranitidine epidemiologist's forest plots and systematically crossed out various studies from it. From one study to another, Mr. Cheffo said not persuasive, not persuasive, not persuasive, exactly what Abilify, Quiet Tech, and Schultz expressly warn Courts may not do in deciding Daubert. That is over the line of gatekeeping, it is asking this Court to enter the arena.

First, Mr. Cheffo summarily rejected the NDMA dietary studies as flawed and irrelevant, but he made no effort to explain how Plaintiffs' experts weigh them, much less how considering that evidence rendered their methodology unreliable.

Mr. Cheffo similarly rejected the occupational exposure study because of his concerns about rubber dust. Again, he failed to address this concern in terms of the experts' actual consideration of the evidence and methodology.

As another example, Mr. Cheffo summarily rejected all non-statistically significant results. Apparently Defendants don't care for this form of evidence, which is a position they are certainly free to take at trial, but what they can't do is argue here that it was an unreliable method for an expert to consider non-statistically significant results in the context of all the available evidence, which is what epidemiologists do each and every day.

In the end, all that remained were the studies that the Defendants like, but each time that Mr. Cheffo asked you to eliminate from your consideration a particular study, he was effectively asking you to weigh the evidence, asking you to evaluate persuasiveness, asking the Court ultimately to play the role of a juror.

This Court should reject that invitation. Mr. Cheffo's arguments might make for a great closing statement or cross-examination, but they have no place in the Daubert analysis.

With that foundation in the law, let's talk about Dr. McTiernan's and Dr. Moorman's methodology. You heard from Mr. Ronca and Mr. Heinz that each of these experts considered all the scientific literature, Ranitidine studies, dietary studies, occupational studies, animal studies, tissue studies, and so forth, and Defendants agree -- let me say it again, Defendants agree that both of these experts considered all the relevant evidence.

Next you heard that both experts carefully and consistently evaluated each study based on criteria that epidemiologists routinely employ. They identified potential biases, accounted for dose and followup, examined each study's design, and a few other factors. Based on those consistent factors, they weighed each study.

Once again, Defendants agree that both epidemiology

experts properly identified relevant factors.

Last, after according each study due weight, they applied Bradford-Hill factors and exercised scientific judgment to conclude that Zantac can cause each of the five cancers. That is what they are supposed to do.

Defendants' criticisms all go to the weight. Defendants argue that the dietary studies receive too much weight. Rather than the moderate to little weight they received, Defendants demand a weight of zero, but even Defendants' case law, Burst and Hendrickson, agree that evidence about the toxin, there Benzene, here NDMA, is relevant and worth considering.

The FDA and the EMA considered NDMA evidence. Giving that evidence some weight is not even close to unreliable and was carefully explained across dozens of pages.

Defendants also argue that the active comparator studies should be weighted double, but Drs. McTiernan and Moorman disagreed. The issue is not active comparator studies at large, but these active comparator studies, which have low dose information, short followup, misclassification, and no information about confounders.

Any one of these would be a sufficient reason to discount a study. Together, they persuasively explain why neither of these experts weighted studies like Iwagami, Norgaard, and Adami highly. Again, that explanation does not

have to be persuasive to the Court, though Plaintiffs believe it is highly persuasive.

It is enough that the explanation is based on valid, consistently applied judgment from qualified experts. That a different expert would give more or less weight to those studies is irrelevant under Daubert.

The Court asked for a factual dose calculation. Drs. McTiernan and Moorman did not supply a mathematically precise minimum dose, though they plainly opine that high doses, many years of use, could cause cancer. Their qualitative doses estimates are on pages 34 to 47 for Moorman, and 291 through 98 for McTiernan.

Cancer specific analyses for Dr. Moorman on pages 110, 134 through 35, 162 through 63, 190 through 92 --

THE COURT: Wait, wait, wait, you lost me. Can you start from the beginning where you started to quote page numbers.

MR. GILBERT: Pages 110 --

THE COURT: Go back to --

MR. GILBERT: I'm sorry. Pages 34 through 47 for Moorman, and 291 through 98 for McTiernan. Cancer specific analyses for Moorman on pages 110, 134 through 35, 162, through 63, 190nine on through 92, and 222 through 24. And for Dr. McTiernan, on pages 203, 222, 236, 254, 283.

McClain, the case Defendants rely on incorrectly to

require a minimum dose, says this in footnote 6, and I quote, "One should not conclude from this analysis that to pass Daubert muster an expert must give precise numbers," unquote.

Drs. Moorman and McTiernan clearly identified an increased risk starting with regular users of Ranitidine after three years of bladder cancer. No study for any other cancer analyzed three years of dose, but Drs. Moorman and McTiernan found NDMA analyses to be comparable.

Plaintiffs' position is that three years of daily use would certainly be sufficient based on this analysis. Maybe less could be enough, but certainly three years is a sufficient dose.

As Schultz explains, an inability to precisely quantify an even lower bound is not required, and that comes from Schultz, at page 432.

Plaintiffs' epidemiology experts should sail through Daubert, your Honor, and the same is true for Drs. Michael and Le. Defendants did not even bother to present oral argument --

THE COURT: You have five minutes left.

MR. GILBERT: Defendants did not even bother to present oral argument against them and their arguments in the papers barely give any reason to exclude them.

Now it is to Dr. Salmon. Defendants' briefing differed dramatically from what you heard over the last two days. Dr. Salmon explained in detail how to convert

occupational inhalation exposure of NDMA into the equivalent dose for a dietary exposure using a well-understood formula. Defendants did not challenge this calculation.

Dr. Salmon also conducted intensive calculations based on statistically significant findings in the dietary and occupational studies. Had he used non-statistically significant associations, he would have found even higher numbers, but his conservative assumptions allowed him to construct a cumulative dose chart showing how much Ranitidine would be sufficient to cause the same levels of risk.

Dr. Salmon calculated this cumulative dose using four different alternative assumptions about the amount of NDMA in Ranitidine.

Defendants protest, but wrongly, that Dr. Salmon picked the highest possible NDMA levels, and the highest possible associations, but in fact he repeatedly used conservative assumptions and calculated using alternative assumptions so the Court can see how different premises affect the analysis.

Your Honor specifically asked for a factual answer on the minimum dose. Plaintiffs' answer remains that a minimum dose is not required, but if it is, minimums are provided from Dr. Salmon's chart on page 223 of his report. That chart lists the number of years necessary to reach a given risk for each of the five designated cancers.

So, if Dr. Najafi is permitted to testify, the far right column would apply. That means that an increased risk of gastric cancer would arise after one year and five months of daily use, or a longer period for less regular use.

For esophageal, cancer, one year and ten months. For bladder, three years and ten months. For pancreatic, three years and ten months, and for liver cancer, six years and eight months.

But even if the Court were to exclude Dr. Najafi, it could use one of the other columns, each of which suffices to show a minimum dose.

Something you heard almost nothing about at this hearing is Dr. Dipak Panigraphy. He also calculated a minimum dose, which is Plaintiffs' third answer. On pages 195 through 99 of his report, and 12 through 16 of his rebuttal report, Dr. Panigraphy calculates minimum doses of 7.5 years of daily use for stomach, bladder, esophageal, bladder, and pancreatic cancer, and 14 years for liver cancer.

Defendants challenged two of his opinions, and only two, both in the catchall brief. Those were his supposed use of FDA's ADI and no threshold opinion, nothing at all about his dose calculation. That is for good reason. Dr. Panigraphy himself, using this identical methodology, was allowed through Daubert in the Valsartan, MDL, yet Defense counsel did not repeat their failed argument against him here.

Today you heard a lot about Dr. Najafi's testing. I am not going to repeat that now based on the amount of time left.

THE COURT: That is one minute.

MR. GILBERT: Thank you. Defendants' Daubert argument is that Dr. Najafi is lying, he is lying about validation, he is lying about internal standards, he is lying about recordkeeping. These attacks are false. These attacks are really not with unreliable science or methods, but Defendants' contention that Dr. Najafi is an unreliable witness, but Daubert is not about credibility of that sort.

Your Honor, you also heard a little bit about endogenous formation. These opinions mostly go to the amount of NDMA exposure. Again, Defendants attack interpretations of the studies and seek to demonstrate certain studies are more persuasive than others. Not a Daubert issue.

Let me close. Early next year, your Honor, juries in this district should be able to learn about what these companies did and what thousands of Plaintiffs went through. Many of those Plaintiffs took Zantac, meaning they consumed NDMA for decades at high doses, and suffered devastating cancers.

Thanks to the FDA in 2019, that won't happen again, but that forward looking relief is cold comfort to the thousands of cancer victims.

Plaintiffs' experts offer reliable opinions about why Zantac was the cause of those cancers. Juries should be able to decide whether the studies they relied on are persuasive, whether they are credible, and ultimately whether Zantac caused these people's cancer.

Thank you.

THE COURT: Thank you.

So, the remaining loose ends that we were going to tie up. How about Plaintiffs, do you have your list, and can you give me a report on that?

MS. FINKEN: Tracy Finken on behalf of Plaintiffs.

Your Honor, I have many of the citations, that you requested. I will try to go slowly because they are numbers.

You asked for the citation from Dr. Le on bioavailability. That is on page 46 to 49 of her report. You asked for citations to where Plaintiffs discuss the Gombar case -- the Gombar study. In Dr. Le's report, it is on pages 46 to 48; on Dr. Marletta's report, pages 35 and 47; in Dr. Michaels' report, it's pages 34 to 35; Dr. Najafi's report, pages 25 to 27; Dr. Panigraphy's report, pages 187 to 188; Dr. Salmon's report, pages 30 to 31.

You asked for the citation for the length of time that Ranitidine can remain in the gut, and those can be found in Dr. Panigraphy's report on page 88; Dr. Le's report on page 8, paragraph 13.

And you asked questions about the study which demonstrates human cells are considerably more active than animals in stimulating mutagenic response to NDMA. This is discussed in Dr. Panigraphy's report on pages 164 and 165, and Dr. Salmon's report on page 50.

And then Ms. Bogdan has some answers for you on the peer reviewed publications, your Honor.

THE COURT: Okay, great.

MS. BOGDAN: You had asked a question, if I remember correctly, with regard to a cite in Najafi's rebuttal report with regard to head space in the containers, and what he is referring to there is the DOE, which is the design of experiment section of the GSK root cause analysis where they assess a statistical study to assess stress, which can be found on page 19, and also referring to page 79 through 82 of the root cause analysis where they do their tablet study in vials that are open which would have unlimited head space.

With regard to the studies that the Court inquired about, one of the studies is a U.S. Department of Agriculture report with regard to the heat that cars can reach. To what I can discern --

THE COURT: I am sorry, back to the root cause, was there a Docket Entry number for that one?

MS. BOGDAN: I would have to look for the Docket Entry. I went to the actual 93 or 5 page.

THE COURT: Maybe if one of your colleagues can look. The Docket Entry would be helpful. I interrupted.

MS. BOGDAN: That's okay. We will get that for you.

THE COURT: Okay.

MS. BOGDAN: With regard to the studies, one is a U.S. Department of Agriculture Report.

THE COURT: Tell me what studies these are.

MS. BOGDAN: These are the studies that you inquired about with regard to the references for the temperatures in the cars that are relied on by Dr. Najafi in his report, and there is one that is a publication of the U.S. Department of Agriculture. I don't see that that is peer reviewed, but it is published by the U.S. Department.

The Vanos study is peer reviewed in the medical physiological journal, which is Taylor and Francis online. The Grundstein is peer reviewed, which is in the International Journal of Bio -- I am getting the pinpoint cite for the Court. I have a friend here who is giving me Exhibit 43.

MR. HEINZ: Plaintiffs' response in opposition to the motion, Exhibit 43, the root cause analysis.

THE COURT: Exhibit 43 to the Plaintiffs' opposition?

MR. HEINZ: Correct. I believe it is the Finken declaration.

THE COURT: The Finken declaration is --

MR. HEINZ: Exhibit 43 to the Finken declaration.

THE COURT: Where is it in here? Is it an attachment? I don't have it in front of me.

MS. BOGDAN: I think it is its own docketed document.

THE COURT: Do you know what the Docket Entry number is?

MR. HEINZ: I don't, I can get it.

THE COURT: What you are saying, is Exhibit 43 to the Finken declaration, because the Finken declaration I think is very long, so just if you have that Docket Entry. You can search. Were there any others?

MS. BOGDAN: The Vanos study is peer reviewed, V-A-N-O-S. I believe I started where the Grundstein study, which is also peer reviewed in a journal. And then there is the Yohoo, Y-O-H-O-O, which is a publication of a university in Japan and it is a research paper that is published on Research Gate, which does not appear to be peer reviewed.

THE COURT: Okay. What about the Aizawa?

MS. BOGDAN: Aizawa and Yohoo are coauthors.

THE COURT: So it's one in the same?

MS. BOGDAN: Yes.

THE COURT: I am going trust your laundry list, other than we are looking for the Docket Entry for the Finken declaration.

MS. FINKEN: There is one more. Your Honor had asked about criticisms of the timing of the dosing of Ranitidine in

the Florian study, and what our experts indicate would be a more optimal time to take Ranitidine, to assess results. I wanted your Honor to note that Dr. Najafi discusses this on page 105, of his report; Dr. Le, in her report on page 45; Dr. Marletta discusses it on page 55.

They discuss several reasons why it is problematic, because taken Ranitidine on an empty stomach is not have the labeling instructs, so it doesn't reflect how patients take it in the real world.

The labeling states to take it before bed time or with an evening meal, the point being you would not take it on a completely empty stomach, like they did with Florian. The fasting stomach will have little nitrates and the addition of food on a fasting stomach will immediately affect the PH, which is an important factor in NFDMA formation from Ranitidine.

The criticism of Florian is also in the published literature. The White article in JAMA in 2021 criticizes Florian, and you can find the citations to White in Plaintiffs' expert reports, particularly in Dr. Marletta's report on page 55, where he discusses the limitations with the Florian study.

THE COURT: Okay, thank you.

Were Defendants going to followup, something on the FDA policies? Then we will circle back to Plaintiffs if there is anything more.

MR. BOSSO: For the FDA guidance document, we were

discussing about validation, that is not part of the record, and we didn't rely on that in briefing. The only reason we brought it up was because it was in Plaintiffs' slides today. We could file it if you want us to. They call it USB, Guidelines.

THE COURT: You need to talk into the microphone.

MR. BOSSO: A screen shot of the guidance on method validation.

THE COURT: To the extent the Plaintiffs have used it min their presentation and it is an FDA document, ids there any objection to there being sort of a joint filing, notice of filing whatever the official name of this document is. It sounds like the Defendants are willing to.

Are the Plaintiffs willing to?

MR. NIGH: Yes.

THE COURT: If you could followup with that.

MS. FINKEN: Tracy Finken for Plaintiffs. Would it be permissible for us to file it with your order for the September 30th completion of the record? We can file it as part of that filing.

THE COURT: Right. That is the certification that everything you have provided to me already is part of the record, or if something is not part of the record that you have provided to me, you will file it and certify that.

MS. FINKEN: Yes, your Honor.

THE COURT: Okay, that is fine. That is fine.

MR. HEINZ: Your Honor, on the root cause analysis.

THE COURT: Yes.

MR. HEINZ: I believe it was the sealed filing that was noticed at Docket 5947. The actual Docket Entry would be on the sealed docket, and I wasn't able to identify it, but it is Exhibit 43 of the Nigh declaration, but I couldn't fine the precise Docket Entry.

THE COURT: Okay. It looks like we found it. Okay.

All right. Hard to believe that it has come to an end. Are we happy about that or sad about that?

It looks like you are exhausted and you can't answer the question.

Okay. I want to again thank everyone. I think it was an amazing amount of information that you conveyed in a very organized and methodical and well thought out, well prepared way. You divided your time, you kept to your time. The only reason that we are over is probably my fault because of injecting my questions and stealing a little time here and there, but even with that, we are only over by an hour.

I hope we haven't caused anybody to miss any flights, that would be terrible. So it is 5:30. To the extent that there are flights to be had this evening, I am going to cut this really short and really just say thank you. I appreciate all of the hard work and effort and patience that everyone has

shown, the professionalism, the collegiality.

I will look forward to seeing some of you back, whoever is arguing next week, on Friday, September 30th, I believe it is for the Plaintiffs' motions on that day.

Let me confirm. Yes, September 30th.

Safe travels, be well, everyone, and we will see you again shortly. Thank you.

That concludes our hearings.

(Thereupon, the hearing was concluded.)

* * *

I certify that the foregoing is a correct transcript from the record of proceedings in the above matter.

Date: September 27, 2022

/s/ Pauline A. Stipes, Official Federal Reporter

Signature of Court Reporter