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
October 7, 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, you may be seated. I can see everybody, no masks. The policy changed since the last time you were here.

All right. All set?

Good morning, everyone. We are here in the matter of 20-md-02924, In Re: Zantac (Ranitidine) Products Liability Litigation. It's nice to see everybody here in person and those of you by Zoom. We have many attorneys, perhaps the same as last time, over 50 attorneys in person, including attorneys who will be presenting the motions here today. We also have attorneys and parties appearing by Zoom, about 98 of you.

I will go through the same administrative matters that we discussed a couple of weeks ago. For attorneys who are presenting, when you present, please come to the podium and make your presentation, speak into the microphone, speak slowly so that everybody can hear you and so that Pauline can make her perfect record of the proceedings.

For those of you on Zoom, please keep your audio and video off at all times. Anybody who has a cell phone should turn it off, and there can be no use of cell phones during the hearings, and no one is to record the proceedings, either by Zoom or in the courtroom.

We have scheduled hearings today on the Plaintiffs' motions, and the attorneys will make the presentations. They have not requested that any expert witnesses be present at the

hearings.

The motions that will be presented today are Docket Entry 5841, Plaintiffs' motion to exclude Defendants' putative expert opinions and general causation under Rule 702, Docket Entry 5839, Plaintiffs' motion to exclude testimony of Dr. Robert Gibbons, and Docket Entry 5838, Plaintiffs' motion to exclude inadmissible opinions of Dr. Bernard Olsen. The Defendants have responded to each of the motions and Plaintiffs have filed replies.

The parties have prepared a schedule for the hearing with my input, such that they were provided with the time they requested to make their presentations.

As I mentioned last time, in preparation for the hearings the Court has received and reviewed the briefing on all of the motions and responses and replies, approximately 25 primary expert reports from the Defendants' and Plaintiffs' experts, including their rebuttal reports, 22 deposition transcripts, 40 science studies and reports. I have had the benefit of two Science Days, one at the inception of the case and one on December 2, 2021.

As with the last hearing, and this time as well, I have shared with the attorneys some of the general topics I may be interested in having the attorneys discuss throughout these hearing and they, in turn, have shared with me their PowerPoint presentations which they intend to show today, over the course

of the hearings today.

We are on a very tight schedule with much ground to cover so, with that, I would like to turn it over to Plaintiffs' counsel who will make the first set of presentations during the beginning phase, which is the introduction phase of the proceeding.

So, with that, I turn it over to the Plaintiffs. Good morning.

MS. FINKEN: Good morning, your Honor. May it please the Court, Tracy Finken on behalf of Plaintiffs.

Your Honor, today's hearing involves our challenge of Defendants' experts who answered the wrong general causation question and blinded themselves to critical evidence that went against their preset conclusions. To be clear, that is why they should be excluded, not because they disagree with Plaintiffs' experts, which reasonable scientists can do.

Defendants would like us to focus on their experts in a vacuum, but the Defense experts we are challenging offer opinions that challenge the Plaintiffs' experts, so the comparisons are necessary.

Unlike Defendants' experts, Plaintiffs' experts easily pass Daubert because they applied reliable methodologies to answer the right general causation question: Was the highest realistic exposure to NDMA from Ranitidine capable of causing any MDL Plaintiffs' cancer?

Plaintiffs' answers to that question are even stronger today because the Wang study, which we spoke about during the last hearing, has been published and it considered much of the very evidence Defendants' experts claim no reasonable methodology should, and it reports an increased risk for every cancer in this litigation.

Wang is notable, too, because it has an active comparator analysis of Ranitidine users, which Defendants wrongly claimed last time is the only sort of evidence that epidemiologists should weigh strongly.

With that in mind, I will start with the proper focus of the general causation inquiry, then move to Defendants' experts on epidemiology, and then move to testing.

If we could pull up slide one. There we go.

First, your Honor, what is general causation? One would think this would be a settled question, and it is. As our slide shows, Judge Rodgers in Abilify captured that general causation analysis. The Eleventh Circuit also articulated that the question is "whether a substance has the potential to cause the Plaintiffs' injury."

Slide two, please.

Since this is an MDL, not a single Plaintiff's case, we need to modify the Guinn test slightly. The Plaintiff's injury is actually the injury suffered by any Plaintiff with any one of the five designated cancers, and the Plaintiff is

actually each and every Plaintiff in this MDL with a designated cancer.

That is really important to ensure this Court is able to address Daubert in a consolidated proceeding, instead of thousands of times in each individual case. That slight shift was not necessary in the cases Defendants cite, like Chapman and McClain and others, which looked at both specific and general causation together, examining a particular Plaintiff.

The only case to address this issue head on, your honor, is the Roundup case, which came to the only sensible conclusion, and that conclusion was the Plaintiffs need not establish any particular level of exposure. It is enough in this litigation, at this stage, for the Plaintiffs to show that glyphosate can cause NHL when people are exposed to the highest dose people might plausibly experience.

The Ninth Circuit affirmed Judge Chhabria's order.

Next slide, please.

Your honor, this is a practical approach and it makes perfect sense. In response to our motion Defendants claim the critical question is the minimum dose, but this is unworkable in a consolidated case with Plaintiffs at a wide range of doses. A focus on the minimum dose would make causation no longer general at all, but only a ruling that the evidence failed for that particular dose.

To reiterate an issue of law, there are no cases that

equate the question of general causation to the minimum threshold exposure to a substance that makes it likely to cause injury. Defendants' legal error is really important today because their experts relied on that misstatement of the law when deciding which question to answer.

So it is no surprise that, with a faulty legal premise, Defendants' experts answered the wrong general causation question. They did not focus on high doses for long periods and opine that Ranitidine could not cause cancer; they focused on small doses for short periods of time then concluded that Ranitidine could not cause cancer.

That opinion is not going to help the trier of fact, your Honor. It is instead going to affirmatively mislead the jury. That alone is grounds for exclusion.

Next slide, please.

So, how is NDMA relevant to general causation, your Honor? NDMA is the toxin at issue in this MDL. This is just like asbestos in Talc, calcium zinc in Fixodent, Benzene in Varsol, and NDMA in Valsartan, yet Defendants' experts fail to even acknowledge the relevance of the studies involving the toxin at issue here, which is NDMA.

Next slide, please.

The Valsartan MDL involves pharmaceuticals containing the exact same carcinogenic molecule, NDMA. The experts looked at NDMA science and Defendants tried the same tactics that they

are trying here. Judge Kugler admitted Dr. Panigraphy and other Plaintiffs' experts that relied on NDMA science because NDMA is the relevant toxin. He rejected Defendants' arguments that only studies of Valsartan itself were relevant. He also, notably, excluded a number of the Defense experts.

Based on the same misunderstanding about what kind of studies are relevant, Defendants' experts offer the same unreliable opinion that they did in Valsartan, that NDMA does not cause cancer, and that opinion should be excluded, your Honor.

Next slide, please.

Now, Defendants make much of the fact that -- about regulatory bodies not reviewing NDMA literature, and that is just simply not true, your Honor. The FDA reviewed NDMA literature when evaluating Zantac. Indeed, unlike Defendants' experts, the FDA relied on NDMA literature in deciding to withdraw Zantac from the market. It did not make that decision based on Ranitidine studies. Instead, the FDA's logic was that NDMA causes cancer, and so NDMA in Ranitidine is dangerous.

The FDA did not ignore NDMA merely because Ranitidine specific studies would be good evidence, and other regulators followed suit, your Honor.

Next slide, please.

Even GSK, the Defendant in this case, reviewed NDMA literature in September of 2019. After learning that NDMA was

in Ranitidine, GSK analyzed and discussed the risks of cancer based on NDMA dietary studies. That is because NDMA is obviously relevant, as everyone outside this litigation, including Defendants, have always agreed.

Next slide.

Now, the published Wang study confirms what Plaintiffs' experts consistently concluded, that NDMA causes cancer; that getting NDMA from Ranitidine is no safer than getting it from any other source; and that consideration of all NDMA science is relevant to the causation inquiry.

Wang is particularly problematic for Defendants' experts because it has everything the Defendants have asked for. It's a human study that looks at Ranitidine users. It is a huge database, the entire country of Taiwan, 99 percent of Taiwan's population of 23 million is included in that database, and it uses an active comparator design that, according to Defendants' own experts, though we believe they are wrong on this point, automatically removes any bias or confounding, and it measures dose response, concluding there is no protopathic bias, the feature Defendants' experts argue affects the results.

Next slide, please.

Now, Wang considered NDMA literature when it evaluated Ranitidine, and Defendants have said that the scientific community disagrees that NDMA literature is relevant, but apart

from the regulatory bodies, which always considered NDMA, look at what Wang says. As Plaintiffs have consistently argued, Wang analyzed the animal and dietary studies Plaintiffs' experts analyzed. Defendants' experts did not.

In other words, even in Ranitidine specific studies, the Wang study extensively analyzes NDMA literature.

Next slide, please.

The Wang study also confirms Plaintiffs' experts' criticisms of Defendants' studies. Just as Plaintiffs' experts did, but Defendants' experts failed to do, Wang looks at the Ranitidine specific studies and identifies limitations, especially "small sample size and short follow-up duration may cause statistical bias and inaccurate conclusions." Wang's outcome data were retrieved from formal cancer registries which are more accurate than other sources.

Recall, your Honor, that Drs. McTiernan and Moorman flagged the importance of a reliable source of cancer diagnoses.

Next slide, please.

Now, defendants' experts talk a fair amount about reverse causation, or what is called protopathic bias. That is what Witte and others say explains many of the associations in the Ranitidine studies. Defendants cannot say that about the Wang study since it considered this and ruled out protopathic bias.

Wang also shows clear dose response for multiple cancers, and overall, it showed that people taking Zantac got significantly more cancer after just one year of use than people taking no Zantac at all, and more than people taking a comparator drug.

Next slide.

So, what did Wang conclude? Defendants' experts disregard or deny NDMA science at every turn. Wang's conclusion exposes their shortcoming, and Wang states and concludes in the published study, "However, the clear data from our real-world observational study strongly support the pathogenic role of NDMA contamination given that long-term Ranitidine use is associated with a higher likelihood of cancer development in Ranitidine users compared to the control groups of non-Ranitidine users who were treated with PPIs or Famotidine."

Defendants' experts' failure makes their opinions unreliable and excludable.

So, let's discuss testing, your Honor.

Next slide, please.

What did the FDA say about real-world testing? Your Honor, no Defendant attempted to test Ranitidine under real-world conditions, despite having in-house laboratories and hundreds and hundreds of scientists. That is not because they dispute the general point that testing is important. Your

Honor, if you look at Exhibit 36, which is the FDA Working Group transcript, day two, at page 129, lines 6 to 24, the FDA actually endorses testing in real-world conditions -- I am quoting -- "such as a hot mailbox, a glove box in a car, a bathroom, or truck in the middle of summer in the southern United States."

Let's look at what Defendants did.

Next slide.

Defendants did none of this; they never tested Ranitidine under real-world conditions.

Next slide, please.

Now, Defendants have the burden to show their methods are reliable. Defendants did not have to provide any evidence on testing, and largely have not. Instead, Defendants' experts focus on criticizing Plaintiffs' experts' actual testing and opinions. This could have been admissible, your Honor, but only if these conclusions had actually demonstrated real problems with the testing based on reliable methodologies which, of course, requires understanding what actually happened.

Defense experts Drs. Olsen and Gibbons failed in this basic requirement. Dr. Gibbons did not understand the testing method or how many pills were tested and tried to turn his own misunderstanding of Dr. Najafi's testing into a critique, but to be reliable, Dr. Gibbons must have actually identified a

reason the testing is wrong, not merely that he could not comprehend an expert report.

Dr. Olsen did address the actual testing on the other hand, but Dr. Olsen misstated that the HILIC column is inappropriate for testing, even though it is specifically designed for polar compounds like NDMA. Worse, he relied on a 2020 source from Waters that contradicts his speculation that testing could form artifactual NDMA.

Next slide, please.

Your Honor, Defendants' expert opinions are simply not reliable. Defendants did not need to produce any experts, but because they did, those experts cannot testify that there is no general causation because Ranitidine does not cause cancer after one prescription. They cannot ignore NDMA science when regulatory bodies and Defendants themselves have said it is relevant.

They cannot testify that Ranitidine studies of short-term use means long-term consumers cannot get cancer, and they cannot cast false doubt on testing methods they clearly misunderstand. That is because expert testimony must be reliable, and Defendants' experts' opinions are not reliable and should therefore be excluded.

Thank you, your Honor.

THE COURT: Okay, thank you.

Defense opening remarks.

MR. BOEHM: Good morning, everybody. Good morning, your Honor.

THE COURT: Good morning.

MR. BOEHM: Paul Boehm for Pfizer, and today and for today's purposes I am speaking on behalf of all of the brand Defendants.

Just a brief note, a housekeeping matter, there were a few slides that were circulated yesterday that we discussed with Plaintiffs' counsel that we believe were outside the scope of the proffer topics for the day. We raised that with Plaintiffs' counsel who respectfully disagreed with our position on that.

We want to register an objection for the record, particularly as to slides 2 and 3 in the first of their decks and to slides 28 through 49 in their deck number 3.

THE COURT: Okay.

MR. BOEHM: Your Honor mentioned during your opening remarks that you had provided a list of some topics for the day, and if we could pull up -- Maryann, if you could pull up the slides and go to slide number 2.

These are some of the topics, your Honor -- if we can go to the next slide.

These are some of the topics that we thought your Honor felt set the framework for the day that will be the background for some of the very specific scientific issues that

the Court will be addressing and some of the criticisms that Plaintiffs' counsel are specifically bringing as to the experts.

In particular, I wanted to start with the first two, the respective burdens of proof that the parties have here and the Court's role in measuring the difference between admissibility under Rule 702, and then just what is persuasive and subject to cross-examination at trial, and these two we think go hand in hand.

Go to the next slide.

This is not controversial, I think Plaintiffs said this themselves, that the party that is offering the expert has the burden to meet the standards of Rule 702. We, of course, agree with that. That means that Defendants have this burden when it comes to the experts we are discussing here today, just as Plaintiffs have the burden with respect to all of the experts that were discussed a couple of weeks ago, again, not controversial.

There is an important distinction between Plaintiffs' and Defendants' burden as it relates to application of Rule 702 in a case like this.

If we could go to the next slide.

The Plaintiff bears the burden of proving causation, and that is important. Defendants do not bear that burden. We do not bear any burden to prove or to disprove anything at all.

As this slide shows, the Plaintiffs have noted that themselves in their briefing on this issue, that we have no burden to disprove causation. We could put forward no expert witnesses, or only rebuttal witnesses.

So, in considering the motions before the Court today, and the motions we discussed a couple weeks ago, this is important context, Defense experts are not offering affirmative causation opinions precisely because we do not have this burden.

The Defense experts are offering opinions that there is no reliable evidence of causation, and Rule 702 still applies to the methodologies and techniques that they apply in reaching that conclusion. Plaintiffs bear this burden alone.

In fact, your Honor, as the Court may know, many judges in toxic tort MDLs reach conclusions about Plaintiffs' experts, that those opinions are not reliable, and then never even get to the motions as to Defendants' experts because you don't need to. That has happened recently in cases that I have been involved in, in Viagra, in the MDL where the Court decided the motions as to Plaintiffs' experts and don't even reach the motions as to the Defense experts. That is a reflection of this burden.

So, how should the Court, in thinking about the briefing and hearing the arguments today, assess reliability of Defendants' experts in this context?

Are they using the same methods here as methods that they have used outside of the courtroom, or are they doing something different here versus there?

In the case of Defense experts, it is the same.

Are they approaching this question consistent with the broader regulatory and scientific community, or are they standing apart doing something new, doing something different?

In the case of Defense experts, they are in lockstep in their techniques and application of methodologies with the broader scientific and regulatory community.

Are they looking at data that is most closely related to the drug at issue, or are they making extrapolations based on other data sets?

In the case of Defense experts, they are primarily looking at the data most closely related to the drug at issue.

Are they honoring the concept of statistical significance, which the Eleventh Circuit says you must do, or are they ignoring it?

In the case of Defense experts, they are honoring that concept.

The answers here, as we will discuss in detail as we go through theses experts one by one, will show that the Defense experts are using broadly accepted methods, the same ones used by FDA, by EMA and others in the scientific community, to specifically look at the question of whether

Ranitidine increases the risk of cancer, specifically the cancers the Plaintiffs are bringing forward here.

Next slide, please.

These are the McClain and Chapman opinions that were referenced by Ms. Finken in her time. This burden, whatever the number of Plaintiffs that were at issue, and it wasn't one -- in some cases, it was bellwethers, in some cases it was whatever number it is. This burden is the same, there is a general causation burden, and that applies here just as it applied in those cases, and that is what those Courts would do.

Maryann, can you take us to the next slide, please.

This is from the Abilify opinion, which your Honor is obviously familiar with, from Judge Rodgers. Ms. Finken also referenced this opinion. Judge Rodgers said that the very best evidence, when you have it -- you don't always have it, but when you have it, the very best evidence is grounded in the epidemiology. Note the language, exposure to the drug. Not exposure to something that might be in the drug at some unknown level that is in controversy, exposure to the drug. That is the question.

Judge Rodgers said this is the sine qua non of general causation. It is an essential and absolutely necessary condition.

I wanted to note, because another of your Honor's topics on the list was specific to weight of the evidence

methodology. Judge Rodgers references that in the Abilify opinion, and she says that whether an expert is using Bradford Hill, whether they are using some other weight of the evidence methodology, this requirement stays the same. You have to start, the threshold issue is, does the epidemiology establish a reliable consistent association between exposure to the drug and the injuries that are alleged in the case.

That is a threshold question, and it goes to admissibility. It is not a matter of persuasiveness, it is not for the jury to decide based on cross-examination and how that goes. It goes directly to Rule 702.

Next slide, please.

In the Eleventh Circuit, in toxic tort cases like this one, Plaintiffs' burden specifically is to show well conducted epidemiological studies that show a statistically significant relationship between the medication and the injury that has been alleged.

We are going to talk about threshold dose. That was referenced kind of in passing by Ms. Finken, threshold dose. We talked at length about that a couple of weeks ago, I will not belabor that now. We will get to that later. We will talk about the reliance on NDMA in occupational and dietary studies as well today. Again, that was something that was discussed at length a couple of weeks ago, so I won't take too much time on that other than to say the Eleventh Circuit law is clear about

what is required under Rule 702. If you fall short on this, you fall short on Daubert.

And that is consistent with the approach that the Defense experts employed in reviewing the data that are available in this case.

They looked first to see, just like the FDA, looked first to see is there this association, is there a consistent signal that we see from the epidemiological studies. You start there and then you can do your Bradford Hill or whatever weighing of the evidence that you need to do.

Next slide, please, Maryann.

Your Honor, of course, is familiar with the studies that are on this chart.

This is a version of the slide that Mr. Cheffo showed your Honor a couple of weeks ago, and we know that your Honor is familiar with these, probably read all of these studies, at least most of them. Again, I am not going to go through all of this again.

By the way, your Honor, everybody here recognizes the work that the Court has done, and the people around you have done to understand this data, and I can speak for our client, for Defendants, and I believe for Plaintiffs' counsel in thanking you for the careful attention to studies like these that you have obviously paid.

The point here is, without going through all of this

again, Defendants' experts did the same thing as the FDA, the same thing as the EMA and others in looking at this data, and now you have -- I know we are going to talk about Wang here in just a minute, I think that gets us over a million Ranitidine users, or at least close, that is in this database.

You heard a reference to Defense experts not looking at the real-world data.

Your Honor, these are the real-world data, over a million users, using the product under all sorts of conditions, being tested based on the gold standard that is the randomized control trial -- or the types of epidemiological studies that are involved here.

You heard a lot about the Wang study, and you are going to hear more about that today. Obviously, it just came out. We can put that up on the slide, we could make it an even dozen, and it wouldn't change anything at all. It wouldn't change anything at all.

A couple of points in passing, and we will talk about Wang a bit more later, of course.

First of all, Plaintiffs have criticized the epidemiology study for having too short of exposure, too short of followup. Wang is shorter than any other studies that were already available in terms of that.

Secondly, when you look at the active comparator results, which is what the FDA and the scientific community

says that is the ideal, that is where you look, only one out of the five cancers shows up with an association. Four out of the five don't.

You heard a couple of weeks ago from Plaintiffs' counsel that it was bladder cancer, that is the one where they said we can rely on the Ranitidine epidemiology, we don't have to look at NDMA data, and we can see an association for bladder cancer. For bladder cancer in the Wang study there is no association. The hazard ratio is almost exactly 1.0.

So, what is the point? Wang, your Honor, demonstrates exactly why the FDA, the EMA, and others in the medical community are using -- and Defense experts are using appropriate scientific methods by looking at these data and considering whether the data tell a consistent story, is there a consistent signal.

Next slide, please, Maryann.

Your Honor is familiar with Florian, no consistent signals. That is what Wang gives, no consistent signals emerge across these studies.

This is an important feature of the causation question. You can read from the study itself. It says that previous studies, including NDMA and Ranitidine studies -- I just wrote this down, page two -- were contradictory, and the data were not sufficient to reach definite conclusions. The conflicting results of studies underlie the lack of concrete

evidence supporting the role of Ranitidine in cancer development. No consistent signals.

There was a reference to Valsartan that I want to mention quickly. In Valsartan, two points. First of all, it's hard to know exactly what to do with that because there is no written opinion, as your Honor knows. From the hearing transcript, the judge, who is in New Jersey, not in the Eleventh Circuit -- let's make it three points.

Two is, this is in New Jersey, not in the Eleventh Circuit. Then third, if you look at the transcript, the basis of the ruling was two things; one, that there was an FDA recall, and two, company documents.

That is the basis of that ruling, and we know it is crystal clear in the Eleventh Circuit that that cannot be a primary methodology to pass Rule 702. So, under Eleventh Circuit law, that would be an incorrect ruling.

Next slide.

I just want to touch base on one last topic that was on your Honor's list of subjects today, and that is the speculation about future science and the concept of law lagging science. Of course, this has been adopted by the Eleventh -- I think it has been adopted by every circuit, this concept of not getting ahead of the science.

The Court's gatekeeper role involves making sure that the scientific theories that are advanced in the context of a

litigation, that they don't get out ahead of what is happening in the real world. That is what this concept stands for.

The scientific methods, and by the way, the conclusions for the Defendants' experts, they are in lockstep with what is happening in the real world. They aren't out ahead of the science, they are in line with that science.

THE COURT: That is 15 minutes.

MR. BOEHM: Which is perfect, because I am all done.

THE COURT: Okay. Everybody is well trained.

Thank you, thank you for the introductions from both sides.

Now we are moving into the epidemiology motion, and Plaintiffs will go first, and you have allotted yourselves an hour and 25 minutes, and then additional time on rebuttal, but for your primary argument.

MR. HEINZ: Good morning, your Honor, Noah Heinz for the Plaintiffs.

THE COURT: Good morning.

MR. HEINZ: Could we get the slides up, please.

I will be setting out the legal framework for Daubert as it applies to epidemiology.

The first critical point is that Daubert is about methodology, not conclusions. That comes from Daubert itself which instructed that in deciding the admissibility of expert testimony, quote, "the focus, of course, must be solely on

principles and methodology, not on the conclusions that they generate," and this is precisely what we told your Honor at the last hearing.

The Court must scrutinize an expert's application of their methodology, but go no further. That means we will not be telling you today that -- to exclude the Defendants' experts because their conclusions are wrong, the jury will decide that. Neither side's conclusions are at issue on Daubert.

Next slide.

Here the methodology all epidemiological experts followed was to compile relevant studies, carefully scrutinize strengths and weaknesses, and interpret them to discern whether an association existed between the NDMA in Ranitidine and cancer, then conduct a Bradford Hill analysis. That is the methodology the Plaintiffs followed, that is more or less the methodology that the Defense epidemiologists followed as well.

Next slide.

For that methodology to be reliable an expert must consider all of the relevant evidence. As the Rezulin case explains, Courts may preclude an expert from testifying in part because he ignored available evidence that was vital to his opinion.

Your Honor may remember that in defending Dr. Moorman, we argued that she undisputedly had considered all relevant evidence, check on this box, and Defendants' experts, as Mr.

Snidow will explain, did not.

Next slide, please.

Then the expert must reliably evaluate the relevant evidence. The general rule under Daubert is that an expert must address any gaps with reasoned explanations. That means that an expert analyzing a study must explain why applying the results of that study are a proper fit with the case.

Experts can't simply assert that the results of a study for short-term smokers holds for long-term smokers. As the Eleventh Circuit has explained, nothing in either Daubert or the Federal Rules of Evidence requires the District Court to admit opinion evidence that is connected to the existing data only by the ipse dixit of the expert.

In the context of epidemiology, that means explaining which evidence is most probative and why.

Next slide.

Recall when I defended Dr. Moorman and listed out the specific consistent criteria that she used to evaluate each and every epidemiological study. Those were factors like the design of the study, whether it was cohort or control, the exposure measurement, followup, OTC misclassification, the quality of the cancer diagnosis information. Criteria like that are essential to a reliable methodology, as the case law confirms.

From the Bair Hugger case, "The key question

in evaluating epidemiological evidence are the extent to which a study's limitations compromise its findings and permit inferences about causation." The same concept appears in the Hardeman v Monsanto Ninth Circuit case, the Abilify decision, Deepwater Horizon, and all of the Daubert cases that each party has cited, and that is because identifying and applying consistent criteria is fundamental to a sound methodology.

The alternative is what happened in Deepwater Horizon where Judge Rodgers explained, "Dr. Williams' report simply contains serial lists of quotes from various studies with no discussion, critique, or assessment of the quality, design, or relevance of any study that she relied on."

That is why Judge Rodgers concluded an expert opinion, even if supported by a lengthy list of case studies and treatises, is not reliable without an explanation of the logical steps supporting it, and, of course, the criteria have to make some sense as in there have to be factors that the scientific community recognizes as important.

As I explained last time, our epidemiologists undisputedly did use criteria just like that that are relevant, and as Mr Snidow will explain, the criteria the Defendants used, to the extent they exist at all, were not of that sort.

Next slide.

Daubert does not allow a District Court to decide for itself which studies are most probative. The Schultz case

explained that Rule 702 does not require or even permit the District Court to choose between two studies at the gatekeeping stage. Abilify, this is within the Eleventh Circuit, quoting the Eleventh Circuit Quiet Technology case, explained "a District Court may not evaluate the credibility of opposing experts or the persuasiveness of competing scientific studies." All about methodology, not at all about the underlying studies, not about persuasiveness.

Next slide, please.

A good example of this is the Roundup litigation. In that case there were studies, including a large Cohort Study that showed no association between glyphosate and non-Hodgkins lymphoma, but there were three smaller case control studies that did show an association. For the Court to choose between them would have exceeded the limited gatekeeping role, and so both sides' experts were admitted.

Next slide, please.

The experts were properly admitted because they had a reasonable basis for picking one set of the studies over the other set. They explained, for example, the Plaintiffs' experts, why the Cohort Study was not definitive, there were misclassification problems in that study, and why the critiques of the case control studies were also not devastating, they could bear the weight. That is why the experts on both sides got through in that case, despite conflicting science.

Next slide.

I am going to linger a bit on Judge Rodgers' approach in Abilify and use it to explain why the framework I just set out is consistent with the Benzene cases which the Court had particular questions on.

Let's start with Burst and Hendrikson, which were about Benzene in gasoline. That was claimed to cause a condition called AML. The Defendants have argued that Burst and Hendrikson show that experts must ignore evidence about the toxin and focus only on the product, but they actually illustrate the two factor test from Abilify, considering all of the available evidence carefully and explaining how each piece of evidence is weighed, and that didn't happen in Burst and Hendrikson.

First on relevance, it is notable that experts from all the Benzene cases, from many different products, including Varsal, Liquid Wrench, gasoline and other solvents, analyzed Benzene science extensively, as the cases cited in Plaintiffs' reply at Footnote 30 confirm. That certainly happened in Burst and Hendrikson where the Court expressly states that literature about Benzene and gasoline were both relevant. Ignoring either one would have been unreliable, and for exactly the reason that Judge Rodgers explained, the first prong.

The problem in those cases was ignoring the gasoline evidence, but that is simply an application of the more general

principle that experts must consider all the relevant evidence. Here the same exact critique applies to the Defendants' experts who failed to adequately consider the NDMA science, which is, just like the Benzene literature, obviously relevant.

The second factor is explaining the relative weight of the different evidence. The problem in Burst and Hendrikson was that the experts failed to explain limitations or perform any weighing for the incomplete list of gasoline studies that they did look at.

The experts here -- the experts there, sorry, just as in Deepwater Horizon, simply listed a number of studies and then their end result, more like a literature review or ipse dixit. That is not reliable.

Weighing was especially important in the gasoline cases because, as the Ryan case explained and as we quoted in our brief, "The Defense experts in Hendrikson and Burst opined that exposure to Benzene in gasoline does not cause an increased risk of AML due to competitive inhibition between the variance components of gasoline that mitigates the carcinogenic properties of Benzene."

Now, that is a mouthful, but what they were basically saying is that the Benzene in gasoline, unlike the Benzene in everything else, does not cause cancer because a specific scientific theory had to do with the ingredients in gasoline and how they worked together.

Because of that theory, which the literature supported, the gasoline evidence was particularly important because there was a good explanation of why the Benzene literature wouldn't be relevant, or as relevant in that case in light of the competitive inhibition. Where that theory is not in the case testimony based only on Benzene has been held to be appropriate, as the Ryan Court held, for example, with Liquid Wrench.

The Benzene cases show that Defendants' experts needed to carefully consider and weigh all of the evidence about the toxin at issue, as every expert in those cases did, but if they had an argument that something in Ranitidine counteracts NDMA that explains on their theory why NDMA in Ranitidine, unlike everywhere else, does not cause cancer, maybe that opinion by itself could be admissible even without looking carefully at the NDMA literature.

But Defendants have proffered no such theory here, unlike the Defendants in the Burst and the Hendrikson case. They have never said that the NDMA in Ranitidine is any different from the NDMA anywhere else, and that is because it is not. That is what the regulators have concluded and that is what both sides have agreed is the case.

Instead, the Defendants' experts have ignored NDMA science and failed to carefully weigh it without a theory for why the NDMA in Ranitidine does not cause cancer, and that is

unreliable.

Thank you.

THE COURT: Thank you.

MR. SNIDOW: Good morning, your Honor, may it please the Court, it's J. D. Snidow for the Plaintiffs.

THE COURT: Good morning.

MR. SNIDOW: Pull up the slides, please. Thank you.

Before I dive into the individual experts, I do want to explain at a high level where they went wrong.

First, the experts answered the wrong general causation question. They answered whether NDMA can cause cancer at low doses and after a short followup time, even though the real general causation question should focus on whether NDMA can cause cancer at high doses, and after a long enough time for the cancer to develop. The reason, your Honor, is because there are many, many Plaintiffs exactly like that in this MDL.

Second, Defense experts fail to consider all the evidence, in particular, evidence about NDMA itself.

And third, Defense experts failed to consider that evidence carefully.

Next slide.

I'll start with the first one. As Ms. Finken and Mr. Heinz just stated, the general causation question is about whether a substance can cause a disease.

As the Court knows, the specific causation question is very different, whether the substance caused the disease in the particular Plaintiff in that particular trial.

I will take the next slide.

There are a lot of places, your Honor, where that distinction is very important. The one I want to focus on for a few minutes is dose because it was the subject we talked a lot about over the last couple of weeks and I'm sure we will talk about today.

In this MDL every Plaintiff is going to have taken a different dose of Zantac, right. Some of our Plaintiffs took Zantac for just a few years, some of our Plaintiffs took Zantac for decades. Some of them took it for just a couple days a week, some of them took it every day.

Then there's storage, of course, too. Some of our Plaintiffs stored Zantac in a cool dry place, others of our Plaintiffs stored Zantac in hot places, like the mailbox Ms. Finken was talking about, or their bathrooms, or in their cars. In those places Ranitidine degrades faster into NDMA.

What that means is that each of the Plaintiffs also ingested a different amount of NDMA. I realize that makes this case a complicated one, but for general causation experts it is just a fact that each of them has to grapple with, that the dose for each Plaintiff is going to be different.

Next slide.

As we pointed out, Judge Chhabria in the Roundup case said that for general causation you have to look at the highest dose that people might plausibly experience. I want to pause for a moment and briefly illustrate why that has to be true.

As I said, every Plaintiff in an MDL like this one is going to have taken a different dose, but if there is some dose that I have is labeled dose A known to be toxic down here, some dose that we can look at the medical literature and say, look, we don't exactly know what the minimum is, but we know if you are exposed to this dose, you have a higher risk. What that means is those Plaintiffs at the top right hand of my chart clearly have a claim, right.

Now, specific causation may be different. If you have the Plaintiff down there on the bottom left who took a dose and we don't really know if it is enough to cause cancer, they might go to trial and they might well lose on specific causation, right. But for general causation, you have to look at the Plaintiffs at the top right, and the reason is, because for those Plaintiffs up there, how could you tell them, we know that you took a dose that is higher than demonstrated to cause cancer in the medical literature, but you lose.

How could that be? It certainly can't be we know you took a dose high enough to cause cancer, but you lose because other Plaintiffs in this MDL maybe took a dose that wasn't high enough. That can't be right. It would defeat the entire

purpose of the MDL, it would arguably be a due process violation for that particular Plaintiff, and that is exactly why law is, for general causation in an MDL, you have to consider the highest possible dose.

I'll take the next slide.

By the way, your Honor, I made it really easy on the first slide by saying there is one dose that we know that can cause cancer, but the reality in the science is much more complicated because the way it works is, every time you do a study you are going to note a different dose that is sufficient to cause the disease. So maybe do one study, and we say, well, now we know that dose A is known to be toxic, we know that is enough to cause cancer from the medical literature.

Then you do another study, look at different data, it might be based on entirely different kinds of data, there are certainly different people, and then you do another dose that you know is enough to be toxic and causes disease, on and on and on, and we have way more than three studies in this litigation, but that is what is going on here, different scientists are looking at different data and they are coming to different conclusions about what dose we know to be enough.

I understand as lawyers we want there to be a bright line, like what is the dose that causes cancer, but that is not the way it works.

Next slide.

The reason why it is not the way it works in particular in this case is because, with respect to this kind of carcinogen, NDMA or even Ranitidine, it is not ethical to do a randomized control trial.

The way this would work for dose with most pharmaceuticals, if you want to know if you have enough dose to cure a certain disease or to cause a certain side effect, you do a dose ranging trial. You do a randomized control trial very early on in the drug's development, you intentionally give certain doses of the drug to different people in different amounts, and from that you can get pretty good data about what the actual minimum dose is to cause a certain outcome.

You just can't do that here when you are trying to figure out whether NDMA or Ranitidine causes cancer, and there are really two reasons. I have one here, it's because it would be unethical to administer Ranitidine to a patient to determine if it causes cancer.

The other reason, of course, is because cancer has this long lag time. It takes a long time for cancer to develop, and so it is something that is difficult to do in a randomized control trial.

So the upshot of all of that is that we have to look at dose information that we can glean from other sources. You can look at NDMA that people consumed in food, which are the dietary studies, you can look at NDMA that people encountered

at work, which is our occupational studies. Yes, you can look at NDMA that people consumed in Ranitidine itself.

From that you can glean information about what dose is for sure enough to cause cancer, or I should say enough to increase the risk of cancer.

Next slide.

What I want to contrast these doses that I show here with is the concept of threshold dose, which is something that Defendants have spent a lot of time on and I believe are going to spend a lot of time on.

Next slide.

So the threshold dose is different than what I have been talking about, it is the minimum dose that could theoretically cause cancer, just theoretically, and for a genotoxin like NDMA our experts opine that dose is very, very, very low, approaching zero.

That is not the kind of thing that is ever going to show up in scientific literature. It's not the kind of thing we are relying upon here to show that we have actually demonstrated that our Plaintiffs took doses that demonstrates that cause cancer, but it is true and it is something that is analytically different than the types of sufficient doses demonstrated that that I have talked about.

Next slide.

That is why Defendants are wrong to put up slides like

this one, that Dr. McTiernan doesn't have an opinion on threshold dose. I'll say i think they are also wrong to use such an unflattering picture of her, but that's neither here nor there.

As they point out here, Dr. McTiernan doesn't really have an opinion on the theoretical minimum dose that is needed to cause cancer, but that is okay, she doesn't need to for general causation purposes. As I said, so long as the literature demonstrates that doses that our Plaintiffs realistically took are enough, then it doesn't matter what the theoretical how low can you go floor is because she has done what she needs to.

Next slide.

As Ms. Finken pointed out, we think the Defendants are just wrong to say that a threshold dose needs to be demonstrated.

We have looked pretty extensively in the case law, and to be totally level with the Court, there is not a ton of case law defining these separate issues, but the closest it comes I think is this case, the Schultz case in the Seventh Circuit.

What the Schultz case did is they looked at two statements made by this expert, Dr. Gore, and I want to focus on them for a moment. The first statement that Dr. Gore made was, if a person is exposed to 11 person years, I believe, of Benzene, then they would be at an eight times greater risk of

developing AML.

That is the kind of dose that I have been describing as the plainly toxic dose, the clearly harmful dose. We know it is enough. If you take 11 years of Benzene, apparently you get an eight times higher risk.

The second box, though, the second statement that Dr. Gore made is that with carcinogens like Benzene it is theoretically possible that any amount of exposure could be enough.

That is similar to the two concepts we have been talking about here. Defendants want to focus on that second one, and they want to say, look, their epidemiologists, they can't say for sure what the floor is, they are telling you it could theoretically be zero, that is grounds for exclusion. That is not what the Schultz case said, in fact it said exactly the opposite.

Next slide.

The Court said it is important to understand the difference between these two statements. The first statement says that scientific studies confirm the danger if you are exposed to at least ten years of Benzene. All right.

The second statement says that no one is sure whether ten years is enough, maybe it is five years, maybe it is one year, or maybe it is none.

That second box is the threshold dose that the

Defendants keep talking about. The first box is about how much is enough as demonstrated in the literature.

What the Schultz Court said is that second box really doesn't matter. The Court said that second statement may have been unnecessary, because it is, but there is no rule requiring the exclusion of expert testimony just because the expert digresses into a collateral issue to explain where the frontier of research lies.

That is exactly what is going on in this case when we talk about -- when Defendants, I should say, talk about threshold dose. As I will get to in a moment, the literature certainly demonstrates that our Plaintiffs took enough NDMA to increase the risk of cancer. Could it be lower than that? Of course it could. That is an academic question, or as the Schultz case says, a collateral issue about where the, quote, "frontier of research lies."

The next slide.

That is why they are wrong to say what they do about Dr. Moorman here, and again not the most flattering picture I have ever seen of her. They say that in her opinion -- they ask her, in your opinion, could a single dose of Ranitidine cause cancer? And she says what is exactly scientifically correct, that theoretically she doesn't believe that there is a threshold dose for this molecule, any level could increase risk.

That really doesn't matter. That is about where the frontier of research is, it is an academic question, but for these purposes, it is not the dose that counts.

Next slide.

Now, to be fair to the Defendants, in a different case that question really could matter because if you had a substance and you had an MDL where none of the Plaintiffs took a dose that was even conceivably enough to cause cancer, or whatever it is, that would matter, right. If the threshold is above anything any of your Plaintiffs took, then Gannon should lose on general causation.

That is what you see in the case law when they talk about dose being a general causation issue, because there are certainly cases where it could be, and there are two that we have talked about in this litigation where that is exactly what happened.

Next slide.

In McClain the Court noted that the dose of ephedrine in Metabolife was about half of what the FDA allowable limits were, which is quite different than what we have here where the doses were so much higher than the FDA limit that the FDA pulled the product from the market. The Court noted that the amount of ephedrine, which is the substance in Metabolife, doesn't exceed the amount of ephedrine in a ton of other products, but then here is the critical thing: In McClain they

didn't have any opinions about what level of exposure was enough.

So, in that kind of situation where there is very little amount of a product -- of a substance in a product, and you don't even know if that amount is enough to cause the disease in any of the Plaintiffs, that is a general causation problem. That is what was going on there. It is just not the situation here where a large, large number of our Plaintiffs, and I will get to them, we know did take enough.

Next slide.

That is also what happened in Chapman, which as the Court noted, all substances potentially can be toxic, and that is true, and that you want to look for a dose and effect, and that is true. Then the Court noted that the experts in that case, nor the articles on which they rely, determined actually how much Fixodent must be used for how long to increase the risk of a copper deficiency.

Again, exactly the same situation, if you do get in a situation where you can't be sure that any of the Plaintiffs ingested enough of the substance to cause the disease, that is a general causation problem.

What I will submit to the Court is that throughout this litigation Defendants have basically been assuming that this is the fact pattern that we are in here, but it is not. The way you know it is not -- turn to the next slide -- is

because there are so, so many of our Plaintiffs who clearly took enough Zantac to have an increased risk of cancer.

I think we said last week in our brief that 60 percent of the Plaintiffs in the registry have more than ten years of use. I will give three examples to the Court just to make it a little more concrete.

Next slide.

Timothy Chilcott, a Plaintiff on the registry, used Zantac from 2001 to 2017, then he got bladder cancer in 2017; Christine Smith used Zantac from 2009 to 2019, she is diagnosed in 2019 with pancreatic cancer, and unfortunately she ultimately passed away.

A similar use situation with Charlotte Carter, she used cancer (sic) from 2000 to 2016, she was diagnosed in 2016, and she ultimately developed bladder cancer.

So, for general causation, your Honor, you have to have in mind these cases because if it is true -- and I am about to show exactly why it is true -- but if it is true that one year is enough, or three years is enough, or frankly, for these three ten years of Zantac use is enough, maybe there will be problems on specific causation for these Plaintiffs, but you can't look at these facts and the use of literature I just talked about and say, you lose on general causation. That just doesn't work.

I'll take the next slide.

I wasn't really making up those numbers when I said one year, three years is enough. As I said, you can't just pick one dose that is demonstrated to cause cancer because the reality is, when you look at different data sources you are going to get different information about doses that are demonstrated to be enough.

I have listed a number of them here. I am going to describe in detail a few of them. Just so the Court knows, the one year is from the Wang study, the three years is from the Cardwell study, and the rest of the figures are the ones that Drs. Salmon and Panigraphy generated by going what I call bottoms up, by looking at what NDMA doses were enough to cause cancer in the NDMA studies, and then looking it up, how much Zantac you need to take to get to those doses.

They are different methodologies, to be sure, but each of these is a dose that is demonstrated in the literature to be enough.

Next slide.

Here is Dr. Salmon discussing the Cardwell study. The Cardwell study looked at three years of usage and noted that there is a statistically significant increase in the risk of bladder cancer.

I think counsel in their opening said the most important thing is to look at exposure to the drug, that is a quote. What happens when people are actually exposed to the

drug. We, of course, think you should look at that plus some other material as well, but even taking just that, this is exposure to the actual drug.

In Cardwell, people took Ranitidine for three years and they developed a risk of bladder cancer that was statistically significant. So for general causation the question should just be, well, are there other Plaintiffs in this MDL who took Zantac for more than three years and developed bladder cancer? The answer to that is yes. I just showed you two examples of them. There are thousands more.

Next slide.

Just to show the Court that Dr. Salmon is exactly correct on this, this is what the Cardwell paper showed: For people who took more than 1,095 daily doses of Zantac, which is three years, they got a 43 percent increase in risk, and that result is statistically significant.

Next slide.

The Wang paper confirms this result and confirms what our experts have been saying all along. This is the graph in Wang for liver cancer, I'm sure we will be talking more about it later, but you can see visually what is going on here. That blue line is the users who took no Zantac at all, and you can see what their risks of cancer were when they followed them over time. Then once you look at people who took it for 90 days, or six months, or nine months, or a year, those lines go

way, way, way up.

This is conclusive evidence of dose response, which is of course, a primary methodology, but for these purposes, the point I am trying to make is that this shows definitively that many, many Plaintiffs in this MDL took Zantac for plenty long enough to have caused their cancer, and to keep beating a dead horse, that is the question that matters for general causation.

I'll take the next slide.

Similar result for stomach cancer for real patients who took Zantac for more than a year, they developed a 33 percent increase in risk.

Next slide.

And I will say that is a tough pill to swallow for Defendants and their experts, as we will talk about, because we have heard for two weeks about how important it is to look at the Ranitidine epidemiology, and not just any Ranitidine epidemiology, but active comparator studies.

They have described them as ideal. They have said that everyone thinks they are more appropriate, and they have criticized our criticisms. I will get to some of the criticisms in a moment, but for these purposes I will say we think they may be overstating the case a little bit, but to the extent they are right, what Wang and Cardwell are, are Ranitidine epidemiology with an active comparator design and it showed that our Plaintiffs took doses that were sufficient to

cause cancer.

I'll take the next slide. One more, actually. Thank you.

So I know that is very long wind up, probably even longer than I wanted to go, but that is really what Defendants' experts got wrong here. They focused on the Plaintiffs all the way down at the bottom who took Zantac for very short periods of time, and they ignored the Plaintiffs up here who took Zantac for very long periods of time. That is just a fundamental error about the question presented at the general causation phase versus the specific causation phase.

Judge, just be clear on one point, it is not that it is never going to matter how much people took of Zantac. In specific causation at this particular trial for one of those Plaintiffs down there at the bottom left, they are, of course, free to argue that for that person they didn't, in their view, take enough Zantac to cause cancer, but it does not provide a reason why there is no general causation for those Plaintiffs way, way up there at the right when we know that those doses in the decades are plainly enough.

The next slide.

The clearest example of the error made by Defense experts on this point is in the studies that they relied upon.

Those studies looked at the weakest cases, allowing patients with just one or two prescriptions of Zantac to be

included in the database, and that is an error when the general causation question has to focus on the strongest case.

Again, in the context of a trial where someone took one prescription, they used it for very short periods of time, those studies are, of course, relevant, but these are supposed to be general causation experts from the Defendants, and if that is true, they have to focus on the much different question of whether it is possible that any of our Plaintiffs got cancer from Zantac.

Next slide.

So, in very simple terms, this is the analytical gap that Defendants' experts tried to jump. They looked at studies that show cancer risk after short usage and short followup, and from those studies, they tried to conclude that Zantac does not cause cancer after long usage and long followup, and that is just the kind of analytical gap that Daubert forbids because that question that I have put in the gray box is the one that matters for general causation purposes, not the one in the other one.

I'll take the next slide.

It is not just about dose, although I have been spending a lot of time on it, but it is also about followup. Over the past couple of weeks I think sometimes these distinctions have gotten blurred, but I want to make it very clear, when we talk about dose, we are talking about the

difference between a person who just took a little Zantac versus a lot. I think the Court understands that.

For followup, though, it is very different. What we are talking about is, did you look at patients who took Zantac and wait for one year to see if they develop cancer or did you wait 30 years? Of course you want to wait for 30 years because if you look at any carcinogen, including smoking by the way, and see if someone gets cancer the year after they started smoking you just are not going to see very much.

Next slide.

That is why the WHO and the IARC preamble says what it does. It says that if you want to disprove the risk of a carcinogen, if you want to provide evidence of lack of carcinogenicity, as it says here, you can't use studies that are shorter than about 30 years.

Now, I want to pause on something because we will get into it when we get into Wang. The opposite of this statement isn't true. You do sometimes see cancer risk in studies that are shorter than that, but that is because if you see a signal that appears in the study that is not looking for as long as it usually takes to develop cancer, that is an especially strong signal.

The opposite just isn't true. If you don't see a signal in a study that doesn't wait long enough, it doesn't tell you very much. If you do see a signal in a study that

doesn't wait very long, that is even more powerful evidence that there is an association.

Next slide.

Turning to the individual experts, Dr. Witte in his report attempts to cure this problem with the literature. If you look at this chart that he prepared about the studies he relied upon, he puts in a column that says time period that makes it look like these studies were very, very long. Yoon says 2009 to 2018, Iwagami says 2005 to 2018. It makes it seem like these studies must have followed these patients, or perhaps looked at patients who had been exposed to the drug for nine years and the 13 years.

The reality is, the Iwagami study only had two years of followup. That was the median amount of time that people were followed in that study.

Your Honor, if you look at a study of a carcinogen and wait two years, you should be surprised if you see an increased risk because that is just not long enough for cancer to develop in most patients.

Next slide.

As far as I can tell, Defendants have realized that this is a problem, because I think they are going to show you a slide that looks like this one.

When you read the slide it looks like the Norgaard, Adami, Iwagami studies have these very, very long time

associated with them, but that is because what they decided to do here is literally blur the concept between exposure of how long people have used the drug and followup time. If you look at the blue chart that is exactly what they said they have done here. I suspect what they have done is added the exposure time and followup periods for all of these studies.

The fact of the matter is, if you look at Iwagami, it says 13.7, but in reality the median followup time in that study was just two years.

In response to that, Defense experts really have no choice but to disagree with the studies' own authors because most of those authors acknowledge that this is a major limitation in their studies. Dr. Yoon writes that the overall followup is not long enough to assess the onset of cancer. He said he saw that and then was asked if he agreed, and he said that he did.

Next slide.

Dr. Vaezi, for his part, did acknowledge in the abstract that you do need to get good data on exposure to make sure you have good data on timing, dose, and duration. He said he thought that was key.

Next slide.

The problem, though, came when he actually looked at the studies because the fact of the matter is, there is not a study that has ten solid years of exposure data where people

took Zantac for that kind of length of time.

So, what Dr. Vaezi did, and frankly what a number of the experts did that I will show you, is they made an assumption, and the assumption was this: If you took ten prescriptions of Zantac, that automatically means that you were using Zantac for ten years, and that is just not true.

I don't even think you need to be a scientist to understand it. If you got ten prescriptions, maybe it was ten months, maybe it was one year, maybe it was two years, but there is not a one-to-one correlation between the number of prescriptions that you have and the number of years you are using the drug.

Next slide.

Because that is not true, one of their experts, Dr. Terry, had to admit that it was wrong. We asked her, do you agree that if they are 30-day prescriptions, perhaps that would mean ten months of use? And she said she had to admit that that would be the lower bound.

Dr. Terry also admits that followup time is critical when doing studies like this. She said that given the long induction time of many of the specific cancer types, you need to look -- sorry, you need to make sure that the medicine has been used for a longer duration prior to cancer diagnosis.

Next slide.

The problem is that Dr. Terry said that she didn't

actually know what the latency for Ranitidine is, but she said that it was ten or 20 years for some solid tumors, and the vast, vast majority of the studies that she and the other Defense epidemiologists relied upon had followup periods that were nowhere, nowhere near that long.

Next slide.

Dr. Chan agreed on the exposure point, again in the abstract. He said in an epidemiological study one would find exposure with the best available data.

Next slide.

The problem was that Dr. Chan said in the case of Ranitidine he didn't understand how exposure levels would be defined.

Instead of doing that -- go to the next slide -- he again made this assumption that the other experts made, that somehow if you take ten prescriptions of a drug, that you would be taking Ranitidine for ten years.

I don't know where these experts got that assumption from. As Dr. Terry acknowledged, it is just not true, and what is really going on here is that they know that they need studies that have that kind of dosage data to be able to say anything meaningful about general causation. In the studies they are looking at is just not there, so to try to bridge that gap they made this assumption that is false, your Honor.

Next slide.

We asked Dr. Chan pretty directly, can you tell us any study that actually looks at what happens when people use Zantac for five or more years? The answer he gave us was the Kantor study.

Next slide.

If you actually look at Kantor, you don't see this five year number here anywhere. In fact, what you see is that people could be in the Kantor study if they used Zantac for most of the days of the week for the last four weeks, and even those authors said they were unable to examine associations by dose or to distinguish short-term versus long-term use.

I'll take the next slide.

Switching to followup for a moment, Dr. Chan also agrees that for there to be an association you need to make sure you have a long enough followup period.

I'll take the next one.

But then Dr. Chan had to admit that he didn't really know what the latency period of Zantac was, that he didn't think they had any data to go on. The reason why that is a problem is because these experts have an opinion that these studies show that there is no association.

If they don't know what the actual lag time is, if they don't know how long you need to look in order to see if Zantac causes cancer, then they can't be sure the studies they are relying on were actually long enough to pick up a signal

that was there.

Next slide.

Dr. Hatten did agree in the abstract that if an outcome has a long latency period that you are not going to see it, if you look at too short of a followup time. I think Dr. Hatten might have said it most directly, it is not possible to see an outcome of interest if the latency period is long and the observation time is short, and that is true.

Next slide.

When it came to analyze the actual studies, Dr. Hatten ignored the fact that the patients had low exposure, ignored the fact that there was short followup time, and then he ignored the other issues with the studies that we have been talking about for two weeks now, misclassification, lack of over-the-counter data, and lack of data on confounding.

I want to pause for a moment and say a variation of what i said before on does, but it's worth repeating with respect to all of these.

To the extent a study that is not well designed does show a risk, that is putting aside certain types of confounding which we will talk about, very good evidence that there is in fact a risk, if it shows up it is sometimes surprising if the studies are designed like these.

For these experts, the important point we need to make to you is, the opposite is not true. If you are going to have

an opinion that Ranitidine doesn't cause cancer in the sorts of cases that are at issue in this MDL, then you need studies that are very, very well designed, that have enough dose in order to replicate the actual Plaintiff population we are looking at and that actually waited long enough to see if those cancers actually developed.

Next slide.

All right. Turning to my second point, the experts failed to consider and assess all of the evidence.

Now, this is a very different criticism that the kinds of criticisms that Defendants made against our experts. I did not understand them to be arguing that any of our experts missed large buckets of evidence, or didn't spend enough time weighing them, or anything like that. Their criticism was just that they though their studies were better than ours.

The criticism I am going to make is plainly a Daubert one because it goes straight to the heart of their methodologies.

I'll take the next slide.

If you look at our methodologies that we employed with our epidemiologists versus the ones that they employed with theirs, I do think you will see a real meaningful difference. Dr. McTiernan and Dr. Moorman carefully considered all the studies, they thoroughly evaluated their strengths and they thoroughly evaluated their weaknesses.

As the Court knows by this point, there are studies in this litigation that help one side more than the other.

What our experts did is, they looked at those studies, they acknowledged the strengths of them, even when they were perhaps more helpful to the Defendants, they acknowledged the weaknesses of them, even when they were perhaps more helpful to us, and they ultimately explained how each of those studies fit into their broader conclusion.

That is not what the Defense experts did.

Next slide. Go back one. Thank you.

Dr. Witte, for example, focused almost exclusively on the epidemiology that compared Ranitidine users with those who used H2 blockers. I know Defendants quibble with this and say he really considered everything, but for this part of Daubert to mean anything it has to mean more than that the expert put a certain set of materials on his reliance list or put them in the discussion section.

In order to really grapple with this literature, which is very complicated, the expert needs to go through each of the studies and actually candidly evaluate what is good about them, what is not. That is what our experts did, that is not what Dr. Witte did.

Next slide.

Dr. Chan, it is even clear, he said in his report there is just no basis to review what he deemed to be less

relevant literature, by which he meant studies that were run on NDMA and cancer risk. In his deposition I think he even said that he didn't look at those NDMA studies until he first noticed them in the Plaintiffs', our expert reports.

Next slide.

The reason why that is a problem is because the NDMA literature is certainly relevant to the general causation question here. There's no dispute that Ranitidine -- NDMA vapor inhaled at work and foods analyzed in the dietary studies all contain NDMA. There is no dispute that this NDMA molecule is identical, whatever the delivery mechanism, and there is no dispute that once it is in the body NDMA behaves exactly the same way regardless of how it first ended up there.

That is critical, your Honor, because it explains why this case is just like the Ryan case of Benzene in mineral spirits, and now Burst or Hendrikson where the Benzene was in gasoline. There they actually were arguing that the underlying chemical behaves differently in gasoline, but Defendants here don't even argue that the NDMA in Zantac behaves differently than the NDMA consumed in foods or inhaled at work.

Next slide. Two more actually. Thank you.

Dr. Vaezi, in his deposition, said that he considered the NDMA studies somewhat irrelevant, so he didn't pursue them any further.

Dr. Terry, in her report, made clear her belief that

only cancer outcome studies of Ranitidine can reliably address potential increased risk. For that reason, she said, she focused on those studies which compared Ranitidine users and she largely ignored the broader literature on NDMA.

Next slide.

So, before I move on to my last point, I want to pause and just give a concrete illustration of what I mean when I say that our experts employed different methods than their experts did when evaluating the literature.

This is Iwagami, and as I said, it has some pretty major limitations. 96 percent of the patients took Ranitidine for less than six months, the median followup was only 2.4 years, 72 percent of the patients were under 50 years old, which meant that they are very unlikely to develop cancer in the first place, and, of course, this study lumped together Ranitidine and Nizatidine.

So what did our experts do with this study? It has real strengths, too, right. It is a very large study, has lots of cancer cases, it had data based on dispensation of the pills, it had some dose data.

Next slide.

What our experts did is, they described the strengths, the large databases, they described the weaknesses, the limited followup, the combination of the drugs, and described what role the study played in their overall conclusions.

Next page.

In fact, if you look at Dr. McTiernan's report, this process goes on for seven pages just for Iwagami alone. Obviously Daubert is not a competition about who can type the most pages. I am not saying that, I get it. But these are very complicated issues over which scientists vigorously disagree and that really deserve a detailed analysis. That is what Dr. McTiernan did just for this study.

Next slide.

That is not how Dr. Vaezi dealt with it. He described the strengths, of course, because Defendants really liked the outcome of that study, but he didn't describe the weaknesses and he did not assess the applicability to this case.

I will show you, if you take the next slide.

This is Dr. Vaezi's entire analysis of the Iwagami study, one paragraph. It is, admittedly, a kind of long run-on paragraph, but that is the entirety of the analysis that he did.

Again, there is no requirement that an expert write a certain amount on a study, it is not a writing competition, but to really analyze a study like this and give it its proper due, given the complexity, I think it is fair to say it takes a lot of time, a lot of effort, and frankly, a lot of pages.

Our experts did all that and theirs did not.

Next slide.

In fact, this is the closest that Dr. Vaezi came to identifying limitations in the Iwagami study. At the beginning we get one opening clause that kind of back handedly acknowledges that the overall median length of the followup on the study was relatively short, 2.4 years, but then he immediately goes on to say that is alleviated by these other features of the study.

The only other limitation that I think he acknowledges is he notes the criticism by Plaintiffs' expert that this study combined Ranitidine and Nizatidine, but he says that ignores the underlying NDMA hypothesis, and that is it.

I think at this point the Court realizes that there are studies that cut in different ways in this litigation, but to give a coherent opinion in this case an expert needs to candidly acknowledge what the strengths and limitations of the study are. That is what our experts did and I just don't think that this qualifies as a candid explanation of what is really going on in Iwagami.

Next slide.

Last, what role did Iwagami play in Dr. Vaezi's opinion? We just don't know. All we have is that one paragraph where he goes through a couple of talking points and then says what the study results are. That is not enough to demonstrate that the methodology he used to analyze this literature is reliable.

Next slide.

My last point: The experts failed to carefully review the evidence as required by Abilify.

Beginning with Dr. Hatten, Dr. Hatten has an opinion that NDMA does not cause cancer, but he did not conduct a Bradford Hill analysis on NDMA itself. He says here that he informally evaluated the NDMA under Bradford Hill, but respectfully, your Honor, an informal Bradford Hill analysis is just not a thing. As the Court knows, Bradford Hill is a complicated method of determining causation. It is not something that you can just say that you did informally.

Next slide.

Aside from NDMA, even Dr. Hatten's Ranitidine specific Bradford Hill analysis is inadequate. Instead of going through each type of cancer, he simply lumps them together under the title of cancer and opines that Ranitidine doesn't cause cancer.

Next slide.

That is not what you are supposed to do, and it is not what our experts did. For Dr. Moorman, these are the pages that she spent talking about each type of cancer. She does a separate Bradford Hill analysis, eight pages for bladder, eight pages for pancreatic, 50 pages in total.

Next slide.

So, for comparison, what did Dr. Hatten do for the

entirety of his Bradford Hill analysis? Again, one single paragraph, not separated out by any cancer types, all cancers lumped together, one paragraph total.

Next slide.

Dr. Witte is similar on this front, instead of doing what our experts did in performing a Bradford Hill analysis of each type of cancer, he simply lumped every type of cancer together, called it human cancer, and then performed a single Bradford Hill analysis on it. That just is not sufficient to qualify as a careful review.

Next slide.

In addition to that general problem, Dr. Witte makes several other errors that demonstrate his lack of careful review. This is his report in the section on bladder cancer. He says that the four active comparator studies did not show an association between Ranitidine use and bladder cancer. But if you actually look at the report, the studies go four for four. Every single one of the studies he identified as a comparator shows an increased risk either numerically or statistically.

In the fourth study, the Habel study, it shows an increased risk as well.

Next slide.

In response to that, he has to do what a lot of the Defense experts do, which is to contradict what the authors of the study said, because the Cardwell study in the discussion

suggestion says the use of Ranitidine, particularly long-term use, was associated with an increased risk of bladder cancer, and Dr. Witte in his deposition has to call this invalid.

Next slide.

Confounders. When it comes to confounders, Dr. Witte noted in his report his view that it is critical to measure the data on smoking, because is the patients taking one drug versus another drug are more likely to smoke, then the cancer rate for that drug might be artificially elevated. In fact, Dr. Witte mentioned smoking more than 50 times in his report.

Next slide.

He also admitted in his deposition that this effect could bias studies in either direction. In other words, he admitted that if patients in the comparator group smoked more than patients in the Ranitidine group, then the results of the study would show an artificially low risk for Ranitidine.

So far, so good on the theory, your Honor, we agree with this wholeheartedly.

I'll take the next slide.

It seems like Defendants agree with that point as well because this is a slide they have from their deck. They know that smoking is a strong confounder in bladder cancer studies, so you want to control for it. So, what you think would happen is that Dr. Porter would place the greatest weight on studies that did control for smoking, given the emphasis he puts on

smoking as a confounder in his report.

Next slide.

So, if you look at the actual studies, the Adami, Norgaard, Yoon, and Iwagami studies don't have any smoking data at all, but Dr. Porter places great emphasis on those studies.

Two of the studies, Cardwell and Kim, do have smoking data. The problem for the Defense experts is that the two studies that do have smoking data cut strongly against the Defendants. The Cardwell study shows a statistically significant increase in bladder cancer risk, even though controlled for smoking, and the Kim Y study showed the Zantac users were less likely to smoke than users of the comparator drug.

Next slide.

So, what is Dr. Witte's response? Dr. Witte's response I think is going to end up being an important one today.

Dr. Witte said that by using an active comparator design the studies were somehow, quote, "indirectly controlling for alcohol and tobacco usages, even though the study didn't actually measure alcohol and tobacco usages."

I suspect that we will see whether Dr. Porter agrees that the Wang study was indirectly controlling for smoking, but for now, my point is a slightly different one.

This is something that a lot of the Defense experts

say, that these active comparator studies by virtue of their design are somehow insulated from any confounding. Your Honor, that is just not correct.

We will talk about it more when we talk about Wang later, and Defendants are probably going to acknowledge that it is not correct, but I'll tell you now, it is just not incorrect. Even in an active comparator study you always have to think about confounders.

To be perfectly fair, that effect can cut in either direction. You can get situations where the results are confounded in a way that makes them look unrealistically high. I think the Defendants are going to show you a chart on coffee and cancer risk that illustrates that point, but you can also get results where the confounding obscures a real association.

Next slide.

Based on the limited data that we have on these confounders, that second option where the confounding obscures the association appears to be what is going on, because the data we have from Kim YD shows that Ranitidine users are less sick, use less tobacco, use less alcohol, and had less of all of these confounders than the comparator groups did.

Active comparators will not fix this problem, that is what Defendants experts failed to recognize.

Next slide.

I have an example here, although I think the Court

probably understands, if it is true that the users of Zantac smoked less than the users of the comparator drug that is going to make Zantac look safer and make the comparator drug look more dangerous for reasons having nothing to do with whether the drug is actually safe or unsafe. That is why you need to -- sorry. That is why the Cardwell study controlled for smoking and why Dr. Porter and the other experts should have credited that over studies that didn't control for it.

What did Dr. Terry do? She did not discount the studies with no smoking data, Yoon, Adami, and Norgaard.

Next slide.

Instead, she did something inexplicable; she looked at one of the only studies that did have smoking data and she criticized it for having incomplete smoking information.

Next slide.

The same for Dr. Porter. These studies are fairly similar at a high level, they use active comparators, they have the same type of comparisons, but one primary difference is that the Cardwell study does control for smoking and the Yoon and Norgaard do not control for smoking.

You would think, based on this, that he would credit the Cardwell study and discount the Yoon and Norgaard study. What Dr. Porter does is exactly the opposite and the reason is obvious, they like the results of Norgaard, they don't like the results of Cardwell, but that kind of litigation driven

reasoning is simply not permitted by Daubert and Abilify.

Next slide.

That kind of litigation reasoning is on display elsewhere in Dr. Porter's expert report. For example, here is his discussion of the consistency prong of Daubert for bladder cancer. Every single one of these studies shows an increased risk. Some of them are higher than others, some of them are statistically significant, some of them aren't, but every single one of these studies showed a higher risk for the patients who took Ranitidine versus the patients who took the comparator drug.

Next slide.

Speaking of consistency, I want to pause on this sound bite from the Florian study that Defendants have shown to the Court a couple of times, showed the Court again today, and I suspect are going to continue to show the Court.

What I think the Defendants want to do with this quote is say, look, Judge, the FDA has looked at the epidemiology and they say no consistent signals have emerged, but that is just not true.

At this point, I know the Court has read the Florian study enough to know that it is really a study about how much NDMA ends up in the patients' urine after taking Zantac. It is not a systematic review of the epidemiology. The best evidence of that is the Florian study does not even cite two of the

studies that existed at that time, McDowell and Liu. of course, Florian is now seriously out of date given that six on point studies have come out after it, including importantly Cardwell and Wang.

Defendants and their experts don't mention this. They just make it seem like Florian is the decisive word on whether Zantac causes cancer, even though that is factually not true and logically impossible given Florian's publication date.

Next slide. One more. Thank you.

The last point I want to make applies to a few of their experts. I don't know if they didn't read the relevant literature carefully, or were just being imprecise, or got confused, or were trying to be intentionally misleading, but a number of their experts, including Dr. Vaezi here, said the public health organizations had looked at the data and decided that NDMA does not cause cancer in humans.

Next slide.

Dr. Chan says essentially the same thing, that he didn't think anyone looked at evidence in human studies and determined that NDMA was genotoxic.

Next slide.

That is obviously not true. The Court knows this. We have gone through many of these by now. I am not going to show each of these classifications, but suffice it to say that health authorities around the world looked at human data and

concluded that NDMA is a probable human carcinogen.

Next slide.

Here is an example of one of them doing it. This is the NTP and its classification on NDMA. It reviews not just literature from animal studies, not just literature from human tissue studies, but literature from human epidemiology studies as well, so Defendants and their experts are wrong to say that this classification is based solely on animals. It is just not the case.

Next slide.

Of course, GSK has done the same thing when they were evaluating NDMA when NDMA was first discovered in Ranitidine. They note that NDMA is a genotoxin and they note that it is highly likely that NDMA is carcinogenic to humans potentially at low dose exposure.

What is interesting about this document is not just what it says, but also what it doesn't say. Over the past two weeks, and I'm sure we'll hear more today, Defendants have made clear their theme, NDMA is carcinogenic in animals and you just don't need to worry about cancer in humans unless the dose is very, very, very high. I think that is a fair characterization of their argument.

But if you look at this document and look at what they were saying before they realized they were being sued, there was no mention of threshold dose, quite the opposite. GSK says

exposure should be reduced to the extent possible. There's no mention of any massive dose required to cause cancer, quite the opposite. GSK says that even low doses are cause for concern. There's no mention of this being a problem that is somehow unique to animals.

GSK says that it is highly likely, not possibly, not theoretically, not even probably, but highly likely that NDMA is carcinogenic in humans.

The next slide.

The reason why I want to end with GSK's own words, is because that is something the Valsartan Court lasered in on. The same molecule was at issue in that litigation, NDMA, the same underlying science. We have here much stronger evidence on Ranitidine than they had here in Valsartan, but the underlying evidence about NDMA is, of course, exactly the same.

The Valsartan Court noted that even the Defendants there acknowledge that NDMA is a carcinogen, relying on the types of documents that I was just showing the Court.

In Judge Kugler's view, at least for these purposes, that was the end of the road, nothing more was required.

Next slide.

In fact, in the Valsartan Court's view, the actions of Government agencies, plus the Defendants' own words were enough to get Plaintiffs there, past the association element, and from there he moved on to Bradford Hill. After going through that

Bradford Hill analysis the Valsartan Court did two things.

First he denied the Defendants' Daubert motions concerning NDMA and cancer, that includes with respect to Dr. Panigraphy, by the way, who employed an analogous method in that case, and he granted Plaintiffs' Daubert motion with respect to some of the Defense experts.

Now, obviously I am not arguing estoppel or that you have to rubber stamp Judge Kugler's opinions on NDMA or anything like that, and that is because, again, the focus of Daubert is about methodology, not conclusions. That said, what the judge did in Valsartan, which is the only other major NDMA case I know of, is instructive.

Next slide. One more.

What the Court did was exactly the right thing, he looked at the methodology of the Defendants' experts and he found them lacking. Obviously every expert has a different methodology, I'm not disputing that, but for Dr. Flack, he noted that the expert had failed to consider a lot of the relevant literature, just like the Defense experts here did by failing to really analyze the NDMA literature, and he noted that they failed to consistently apply a recognized methodology.

For Dr. Wei the effect was also similar. Dr. Wei essentially opined that because one of the Plaintiffs' experts had bad methods that meant NDMA did not cause cancer. The

Court realized why that didn't work logically.

With respect to NDMA, that is by and large what Defendants' experts do here as well, they criticize our experts and the underlying studies and say that they have limitations and then jump straight to the conclusion that NDMA doesn't cause cancer. The Court in Valsartan wouldn't let them do that, and I don't think the Court should do so here either.

Next slide.

I will close where I started. Our experts answered the right general causation question, whether any Plaintiff in the MDL could have plausibly gotten cancer from Zantac. Their experts answered the wrong question, relying on studies showing what happens to patient populations that were much younger, exposed to far less Zantac, and with much shorter followup times.

Our experts carefully considered all the evidence, even the ones relied upon heavily by Defendants' experts, and carefully explained them. Their experts did the opposite, ignoring huge swaths of evidence and failing to give them an explanation.

Finally, our experts reviewed the evidence carefully. You have heard very little of this over the past two weeks from the Defendants. They don't say our experts identified the wrong literature. They don't say that they used the wrong methods to identify it. They don't say they didn't call out

the right strengths and weaknesses. They just don't like the conclusions, but that is not our criticism of their experts.

As we pointed out, methodologies are quite different in their rigor. Their treatment of Bradford Hill was sometimes nonexistent or broadbrush or woefully brief. Their treatment of confounders reveals results oriented reasoning made for litigation, and more than one of them was simply confused about what the scientific community really says about NDMA.

For these reasons, and those stated in our briefs, we ask the Court to exclude the opinions of Dr. Terry, Dr. Witte, Dr. Porter, Dr. Chan, and Dr. Hatten.

For Dr. Guengerich and Dr. Chodosh we ask the same thing, but we rest on our brief due to time constraints.

THE COURT: Thank you.

MR. SNIDOW: I will turn it over for Dr. Wang to Ms. Goldenberg.

THE COURT: Okay. I thought you wouldn't come in that short. You still have about twelve minutes.

MS. GOLDENBERG: Good morning, your Honor, Marlene Goldenberg for the Plaintiffs, and may it please the Court. I am here to talk about Dr. Wang.

Go to the next slide, please.

As the Court knows, Daubert is not about conclusions, but about methodology. So, to be clear, we are not disputing that Dr. Wang is qualified to offer his opinions, and we are

also not disputing that Dr. Wang could have offered his conclusions about Ranitidine and cancer risk if he had employed a reliable methodology in support of them. The problem is that Dr. Wang made several errors that rendered his methodology unreliable and inadmissible under Daubert.

Next slide, please.

Dr. Wang appears to apply a weight of the evidence approach to evaluating the risk of cancer from Ranitidine. There is no problem with that approach. Many of our experts used that approach, too, as the Court will see from the Abilify opinion quoted here, and other Courts in the Eleventh Circuit have blessed that approach, too.

But when an expert uses the weight of the evidence approach, as Dr. Wang did, it comes with three strings attached. First, the expert must consider all of the available evidence, not some of it, not just a select bit of it, not just the evidence that is helpful to his or her side; all of it, and that is what our experts did.

Second, the expert must consider each piece of evidence carefully. That means the expert needs to give more than lip service to having read a study.

And third, the Court (sic) must explain how the relative weight of each piece of the evidence led to his or her conclusion.

Next slide.

Dr. Wang failed to do each of these things. Let's start with the first string. Dr. Wang simply did not consider all of the available evidence.

Next slide, please.

As the Court surely remembers from last week, Plaintiffs' experts relied upon several different categories of evidence, including dietary studies, occupational studies, animal studies, and human epidemiology, but Dr. Wang relied almost exclusively on human Ranitidine epidemiology and did not meaningfully consider the other categories of evidence.

As the Ranitidine epidemiology has been discussed by others in our group, I will only add that studies purporting to study Ranitidine users are hardly grounds for ruling out carcinogenic effects when, like the Adami and Norgaard studies, they only require levels of use that are far less than what Plaintiffs in this case took.

Yet, these Ranitidine epidemiology studies are the basis Dr. Wang uses to conclude that Ranitidine does not cause cancer at the allegedly low doses, which we will discuss momentarily.

Next slide, please.

Now, to be clear, Dr. Wang paid lip service to these other kinds of studies by listing them in the background section of his report, but when it came time to actually perform his Bradford Hill analysis, everything except the human

Ranitidine epidemiology all but disappeared. He mentions them in one single sentence in the analogy section.

In all of the other sections it's just human Ranitidine epidemiology alone. Dr. Wang could have testified that he was unpersuaded by these other forms of evidence, but he didn't. He just pretended that they weren't there. This can't be enough to meet the standard for considering all of the available evidence required under Daubert.

Next slide, please.

Even if that were enough to somehow check the box in considering all of the available evidence, there is no question Dr. Wang did not do so carefully.

Next slide, please.

For starters, there just wasn't enough time for Dr. Wang to have done a careful review. In his report he says he reviewed more than 580 documents, but his timekeeping records reveal that he spent only 18 and a half hours reviewing them. That works out to one to two minutes, not per page, per document. As everyone in this courtroom knows, it takes more than one to two minutes to read these studies and that shows in Dr. Wang's report.

These are dense, extremely complicated, and often quite lengthy pieces of medical literature. It is simply not enough time for Dr. Wang to have performed a careful review as required under Abilify and by Daubert.

Next slide, please.

Perhaps unsurprisingly, given the time he spent, Dr. Wang's lack of careful review led to serious errors in his report. For example, he relied on a 2022 study by Chan which looked at the cancer risk from Valsartan. The problem with that is that the Chan 2022 study looked at Valsartan before the drug was ever contaminated with NDMA.

Next slide, please.

Now, that is obviously a huge error given that it is entirely irrelevant whether Valsartan without NDMA causes cancer. We confronted him with that in his deposition and he essentially admitted the slip up on pages 142 and 143 of his transcript, acknowledging that if the Valsartan in the study wasn't contaminated with NDMA, then the study would not be informative about NDMA, which is an obvious point. That means the study cannot form the basis for a reliable opinion in this case.

Next slide, please.

Then in his deposition Dr. Wang also admitted he had no idea when the Valsartan actually become contaminated with NDMA.

Next slide, please.

For another example, Dr. Wang testified to his belief that NDMA is not carcinogenic in primates, namely monkeys, and in support of that, he testified that he was relying upon

the Thorgeirsson study.

Next slide, please.

Now, this opinion about NDMA not causing cancer in monkeys was something of a surprise to us, given that the WHO says that NDMA is carcinogenic in all species examined, and the WHO said that almost a decade after the study that Dr. Wang said he was relying on. So then we went and looked at the Thorgeirsson study to see what it actually said.

Next slide, please.

What it actually says is nothing at all like what Dr. Wang thought. It notes that DMNA, which is another abbreviation for NDMA, was given to 11 monkeys, then it appears that four of them died after six months. For the seven that lived longer, one died of cirrhosis and the other six died of toxic hepatitis.

Now, I guess we can debate exactly what that shows about the safety profile of NDMA in monkeys, but it certainly does not suggest that NDMA is somehow not a carcinogen in primates.

Next slide, please.

Dr. Wang also testified in his deposition that the primates in the study lived long enough to develop cancer in response to NDEA, another nitrosamine that is so much more potent than NDMA that the FDA's interim threshold limits for NDEA are one-third of what they are for NDMA. That another

more potent carcinogen killed the monkeys first says nothing about the absence of NDMA's carcinogenicity in primates, but that is what Dr. Wang read it as. This again is not evidence of the kind of careful review required by Daubert.

Next slide, please.

The last point I want to make about Dr. Wang's lack of care in reviewing the evidence relates to dose. Dr. Wang does not know how much NDMA is actually in the Ranitidine that these Plaintiffs took because he only relied upon baseline testing results performed on pristine Ranitidine. He doesn't know how much NDMA formed in real-world conditions, over time, at increased temperature and humidity levels, during storage and shipment, and endogenously in the body.

Next slide.

He basically admitted this in his deposition, conceding that he had no information abut how much NDMA forms when Ranitidine ages or is exposed to real-world conditions.

Next slide, please.

And the reason that this is a problem is because Dr. Wang's opinions are based on an assumption about how much NDMA was actually in the Ranitidine that patients consumed. Indeed, Dr. Wang goes so far as to say that it is not biologically plausible for Ranitidine to cause cancer given the amount of NDMA in the drug that Plaintiffs consumed.

As we just saw, Dr. Wang actually has no idea how much

NDMA was in the Ranitidine that Plaintiffs took. He can't even give a ballpark. Despite his admission in the deposition that more NDMA forms with time, temperature, and humidity, Dr. Wang made no effort to account for this in giving his opinions. He just ignored this universally acknowledged fact and pretended it didn't exist. That methodology is not reliable.

Next slide, please.

Going back to our slide on dose, you can see why that is a problem. If Dr. Wang does not know the maximum amount of NDMA that a patient could have taken, then he has no basis on which to say the dose was lower than the amount necessary to cause cancer.

Next slide, please.

And he certainly has no basis to say that the highest dosed Plaintiff was too small to cause cancer, and that is the relevant question for general causation. He just assumed without any basis whatsoever that the dose was too low.

Next slide, please.

The last reason to exclude Dr. Wang is straightforward. An expert has to explain the relative weight that he or she applied to each piece of evidence, and Dr. Wang didn't do this at all. As we have discussed, he essentially failed to analyze the studies other than human Ranitidine epidemiology at all, and he certainly did not explain the weighting that he gave to varying pieces of evidence that he

did not consider.

For these reasons, your Honor, Dr. Wang's testimony should be excluded under Daubert.

Thank you.

THE COURT: Thank you. All right. Perfect. You came in within your time.

Our schedule shows that we are going to take a 15-minute break now. It is 10:30, that means we come back at 10:45 and we will see everybody at 10:45.

(Thereupon, a short recess was taken.)

THE COURT: All right. You may be seated.

Okay, are we all set from Defense?

MR. BOEHM: Yes. Good morning, your Honor. Paul Boehm for Pfizer and speaking on behalf of all of the brand Defendants.

My colleague, Angela Pyo, and I will be addressing several of the issues that Plaintiffs have raised in their brief that they dub the general causation brief. It has been referred to also as the epidemiology brief. We will be addressing some of the issues that cut across the experts, so they will apply to not just one, but more than one, and in some cases all of the experts.

If we can go to the next slide, Maryann.

These are the four specific issues that Ms. Pyo and I will be addressing. Ms. Pyo will take the first two and then I

stand back up and take numbers three and four.

Before I hand the microphone off I wanted to note that although Ms. Pyo is not technically part of the Leadership Development Committee, she is an associate at our firm and otherwise would meet all of the requirements for that and I am pleased to be presenting with her this morning.

THE COURT: Okay, excellent, welcome.

MS. PYO: Angela Pyo for Defendants.

I will start with Plaintiffs' claim about active comparator studies.

Next slide, please.

Your Honor has already heard a bit about this a couple weeks ago in the context of why Plaintiffs' experts are unreliable for discounting and ignoring the active comparator studies.

As a quick refresher, the active comparator studies are those that compare groups of people taking drugs for similar indications, and because they are taking drugs for similar indications we know that they are similar groups of people, that we are comparing apples to apples, and that reduces confounding.

Of course, because this case is about Ranitidine the active comparators here will be other H2 blockers and PPIs. Today we are talking about the flip side of the coin from a couple weeks ago. Plaintiffs are faulting Defense experts for

relying on these active comparator studies.

They claim that the comparators themselves, the other H2 blockers and PPIs, might be carcinogenic, and if that is true, that would reduce any contrast between the group that took the Ranitidine and the group that took the comparator.

There is just no evidence to support these claims. Plaintiffs' own experts don't support them, the FDA doesn't support them, and the broader scientific community doesn't support them.

Next slide, please.

Plaintiffs lack evidence showing that the comparators themselves can increase the risk of cancer. Although Plaintiffs' experts in their reports suggest that these comparators might increase the risk of cancer, they walk those statements back in their depositions.

Both Drs. McTiernan and Moorman, when asked, they stated that they had not done an evaluation of the science behind their assumptions that these comparators could increase the risk of cancer, and when asked, Dr. Moorman said that she couldn't point to a single regulatory agency or medical guideline that suggested other H2 blockers could increase the risk of cancer.

Next slide, please.

What the regulatory agency, what the FDA has said is that the active comparator design is ideal. In a guidance for

industry on the best practices for conducting pharmacoepidemiologic safety studies the FDA said that selecting an appropriate comparator is a critical part of designing such a study, and that it is ideal to use an active comparator.

Next slide, please.

The broader scientific community agrees. Yoon explains that pharmacoepidemiologic studies are needed for clinically relevant causality assessment, and then goes on to say that the most appropriate way he found to design such a study is to use an active comparator.

As your Honor is familiar with the several recent studies addressing the carcinogenicity of Ranitidine, several other experts in the scientific community have concluded the same and have also designed their studies to include an active comparator.

Next slide, please.

This all ties into the Daubert standard that Mr. Boehm was talking about earlier. A key factor in assessing reliability is to look at whether the expert and their methods have enjoyed general acceptance in the broader scientific community, and as we just discussed, the FDA and the broader scientific community, they have endorsed active comparator studies as a way to look at cancer risks.

Defense experts and their methods enjoy widespread

acceptance. It's Plaintiffs' criticism that stands alone, and that opinion should be viewed with skepticism.

Next slide, please.

I will next discuss Plaintiffs' criticism of Defense experts' reliance on the existing body of Ranitidine epidemiology because they claim that several of the studies fail to account for over-the-counter use.

Several of these studies are designed so that there is a group that took prescription Ranitidine and a group that did not. Plaintiffs claim that some of the people in the nonexposed group may have been exposed to over-the-counter Ranitidine. They were therefore misclassified and that could reduce the contrast between the group that was supposed to be exposed to Ranitidine and the group that was not.

Once again, your Honor, there is no evidence that this occurred. When asked at her deposition, Dr. McTiernan said that she couldn't identify a single person in any of these studies who had actually been misclassified.

Moreover, all of the comparators during the time period of these studies also had over-the-counter counterparts. There is just no basis to believe that the usage for Ranitidine over-the-counter use was materially different than over-the-counter use for any of these comparators.

Next slide, please.

Most importantly, the study authors themselves

considered whether there could be misclassification bias and concluded that there wasn't. Adami notes that because all the comparators were similarly impacted by over-the-counter use over time the effect, if any, would be limited.

Norgaard observed that because the proportion of over-the-counter sale of Ranitidine increased during the study period, if there really were misclassification bias, we would expect to see different risks for someone who took Ranitidine in the 1990's compared to someone who took it in the 2000's, but we didn't see that kind of attenuation.

No other researcher or peer reviewer in the medical community has looked at these studies and said that misclassification bias invalidates the results.

So once again, your Honor, Defense experts are in line with the medical community and that is a signal of reliability.

Thank you, your Honor.

THE COURT: Thank you very much.

MR. BOEHM: Again for the record, Paul Boehm for Pfizer and for all of the brand Defendants.

Your Honor, I am going to turn to the next slide which shows us the third of Plaintiffs' criticisms that Ms Pyo and I will be addressing. As your Honor knows, some of my colleagues will be standing up and talking about applications of these criticisms as they apply to individual experts, and also there are some individual specific issues that will be addressed

during that portion of today's discussion.

The third criticism that Plaintiffs make that we will be addressing, your Honor, is, as you know, they criticize the Ranitidine epidemiological data. They say that it leaves a gap, that is in their brief, it leaves a gap, and we already heard all about how their experts purport to fill that gap, and we have discussed whether or not that is permissible.

The issue today is whether it was methodologically reliable or unreliable for Defendants' experts to use these Ranitidine epidemiological data in the way that they have, in a way that is consistent with how FDA treated it, how EMA treated it, how others in the scientific community have treated this data.

It is important, your Honor, just to start by going back to something that we discussed earlier this morning, which is, what is the law in the Eleventh Circuit.

The law in the Eleventh Circuit specifically asks Courts, when evaluating Rule 702, to consider whether or not the epidemiology related to the drug shows an association, and that is fundamentally the issue that we are addressing here as it relates to Defendants' experts. That is what they did, and you remember Judge Rodgers in the Abilify opinion said, that is the sine qua non of general causation.

If we can go to the next slide. Thank you.

If the studies have limitations, the way science works

and what the law in this circuit says, it doesn't mean you make the test easier. You don't move the goal posts a little closer. You don't look to find other paths to get to causation.

In science you might do more studies, you are always looking for more information, that is a process that is ongoing, but one of the core tenets is the null hypothesis. Some people have told me not to talk about the null hypothesis here today because it sounds too wonky, but it is a key premise of all scientific inquiry.

You start with it and the null hypothesis basically says you have an assumption that there is not an association, and then you try and disprove that null hypothesis. In the courtroom the way that gets translated is in the form of Plaintiffs burden of proof that we discussed earlier.

If the epidemiology doesn't reject the null hypothesis, which is what FDA and EMA and others have said when they say there is no consistent signal, that is their conclusion, then you don't fill the gap with extrapolation, with deductive reasoning, with in some cases speculation.

Here Plaintiffs' characterization of the Ranitidine epi aren't even quite right based on testimony from their own experts. This is Dr. Moorman referring to the Adami study. This study in particular, along with some others, has a longer followup than the Wang study that we have heard about a bit

this morning.

Next slide, please.

Again, Adami. Adami had a median followup of 14 years. Norgaard the same, a median followup of 14 years.

Next slide, please.

Again, looking at the epidemiology about exposure to the drug and looking for consistency and replication, that is the first step. That is the threshold issue under Rule 702 when you are talking about toxic tort cases.

Again, that is how FDA did it, that is how EMA did it, that's how Defendants' experts did it, and that is how the broader scientific community has done it.

That is the question when it comes to this issue, was it okay, under Rule 702, for Defense experts to use the Ranitidine epidemiological data in the way they have? They did it in the way that is broadly accepted in the scientific community. They did it in the way they have done it outside of the courtroom. It is reliable.

Now, Mr. Snidow, at one point he said something that I thought was interesting. He said associations that you see in poorly designed studies, that is especially strong evidence of causation. I was just waiting for where it says that in the reference manual. That is not in any case I know of, it's not in the reference manual. The reference manual says the opposite. That is not the law.

You look for replication and consistency. That is what you do, you look for replication and consistency. That is what the reference manual says.

He also talked about criticisms that they have about our experts' use of Bradford Hill analysis, and they said it was too shallow, they didn't go deep enough into Bradford Hill. Some of the people here at the table will talk about the specific application that certain of the experts applied in doing their Bradford Hill analyses.

The point I am going to make now is simply that Bradford Hill applies when you have an established consistent association. That is what the law says, that is what the reference manual says.

If you don't have a consistent, replicated, reliable, unbiased association, you don't get to the Bradford Hill criteria. The experts on the Defense side, they did it kind of like belt and suspenders, go ahead and look at some of the issues, but their conclusion was that you didn't actually get past that threshold issue.

Let's go to the next slide, please.

This is the Florian article, FDA statement. I believe Mr. Snidow called it a sound bite and he said it was out of date.

The point is that what the FDA said in this publication remains exactly true. That is the point. You can

look at the two studies that Mr. Snidow referenced, he said this came out before Cardwell and it came out before the Wang study.

Well, if you look at those two studies, they come out totally different on bladder cancer. Cardwell had the bladder cancer finding that the Plaintiffs like, and Wang shows 1.0 hazard ration on bladder cancer.

On Wang you have four out of the five cancers at issue here, no association. The only one they have is liver. That is the point. That is the point. You are looking for consistency, you are looking for replication, and here we have the opposite.

And when you don't have a consistent signal, you don't just get a look for alternative routes to causation.

Next slide, please, Maryann.

We heard some discussion at length, actually, about a threshold dose issue, which your Honor knows was a subject that the parties discussed at great length a couple of weeks ago. It wasn't clear how, if at all, Mr. Snidow meant to apply that discussion. Slides 28 through 49, those are the ones I objected to at the beginning.

It wasn't clear to me how he intended to apply that discussion to the opinions of the Defendants' experts. It took 52 slides, I kept track, before Mr. Snidow said anything about Defendants' experts.

In any event, he is wrong on the law.

Let's look at what the Courts have to say. He mentioned McClain, he tried to make it sound like McClain said something that it doesn't.

In McClain the issue was that the expert couldn't say how much was too much, could not establish any minimum threshold dose, and noted that issue is the single most important factor to consider. Same issue in Abilify, a general causation expert has to establish -- who is trying to establish causation affirmatively should address what levels of exposure the risk emerges as. Where is it that you have it pop up.

They have flipped this, and you heard a reference to Judge Kugler, the Valsartan Judge, and you saw what I said earlier. Remember this morning I said we don't have an opinion, we just have a transcript. It is not in the Eleventh circuit, but we know that judge actually made his ruling based on two things: One, company documents; two, the withdrawal of the product from the market.

I believe Mr. Snidow said for that judge that was the end of the inquiry, he stopped there, that was enough. If you look at the jurisprudence in the Eleventh Circuit, it specifically says you can't do that. That is not enough to get past Rule 702.

I haven't investigated what the is law in New Jersey, but I know that is not the law here.

Next slide, please.

Here are some of the statements the Plaintiffs have made in the briefing about this issue. It is important because they say there is some threshold dose, there is some amount of exposure, and we are not saying that every Plaintiff who has had every amount would meet this threshold. There is some threshold dose, we are just not quite going to tell you what it is.

Then we had that slide that Mr. Snidow showed, I think slide 33, where he put down -- he pointed down at the left-hand corner and he said minimum dose, that means the lowest dose that theoretically could cause cancer.

It is not about theoretical, you have to have scientific evidence, that's what the law is. You have to have scientific evidence that establishes that association at that level of exposure, not theoretical speculation. That is a misstatement of the law, completely wrong. We didn't see any cases that said that. It is not the law.

I put up this quote from the transcript of the September 21st hearing when your Honor was asking some questions about this. We heard Plaintiffs' counsel respond to those question by saying, well, there might be a conflict of interest with a particular Plaintiff, and maybe they would have to come in, and they might disagree with something that is being said here about dosage, might be a little unfair to hold

that against them. You heard kind of a muddled version of that again here today.

We have all these Plaintiffs, we will deal with all this later, that is the idea. Let's just push that question aside, we'll deal with it later. It all goes to specific causation. That is not the law, you can't do that.

Next slide, please.

Now, Plaintiffs' counsel suggested that we used an unflattering photo of Dr. McTiernan. If that is the case, we apologize. I am personally sensitive to unflattering photos.

The point here is, Dr. McTiernan didn't have an opinion as to threshold dose. If you apply that to the law we just looked at, if you look at Abilify and look at McClain, that means you don't have a causation opinion under Rule 702.

Next slide, please.

And we know that this also is not permissible under Eleventh Circuit law. You can't just say any exposure at all, a single pill, that is enough. Again, you can't do that. You can't skip this inquiry at this stage.

Next slide, please.

All right. This is the last of the four issues that Ms. Pyo and I will be addressing during this section. It is the argument that the Defendants' experts don't consider the NDMA studies that the Plaintiffs' experts have used to fill the gap, that gap that you heard as it relates to the Ranitidine

epidemiology. They say we ignored them, and I think we heard that again from Mr. Heinz, I think he said they ignored them.

We want to clarify, and you will hear more about this when we get to the specific individual experts, it is just not correct. The reality is they looked at those studies and they concluded about those studies the same thing that everybody else in the scientific community outside of this courtroom has concluded about them, which is that you cannot use them to establish risk when it comes to Ranitidine, and you cannot use them to measure risk when it comes to Ranitidine.

It doesn't mean you have ignored them. You don't have to put them in a closet and pretend like they don't exist. They have a purpose, they generate hypotheses, you look at them for various other ideas and reasons, but the point is, under the law and actually as it works in the real world, you can't use them for that purpose.

That is the point and that is the point we are making and that is the point that Defense experts are making and that is the issue.

Next slide, please.

The Plaintiffs engaged Dr. Hidajat. You have heard a lot about the Hidajat study. They engaged her as an expert in the case probably in hopes that they might be able to get her to endorse the use of her study for the purposes that they were trying to use it for, and she didn't quite go along with that.

When she was actually asked specifically about whether you could use the study for this purpose, she said, no, it was designed to look at occupational exposure and that means in a working day, long exposure over a lifetime. It's a totally different setting.

Next slide, please.

Dr. McTiernan, this is in the Talc litigation, she was an expert in the Talc litigation. You will remember this from a couple of weeks ago.

In that setting she said, you can't really use these dietary studies to establish risk or to measure risk, they are just not reliable for that purpose. It doesn't mean you pretend like they don't exist or you have to put them away in a closet, you just can't use them for this purpose. That is what she said in the Talc litigation, and we are hearing something different from Plaintiffs here in this case.

Next slide, please.

Now we get to these two cases that we have heard a lot about, the Fixodent and the Benzene case. I want to talk briefly about those.

The law here in the Eleventh Circuit, and in other Courts, it lines up with how this works in the real world.

Courts have found that this kind of extrapolation from adjacent or different bodies of data, it is interesting, you can come up with ideas and theories about it, but it is

impermissible, it's impermissible under Rule 702, because it is not sufficiently reliable to actually sustain the causation burden that Plaintiffs have.

It goes to reliability, doesn't go to weight. This wouldn't be a cross-examination point, it is an admissibility issue. Mr. Heinz said -- you know, again, Mr. Heinz said Defense experts are just completely ignoring it, and I want to emphasize again, not saying that, you just can't use it to establish and measure risk. There are too many analytical gaps, too many leaps of logic, too much deductive reasoning and not enough hard actual data. That is what the cases say about this.

Go to the next slide.

One of the topics on the Court's list for today is the role in determining admissibility rather than weighing persuasiveness, and again, this is an issue that goes directly to admissibility and reliability.

Defendants' experts' treatment of these studies was not to ignore them, but it was to properly situate them in a way that accords not only with the scientific practices, the same things that the regulatory bodies and other scientists have situated then in the context of Ranitidine, they have done the same thing, but in the context of what we see in the law that, under Rule 702, you can't do this type of leaping.

Your Honor, thank you for your time. I am not sure

how many minutes we have used up, but it might be helpful if you could help us out on that.

THE COURT: 25.

MR. BOEHM: With that I thank your Honor and pass the microphone to my colleague, Mr. Tobey.

THE COURT: All right. Thank you.

MR. TOBEY: Good morning, your Honor.

THE COURT: Good morning.

MR. TOBEY: My name is Stanley Tobey and I will be defending Dr. Witte on behalf of all the brand Defendants today.

As background, your Honor, Dr. Witte is a world-renowned cancer epidemiologist. There is really not a major challenge to his experience or credibility, but just for background, for over a decade he was the head of the division of cancer epidemiology at UCSF, and now he serves as the vice chair of the Department of Epidemiology and Public Health at Stanford University. He is actually a senior editor of one of the leading epidemiology journals which published about twenty of the papers that people have been presenting to you in this case.

Next slide, please.

So, your Honor, there are four main critiques that Plaintiffs have lodged against Dr. Witte, and we are going to take on all of those, but what I would like to do is walk

through Dr. Witte's methodology and how he approached this question, the same way scientists all over the world approached this question. In doing so it will provide a window into how credible scientists around the world decided what was a reliable set of evidence and what was not.

Next slide, please.

To level set on the law, your Honor, as you know from the Rider case, scientific evidence must fit the Plaintiffs' theory of causation. That is going to be a theme I keep returning to. There must be that fit. You have to look to the reliable evidence that addresses specifically the proper research question, otherwise your results are simply unreliable.

Next slide, please.

What did Dr. Witte do first? He defined the relevant research question. I know there is a lot on this slide, your Honor, but what it shows is remarkable consistency.

Everybody, including Plaintiffs, began with the same issue, the question of finding small amounts of NDMA in some lots of Ranitidine. So, what did scientists do? They went to work and they formed the research question, and the proper research question was, does Ranitidine cause cancer? That is exactly how your Honor framed it in PTO 77, the limited question is whether Ranitidine can cause one of the five designated cancers.

That is exactly how Dr. Witte framed it, too. It is how EMA framed it, it how FDA framed it, it is how the vast majority of researchers outside of this courtroom framed the question. Plaintiffs stand alone. Only Plaintiffs have asked this Court to focus on NDMA rather than Ranitidine when Ranitidine is the exposure in question.

Next, Dr. Witte said what is the reliable body of literature that addresses that properly framed research question? This is an important methodological step, your Honor. Even the best intentioned researchers can have a tendency, when they don't find the answer they want in one body of evidence, to continue looking to other bodies of evidence in hopes of finding something that supports their hypothesis.

Dr. Witte points out in his report scientists approach it differently. They set the relevant body of evidence, he uses the phrase of priority, in advance, and that restrains them from making analytic leaps, or resorting to unreliable bodies of evidence. Again, you see, your Honor, Plaintiffs stand alone, only they said let's broaden this universe beyond the evidence that fits the question and port in these other bodies of data.

Just one point, we mentioned Florian on this slide, and you heard from Mr. Snidow that, in Plaintiffs' view, Florian is old news. What is critical about Florian is the methodology. How did FDA address this question? They looked

at Ranitidine epidemiology and they applied active comparators to reduce confounding and bias. That is the methodology that they found reliable and that remains true today.

Next slide, please.

Your Honor, Dr. Witte did not just look at Ranitidine evidence and he certainly did not ignore the so-called NDMA science, by which Plaintiffs just say means dietary and occupational studies. He spent a great deal of his report looking carefully and explaining why those studies don't fit the question before the Court.

Now, to zoom out, Dr. Witte has published over 250 peer reviewed epidemiology studies, including nutritional and dietary studies. He is certainly familiar with those methodologies, and he appreciates that they have their place, but he also explains very carefully why they don't have a place here. They simply do not fit the question.

So, what does Dr. Witte say? Two broad points and then we will drill down a little bit.

First, he points out that from a scientific perspective, extrapolating from NDMA studies requires speculation, whereas studying Ranitidine specifically reflects the actual real world question here.

Dr. Witte said there is only one way to test what the effects of NDMA in Ranitidine are at the doses people actually took them and with whatever quantum of NDMA may or may not have

been in those particular pills, and that is to look at the studies of Ranitidine human epidemiology.

Dr. Witte makes another really good point. He says looking at NDMA alone does not account for the real-world net effects of NDMA in Ranitidine. Everything happens within a biological context. The way NDMA is consumed in radishes or rubber fumes is not the same as when NDMA is consumed with Ranitidine.

We have heard all kinds of things about Ranitidine adjusting pH, and the effects of Ranitidine with or without food. All of that has to be taken into account, and there is only one body of evidence that does that. That is looking at the real-world exposure, which is Ranitidine.

Next slide, please.

Dr. Witte drills down and talks a little bit about the Hidajat study and why that study and others like it do not fit the question before the Court, and what Dr. Witte says is, first let's look at the internal limitations of that study, and he points out several, but the big one here that is indicative is Dr. Hidajat took a single year of data from a rubber factory and she extrapolated it over decades to make assumptions about the effects of that exposure.

Now, Dr. Witte points out that is a pretty shaky basis within Hidajat for Dr. Hidajat's own conclusions. Then Dr. Witte points out that is not what Plaintiffs are doing. They

are trying to take that shaky foundation and extrapolate it to a wholly unrelated question. That is simply not a reliable method. It is why nobody outside this courtroom has done it.

Now, Dr. Witte also talks about some of the specific problems of Hidajat in terms of extrapolating. So, let's zoom out. Why do Plaintiffs believe it is okay to look at NDMA and other exposures? They have said this in their briefing. They say NDMA is NDMA, it is the same molecule. They believe these studies can isolate the effects of NDMA and then they can port those effects into Ranitidine and say, see, there is no difference. If it is like that here, it is like that there.

Dr. Witte points out even Dr. Hidajat doesn't believe that basic assumption holds up. Dr. Hidajat talked about the challenges and the impossibility of disentangling the effects of NDMA from the dozens of other chemicals in rubber fumes, including known human carcinogens. She said, I can't disentangle which thing is causing which. That directly undermines Plaintiffs' whole assumption that they can isolate NDMA and then apply it through some conversions and assumptions here.

Even Dr. Panigraphy, one of Plaintiffs' experts, has said, and it is obviously true under Rule 702, if Dr. Hidajat's measurements are unreliable here, then all the people who piled on to Dr. Hidajat's work, Dr. Panigraphy, Dr. Salmon, all of that is also unreliable.

Next slide, please.

Your Honor, this is a busy slide, and we are not going to go through it all, but the busyness is by design. We thought it would be helpful to show you just the number of compounding assumptions that it takes to translate, in Plaintiffs' view, from rubber factories or dietary studies to the people here, people who actually took Ranitidine.

At the bottom of this tower you see the problems internal to those bodies of evidence, like you heard Mr. Boehm say, the World Cancer Research Foundation found limited evidence in the dietary studies, but then Plaintiffs keep piling assumptions. They don't have a direct dose in Ranitidine because they are extrapolating, so they use Dr. Najafi's estimations and they extrapolate from those, and it keeps going.

In fact, on the rubber factory side they have to travel through animal models. There is a mouse model in there, your Honor, because they don't know how else to go from inhaling NDMA to consuming it in a pill. That is simply not a reliable basis.

Let me say one thing, your Honor, about the burden of proof because they talked about the Fixodent case and the gas cases, and you heard them say, well, you haven't proved that our tower here is unreliable. That is simply not the law. Plaintiffs, under Rule 702, bear the burden to show that their

extrapolations and analytic leaps are reliable, that they can make these comparisons. They simply cannot do it.

Next slide, please.

Obviously Dr. Witte did not ignore NDMA science, he explained why it didn't fit.

Then he turned to the reliable body of evidence, and what he did was, he tested the Ranitidine data for valid associations. Plaintiffs claim that apparently "none of these associations are valid, but Witte does not explain why."

Well, Witte does explain why. He defines validity very clearly, and consistent with the reference manual, a valid association is one not due to chance, bias, or confounding.

So, how did Dr. Witte and other credible epidemiologists rule out chance, confounding, and bias? Your Honor, you have heard all of these generally accepted techniques. I will run through them quickly.

He applied the standard control for bias and confounding of active comparators. To hear Plaintiffs talk about it, active comparators are something Defense experts concocted up for this case. Ms. Pyo showed you the evidence, FDA, EMA, all the reliable authorities say this is the best in class for controlling bias.

But Dr. Witte didn't stop there, he evaluated dose response and he said you have to find a consistent dose response across the various studies. He also reduced the role

of chance by applying the statistical test of significance. You set the threshold in advance and you don't depart from it like Plaintiffs' experts did.

And finally, he also assessed bias and confounding by looking at effect size. Dr. Moorman, one of Plaintiffs' experts, agreed here. She said, results under 2.0 are suspect, they are simply too small and you need to be very, very suspicious of them because they can reflect noise, confounding, and bias that is residual despite your best efforts to control.

I am not going to retread active comparators, I think you probably have heard enough for a lifetime on active comparators. But Dr. Witte makes a really interesting example in his testimony about the importance of active comparators, and he actually looks to the study that Plaintiffs like so much, the Cardwell study, and what he says is that database had some information on smoking, and so McDowell, the first person to study it, tried to control for smoking, took that data and controlled.

What Dr. Witte planned out is, you would suspect if you had isolated and controlled all the smokers, you wouldn't see any remaining effects for prescription nicotine because it just kind of stands to reason, if you take out everyone who ever smoked there is really not any reason for them to take prescription nicotine except to quit smoking.

What Dr. Witte found when he looked, though, was even

after McDowell controlled for smoking, there was a 1.54 association in that database between prescription nicotine users and cancer. That is an effect size bigger than the one they claim for Ranitidine.

What does that tell you? Residual confounding, even when you try to control for specific variables, exists. That is why you want active comparators. Dr. Witte doesn't say active comparators magically cure everything, you want to control measured and unmeasured bias with all the techniques available given a certain data set.

That is what he did when he looked at the data, and as your Honor knows, when Cardwell added an active comparator to that same study the bladder finding went away.

Next slide, please.

Another interesting point, your Honor, we haven't really talked yet about why active comparators are critical to the dose response analysis that you have seen. As you know, dose response is another one of the factors that Plaintiffs are trying to show.

What Dr. Witte explained was, you can have confounding within a dose response if you don't apply active comparators. The reason is, if you are just comparing to nonusers, people at the low end of the dose curve are typically healthier, people at the high end who need more medication tend to be sicker.

So, just comparing them within the curve could be

reflecting bias of different populations, but if you compare all of those points to other people taking the same type of medication, the same class, you get rid of that confounding to some degree and leave only the effect of the drug in question. That is a very important thing to keep in mind when we look at some of these studies.

Next slide, please.

So, what did Dr. Witte find, your Honor? We use bladder as an example here because, until this week, bladder was the cancer that Plaintiffs were very excited about.

Dr. Witte looked at this evidence and he didn't cherry picked, he had non-use comparisons, PPI comparisons, active controls, H2RAs all in his chart. He put the best evidence at the top, which is comparisons to other drugs in the same class, then he put the intermediate comparisons in the middle, and then he put the least controlled, most subject to bias comparisons at the bottom, and he looked at what that showed.

He noted that when you applied active controls signals in the non-user population disappeared. He looked and said all of these risk ratios are well below 2.0, which Dr. Moorman tells us makes them highly suspect for residual confounding. He noted that there were no statistically significant findings, not even a consistent pattern of statistical significance.

If we can go to the next slide.

He also looked at the dose response relationship, and

as you see here, two strong studies doing dose response, one shows an upward trend, one shows a downward trend. That is not the consistency in the data that would let Plaintiffs meet their burden.

And merely as a side note, your Honor, I don't want to get in the weeds, but Plaintiffs keep saying that Norgaard is shorter than Cardwell and it's only ten months long. If you look at Plaintiffs' own expert, Dr. Le, who assessed the Pottegard study, those prescriptions were three-month prescriptions in Norgaard, so it is actually 2.5 years versus three years respectively looking at a similar exposure period.

Next slide.

Let's talk about Wang a little bit. Does Wang change the picture?

One thing that the Wang authors and Dr. Witte clearly agree on is following statement: "Conflicting results of studies underlie a lack of concrete evidence supporting the role of Ranitidine in cancer development."

That is on page two. That is what the Wang authors said when they assessed the entire body of literature up to their study. That is what Dr. Witte did and he came to the exact same conclusion. So, does Wang move the needle? As you have heard from Mr. Boehm, Wang only has one statistically significant active comparator result and that is liver, which is a cancer you heard barely anything about before today, but

now Plaintiffs are rallying around it.

When you look at the totality of the data and you apply the FDA criteria of consistency and replication, you see here, your Honor, there is simply no pattern that anyone could hang their hat on. You have one significant result below 1.0, you have one significant result above 1.0. You have two others that are below the risk line, so decreased risk, but not significant.

Over on the right you have a similar comparison of dose responses, Wang found an upward trend. Adami, and they like to pick on Adami, he was the chair of the Department of Epidemiology at Harvard School of Public Health, he can do a study. He saw a downward trend, and an important thing here, your Honor, is Adami's was an H2RA active control.

The dose response that Plaintiffs want to rely on in isolation is compared to non-users. It doesn't have that control for bias, but even if you took Wang's numbers at face value, and there are certainly methodological flaws that one could spend a lot of time pointing out, at face value this is not the picture of consistency that is any reliable basis to draw an association, much less causation.

Next slide, please.

Dr. Witte, applying these generally accepted methods, reached the same conclusion that everybody else has reached, all the regulatory bodies, the vast majority of independent

experts, there is simply no valid association free of chance, confounding, and bias in the data that exists.

Next slide, please.

Mr. Snidow put this slide up, let's talk about it. Dr. Witte responded in advance to McTiernan's and Moorman's criticism that the Ranitidine data is somehow too short to draw conclusions from.

What Dr. Witte did was, he said, hey, Dr. Moorman, she cites an IARC study. We know how Plaintiffs like to analogize to diet. IARC did a dietary study of red meat and found an association with colon cancer, and Moorman held that up and said, see, this is a dietary study, it caused cancer, so therefore NDMA in Ranitidine must cause cancer.

What we showed here, your Honor, is there is no meaningful difference in the length of studies, in the IARC red meat study that Plaintiffs liked and in the Ranitidine cohort studies that should be the focus of this analysis.

Now, A couple of interesting points. Mr. Snidow seemed to imply there was some duplicity in the calculations here. This is how IARC calculated duration, this was their study. We made the same calculation that IARC used and showed apples to apples that their study that did find a valid association, where one existed, was no longer than the studies we have.

As Dr. Witte said, this length of study that we see is

par for the course in cancer epidemiology and it is certainly sufficient to find real associations where they exist, which is not the case here.

Next slide, please.

Dr. Witte didn't stop there in responding to this strawman of studies are too short. He said, let's look at Cardwell. Plaintiffs love Cardwell, Plaintiffs called Cardwell a study of long term risk, 18 years total. They say finally a study with the length they want.

Well, Witte says I agree, and look at the finding. When you apply the best controls for bias and confounding, active comparators, quote, this is Cardwell, "there was little evidence of a difference in bladder cancer." The lone finding that they want to hang their hat on simply goes away when you apply the best controls in a study that they concede is of sufficient length.

Next slide, please.

So Mr. Snidow said something interesting, and I think maybe it was a Freudian slip, but it is really telling. He said, IARC says it takes 30 years duration to disprove a cancer risk.

That is not what this court of law is about. No one is trying to disprove a cancer risk, and they do this throughout, your Honor, and it is something to watch out for, the flipping of the burden. They have the burden to establish

the totality of reliable evidence as it exists supports a valid causative effect.

They can't even get to association, but they don't get to flip the burden and say, well, you don't have 30 years to disprove it. That is simply not the way science works and it is certainly not the way Rule 702 works.

Now, this is a point that Mr. Boehm made and I won't belabor it, but going back to that question of fit from Rider, let's assume that Dr. Witte is wrong and there is some gaping hole in the Ranitidine literature, it is not long enough or whatever. That is not an invitation to fill that gap with evidence not deemed reliable in the first place to answer the question. That is exactly why we set the body of evidence on priority so that you don't then resort to NDMA in radishes or NDMA in rubber when the question is NDMA in Ranitidine. It is simply too great an analytical gap.

Just a point on dose, your Honor. You heard this theoretical debate, dose above the line, dose below the line, what do people have to show. It is kind of missing the point. There is no reliable evidence here of any dose being associated with cancer in actual studies of humans who took Ranitidine in the real world. They can argue all day about where they want the dose to be. They don't have an association, there is no dose at all right now to talk about.

Next slide, please.

Dr. Witte, consistent with Bradford Hill, consistent with the reference manual, said there is not even an association here, certainly not a perfectly clear-cut association like Bradford Hill required to proceed to that next analysis, so he says, I am not doing it, it stops here.

But as a rebuttal expert, he saw that Plaintiffs did it, and so he pointed out some factors that negate their Bradford Hill analysis. He wasn't doing his own primary Bradford Hill, and so when they critique him for not talking about everything that is missing the point.

He was showing how they can't win even on their own terms, the science simply isn't there.

So, in sum -- next slide, please -- Dr. Witte is a window into the generally accepted methods of the larger scientific world. He picked the right question, he picked the right body of evidence, and he applied the standard controls for chance, confounding, and bias, and found that there was no evidence of any relationship between real-world Ranitidine use and any of the cancers alleged that survives true scientific scrutiny.

That is the problem fundamentally that Plaintiffs have here in all of these motions is, when they ask you to strike the methodology of Dr. Witte they are asking you impliedly to strike the methodology of FDA, EMA, Harvard, all of these people that you have heard about. There is simply no one out

there doing what Plaintiffs want you to do, so that is why it is their motions that must be stricken as unreliable and the motion against Dr. Witte should be denied.

Thank you, your Honor.

THE COURT: Thank you. That is 51 minutes.

MS. CANAAN: Good afternoon, your Honor, Eva Canaan for Defendants. Can you hear me well?

THE COURT: Yes.

MS. CANAAN: Your Honor, I am going to argue Defendants' opposition to Plaintiffs' challenges to Drs. Chan, Vaezi and Porter.

Next slide, please.

Dr. Chan, your Honor, he has impeccable credentials, he is the director of cancer epidemiology at Massachusetts General Hospital, he is the co-leader of the cancer epidemiology program at Harvard. He is also a practicing gastroenterologist and vice chair of clinical research in gastroenterology at Massachusetts General Hospital.

He is one of the most cited researchers in the world. He is the director of the National Cancer Institute's Board of Scientific Advisers. I also want to point out that Dr. Chan was an advisory group member at IARC. I only raise that because Plaintiffs have claimed at the last hearing that none of the Defendants' experts have served on an IARC panel. That is obviously not true.

Now, Dr. Chan's expertise is really uniquely suited to this litigation. As a gastroenterologist, he treats GERD and other conditions for which acid suppressants are taken. He routinely prescribes H2 blockers and PPIs, and there is really no one more qualified than Dr. Chan to talk about these medications, to talk about the populations that take them, right.

For example, he sees literally on an everyday basis how likely his patients with GERD are to be obese, to smoke, or to use alcohol, and so Dr. Chan brings this unique clinical expertise to the study of cancer epidemiology, with a particular focus on the four GI cancers alleged in this litigation.

In fact, your Honor, Plaintiffs themselves have recognized Dr. Chan's unique fit, so to speak, for the issues in this litigation and they have approached him as a potential expert candidate.

Next slide, please.

Dr. Chan has reviewed the totality of epidemiological evidence in this litigation and he has concluded that it does not support a conclusion that Ranitidine has a true association, let alone a causal relationship, with any type of cancer.

Next slide, please.

Plaintiffs' challenge to Dr. Chan really boils down to

three claims. First, they contend that he ignored NDMA epidemiology; second, they claim that he failed to account for dose and duration of use in the Ranitidine studies; and third, they claim that he failed to account for length of followup in the Ranitidine studies.

Next slide, please.

So, let's start with Plaintiffs' first claim, that Dr. Chan purportedly ignored NDMA epidemiology. Simply put, the claim is false.

Next slide.

Although Dr. Chan appropriately focused on the Ranitidine epidemiology in his causation analysis, he did not ignore any NDMA studies. In his report Dr. Chan has a section titled Epidemiology Studies of NDMA and Cancer Outcomes. That section, your Honor, is literally 33 pages long, so it is pretty hard to miss. Dr. Chan states unequivocally in his report that he systematically reviewed the entire body of epidemiological literature on NDMA and the cancer outcomes alleged by the Plaintiffs.

Now, today we heard a somewhat different story from what Plaintiffs put in their brief. Today we heard, oh, Dr. Chan, he never looked at the NDMA studies until he saw them in Plaintiffs' reports.

First of all, even if that were true, there is nothing wrong with that. He is a rebuttal expert, that is what

rebuttal experts do.

Secondly, it happens to be not true because he was asked this precise question at his deposition, and at page 38, line 25 to page 39, line 9 he explained that he had reviewed many of these NDMA studies even before he saw the Plaintiffs' reports. He didn't think they were important enough to include in his report, but when he saw Plaintiffs' reports he systematically reviewed the entire body of literature and he included 33 pages discussed in his report.

Next slide, please.

Now, in their brief Plaintiffs go even further and they say because Chan ignored the NDMA epidemiology he offers no opinion on the carcinogenicity of NDMA. Again, nothing could be further from the truth. After his 33-page long review of NDMA epidemiology, Dr. Chan concluded that the extant epidemiological literature does not establish a true association between either medication related, dietary, or occupational NDMA exposure in any of the five cancers.

Moreover, your Honor, he reaffirmed this opinion time after time after time at his deposition when he was asked questions about these issues.

So, the bottom line here is Plaintiffs' claims that Dr. Chan didn't review the NDMA epidemiology or didn't have opinions about it, they are just flatly contradicted by Dr. Chan's report and his sworn testimony, your Honor.

Next slide, please.

Now, Plaintiffs' second claim is that Dr. Chan purportedly failed to account for dose and duration in the Ranitidine studies.

Next slide, please.

Again, your Honor, the claim is plainly contradicted by the language of Dr. Chan's report. In fact, literally for every single type of cancer alleged in this litigation, Dr. Chan specifically analyzed the Ranitidine study findings for both high exposure and long-term use and concluded that they simply do not support an increased risk.

Next slide, please.

Now, what is also critical about Dr. Chan's assessment of dose and duration of Ranitidine use is his unique clinical expertise. So one of the criticisms that we heard earlier today from Plaintiffs is that for some of the studies, like the Adami study, for example, we know that the patients redeemed more than ten prescriptions, but we don't know exactly how many months or years of Ranitidine use that is.

So, at his deposition, Dr. Chan explained that GERD and peptic ulcer disease are chronic conditions, much like diabetes, for example, and so especially for patients that have redeemed more than ten prescriptions of an acid suppressant medication like Ranitidine Dr. Chan said these are chronic patients, they are taking it on a long-term basis.

Again, plaintiffs don't like this opinion, your Honor, and that is not surprising. That is not surprising because they don't have a gastroenterology expert. In fact, they don't have a practicing clinician expert who can contradict Dr. Chan on these points.

Next slide, please.

So, Plaintiffs' last claim is that Dr. Chan purportedly failed to account for the length of followup in the Ranitidine studies.

Next slide, please.

Again, however, the claim is flatly contradicted by Dr. Chan's expert report. Dr. Chan explained that in study after study after study longer follow-ups simply did not result in higher risk estimates for cancer. As you can see on the screen, your Honor, in many cases the opposite was true, longer followup resulted in decreased risk estimates for cancer.

Next slide, please.

Moreover, and this is important, your Honor, Plaintiffs' claims that the followup in the Ranitidine studies was not long enough are also contradicted by Plaintiffs' own cancer biologist, Dr. Panigraphy. Dr. Panigraphy testified at his deposition that he would see a measurable effect of NDMA on cancer outcomes from a year to a couple of years.

Your Honor, every single Ranitidine study followed patients for much longer than that.

So, the bottom line is this: Plaintiffs' attacks on Dr. Chan are objectively contradicted by his report and his deposition testimony and your Honor should deny Plaintiffs' motion as to Dr. Chan.

Next slide, please.

So now moving on to Dr. Porter. Dr. Porter is an expert on bladder cancer. He is a practicing urologist as well as an epidemiologies. He has served on the National Cancer Institute's bladder cancer task force, he has coauthored national comprehensive cancer network clinical practice guidelines for bladder cancers. He really brings unique expertise to the review of the data on bladder cancer in this litigation.

Again, Plaintiffs do not have an expert with actual clinical expertise on bladder cancer, nor do they have an expert who has focused on the epidemiological study of bladder cancer in the way that Dr. Porter has.

Next slide.

So Dr. Porter proffers an opinion that the existing epidemiological evidence does not support a true increased risk or causal association between Ranitidine exposure and bladder cancer.

Next slide, please.

Now, Plaintiffs' challenge to Dr. Porter is based on two claims. First, they claim that he improperly found no

association between Ranitidine and bladder cancer; and second, they contend that he didn't perform a proper Bradford Hill analysis. As I will show, your Honor, both claims are meritless.

First, Plaintiffs claim that Dr. Porter improperly found no association between Ranitidine and bladder cancer. However, this claim is premised, first of all, on a misrepresentation of Ranitidine data on bladder cancer; and secondly, it is premised on a rejection of the principles of statistical significance.

Next slide, please.

So, first of all, Plaintiffs included this forest plot of Ranitidine and bladder cancer in their brief and today they put it up on a slide with the title, How Is This Not Consistency?

And they claimed in the brief and today that this bladder cancer forest plot shows every result reported by Defendants' bladder cancer expert report, every result exceeds the 1.0 null hypothesis and therefore each result shows an increased risk.

And yet, despite emphasizing that they purportedly included every result, Plaintiffs have excluded numerous risk estimates, specifically noted in Dr. Porter's expert report, from this forest plot.

Next slide, please.

So, what you see here, your Honor, are all the risk estimates from Dr. Porter's report, including the ones Plaintiffs omitted.

As you can see, when all the risks are added to the forest plot there are at least four risk estimates to the left of 1.0, and importantly, those include the analyses from the Norgaard study with the highest dose and the longest duration of use -- the longest followup. I apologize.

Of course, the recently published Wang study that we have heard so much about today, your Honor, also found absolutely no association between Ranitidine and bladder cancer. The risk estimates were 1.03 and 1.04. That is absolutely no association, contrary to what you have heard today.

Equally important, your Honor, the vast majority of the risk estimates in this forest plot are not statistically significant. As you can see, they overlap the line of unity, they overlap 1.0.

Next slide, please.

While Plaintiffs reject the principles of statistical significance and claim that every single study of Ranitidine showed an association with bladder cancer, their own expert, Dr. Le, disagrees with them. Dr. Le testified unequivocally at her deposition that when a confidence interval includes 1.0, that shows no statistical association. That is how she

interpreted risk estimates in her report.

So, Plaintiffs' views on statistical significance are not shared even by their own expert, much less the rest of the scientific community.

Next slide, please.

Now, Plaintiffs also accuse Dr. Porter today of not being consistent in the way in which he assessed confounding by smoking in the Ranitidine study, but Dr. Porter's methodology was entirely consistent.

First of all, Dr. Porter explained that smoking is by far the strongest risk factor for bladder cancer. In fact, he notes in his report that 50 percent of bladder cancers in the United States are directly attributable to smoking.

And third, and this is a really critical point, your Honor, Dr. Porter explains that it is extremely difficult to control for smoking through statistical adjustment in epidemiological studies, and that is because people do not accurately report if they smoke, how much they smoke, and how often they smoke. When you have a disease like bladder cancer that is so heavily determined by smoking, even a small amount of residual confounding by smoking can result in false or spurious increased risks.

Next slide, please.

This is an example that Dr. Porter provides in his expert report and one that your Honor can readily find simply

if you Google, your Honor, bladder cancer and coffee.

What you will find is that epidemiological studies have consistently reported a statistically significant increased risk for coffee in bladder cancer, and not just a statistically significant increased risk, but consistent evidence of dose response.

For example, in this meta analysis that Dr. Porter cites in his report, this is a meta analysis combining 17 studies, they all control for smoking, and you see a statistically significant dose response for every additional daily cup of coffee.

So, what does that mean for coffee drinkers like myself? Well, your Honor, the generally accepted explanation among epidemiologists, as well as IARC, is that all of the studies of coffee and bladder cancer are confounded by smoking. Coffee drinkers tend to smoke more and so smoking confounds the association between smoking and bladder cancer even though all these studies attempt to adjust for smoking in their statistical analyses.

Because smoking is such a strong confounder it really acts like a surrogate for exposure and creates this false appearance of a dose response.

Again, even though all these studies attempt to control for smoking there is still residual confounding that leads to false evidence of increased risk and false evidence of

dose response.

Earlier we heard today Plaintiffs saying that the Cardwell study purportedly controlled for smoking, but what the Cardwell authors actually said, and this is on page seven of their study, they say smoking and alcohol were incomplete and did not capture detailed information on the extent of exposure, and consequently there remains the possibility of residual confounding.

That is exactly why it is so difficult to control for smoking in statistical analyses, your Honor.

Next slide, please.

So, because smoking information is so difficult to accurately ascertain and then so difficult to control for statistical analyses, Dr. Porter concluded that an active controlled analysis is the best way to control for smoking.

Dr. Porter also notes in his report that because of their side effect profile, PPIs are less likely to be prescribed to smokers than H2 blockers, and for that reason he concluded that other H2 blockers are an ideal comparator group for Ranitidine. Of course, as you can see on the left side, the Ranitidine study authors reached the exact same conclusion.

Next slide, please.

Now, once we focus on the studies that compare Ranitidine to other H2 blockers, we see absolutely no statistically significant increased risks in any primary

analysis for bladder cancer, nor do we see any evidence of dose response, because the only evidence of dose response, as was mentioned earlier, was from the Cardwell study that came from a non-user analysis, not from an active controlled analysis.

So Dr. Porter's conclusion that there was no reliable association between Ranitidine and bladder cancer, it flowed naturally from his stated methodology in his expert report.

Next slide, please.

Again, your Honor, Dr. Porter's conclusion is entirely in line with the conclusions of the Ranitidine study authors. Plaintiffs' claims to the contrary are really belied by the plain language of these studies.

Next slide.

Now, Dr. Porter also looked at the dietary and rubber worker studies, and he concluded that they simply do not support an increased risk. Jakszyn, 2011, a cohort study of dietary exposure and bladder cancer, found no increased risk of bladder cancer with dietary NDMA. As you may recall from the last hearing, dietary cohort studies are the only types of studies that WCRF, World Cancer Research Fund, even considers in their assessment of diet and cancer risk. They don't consider case control studies because of the issues with selection and recall bias with those studies.

On the other hand, we have a study like Ronco, 2014, which is a case controlled study, the type of study that WCRF

would not consider, and they did report an increased risk with NDMA, but they also reported an increased risk for cheese, whole milk, and total eggs. In fact, if you look at the odds ratio for eggs, your Honor, 4.05, that is over a 300 percent increased risk. It is twice as high as what they reported for dietary NDMA.

Finally, as you heard earlier so I won't belabor it, the Hidajat study of the rubber workers, it is simply not relevant, and Dr. Porter concludes this in his report, because these rubber workers are exposed to a variety of different chemicals, including Class I carcinogens, and the authors in the peer reviewed study explicitly acknowledge that it is very hard to disentangle what exposures in this industry cause which types of cancers.

Next slide, please.

Plaintiffs' second challenge to Dr. Porter is that he purportedly did not perform an accurate Bradford Hill analysis.

Of course, as you have heard before from Mr. Boehm, Dr. Porter did not even need to conduct a Bradford Hill analysis because he reliably concluded that there is no true association that is not due to chance, bias, or confounding for Ranitidine and bladder cancer.

So, for all of the other points raised in Plaintiffs' briefs, we will rest on the papers and we ask that your Honor deny Plaintiffs' motion to Dr. Porter.

Next slide, please.

Lastly, I am going to address Plaintiffs' challenge to Dr. Vaezi. Like Dr. Chan, Dr. Vaezi is a gastroenterologist, as well as an epidemiologist. He is the associate chief and clinical director of the division of gastroenterology at Vanderbilt University. He is the coauthor of the American Gastroenterology Association's guidelines on GERD, which specifically address the management of GERD with acid suppressant medications like Ranitidine.

Next slide, please.

Dr. Vaezi proffers the opinion that the epidemiological evidence does not support a reliable association or causal relationship between Ranitidine and any cancer type.

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Plaintiffs' challenge to Dr. Vaezi again boils down to three claims. First, they say he ignored NDMA epidemiology; second, they contend that he misrepresented opinions of scientific organizations on NDMA; and third, they claim that he failed to account for and misinterpreted dose and duration of Ranitidine use.

Next slide, please.

Focusing on the first claim, that Dr. Vaezi purportedly ignored NDMA epidemiology, I think we can dispense with this one quickly.

Next slide, please.

Dr. Vaezi's report states very clearly that he reviewed all studies that reported on quantifiable NDMA exposures and risks of the five alleged cancers. Then he goes on to explain that these studies that he reviewed included NDMA contaminated non-Ranitidine medication studies, they included dietary NDMA studies, and they included occupational NDMA studies.

Next slide, please.

Again Plaintiffs misrepresent Dr. Vaezi's sworn testimony when they claim that Vaezi testified under oath that he never once reviewed a single NDMA epidemiology study.

Again, your Honor, even a cursory glance at Dr. Vaezi's deposition testimony you can see that is simply not true. He made clear that he reviewed the dietary studies, he reviewed the rubber manufacturing studies, again underscoring what he already stated very plainly in his expert report.

Next slide, please.

Plaintiffs' second claim that Dr. Vaezi misrepresented opinions of scientific organizations on NDMA, your Honor, this claim is equally meritless. To the contrary, Dr. Vaezi made it perfectly clear that NDMA is not a known human carcinogen. That is unassailably true, your Honor, and exactly what IARC, EPA, and ETA stated their guidelines.

Next slide, please.

Now, Plaintiffs twist Dr. Vaezi's words. This is what we heard earlier today, that they claim that he testified that IARC and other organizations had concluded definitively that NDMA does not cause cancer in humans.

That is a complete misrepresentation of Dr. Vaezi's opinion. What Dr. Vaezi actually testified to and what you see on the left side, your Honor, is that these organizations have not determined that NDMA is definitively a cause of cancer in humans. Again, that is unassailably true.

Next slide, please.

And Plaintiffs' last argument is that Dr. Vaezi failed to account for and misrepresented dose and duration of Ranitidine use in Ranitidine studies.

Next slide, please.

The claim is squarely contradicted by Dr. Vaezi's expert report. As you can see, your Honor, Dr. Vaezi routinely assessed dose and duration in the Ranitidine studies and he concluded as part of his Bradford Hill analysis that not only he is there no evidence of a reliable gradient, meaning no evidence of dose response, but many studies showed the risk estimates decrease with higher doses or longer durations of use.

Next slide, please.

Finally, Plaintiffs' claim that Dr. Vaezi somehow confused followup with the exposure period because he testified

that, for example, for the patients in the Adami study who filled at least ten prescriptions and were followed for more than ten years, that these were long-term users of Ranitidine.

In fact, Dr. Vaezi testified, based on his clinical experience as a gastroenterologist, that these are chronic patients who are taking the medication to treat their chronic disease. He said when patients fill ten prescriptions of Ranitidine, there is no reason to expect that they are not going to fill the 11th prescription.

There is every reason to expect that they would continue to use their medication to treat their chronic disease. Frankly, your Honor, if the Plaintiffs had a practicing clinician expert who prescribes these drugs, I suspect he or she would tell them the exact same thing.

The Adami authors in fact reached the same conclusion. In their published peer reviewed paper they state that the analysis of ten plus prescriptions were meant to capture long-term users of Ranitidine.

So, for all of these reasons, your Honor, Plaintiffs' challenge to Dr. Vaezi has no merit and should also be denied.

Thank you, your Honor.

THE COURT: Thank you. That's an hour and 18 minutes.

MR. SHEEHAN: Tom Sheehan, your Honor, on behalf of the Defense. I am going to try and be quick here. I won't be too quick on your fingers, Pauline, but I will try and move

along here.

I am going to be defending the motions against Dr. Terry and Dr. Wang.

This is the Wang study, so very careful and important point of clarification here, Tim Wang, Defense expert, is not the author of the Wang study you have heard so much about, and these are not the slides I need, actually.

So, if we could find -- I want to start with Mary Beth Terry. I don't know who has that, somebody behind the curtain here.

THE COURT: I will stop the clock. Are we going a little out of order?

MS. POWER: Yes, your Honor, Caroline Power for the Defense, and I will be speaking to Dr. Hatten.

If we could have the slides up for Dr. Hatten, please. If I could have the first slide.

Your Honor, Dr. Benjamin Hatten is a medical toxicologist and emergency physician with training in epidemiology and biostatistics. He offers the core opinion that there is no reliable basis supporting that either Ranitidine or NDMA exposure from Ranitidine causes any of the five designated cancers.

Next slide, please.

He incorporates a number of scientific principles in his methodology, and I won't rehash them all, but I do want to

revisit the null hypothesis that you have heard about today. We talked about the burden of proof. It remains Plaintiffs' burden of proof to show causation in this case, and the scientific community has a parallel framework.

Scientists in the real world begin with the assumption that there is no association, there is no causation, and it is on the burden of the evidence -- it's the evidence burden to show that there is consistent, replicated, and convincing scientific proof that there is, in fact, an association.

When experts like Dr. Hatten and others opine that the evidence is insufficient, they are not taking on the burden of proving no causation, they are simply stating that the null hypothesis persists and this is an appropriate approach under accepted scientific principles.

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In their papers Plaintiffs levy four main criticisms against Dr. Hatten, and like in many instances in this case, they conflate the Ranitidine aimed criticisms and the NDMA criticisms all together.

So, starting with the first one -- next slide, please -- Plaintiffs argue that Dr. Hatten did not assess the Ranitidine studies with his evaluation of the -- excuse me -- NDMA studies, but that is besides the point, your Honor. Dr. Hatten focused on what he found to be the most reliable studies, the Ranitidine studies.

I would like to pause here for a moment and address some of the things that Plaintiffs' counsel said earlier today.

First, we heard so much about dose, and dose is precisely why Dr. Hatten found the Ranitidine studies to be the most reliable because, as he states here, Ranitidine use inherently accounts for the level of NDMA exposure related to Ranitidine use.

Mr. Snidow mentioned that NDMA levels could vary drastically based on things like storage conditions or an individual Plaintiff, but that is captured in these studies.

Second, Mr. Snidow mentioned that Dr. Hatten ignored dose duration and followup, and your Honor, that is just not true. On pages 63 to 65 of his report he looks specifically at studies that have the longest use, the longest followup, and on page 65, he concluded there were no associations seen between long-term use of Ranitidine and any of the five designated cancers even when limiting the literature to cohort studies with at least ten years of followup.

Finally, Plaintiffs have asserted today and at the last hearing that all NDMA is the same, but, your Honor, that also is not true. As Dr. Hatten explains with regard to the dietary NDMA studies, those are indirect evidence because dietary studies necessarily involve a number of different nitrites, not to mention all the other components of food.

With regard to occupational data, at page 54 of his

report Dr. Hatten explains that inhalation exposures do not involve first pass metabolism in the liver, unlike oral exposures. In addition, "reliable quantitative information on the absorption of NDMA following inhalation," is not available. There Dr. Hatten is quoting the Liteplo 2002 WHO study that has been submitted to the Court, your Honor.

So, getting back to some of the criticisms Plaintiffs levy in their briefs, while Dr. Hatten did base his core opinions on Ranitidine studies, he did consider that NDMA data.

Next slide, please.

What did he conclude? The evidence is indirect, the associations are weak and unreliable, and there are sporadic and inconsistent associations based on assumptions.

Next slide, please.

Plaintiffs argue that Dr. Hatten failed to conduct a formal Bradford Hill analysis, and I think Mr. Snidow said there is no such thing as an informal Bradford Hill analysis. As you have heard throughout the day, your Honor, there is no such thing as a Bradford Hill analysis in the absence of an association, and here Dr. Hatten concluded there was no reliable association.

Next slide, please.

To the extent Plaintiffs point to Bradford Hill factors in levying their criticisms, Dr. Hatten considered those factors when assessing if an association exists. For

instance, we just talked about his review of the longest studies with the longest followup. That dose response Bradford Hill factor is inherent in that analysis.

Next slide, please.

Finally, as a belt and suspenders approach, your Honor, Dr. Hatten did walk through the Bradford Hill factors and how they apply to the Ranitidine studies as a whole.

Next slide.

Now, switching gears to the NDMA focused criticisms, the Plaintiffs argue in their papers that Dr. Hatten misrepresents how the scientific organizations classify NDMA. To be clear, Dr. Hatten opined that NDMA is not a human carcinogen, which is to say an established human carcinogen. This is consistent with scientific organizations that consider it a probable human carcinogen, potential, or of unknown relevance.

Your Honor, this is more than just semantics, these specific labels are the kind of precise language that scientists use and rely upon to accurately reflect the data and the significance of that data.

Next slide.

And again, your Honor, the Plaintiffs argue Dr. Hatten should have conducted a Bradford Hill analysis on the NDMA data, but there is no Bradford Hill analysis in the absence of an association.

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To bring it all together, your Honor, Dr. Hatten's considerations of all these different kinds of evidence, which he carefully weighed, he explained his conclusions on each, all of this gets to the core question of why we are here today. He looked at them within the context of how they inform the potential NDMA exposures related to Ranitidine use.

For those reasons, your Honor, and all the reasons explained in our papers, the motions against Dr. Hatten should be denied.

THE COURT: Okay, thank you very much. We are at 126.

MR. SHEEHAN: All right. We should be good to go. I will try to be brief in the interest of time. Tom Sheehan on behalf of the Defense.

If we could bring up the slides for Dr. Terry. I was told we were good to go, and yet here we are. Okay. I think I will get into it, your Honor -- oh, my gosh, there is a ghost in the machine when I get up here I guess.

I am speaking on behalf -- I am going to defend the motion against Dr. Terry.

Go to the next slide, please.

Dr. Terry, I will not belabor her qualifications, she heads up the Comprehensive Cancer Institute at Columbia University, she's on the board of scientific advisers for the National Cancer Institute. Obviously her qualifications to

opine are not challenged here.

She offers the opinion that, after reviewing the epidemiologic evidence, there is not support for a valid association or causal relationship between use of Ranitidine and development of any of the five designated cancers, much like other experts you have already heard about.

Next slide, please.

What are the challenges then? You have heard many of the same criticisms, Plaintiffs allege that Dr. Terry ignored NDMA studies, that she ignored limitations in the Ranitidine epidemiology studies relating to dose, relating to length of followup, duration, that type of thing. And finally, there is sort of an individual attack on Dr. Terry related to a supposed inconsistent approach to case control studies.

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So, with respect to ignoring NDMA data, you know, it doesn't take much to look at a report and see she that evaluated the NDMA data. She spends about 25 pages going through it, and when you get right down to it, the Plaintiffs don't like her interpretation of that data. Much like the scientific community at large, much like regulators, she basically offers the opinion that those data, two-fold.

They do not provide reliable evidence to establish that exposure to NDMA in either the diet or occupational setting is a cause of human cancer, but more importantly, you

can't take those studies and extrapolate from them to draw reliable conclusions about cancer risk with Ranitidine use.

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This is very, very similar to what the EMA determined when they looked at this data. The Plaintiffs cite to the EMA document in their challenge to Defense experts, but what they don't provide the Court is the interpretation that EMA had of the exact same body of data.

The EMA looked at exposure to NDMA in the diet, they looked at exposure to NDMA in occupational settings like Hidajat. In fact, they looked at 33 separate studies evaluating exposure to NDMA separate and apart from anything to do with Ranitidine.

What did they find? They said definite conclusions cannot be drawn at this stage. Effect sizes and especially dose response relations should be interpreted with great caution, and they called for further research. That is just with respect to NDMA itself, again, nothing to do with Ranitidine.

What does EMA then say about how to assess cancer risk with Ranitidine?

If we could go to the next slide.

They then go on to say there is a way, a method to reliably assess cancer risk with Ranitidine, and here is what you should do. You should focus on Ranitidine specific

epidemiology. You should employ methodologic principles that we have listed here. You should compare Ranitidine to an active control, like an H2RA or a PPI. You have heard it ad nauseam at this point, that is the best way to control for confounding that relates to the underlying conditions for which these medications are prescribed.

You should employ a lag time. You should evaluate reverse causation and protopathic bias and confounding within these studies.

The reason I bring this up, your Honor, is because this is the methodology that EMA set out to investigate, whether or not there is an increased risk of cancer with Ranitidine use. It is exactly the methodology that Dr. Terry employed when investigating that same question, much like other Defense experts.

Go to the next slide.

So, what is the next claim? That she ignored limitations in the Ranitidine studies.

Go to the next slide.

I think even a cursory glance at a report, you know, sort of belies this allegation of ignoring certain features. So, Dr. Terry provided at the end of her report a table that listed various methodologic considerations and study design features for all of the Ranitidine studies that she evaluated, and you can see across the top here she looked at how those

studies assessed exposure.

She looked at how long those studies followed patients who had been prescribed Ranitidine. She looked at whether there were any analyses done to assess intensity of exposure or duration of exposure, and she listed and evaluated all of the confounders for every Ranitidine epidemiology studies.

We have a couple of questions here. These are basically the allegations that were put forth by Plaintiffs, that Dr. Terry had assumed higher exposures or longer followup periods, or cherry picked certain confounders to analyze. What is the answer to that question?

If we could go to the next slide.

I am hoping it is -- it is a no, she did not cherry pick anything to analyze.

If we could go to the next slide.

So, how did she apply this? It is true, your Honor, that there are studies that assessed exposure differently. It is true that there are studies that within their database followed patients for shorter or longer periods of time, and that actually provided reassurance to Dr. Terry that there was no signal of increased risk associated with exposure to Ranitidine.

She actually looked at that and said, hey, this study -- for example, I think we heard about Iwagami earlier today -- had a shorter median followup. There are studies like

Adami or Norgaard that have longer periods of followup, 15 years. If you extend it out to the absolute maximum, over 20 years in some cases.

Nowhere across those different methodologic features, different ways of assessing exposure, different ways of assessing duration of use, was there any consistent signal of even an association between use of Ranitidine and any of the five designated cancers.

Go to the next slide.

So, what is the last claim? I won't spend a lot of time on this. They say she approached case controls differently with respect to Ranitidine litigation than she did in an interview or a lecture that she gave.

Go to the next slide.

And she explained very clearly at her deposition that case control studies have their place, and they can be very useful under certain circumstances if you can reliably execute them.

So she gave the example, if you are asking a woman who gave birth whether she breastfed her child, that is a very different construct methodologically than asking that same woman how much broccoli did you eat six months ago, a year ago, five years ago. It is very exposure dependent. It is also very dependent on the magnitude of the association.

Where you have small risks, like we do here, 1.2, 1.4,

1.6, that type of thing, those are exactly the types of risk estimates that are subject to the biases that are inherent to the case control design, and that's exactly why the World Cancer Research Fund elevates cohort study designs over case control study designs in evaluating dietary factors and cancer risk.

THE COURT: So that is 1:35. I misspoke when I said 1:45. You allotted yourselves an hour and 35. So it is 1:35 now. If I have confused anyone -- are you the last speaker for the Defense or are there others?

MR. SHEEHAN: I have one more expert to do. I can do it in a matter of just a couple minutes honestly.

MR. BOEHM: Your honor, I believe each side had a total of one hour and 40 minutes, unless that was changed.

THE COURT: That is fine. The agenda I have says 10:40 to 12:15, but you think it is 1:40?

MR. BOEHM: That is my understanding.

MS. FINKEN: Your Honor, in the revised schedule you changed it and took five minutes off each side on this motion.

THE COURT: Okay. I know there has been some back and forth. Why don't you try to get through your presentation and whatever additional time you get in, the Plaintiff will be given as well.

MR. SHEEHAN: Okay. For all the reasons I have explained, the motion as to Dr. Terry should be denied.

If we could pull up the next section here, Dr. Wang. As I said before, he is not the author of the Wang study.

THE COURT: State clearly on the record which doctor this is so there is no confusion.

MR. SHEEHAN: I am defending the motion against Dr. Timothy Wang, Defense expert.

Dr. Wang is very well qualified, and he combines two areas of expertise, really he is a clinician, treats patients with gastrointestinal diseases, and he is a cancer researcher that looks at the biological mechanisms specific to gastrointestinal cancers.

Go to the next slide.

He offers the opinion, much like other Defense experts, that there is not evidence supporting that therapeutic use of Ranitidine causes any of the GI cancers being alleged.

Next slide.

This is just for your information, your Honor, there is a lot of opinions that he offers that are simply not challenged. For example, he looked at all of the Ranitidine lifetime animal carcinogenicity studies, and he did that because that is the exposure of interest here. Animals given high doses of Ranitidine over their lifetimes did not develop cancer.

He looked at whether there was evidence that Ranitidine caused a mutagenic effect in like test tube in vitro

type studies. It didn't, and offered those opinions. Those are unchallenged. In fact, all of the opinions here are unchallenged.

If we could go to the next slide.

So they claim certain challenges to Dr. Wang's opinion. I don't think you heard a lot about them today during the argument. For example, they didn't articulate the challenge with respect to a threshold level of NDMA in animals. I will quickly go over it.

Dr. Wang -- keep going.

Dr. Wang evaluated that issue looking at the animal data to see where there is actual evidence of a statistically significant difference in tumor formation in animals versus those animals that did not get NDMA. Lo and behold, you needed to get to 65,000 nanograms per kilogram per day before you would observe a statistically significant difference in the rate of tumor formation.

In these studies, such as the Peto study, they examined much lower doses, but they did not observe a statistically significant difference at those lower doses. Obviously that is the basis for his opinion with respect to the level of NDMA required to induce tumor formation in animals.

Next slide.

They say that his opinions about the monkey studies, the primates, are wrong.

Go to the next slide.

Plaintiffs are just wrong about this. The study authors themselves clearly state all of the compounds except DMNA -- that is just another acronym for NDMA -- were hepatocarcinogens, caused cancer in the liver of the monkeys. They specifically call out NDMA and say that didn't happen.

So the Plaintiffs next approach is to say, well, in 2002 the WHO said all animal species. You can take a look at that document for yourself, your Honor. The WHO document from 2002 actually articulates the species where cancer was observed. It does not include any primate species, and it's not just mice, rats, and hamsters, but I will freely admit there are other animals, there's frogs, there's newts, there's amphibians.

They simply don't address the primate data in any way, shape, or form. There is not a single reference or citation to any of the primate data, so that is a bit of a red herring there.

Go to the next slide.

They say his levels about endogenous NDMA, this is again separate and apart from anything to do with Ranitidine, just background levels. You and I sitting here are probably generating some level of NDMA just as natural human physiology. Dr. Wang offered opinions about those levels based on the data.

If we could go to the next slide.

He freely admits that they are variable, that they are estimated, but the important point, your Honor, is that the primary route of exposure -- we can see down at the bottom of this slide, the Plaintiffs cite to this document, the ATSDR report, the draft document from 2022. The primary route of exposure to NDMA is through endogenous production, again, nothing to do with Ranitidine at all.

Where there is no evidence that ingestion of Ranitidine contributes to endogenous formation of NDMA, setting that aside, the primary route through which human beings are exposed to NDMA is just natural human physiology.

If you could go to the next slide.

Finally, they say his Bradford Hill analysis is not reliable. I won't belabor this point.

Next slide.

You have heard from numerous people today you don't even get to Bradford Hill if you don't have a reliable valid association. Plaintiffs complain that he failed to consider the non-Ranitidine epidemiology, not true. He considered it.

Like many, many others, he determined, number one, that it did not rise to the level of a valid association between exposure to NDMA and dietary and occupational studies in development of cancer. Number two, it is not appropriate to apply that data to draw conclusions about Ranitidine.

He also considered the Ranitidine data, did not see a

valid association. There was no reason to apply Bradford Hill. He did it again in response to the Plaintiffs' experts. There was no consistent association, no magnitude of association, not even temporality, given some of the designs where you are unsure whether protopathic bias is at play.

For those reasons, his Bradford Hill analysis was entirely reliable and the challenge to Dr. Wang should be denied.

Thank you, your Honor.

THE COURT: Thank you very much. The Plaintiffs can take some additional time if they want, if you need it. You are otherwise allotted ten minutes for your rebuttal. So if you need some more time, that is fine.

MR. SNIDOW: Good afternoon, your Honor. Do you mind if I have my laptop up here?

THE COURT: That is fine. I have mine here.

MR. SNIDOW: I want to start with their experts. Counsel said that I waited too long before getting into it the last time, although I might ask why they had slides about Dr. Moorman and Dr. McTiernan in their deck, but this time I will start with theirs and then go to some of the more general themes.

What I noticed in their presentation, and perhaps the Court did as well, is that they were very long on talking about what their experts' conclusions were and how well supported

their experts' conclusions were in the medical literature, but you heard very little on why the methodologies that they employed were reliable under Daubert.

The reason why that is important, your Honor, is of course, as we keep emphasizing, Daubert is about methodology. Perhaps if their experts had employed different methodologies and, frankly, done a more careful review, they could have still given some of the same opinions, but that is not what they did.

If I could have my slide deck up, please. Might not get it.

MR. SHEEHAN: Now you feel my pain.

THE COURT: You can keep talking until it comes up.

MR. SNIDOW: I will. I was going to show the slides. You have heard no explanation for the slide that I showed about why it is appropriate to make a one paragraph Bradford Hill analysis that lumps all cancers together. We heard no explanation of why it is okay to spend just one paragraph on these very complicated studies and not talk about the limitation hardly at all.

We heard no explanation at all, at all, of why ten prescriptions automatically means ten years of use, and that is because it doesn't. That is something that their experts used as an assumption in their opinions.

We heard no explanation of how active comparators indirectly control for any confounding. We heard not

explanation of why a reliable expert would rely on a study about Valsartan from before Valsartan was contaminated with NDMA. We've heard no explanation of how an expert can review 500 studies in under two minutes per study.

The reason I am focusing on this stuff is because this is about the methodologies. I know at some point these types of hearings can start to sound like people sniping at each other and nitpicking experts.

What I want to emphasize is there is a categorical difference between the kinds of criticisms that the Defendants make about our experts and the kinds of criticisms we are making. They are attacking our conclusions. We are attacking their methodologies and that is fundamentally different.

I will take Bradford Hill as an example. I pointed out how short their Bradford Hill analyses are and how, frankly, cursory.

The only response that I heard from them is, I think a fair characterization, something like, well, we didn't have to do that anyway. That is fine. If they didn't think they had to and didn't want to include that in their expert report that is up to them, but the fact is they did include Bradford Hill analyses in their report.

Counsel said there is no Bradford Hill without an association. Apparently there is because it is in all of those expert reports, they are just not very detailed and they just

don't analyze the literature in a way that allows them to do it reliably.

Under Daubert, if you are going to apply a methodology, you have to do it reliably. You don't have to do it if you don't want to, but if you do, you have to do it reliably.

Turning to threshold dose, counsel said that I said two things about threshold dose that I want to clarify. The first thing he said is that I said that it was irrelevant. I want to pull up slide 39 and make this crystal clear, because I hope I didn't say that and it is not what I meant to say.

Slide 39, please.

Right. What I said was, no, threshold dose can be relevant in a case where the evidence shows that all of the Plaintiffs took a dose that is well below even the minimum theoretical dose. My point was just that it is not this case. It is relevant perhaps in other litigations, just not here.

The second point was he said I didn't show any case law on this issue of threshold dose. I want to make clear that is not accurate either.

If I could go to slide 36.

This Schultz case is directly on point. What they are criticizing Dr. McTiernan and Dr. Moorman for is what is going on in that second bucket, for having an opinion about what the theoretical minimum dose of NDMA that could pose a cancer risk

is. Again, there is an academic debate about that, I am not going to get into it because I, frankly, don't think I have to.

Yes, our experts, and a number of other authorities, have the opinion that if you want to know the truth, the real threshold dose is very low. This is not the only substance that works that way. It is true of a lot of carcinogens.

One example is actually ultraviolet sunlight. Scientists -- obviously if you stay out in the sun a long, long time it increases your risk of cancer. Scientists, if you look, say ultraviolet light, there might not be a threshold. That is obviously at the small limit, it is a theoretical possibility, but that is what is going on in the second box.

Next slide.

I don't think there is any way to get around this case law because it's crystal clear. The Schultz Court looks at that second box about the opinion that the threshold is very, very low or nothing, and says although it is unnecessary, that doesn't mean that the experts' opinion should be excluded.

Again, that makes perfect sense in a world where we know, as we do here, that the Plaintiffs in this actual MDL took doses that were much, much higher, not just in zero, not just in the theoretical threshold, but doses demonstrated in the medical literature to increase the risk of cancer.

Now, counsel says on active comparators that we categorically don't like them, we are opposed to active

comparator studies. I want to make clear that is not true. Active comparators are useful to the extent that they are well designed and to the extent that they answer the actual question presented. But there are a couple -- on the point of active comparators, we don't think it is the only thing that you should focus on, but we agree they are useful.

What counsel said was, and I'll quote here, they don't have any association at all between human Ranitidine and any dose at all, and they also said that we have to look at what happened out there in the real world, and we have to look at studies that, in their view, "inherently account for dose of NDMA," by which they mean active comparator studies.

Let's look at slide 46.

This is Cardwell, this is out there in the real world. This is a study that is human Ranitidine data and includes dose. This is a study that apparently inherently accounts for the amount of NDMA that people consumed.

What it showed for bladder cancer is that when people took more than three years, they had a 43 percent statistically increased risk.

Counsel said he didn't want to get into null hypothesis, he thought it was too wonky. I am happy to spend a few words on it. When the study here says that it is statistically significant, what it is saying -- I don't think you will hear any dispute about this -- is that the authors

were able to rule out the null hypothesis. That is 1 in the confidence interval there you see in parentheses.

So, it is actually not true. Sure there is a null hypothesis. In Cardwell they were able to rule it out, and you see that by the fact that that 1.05 there is greater than 1.

Slide 47.

The Wang paper confirms this result. This is an active comparator analysis done in Wang. This study shows actual dose. This study shows -- this study "inherently accounts for the dose of NDMA," as Defendants put it. What they are saying there is whatever the dose of NDMA that can cause cancer is, that dose has to be embedded in Ranitidine. Well, if that is true, the people who took Ranitidine in this Wang study took that dose and we know what happened. For people who took it for just 90 days, they go a little bit more cancer. For people who took it for six months, even more cancer, and people who took it for nine months, even more cancer, and after a year that gap is large.

The other thing I meant to point out about this chart this morning and just forgot is this X axis, the line there at the bottom, the one that ends at 18. What that is showing is years of followup. That is the other point that we keep coming back to.

What we have to understand about this literature, the longer you wait when looking at patients, the greater that risk

shows in this gap, and does your Honor see where it says 3 there at the bottom? That is the risk after three years.

You can probably tell where I am going with this. If you cut the Wang study off at three years and only look at what happened, you probably see some small difference in risk, but it is, frankly, not very big.

It is only until you wait until the full followup periods are established that you really see that, yes, it is true that people who took Zantac for more than one year got a lot more cancer than people who took it for shorter periods of time, and certainly more than people who didn't take Zantac at all.

That, of course, is the problem that we identify with the active comparators the Defendants brought up. It's not that active comparators are bad, it's not that they don't reduce confounding somewhat. They definitely do those things.

If I could have slide 83.

But what active comparators do not fix are problems like these. You can compare Ranitidine to people who didn't take Zantac, or you can compare it to a PPI, or you can compare it to an H2 blocker, or whatever drug you want, but if you are looking at patients who didn't take Zantac for very long and you have a Plaintiff population, some of whom took Zantac for a very long time, it is just not answering the question.

The same thing with followup, if you cut off this --

not cut off. If you have a median followup of 2.4 years in a study, that is really not telling you very much about what happens after ten years, 15, or 30 years of followup.

Counsel asked for a citation for the proposition that poor followup time, poor exposure information can -- even studies that have those features, when they do show up it shows -- it means that there might be even greater association. I want to show two points on that.

The first is on slide -- sorry, not a slide, it's a citation to the reference manual. In the reference manual, on pages 589 and 625, or I know your Honor sometimes does control F for certain terms, if you control F for bias toward the null, you will see discussions on this.

I know I am running out of time, but I want to be clear on one thing because we will get to this in a moment.

What I actually said was there are certain types of ways in which studies are poorly designed where if you do see a signal that means that there might be something even greater there. Those types are the following things:

If you have poor exposure classification, if you have short followup time, and if you have non-differential misclassification, if you are just not categorizing the Plaintiffs very well.

If you look at those kinds of studies that are not accurately capturing the signal from the noise and you still

see an association, that is very powerful. If you don't see an association that doesn't mean that there isn't one necessarily, because a better designed study might have picked it up.

There is one exception to that that I want to lay down because I don't want to be accused of misstating it, and that is when you have confounding. If you have confounding -- she is right about the coffee and the tobacco and the cancer stuff. If it is true that coffee drinkers smoke more and you compare people who drink coffee to people who didn't drink coffee and you measure cancer outcomes, you are going to think that coffee causes cancer, even though it doesn't.

But, and there is an important but here, all the evidence we have suggests that in this case it cuts in the other direction. On that, I want to show slide 104.

What we are almost certainly dealing with, based on the limited data that we have, is a situation where the people who took Zantac actually smoked less. It is the opposite of the coffee situation.

If you want proof on that just look at the next slide, or maybe the one before, 103. These are the results from the Kim study, which is one of the few that actually had data on tobacco use. What this it shows is the opposite of the coffee example. People who took Ranitidine smoked less than the people who took Famotidine. That is going to make Ranitidine look safer than Famotidine for reasons that have

nothing to do with whether Zantac causes cancer or not.

I will close with slide 121.

Returning to our criticisms, if you start out answering a different general causation question, that is a problem under Daubert, and a methodological one. If you fail to consider and assess all of the evidence carefully, that is a problem under Daubert. If you fail to carefully review the evidence, that is a problem as well.

If Defendants' experts had answered the right question and applied more reliable methods, they probably still could have reached some of the conclusions, but they didn't, and for these reasons we ask that you exclude them.

Thank you.

THE COURT: All right. Thank you.

Have we settled on 45 minutes for lunch? Okay. Let's make it even, let's call it 40 minutes, and we'll say 1:30. We will be back at 1:30 and pick up from there.

Have a good lunch.

(Thereupon, a luncheon recess was taken.)

THE COURT: You may be seated.

All right. I am going to ask a few questions. I know we are a little tight on time so I might stop and pick them up later if we have time. We have a lot of different parts of the schedule this afternoon for some questions.

Okay. So this is going to be for both parties, so

both of you listen carefully, and when it is time for one of you to answer you can come to the podium.

I have to state a preface first, so bear with me.

Plaintiffs, in your briefing you rely upon regulatory agency findings and methodologies in assessing causation for NDMA and Ranitidine. For example, in your omnibus motion, on page 75, you criticize Defense expert Dr. Witte because, as you argue, he did not rely upon human studies of NDMA.

You assert that his methodology is not permissible and support you assertion by stating that, quote, "The FDA obviously did not consider only studies focused on Ranitidine in deciding to pull Zantac from the market," end of quote.

You also cite to findings by the World Health Organization's International Agency for Research on Cancer, IRAC, and the National Toxicology Program, NTP. That is your motion at page 11.

Defendants, in your response you state that, quote, "Plaintiffs' approach to epidemiology wrongly conflates precautionary regulatory standards with the scientific rigor required by this circuit in a causation analysis," end of quote. That's at Docket Entry 5968 at 47.

I did ask both parties to come prepared today to discuss case law regarding regulatory thresholds and the role of agency findings in assessing causation. The Eleventh Circuit has clear case law regarding the role of regulatory

findings in assessing causation.

In the case Williams versus Mosaic Fertilizer, LLC, 889 F.3d 1239, Eleventh Circuit, 2018, the Eleventh Circuit cautioned against what they described as the methodological perils of relying on regulatory thresholds to establish causation. That's at pages 1246 to 47.

The Court explained that the biggest problem stems from the potential difference in purpose between regulatory standards and toxicological dose response calculations. Regulatory standards often build in considerable cushion in order to account for the most sensitive members of the population and prophylactically protect the public; in other words, they are protective, while dose response calculations aim to identify the exposure levels that actually cause harm; in other words they are predictive. That's at page 1247.

Likewise, the Eleventh Circuit in McClain versus Metabolife International, Inc. 401 F.3d 1233, Eleventh Circuit, 2005, explains the agency approaches, and specifically the FDA's approach, differ from the analysis of causation in a courtroom because "the FDA will remove drugs from the marketplace upon a lesser showing of harm to the public than the preponderance of the evidence or the more likely than not standard used to assess tort liability."

The Court in McClain clarifies that it, quote, "is not rejecting public health rules from consideration in a Daubert

analysis," and clarifies that, rather, the trial Court needs to understand the meaning of agency rules, 1249 to 50.

For both parties, Plaintiff first, then Defense -- and you can answer from your desk, just speak into the microphone because I am going back and forth.

Do you agree that, under Eleventh Circuit case law, regulatory threshold levels and regulatory findings regarding public health are made using a lower burden than the preponderance of the evidence standard required in this courtroom for establishing causation?

MR. SNIDOW: Your Honor, this is JJ Snidow for the Plaintiffs. We do agree. May I elaborate?

THE COURT: You agree?

MR. SNIDOW: I do.

THE COURT: Defense, do you agree?

MR. BOEHM: Yes, your Honor, we do agree.

THE COURT: Okay. Back to the Plaintiff, do you agree that the Eleventh Circuit has determined that regulatory standards are not intended to serve the purpose of establishing exposure levels that actually cause harm, but rather, are usually overly cautious in order to protect the public?

MR. SNIDOW: I think it depends on the substance at issue, your Honor.

THE COURT: Okay.

MR. SNIDOW: If you want a little more, I can provide

it.

THE COURT: A sentence more.

MR. SNIDOW: I would say I think there was an adjective that was usually or generally in there that you read. I think that's correct.

THE COURT: Yes.

MR. SNIDOW: Obviously, we are not arguing that just because the FDA pulled Zantac from the market that is by itself enough evidence of general causation, which I think is probably what the Court is getting at. It is obviously not. We are not saying, look, they pulled it from the market, there is nothing else to do. We wouldn't have done the expert reports if that were enough.

THE COURT: Okay. From Defense.

MR. BOEHM: Your Honor, we certainly agree with the fact that a recall or a withdrawal would not constitute reliable evidence under 702. Beyond that, I don't think that is all that these cases state.

They state that there is a different standard that regulatory agencies are applying in contrast to the one that the Court applies in applying Rule 702 analysis, that they are distinct and different and have different purposes. It is not just as to a recall, but it is a more robust case law on that point.

THE COURT: Okay. Thank you.

Plaintiff, in your slide you cite to the hearing transcript from Valsartan in New Jersey, 2022, in which Judge Kugler asked the Defendants to explain why there was a recall by Government agencies if, as Defendants claim, there was no association between NDMA and cancer. Judge Kugler confirms that "the association element has been clearly demonstrated both through all the action by the Government agencies and through the words of the Defendants themselves."

For the Plaintiffs, can you explain how you reconcile Judge Kugler's opinion, which is from the District of New Jersey, with the Eleventh Circuit's precedent?

MR. NIGH: Your honor, I would start out by saying that in the Valsartan decision Defendants made all the same arguments that they have made here, many of the same arguments on not to look at NDMA literature, our arguments on threshold, we have calculated lifetime cumulative exposures.

All the same arguments were well briefed, and there are many more statements in that transcript, and all those Defendants' arguments were denied.

Now, specifically on this point, the question on association, it is not just the regulatory statements, but it is also the statements that were made by company witnesses and some of those same sort of things we have at play here where company witnesses have recognized that NDMA itself is a carcinogen.

So, we do believe that there is association here on that, but we have way more evidence here as well on association, and that was presented thoroughly here this morning.

THE COURT: Thank you. Any response from the Defendants?

MR. BOEHM: Your Honor, we take it that the premise of the question is one that we would agree with, that Judge Kugler was not applying Eleventh Circuit law in reaching his determination in that case.

THE COURT: Okay. I am going to go back to Plaintiffs for a moment. You focused on, it seems from the statement I read, not on the Government agency portion of what he said because that would not necessarily be consistent with what you have just agreed is Eleventh Circuit law. So, is the emphasis there on the words of the Defendants themselves, and is that consistent with Eleventh Circuit law to satisfy Daubert, what company witnesses say?

MR. SNIDOW: Well, a couple things. One, in our view, the Third Circuit law on this point is nearly identical to Eleventh Circuit law. I think that the Hardeman Court in the Ninth Circuit --

THE COURT: Use the microphone.

MR. SNIDOW: Sorry. If the Court looks at the Hardeman versus Monsanto opinion from the Ninth Circuit, there

is that paragraph where it talks about Defendants' arguments that the law in different circuits is more or less leaning on Daubert. What the Ninth Circuit there says is that the Ninth Circuit law on Daubert is the same as the Eleventh Circuit and the Third Circuit. So, I don't think there are materially different Daubert rules between the circuits.

On the Court's general question about the importance of regulatory agencies, just two points. One is WHO and IARC are not actually regulatory bodies. The FDA, of course, is.

The second point is, we are not relying exclusively on the FDA's recall or, frankly, even what the FDA has said, but those are obviously relevant. It's relevant both what the FDA said about Zantac and what the FDA said about NDMA when evaluating Zantac, and that is, of course, what we say the Defendants should have done. They should have certainly considered the underlying NDMA literature, that it is relevant, and they didn't.

THE COURT: Are you familiar with any Eleventh Circuit case that says that the law in the Eleventh Circuit is the same in other circuits, or any other circuit case that analogizes to the Eleventh Circuit offhand?

MR. SNIDOW: Not offhand, your Honor. Hardeman qualifies for everything you have asked for except it being from the Eleventh Circuit. I don't know of an Eleventh Circuit analog.

THE COURT: Okay. Thanks. Defense, your position on regulatory standards, relevant or not relevant to the question of general causation?

MR. BOEHM: Certainly how the regulatory community, alongside the scientific community, more broadly approach the scientific question informs the general acceptance prong of the reliability analysis under Rule 702. That is part of what we were saying about Defendants' experts, that the methods that they apply, the approach that they take in evaluating the relevant data here is consistent with those that are used and applied by the broader regulatory and scientific communities, and that is an indicia of reliability under Rule 702.

In terms of regulatory findings, decisions to, for example, take the product off the market or take other precautionary measures, that in the Eleventh Circuit has been found to be a separate analysis, one that is fully distinct from the Daubert trilogy that this Court undertakes in assessing reliability of experts' testimony in litigation.

THE COURT: Thank you. Plaintiffs, on pages 103 to 104 of your omnibus motion you argue that Dr. Guengerich's opinion that there are threshold levels of NDMA below which Ranitidine does not cause cancer in humans is flawed. You explain that Dr. Peto concluded otherwise and found no indication of a threshold.

In the next sentence you state, "The FDA utilizes a

non-threshold linear dose response methodology based on the Peto data to calculate an acceptable daily limit, ADL, for NDMA of 96 nanograms a day."

Can you explain further how the FDA's calculation of the acceptable daily limit of 96 nanograms a day supports your argument that there are no threshold levels of NDMA below which Ranitidine does not cause cancer?

MR. NIGH: Your Honor, those are really two different ideas, but the idea of a threshold means is there any -- is there a level as to which below it there is no increased risk at all. The 96 nanograms is an acceptable increase risk that the FDA has stated, but they don't say there is no risk at 96 nanograms. In fact, they have multiple FDA statements where they recognize that they would there be no NDMA in the medications, but they are going to set 96 nanograms as the acceptable risk.

THE COURT: Okay, thank you. Plaintiffs, let's see, in your reply and your presentation this morning you cite to a hearing transcript from Valsartan to argue that NDMA which has been found in Ranitidine is the relevant toxin in this litigation. That is at Docket Entry 6011, at page 31.

You also cite to Burst versus Shell Oil Company, 2015 WestLaw 3755953 in support of the proposition that studies of NDMA are relevant to the carcinogenicity of Ranitidine.

In Burst, on page 9, the Court states, "Because

Benzene is a known human carcinogen and because all gasoline contains Benzene, the Court recognizes that literature pertaining to Benzene is generally relevant to the causation question at issue."

This first question is for the Defendants.

Is it your argument that NDMA is not generally relevant to the question of whether Ranitidine is carcinogenic, that is, do you concede that the question of whether NDMA is carcinogenic is relevant to the question of whether Ranitidine is carcinogenic or not? What is the Defendants' position on that?

MR. BOEHM: We'd have to concede that there is some level of relevance. The point that we have made is that it is not enough. Even if you establish that fact, it is not enough to meet the requirements under Rule 702 for reliability as applied by Courts in the Eleventh Circuit, which very specifically indicate you have to look at exposure to the drug and it would be too great a leap of logic, it would be too great an analytical gap to extrapolate based on NDMA data, shoving aside the existing robust database of Ranitidine epidemiology.

THE COURT: Okay. Plaintiffs, in Burst the Court goes on to state the following on page ten: "The Court finds that although evaluation of the Benzene literature is generally relevant to Dr. Infante's ultimate opinion, it alone cannot

provide a reliable basis for Dr. Infante's opinion. While seemingly all scientific authorities recognize Benzene as a carcinogen, none recognizes gasoline as a carcinogen and Defendants have offered several justifications for why exposure to Benzene in gasoline should be evaluated differently than exposure to Benzene generally."

The Court ultimately finds that the Benzene studies alone did not provide sufficient grounds to support the expert's general causation opinion.

Can you explain why the Defendants' expert's reasons why exposure to NDMA from dietary and occupational sources should be evaluated differently from exposure to NDMA in Ranitidine, why that is not an acceptable justification such as the one in Burst for why exposure to Benzene in gasoline should be evaluated differently than exposure to Benzene generally?

MR. HEINZ: Yes, your Honor. Noah Heinz for the Plaintiffs.

I would say that the type of explanation in the Burst case was about competitive inhibitions, so that they said it is not just a question of the amount of Benzene, which if you are just talking about the amount, you could look at Benzene specific literature addressing that.

The issue was that within gasoline it was counteracted by Toluene, and so was not carcinogenic in that context. The Defendants' experts, to my recollection, do not provide any

similar explanation for why the NDMA in Ranitidine would act differently. All they say is that there is too little in it.

To the extent you are talking about the amount, you should still look to the NDMA literature to see how much NDMA you need.

It is also notable that I think a lot of the experts, I'm not sure if all of them do, but certainly many of them say they don't know how much NDMA is in Ranitidine, so the nature of the justification is much smaller in this case as compared to Burst.

THE COURT: Thanks. Any response from Defense?

MR. BOEHM: Just, your Honor, that the form of reasoning by analogy that we just heard from Mr. Heinz and that we have heard at other points in our discussions and in the briefing is in cases like Abilify and McClain and others in the Eleventh Circuit found not to be reliable under Rule 702. You cannot make that leap. It is reasoning by analogy, it is not evidence as to the actual drug at issue.

THE COURT: Thank you. I will try to get in two more questions and then I'll pause, and then if we have time at the end, I might pick up some more of these questions.

For Plaintiffs, in your reply and in your slides you explain that a District Court's role at the Daubert stage is not to evaluate experts' conclusions, the credibility of opposing experts, or the persuasiveness of competing studies.

You state that, rather, the Court's role is to assess whether experts employed a reliable methodology, at Docket entry 6011 at 27.

You are correct that the Court's role is not to evaluate the persuasiveness of any study, nor the conclusion as to the credibility of any expert.

Do you agree, however, that in order to fulfill the Court's role of evaluating the reliability of the methodologies followed by the experts in this litigation the Court needs to examine the studies each expert relies upon to determine how the experts reach their conclusions and whether it was reliable to reach the conclusions that they did based on the literature, and that this process is different than considering the persuasiveness of the studies or the experts' conclusions because it looks at the process of how and why the conclusion was reached, not the persuasiveness of the conclusions or studies themselves?

MR. HEINZ: Yes.

THE COURT: Defense, do you agree as well?

MR. BOEHM: We agree as well, your Honor.

THE COURT: Okay. Plaintiffs, in your slides and in your omnibus motion at Docket Entry 5841 you quote In Re: Abilify, 299 F.Supp.3d 1291, at 1311, Northern District of Florida, 2018, stating "A scientific methodology that turns on weighing the totality of the evidence is reliable only if the

expert considers all available evidence carefully, and explains how the relative weight of the various pieces of evidence led to his conclusion."

In your reply you argue that "only Defendants' experts consider less than all the evidence, gerrymandering the studies in a manner at odds with how IRAC, the WCRF, and their ilk approach causation." Docket Entry 6011 at 14.

You argue that Defense experts Drs. Chan, Witte, Terry, Vaezi, and Hatten "ignored" or "did not consider" -- and that is in quotes, ignored is in quotes and did not consider is in quotes from your brief -- the NDMA epidemiology.

In their response and in their presentation today the Defense argued that their experts, Chan, Witte, Terry, Vaezi, and Hatten considered all of the evidence, including NDMA studies, and that is at Docket Entry 5968, at 58.

Can you, Plaintiffs, explain what you mean by the terms "considered" and "ignored". Is your argument the Defendants' experts did not review the NDMA epidemiology at all, or that although they reviewed it, they did not rely upon it, or something else?

MR. SNIDOW: Yes, your Honor. Our argument is not, at least for most of them -- I don't have it in front of me. For most of them the argument is not that they didn't consider it in the sense of it doesn't appear in their report, they don't have it on their reliance list, something like that.

But to read Abilify fairly, the word "consider" has to mean more than just did you put it on your materials considered list. If the Court looks at the reports and depositions, especially if the Court compares those reports to the reports that our experts prepared, you will see a real difference in how thoroughly the experts considered the NDMA literature, and, frankly, the Ranitidine literature.

Our experts went through it in great detail with respect to the NDMA literature, their experts -- it varies expert to expert, but by and large didn't. Does that answer the Court's question?

THE COURT: Yes. Any brief response? Then we will move on.

MR. BOEHM: To the extent I just heard Plaintiffs' counsel, as I believe I did, concede that Defense experts did review the NDMA data, then we certainly agree with that, and we have discussed at length how they approached that data, and I won't repeat that now.

THE COURT: All right. Thank you. We will maybe pick up with some more epidemiology questions in a bit.

Now a bit off schedule, but hopefully not -- no one is going to miss their flight. I am going to end on time regardless of where we are for all of you to make your flights. Don't worry about that.

Now we will move into the Gibbons motion at Docket

Entry 5839. Is that where we are, just ten minutes?

MR. NIGH: Yes. i might take a little time for rebuttal.

THE COURT: You have rebuttal time, five minutes. Ten minutes now.

MR. NIGH: Can we go ahead and pull up the Gibbons slides.

THE COURT: State your name again for the record.

MR. NIGH: This is Daniel Nigh for the Plaintiffs.

Your Honor, I will argue that the Court should exclude Defendants' expert Dr. Robert Gibbons under Rule 702 and the Daubert line of cases.

Defendants offer Dr. Gibbons as a rebuttal witness against Dr. Davis' statistical analysis. Much of Dr. Gibbons' opinion is actually an attack on Emery Pharma's testing. Dr. Gibbons' opinions are predicated on pervasive misunderstandings of the facts of Emery Pharma testing. His methodology in reaching those opinions is thus unreliable and his opinions therefore should be excluded.

Next slide.

First, Dr. Gibbons critiques Dr. Davis' analysis for purportedly using too small a sample size, but Dr. Gibbons' opinion is based on a misunderstanding of Emery Pharma's testing. Dr. Gibbons' error is straightforward, he doesn't even know how large a sample size Emery Pharma used. For

example, in Emery Pharma's consumer experience testing Dr. Gibbons simply didn't know how many pills were tested.

"Question: Do you know how many total samples were run in looking at whether or not NDMA increases as a result of sun, shade, and shower? How many total pills were tested?" His answer is: "I believe it was a total of 25."

He is wildly off. In reality, the sun, shade, and shower study tested at least 400 pills and had over 200 observations of the average amount of NDMA. And the climactic zone study tested at least 150 pills and 80 observations of average amount of NDMA.

He was wildly off on the total amount of samples that he thought were tested, yet he criticized that issue. In fact, Emery Pharma tested substantially more than the FDA.

Dr. Gibbons' critique of Dr. Davis' statistical analysis thus ignores the facts in the record that show the significant sample sizes that Emery used in its testing. Because his opinion is disconnected from the facts, it should be excluded in its entirety.

Next slide.

Dr. Gibbons did not understand Emery's study design. Second, Dr. Gibbons critiques the study design that Emery Pharma used in its testing, but as Defendants concede, that critique is based on the failure to understand how Emery Pharma's testing was done, and this was found in the

Defendants' briefing at page eight where they quote, "although he carefully reviewed Dr. Najafi's report, it was unclear how Emery actually designed the experiments."

Defendants try to recast Dr. Gibbons' failure to understand Emery Pharma's testing as a problem with the testing. That places the burden in the wrong place. For Dr. Gibbons' opinion to be reliable it must be based on the actual facts of Emery Pharma's testing, not his false misimpressions of it.

Next slide.

Indeed, Dr. Gibbons' basic misunderstanding of Emery Pharma's pill testing undermines his opinion. For example, Dr. Gibbons' inaccurate guesses about Emery Pharma's sample sizes were the result of his failure to understand how that pill testing is conducted. He assumes that the ID numbers in Dr. Davis' report identify an individual pill that was subjected to all possible numbers of, for example, shower cycles, and that the same pill was tested after each number of cycles.

That is completely incorrect. As Dr. Davis' report explains, the ID numbers refer to the lot or batch number for a collection of pills. Because testing pills using LC/MS-MS necessarily destroys the pill tested, it can't be tested multiple times.

Emery Pharma tested multiple pills from each batch or lot. A different pill, and usually multiple pills, would be

tested after each different number of cycles, but the total number of pills tested was therefore much higher than Dr. Gibbons inaccurately assumed.

That is just one example of Dr. Gibbons' pervasive misunderstanding of how Emery Pharma's testing was conducted. Those misunderstandings undermine the reliability of all of his opinions, which should therefore be excluded in their entirety.

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In addition to these factual misunderstandings, Dr. Gibbons also levies entirely unsupported criticisms of Dr. Davis' statistical analysis likely because, as he admitted in his deposition, Dr. Gibbons has no experience running statistical analyses on results from pill testing whatsoever, and that led to many of these problems.

Next slide.

Next, for example, Dr. Gibbons critiques Emery Pharma for not using a random sample of pills in its testing. That purported requirement is inapplicable to pill testing, and indeed impossible to satisfy. Emery Pharma tested pills that it received from the Defendants. At that point Ranitidine had been withdrawn from the market.

Dr. Najafi testified at his deposition that Emery Pharma tested a sample of the pills that it received. It was impossible to test a random sample of pills that millions of people had already purchased and millions of people had already

ingested.

For that reason, GSK did not use a random sample of pills when it performed its root cause analysis, nor did the FDA use a random sample of pills when it conducted its own testing of Ranitidine, nor, for that matter, did any other laboratory that has conducted pill testing of Ranitidine.

Dr. Gibbons cites no source to support his unorthodox view that Emery should have used an impossible random sample, and he gives no reason whatsoever why that impossible standard should apply to Emery Pharma, but not to the FDA or to the Defendants themselves.

Dr. Gibbons' baseless opinion is thus inconsistent with widely accepted scientific practice and should therefore be excluded.

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Finally, Dr. Gibbons opines that Dr. Davis failed to perform a power calculation prior to Emery Pharma selecting the pills that it tested. That once again demonstrates Dr. Gibbons' failure to understand pill testing, a field in which he admits he has no experience.

If Dr. Gibbons understood pill testing he would know that a power calculation is not commonly set up beforehand to establish how many pills need to be tested, nor to extrapolate results to the population. For that reason, when the FDA tested the pills and reported the results the FDA did not

perform a power calculation before testing to determine how many pills needed to be tested to extrapolate the results to all Ranitidine pills in the market.

In addition, GSK, when testing for their root cause analysis that was later peer reviewed and published, also did not perform power calculations. Dr. Gibbons does not explain why Dr. Davis and Emery Pharma should be held to a novel standard that the FDA itself does not consider applicable to pill testing.

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Dr. Gibbons ignores the statistical tests that are applicable. As Dr. Davis opined, his results are statistically significant. Dr. Gibbons provided no response to Dr. Davis' P test regarding the sun, shade, shower, and zones consumer experience testing.

As Dr. Davis opined, all 25 slopes, 25 of 25, of Emery Pharma's consumer experience testing were positive in the shower test, that is, all 25 slopes show that the more heat and humidity that Ranitidine is exposed to, the more NDMA forms. The likelihood that all slopes would be positive by random chance is 6 in 100 million, which is a lower chance than getting hit by lightening in any given year. Dr. Gibbons does not refute this.

Because Dr. Gibbons' opinion regarding power calculations are disconnected from the generally accepted

practices in the field, it should be excluded.

Thank you, your Honor.

THE COURT: Okay, thank you.

And from the Defense.

MR. TOBEY: Good afternoon, your Honor.

THE COURT: Good afternoon.

MR. TOBEY: Danny Tobey on behalf of all brand Defendants. I will be presenting our opposition to Plaintiffs' motion against Dr. Gibbons.

Pull up the slide, please. Next slide.

So, at the outset, your Honor, it is helpful to frame what Dr. Gibbons did and didn't do.

As this Court is well aware, Plaintiffs hired a chemist named Dr. Najafi to perform pill testing on samples of Ranitidine to ostensibly detect levels of NDMA under various simulated conditions.

The Court has already heard Defendants' critiques of those chemistry methods, not least of which that Dr. Najafi used different testing techniques before litigation, and then once he was hired as a litigation consultant of course got different results as a consequence.

Plaintiffs also hired a statistician, and that doctor's name is Dr. Davis. His job was to take the outputs from Dr. Najafi and be able to extrapolate them through statistics to presumably all people or all Plaintiffs in the

case who took samples of Ranitidine.

Now, Defendants hired their own statistician, Dr. Gibbons, to review Dr. Davis' statistical methods and that is what we are here to talk about today.

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The first take home point, your Honor, is, like Drs. Salmon and Panigraphy, which you heard at the last hearing, Dr. Davis' model relies on the inputs from Dr. Najafi's testing. So, if Dr. Najafi's outputs, which become the inputs of these statistics, are unreliable, then these models are also unreliable, too. That is the core of Rule 702, that valid opinions must be based on sufficient facts and data.

If the Court were to strike Dr. Najafi's unique testing, the all the follow on models would also fall without further analysis.

Next slide, please.

We are going to put Dr. Najafi and his chemistry methodology to the side now and talk about statistics. Dr. Gibbons is a statistician, he is here as a rebuttal expert to talk about Dr. Davis, and what Dr. Gibbons did was point out several very, very basic statistical flaws when someone sets out to do what Dr. Davis did, which is create a statistical model that can be reliably generalized to a much larger population.

What did Dr. Gibbons point out? Dr. Davis did not use

random samples, he did not power his study for generalizability, he did not correct for false positives from multiplicity, and he treats related variables as independent.

Next slide, please.

So, what do Plaintiffs say in response? You heard a lot of this, Dr. Gibbons simply doesn't know what he's doing, he is unfamiliar with pill testing. Dr. Gibbons never said that, but in reality, Dr. Gibbons is a biostatistician. That is the same discipline that Dr. Davis is trained in.

In particular, Dr. Gibbons has received the Harvard award for lifetime contributions to the field of biostatistics, he received the Outstanding Statistical Application Award for Drug Safety Studies, and he actually authored the National Academy of Medicines's recommendation, which was adopted by the U.S. Congress and enacted by the FDA to create a statistical drug safety monitoring network. Needless to say, Dr. Gibbons knows how to apply statistics to pharmaceuticals.

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Plaintiffs then critique Dr. Gibbons and say, well, he didn't understand Dr. Najafi's testing methodology, so clearly he can't opine because he doesn't know these basic things.

This is a bit putting the cart and the horse in the wrong position. What they don't realize is, Dr. Gibbons was clearly criticizing the information that was missing from Dr. Davis' report that he should have had from Dr. Najafi in order

to make reliable assessments.

You can see this in the chart here, the things that they criticize Dr. Gibbons for on the right-hand side. Dr. Gibbons is actually saying I should have known these things, these things should have been available. He says there is a lack of any details on how these were collected by Dr. Najafi. They don't provide any specific information on how the samples were identified.

On the left-hand column, your Honor, you see that Dr. Davis doesn't know these things either. He says, no, I wasn't involved with that. Do you have any idea how those samples were chosen? No. He says, I don't know that, I have no way of knowing that. So, Plaintiffs can't criticize Dr. Gibbons, one, for pointing out that important information was missing that, two, their own expert didn't know. At the end of the day, your Honor, no one knows exactly what Dr. Najafi did.

Next slide, please.

So another critique that you heard here, your Honor, is that Dr. Gibbons criticized that the sample size is too small, and they say, well, he doesn't understand pharmaceutical statistics, but Dr. Davis said the exact same thing, your Honor. This is a trend, you have seen it in the last side and you see it in this slide, that often times they are criticizing Dr. Gibbons for things their own expert conceded.

Dr. Davis said many times the sample sizes were too

small. He had to amend his protocol post hoc because once he got the actual samples it was too small to analyze, extremely small sample size.

Next slide, please.

You also heard Dr. Gibbons was criticized because he didn't know the number of pills that were destroyed in the making of these chemistry analyses. That is a bit of a gotcha, your Honor, because the number of pills is entirely irrelevant to the statistical question that Dr. Gibbons was looking at.

As you know, your Honor, statisticians look at the number of observations, and observations have to be defined, and here Emery's spreadsheet and Dr. Davis' report said clearly, the spreadsheet includes one record for each unique observation as defined by batch or lot number. The observations were batches. If Dr. Najafi used two pills from that batch, or ten pills from that batch, or a hundred, it doesn't matter. What he ended up with was an average NDMA level for each particular batch.

That was the unit of currency that Dr. Davis analyzed, and therefore it was the unit of currency that Dr. Gibbons analyzed. As Dr. Davis said, from each observation in the data set, it is the average level from more than one pill tested from the lot number.

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Next, you just heard this from Plaintiffs, they

criticize that Dr. Gibbons was wrong for suggesting that basic statistical concepts like randomization and power calculations should not apply here, and Dr. Gibbons disagrees, for sure. He says, as a preliminary matter, it is important to note you can't generalize to a large random population if you start with a biased sample. That is statistics 101.

Likewise, if you don't do a power calculation, you have no reliable measurement of whether your results have the statistical power to be generalized.

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Plaintiffs kind of create a strawman, and I am not going to belabor this because the Court was just asking questions clearly delineating between what regulators do for a precautionary measure, such as a recall, and what scientists do when they are assessing biological truths, statistical generalizations, things where the actual numbers matter because you are going to be extrapolating from them to a larger population.

It is true, when the FDA wanted to answer a simple question, is there really NDMA in some lots of Ranitidine, they grabbed a few samples, they tested them, they found very small amounts, they likened it to amounts in food, but that is all they needed to know. Same thing with GSK, those were spot tests to see is there something here at all.

What did FDA do when it published a scientific study

where the results mattered because they wanted to generalize conclusions from those data to larger data? That is the Florian study. They randomized their sample so it would be generally applicable, and they calculated the power. The USP General, the U.S. Pharmacopeia says the exact same thing, when possible, use of a random process is considered the most appropriate way of selecting samples.

Dr. Davis is not here performing a precautionary regulatory function, he is setting up a framework where they can ostensibly extrapolate from Dr. Najafi's flawed chemistry to speculate about what any given Plaintiff might have taken in a particular pill, and that is where power and randomization and all those important safeguards come in because that is not a reliable methodology.

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Another critique that Dr. Gibbons made was Dr. Davis ran hundreds of experiments without correcting for the effect of multiplicity. Multiplicity sounds complicated, but it is actually really understandable in the sense of if you just run enough tests, eventually you are going to get some false positives. I like to think of it as throwing darts at a dart board. I could be the worst dart player on earth, but if I throw enough darts, some of them are going to land in the middle.

It is not an insurmountable problem. Statisticians

have ways to correct for multiplicity to say I have run this many trials, therefore I am going to adjust my parameters.

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Dr. Davis did not do that, and he specifically said in his protocol I am not adjusting for multiplicity. He knew the right thing to do, but he did not do it because he knew his effects would go away.

What did the Plaintiff say in their briefing in response to that? They said, well, goose, gander, glass houses, Dr. Gibbons did not even adjust for multiplicity when he conducted his own analysis. What Plaintiffs aren't realizing here is, Dr. Gibbons was running a simulation of the effect of multiplicity.

He took all of Najafi's data, scrambled it so it was random, then ran the number of tests that Dr. Davis ran and showed that even when the data was scrambled so it was all random chance he generated multiple, multiple false positives. He was demonstrating the effect of multiplicity and it would have been a strange way to conduct that experiment to correct for multiplicity.

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Now, another critique that Dr. Gibbons made was that Dr. Davis treated variables that were interrelated as if they were independent. Again, this is just a basic statistical error. If your variables have interdependence, there are ways

to test for that, and then there are ways to extrapolate taking that into account.

Dr. Davis didn't do that, he treated every single one of his parameters as if it were its own independent variable. Take, for example, manufacturing plant and then temperature control. He treated those as two completely separate tests. When he got a positive one, he said great. When he got a positive on the other, he said great, look at all these things I am finding.

What he didn't account for was these things are interrelated. Each manufacturing plant has its own related temperature control, has its own storage, has all kinds of variables that are interrelated. There are corrections for that, Dr. Davis didn't make them.

What happens then as a result is, not only are there all the false positives from multiplicity, there are false positives because you're double counting your findings. You are saying, ah-hah, temperature matters and factory matters, when in fact that is really one finding, not two, and this error was propagated over and over.

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So, in sum, what did Dr. Gibbons do? He is a renowned biostatistician, but it didn't take his skill level to make these assessments. He said if you want to create a reliable sample to randomize and extrapolate from, you have to have a

random starting point so it's reflective. You have to power your study so there is some objective criteria about extrapolation. You have to correct for false positives and you have to correct for interdependence. Dr. Davis did none of these things.

This is not something disputed by Plaintiffs, they just try to minimize these critiques. That does not rehab Dr. Davis' unreliable statistical methodology, and it certainly doesn't disqualify Dr. Gibbons. There is nothing unreliable about pointing out a failure to apply the most basic statistical controls.

Thank you, your Honor.

THE COURT: Thank you. Any rebuttal?

MR. NIGH: Yes, your Honor. Daniel Nigh for the Plaintiffs. I will be brief.

Defendants discuss Gibbons' experience with monitoring for drug safety, but monitoring for drug safety is much different than pill testing for impurities or carcinogens.

Next, Defendants defended Gibbons' multiplicity criticisms, however, Dr. Davis testified that multiplicity adjustments are not applicable to safety issues, and that makes sense.

Think about all the epidemiology studies in this case that your Honor has reviewed. Some of them have many analyses that the authors have investigated and not a single one of

those study authors in those epidemiology studies have adjusted for multiplicity.

Defendants raise Florian, and again, Florian has numerous statistical analyses conducted and multiplicity was never applied. In Defendants' own root cause analysis, including GSK's root cause analysis that was published in the King study, also had no multiplicity applied to those analyses.

That is because the clear majority view is that applying multiplicity to safety issues, including pill testing for a carcinogen, is not appropriate, and therefore Gibbons' opinions related to multiplicity would be confusing to the jury and should be excluded.

Now, power calculations. The only support Defendants cite to for power calculations is the Florian study. Defendants discuss Florian's power calculation and suggest that because Florian did it, then Gibbons should have, but this reasoning is very flawed.

First, Dr. Gibbons did not cite to Florian or even consider it. This is because Florian's power calculation is irrelevant and for an entirely different purpose. Florian did a power calculation to see if they had enough subjects for measuring urine and plasma differences within individuals, and because of their concern with only having 17 individuals and understanding these individual differences, whether they were testing enough individuals to possibly detect statistically

significant differences.

This power calculation by Florian was on patients, not pill testing, and as Dr. Davis explained, the power calculation for whether enough pills were tested to possibly detect statistically significant results is irrelevant. Why? Because Dr. Davis' analyses showed clear statistically significant results, including a six in a hundred million chance that the findings were due to chance, clearly statistically significant, so clearly enough power to reach statistical significant findings.

Again, Florian wasn't about pill testing. GSK's root cause analysis that tested pills and was peer reviewed and published in the King study, GSK did not perform a power calculation, and the FDA did not perform a power calculation.

Further, for randomization neither GSK's testing or the FDA, or any other testing for pills, has this sort of randomization requirement that the Defendants suggest because this is simply not required.

Defendants try to excuse Gibbons' pervasive misunderstandings of Najafi's testing because there are a few things that Davis didn't know. The key difference is that Davis didn't know about a few issues related to Emery Pharma's testing, but those issues were irrelevant to his analysis. He didn't need to know those issues.

The issues relevant to Gibbons' analyses regarding how

many pills were tested and his criticisms were clearly relevant.

And finally, Defendants conflate the number of samples and observations for a particular statistical tool with overall number of samples and observations, and they do this to try and rescue Gibbons' pervasive misunderstanding of important relevant aspects of how pill testing is done, including that each pill can only be tested once and that power calculations and randomization are generally not done for pill testing.

Dr. Davis also confirmed that the sample sizes used for the analysis that he did perform were sufficient.

Thank you, your Honor.

THE COURT: All right. Thank you.

Let's move into the Olsen motion, Docket Entry 5838. From the Plaintiffs.

MS. BOGDAN: Good afternoon, your Honor, Rosemarie Bogdan for the Plaintiffs.

May it please the Court, I will argue that the Court should exclude the opinion of Dr. Bernard Olsen, a rebuttal witness against Dr. Najafi and Plaintiffs' other experts who reference Emery Pharma's testing. I will focus on three of Dr. Olsen's opinions.

First, he claims that Emery failed to follow irrelevant laboratory standards, which they now concede are inapplicable. In truth, Emery followed detailed protocols that

confirmed the reliability of its testing.

Second, he claims that Emery's LC/MS-MS technique created artifactual NDMA resulting in inaccurately high measurements. In truth, the published literature and Emery's own data confirmed that its technique is accurate and reliable and does not create artifactual NDMA.

Third, he claims that Emery's testing results are outliers. In truth, Emery's results are comparable to Defendants' own testing of non-pristine product like Sanofi's 21-month plus room temperature stability testing and the Braunstein study's baseline testing. Olsen's opinions are thus disconnected from the facts of Emery's validated reliable testing and should therefore be excluded.

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First, Dr. Olsen criticized Emery for allegedly failing to follow proper protocols. That is a bait and switch. He first accused Emery for failure to follow GLP and cGMP standards, but now Defendants concede on page six of their brief that these are specific regulatory requirements that do not apply in this context.

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And Defendants' experts like Dr. Lindsley concede that they themselves do not comply with cGMP and GLP either when doing research and development testing. Defendants thus fall back to the position that Emery allegedly did not follow any

standards at all. This is simply false.

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Here are Emery's extensive experimental protocols governing its testing. These pages and pages of protocols draw directly from the FDA, GSK's root cause analysis, from peer reviewed studies like Braunstein and Gao. They specified the equipment, materials, reagents, calibration standards, quality control samples, detailed testing procedures, and much more.

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By contrast, let's look at the protocols Dr. Olsen himself used for his own testing in a different case, Cephalon versus Watson Pharmaceuticals. This is his protocol in its entirety for his testing of CO2 in fentanyl. It fails to specify much of what Emery's protocols detail, and it lacks numerous parameters that Olsen now claims are necessary, like dated protocols, an explanation of how the analyst chose the tablets, missing sources where the analyst purchased materials, lists of common laboratory equipment like a mortar and pestle.

Dr. Olsen basically testifies that Emery should do as he says, not as he does, but Dr. Olsen used those protocols that you see because he recognizes they are more than sufficient, as are Emery's.

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The truth is that Emery followed generally accepted scientific principles and standards that confirm the

reliability of its reproducible testing results. Dr. Olsen's opinion should therefore be excluded.

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What is Olsen's theory about the column? Dr. Olsen suggests that artifactual NDMA "could be created" in Emery's LC/MS-MS testing technique by heating the sample, leading to inaccurately high results. That contention is rank speculation that flies in the face of refuting facts that Dr. Olsen ignores.

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Emery's data itself shows that its testing using a HILIC column did not create artifactual NDMA. If it did, then every single test would show high levels, but that is not what Emery's data showed. For example, this sample showed an NDMA level of 5.2 nanograms, other tablets tested at 7.2, 21.4, 15.2, 19.4 nanograms, and so on.

Emery's validation, including in matrix accuracy testing, conclusively demonstrates that any hypothetical artifactual NDMA would be consistent across runs, and given the low testing results just discussed, is non-existent.

Dr. Olsen's speculation that Emery's testing was consistently biased high by artifactual NDMA is impossible to a core with these low testing results, which again confirms that Emery's testing is reliable and follows generally accepted scientific standards.

Emery's other data confirms this point. Emery tested the exact same sample lot with HILIC and the reverse phase column that Defendants prefer, and those two tests of the exact same lot using the two columns show strikingly similar results.

Emery tested pills from Sanofi lot 19D452U using both the HILIC and reverse phase columns. For the HILIC the measurement was 11.9 nanograms. That is reflected in Figure A on page 162 of Najafi's report.

For the reverse phase, that exact same lot ranged from 3.6 to 16.3 nanograms, that is on page 190 -- excuse me, 90 to 91 of Najafi's report. Those results were essentially identical. That again refutes Dr. Olsen's speculation that the HILIC columns lead to artifactual NDMA.

Next slide, please.

Olsen's unfounded theory misunderstands the relevant scientific facts and literature. Defendants ignore a critical fact about this allegation, any artifactual NDMA due to heat would occur during the mass spectrometry stage of the testing when an analyte is ionized, but Defendants' and FDA's testing also exposes the alluded analyte to an MS source, and all of these MS stages heat the sample for mere milliseconds, many orders of magnitude shorter than the fifteen minutes of heating that created artifactual NDMA in Valisure's gas chromatography technique.

Next slide, please.

As we explained at the previous hearing, HILIC columns are specifically designed to separate highly polar compounds like NDMA. Defendants offer no rebuttal to that, so Defendants speculation that it won't adequately separate NDMA in Ranitidine is worse than speculation, it is demonstrably false.

Even if a HILIC column eluted NDMA and Ranitidine at the same time, Dr. Olsen's speculation that the MS source would convert that Ranitidine to NDMA is again refuted by the facts.

Next slide, please.

Here is Figure 10 in the Waters note that Olsen cites as support for his, quote, "theory". But it actually shows the opposite. Figure 10 shows the chromatographic data when the LC column eluted the Ranitidine into the MS source, and the chromatographs in the red box slow a spike for NDMA when the NDMA eluted. Below that red box the chromatograms show a spike for Ranitidine when Ranitidine eluted.

Next slide, please.

If there were artifactual NDMA creation it would show a second NDMA spike in the area shaded in yellow, but that second spike doesn't exist. That confirms that the MS source does not convert Ranitidine into NDMA.

Next slide, please.

And indeed, the Waters note labels this chromatograph as confirmation of endogenous NDMA. In other words, the authors concluded that the NDMA was not an artifact

caused by the MS source.

Dr. Olsen's contrary opinion thus conflicts with the data in the Waters note that refutes his speculation, which Daubert forbids. Indeed, the Waters note confirms the reliability of Emery's testing. Olsen also misunderstands the Yamamoto study. In fact, this paper discusses the possibility of a matrix effect for detecting NDMA, meaning the measurements of NDMA would be suppressed, not artificially elevated.

Dr. Olsen ignores these facts which demonstrate that Emery's testing was reliable in accord with scientific standards. That failure to consider all the facts in forming his opinion is fatal under Daubert. His speculation about artifactual NDMA should therefore be excluded.

Finally, Dr. Olsen's claim that Emery's testing results are outliers ignores the relevant evidence. The results he looks at largely tested pristine product which yields lower results.

Emery's results are fully in line with results of comparable testing of real-world conditions, like Sanofi's 21-month room temperature stability testing ranging from 110 to 786 nanograms, and the Braunstein study baseline testing ranging from 824 to 1,440 nanograms, and note that the low end of this range was comparable to Emery's average.

This shows that when you look at the relevant evidence, studies that tested NDMA levels in comparable

real-world conditions, Emery's results are no outliers. Dr. Olsen's opinion ignores that evidence and so should be excluded.

Thank you.

THE COURT: Thank you. And from the Defense.

MR. FRIEDMAN: Good afternoon, your Honor, Robert Friedman for the Defense.

I am going to address the first criticism of the Plaintiffs, then I will turn it over to my colleague, Mr. Bosso, to address the more complicated scientific criticisms.

Meanwhile, a little bit about Dr. Olsen, and we will get the slide in a second, but he has a Ph.D. in analytical chemistry, he has served on the Board of the U.S. Pharmacopeia for about 25 years, including sitting on their expert subcommittee on nitrosamine impurities, and importantly, he has written over 55 publications, including a treatise on the HILIC analytical chemistry method that we are going to talk about in a second.

So needless to say, his qualifications are not being challenged here.

If I could have the next slide, please.

What Dr. Olsen did is what most rebuttal experts do, is he reviewed Dr. Najafi's work and identified problems with it, and this slide is not meant to be exhaustive and I am not going to really go through it, it is just some examples of how

Dr. Olsen looks at part of what Dr. Najafi did and identified an issue.

So, for example, the last one, Dr. Najafi wants to tell the jury that the Defendants' product -- that the testing that he did was validated and consistent and Dr. Olsen's opinion is, it is not, and he goes on to explain why.

This is perfectly appropriate -- next slide -- because this is what rebuttal experts do. They do not have to disprove the work of the expert they are challenging. They simply are allowed to criticize or rebut the methodology or opinions of another expert, and that is precisely what Dr. Olsen did here.

There are some criticisms in the briefing that Dr. Olsen didn't actually do his own testing and disprove the results, or he can't say as a factual matter that the results are wrong, but that is not required of a rebuttal expert like Dr. Olsen.

Next slide, please.

These are the four criticisms laid out in the motion and I am going to start with the first one related to the standards.

Jump two more slides, please.

What is Dr. Olsen's opinion? Which we say is undeniably correct. It is that Dr. Najafi did not apply any standards, and what he saw when he looked at Dr. Najafi's report is, Dr. Najafi said, well, my lab is cGMP/GLP compliant,

implying that he followed those standards, and Dr. Olsen said, no, he didn't.

At his deposition, Dr. Najafi said that is true, I didn't, but I didn't have to. Well, we never -- Dr. Olsen was never arguing that he had to. The point Dr. Olsen was making is that he doesn't identify any standards that he used.

Now, the Plaintiffs have come back and said, no, no, here are some protocols he followed, but protocols are not standards. Protocols are specific to particular tests, and they are step by step how you do a particular test. They are not how you conduct tests as a general matter, how do you document them, how do you run your laboratory properly so that other scientists can review it.

We know they are different because Dr. Najafi admitted it. At his deposition he was asked, what standards did you apply? On page 140, lines 4 to 14, he said, well, the standards I applied are "generally acceptable scientific principles. They are not written anywhere that I can go and point you to."

If the answer to the question was, well, they are the protocols, he would have just said they are the protocols, but he didn't. He said my standards are not written down anywhere, they are not the CGMP standards, they are not any NIH standards, they are not any standards that different companies and different organizations can follow.

So, Dr. Olsen's opinion that Dr. Najafi didn't follow any standards in doing his testing is undeniably correct.

With that, I will turn it over to my colleague, Mr. Bosso, to address the other two criticisms.

THE COURT: Okay. Thank you.

MR. BOSSO: Good afternoon, Luke Bosso for BI and on behalf of all brand Defendants.

THE COURT: Good afternoon.

MR. BOSSO: Plaintiffs also argue that Dr. Olsen cherry picked data. This is essentially the outlier opinion you just heard about. Normally, when people say that an expert cherry picks data it is because there are some data they ignored which would undermine their opinion. Plaintiffs have not identified any true apples to apples data set that would undermine Dr. Olsen's opinion.

What you see on the screen -- I know we have given this graph in various forms before and a version of this was in Dr. Olsen's report -- is an apples to apples comparison because it compares baseline to baseline and it compares unexpired tablets to unexpired tablets.

Now, what Plaintiffs just got up and compared their results to is saying Emery's baseline testing is similar to Sanofi's stability testing and similar to Braunstein's simulated gastric fluid study where you put it in with -- in a simulated incubation and then test it. Those are not baseline

testing results, those aren't comparable, these are the data that you can actually compare them to.

They also criticized them because they were pristine samples. I want to note that Emery, pre-litigation, a hundred percent of those samples were from the market, so if those were pristine samples, that is because the storage and transport processes ensured that the products got to the market with very little NDMA present.

FDA, that included samples from the market, Cabillo included samples from the Spanish marketplace, Al-Shiri included samples from the Saudi Arabian marketplace. These are real-world samples that you compare them to.

The true issue is that Dr. Najafi wants to tell the jury, I tested these Ranitidine products and my samples are actually representative of what you get on the market, and Dr. Olsen says, wait, we have all this data that is actually from the market and it is entirely inconsistent. Plaintiffs have no good answer but to point you to stability results and simulated gastric fluid studies which are just inapplicable.

The next slide.

Next I am going to address the third argument. Defendants' position is that Plaintiffs are misconstruing Dr. Olsen's opinions so I want to start by first outlining exactly what his opinions are.

First, Dr. Najafi in his report and his deposition

continuously says that Ranitidine is highly unstable and affected by temperature. This is critical because his testing actually exposes Ranitidine to 300 degrees Celsius. Plaintiffs can speculate that while Dr. Najafi says, you know, Ranitidine degrades everywhere, in a hot car, in a bathroom, even at room temperature, at around 20 degrees Celsius, in this testing that uses even higher conditions, this is the one place on earth where Ranitidine is stable.

Now, Plaintiffs can speculate, but outside litigation researchers actually prove that their methods do not cause artifactual NDMA formation.

So, we heard a lot about the Waters 2020 note today. Those researchers were actually doing the work necessary to validate their method, and they can actually point to testing that they did to show we considered this issue, we confirmed it was not causing artifactual formation, and therefore the method is validated.

Dr. Najafi has never demonstrated that for his method, and since that is required to say that your method is validated, he cannot continue to say that he sufficiently validated his method. Plaintiffs essentially recast this as a "volatilization theory" which is a term that does not appear anywhere in Dr. Olsen's report or in his deposition.

Next slide, please.

Essentially the scientific community agrees with Dr.

Olsen's criticism about how Emery or Dr. Najafi failed to validate his method. In fact, as you heard earlier, Dr. Olsen relies on Waters 2020, which has that same graph you saw earlier. I will explain exactly why.

Now, Dr. Najafi's reliance on Waters 2020 is completely misplaced, and this was discussed both by Dr. Olsen and Dr. Guengerich.

Waters 2020 uses a different method than Dr. Najafi. Waters uses a reverse phase separation followed by an ionization technique called APCI, whereas Dr. Najafi used the HILIC separation followed by an ionization technique called electrospray.

This is saying trying to extrapolate from Waters to Emery is just a complete apples to oranges, yet Dr. Najafi is forced to do this extrapolation because he has not conducted that testing himself.

Likewise, while Dr. Najafi attempts to use Waters 2020 to justify the fact that he didn't actually do this demonstration himself, and that he doesn't need to demonstrate separation of Ranitidine API from the other impurities, Waters disagrees and specifically says, despite the finding in Table 10, separation of API from the impurities is critical.

And finally, it cannot be lost that in Waters 2020, those lines you saw on those graphs, those were chromatograms, processed chromatograms that those researchers put forth into

the scientific community to prove that their methods were validated.

Still to this day, in this MDL there has not been a single processed chromatogram produced by Plaintiffs that Dr. Najafi will authenticate on his own. I am going to show you a chromatogram that our consultant has generated, but that they dispute as being an accurate representation.

Let's go to the next slide.

I want to show you empirical evidence because you said that Dr. Olsen doesn't have a bit of proof for this, but I actually want to show you the real empirical evidence we have.

As you can see here, there are four chromatograms. Two of the chromatograms on the left are Dr. Najafi's calibration solutions, meaning that there is no Ranitidine in these samples. The top chromatogram measures NDMA and the bottom measures the internal standard version of NDMA.

Contrast that with the left side, the sample contains -- or the right side, this has Ranitidine in it, the top measuring NDMA, and the bottom measuring internal standard version.

On three of these four chromatograms you see clean and well-resolved peaks, and importantly, in these three chromatograms there is no potential for artifactual NDMA formation either because, one, there is no Ranitidine in the sample or, two, because internal standard version of Ranitidine

molecule never degrade into internal standard version of NDMA. But the place where you can actually get artifactual NDMA formation is this red circle. This is all NDMA appearing in the Ranitidine sample.

Dr. Olsen has reviewed these chromatograms, and chromatograms like this, and said that there is no way that a reliable chromatographer would look at this and proceed to actually rely on this result.

It is hard to tell on this figure, but there is an asterisk next to this 1.803, and that is because although the computer didn't recognize this as a valid peak, an analyst at Emery manually went in and overrode the decision and said, I am still going to use this as a peak.

This is the same type of chromatogram that has been used for all of the baseline, stability, and zone testing that serves as the basis of extrapolation by other experts, like you heard Dr. Davis, Dr. Salmon, Dr. Panigraphy, and I believe Dr. Le.

Last, I want to address just a few points made by Plaintiffs. First, Plaintiffs -- this is about the low findings argument. Plaintiffs argue that if artifactual formation was occurring, it would occur in every sample of Ranitidine. This argument, however, is belied by Dr. Najafi's own opinions.

In his rebuttal report, on page 13, Dr. Najafi writes

"The exact batch/lot of products dictated the course of NDMA formation from Ranitidine. In fact, no two Ranitidine batches have behaved identically when exposed to stress or stability conditions." He goes on to say, "It is possible that some Ranitidine drug products may only generate a few nanograms of NDMA."

So having low artifactual formation in some samples and high artifactual formation in other samples is entirely consistent with Dr. Najafi's own opinion.

Additionally, n matrix accuracy, they argued that, and as far as I can tell based off the current record, there is no evidence that Dr. Najafi ever conducted n matrix accuracy testing for his HILIC method, and I will give you a cite. I know it is generally hard to cite a negative, but on page 11 of Dr. Najafi's rebuttal report he indicates that he performed n matrix accuracy only for two types of samples, effervescent tablets and injectables.

Notably, the methods for these two types of samples was reverse phase and not HILIC.

Lastly, conceptual separation. Plaintiffs continue to argue that they have evidence that the HILIC method should separate NDMA from Ranitidine. First, this is something that needs to be tested with empirical evidence; and second, there is a fundamental flaw in Plaintiffs' reasoning.

The true issue is whether NDMA is separated from

Ranitidine, but Plaintiffs do not put forth even conceptual evidence of how Ranitidine reacts within the HILIC column. So, looking just at NDMA is insufficient to tell you whether there will be separation between NDMA and Ranitidine.

As for the remaining arguments, we are fine to rest on the papers and ask this Court to deny Plaintiffs' motion.

THE COURT: Okay. Thank you very much.

Any rebuttal from the Plaintiffs?

MR. SELIGMAN: Yes, thank you, Matthew Seligman for the Plaintiffs on rebuttal.

Can we pull up the first rebuttal slide.

I am going to focus today about this issue about artifactual NDMA formation and whether that is apparent in the chromatograms that Emery itself produced.

This is Figure 2 that appears on page 15 of Defendants' opposition brief, and so, what is going on here is that the Defendants are suggesting that the NDMA peak in the chromatogram on the left, which was created by the FDA, shows a clear spike without any indication of an artifact, an unidentified detector response, and so it is reliable, whereas Dr. Najafi and Emery's NDMA peak on the right is more complicated and therefore is unreliable.

Now, this comparison is inapt and misleading for a variety of reasons.

Next slide.

The FDA chromatograph that was displayed in Figure 2 of the brief was not from LC/MS-MS chromatography, it was from LC/HR-MS chromatography, a completely different technique, and that really matters. The difference here is that in LC/HR-MS chromatography the separation -- difference between LC/HR-MS and LC/MS chromatography really matters in this context.

The difference is that LC/HR-MS chromatography separates the analyte from the sample only using the column, not using the mass spectrometry. What the means is, as is widely recognized in the scientific community, LC/HR-MS is just not as accurate and not as precise in fluctuations in a sample.

As a result of that -- if we go to the next slide -- you can see that the chromatograph on the left is just smoother than the one at the right, and that is because the technique is not picking up small variations.

Now, you will also note that on the left, the chromatogram, the baseline is not zero, the baseline is at about 50 to 60 of the relative magnitude, so there is a detectable response there, and that matters for another reason as well, which is that the Defendants here are comparing apples and oranges, even taking aside the different techniques in these two chromatograms.

Next slide.

This is -- unfortunately, the slide is a little bit off, but what this slide will show is that in that very same

FDA report using the LC/HR-MS technique, what you don't see here is actually the baseline is about 90 to 95 of what the ultimate peak is, so I will just describe it to you. It is basically a horizontal line with some squiggles on it and then a tiny little hump.

What that shows is that when the FDA, using its LC/HM-RS process, and actually and tested drug product, that is a pill that has all of the complications in the matrix that Emery tested, then it found that you have an extremely high detector response with just a tiny little hump on top of that.

So, that is why Emery decided to use LC/MS-MS, rather than LC/HR-MS, which is what so many other of the Defendants did. The FDA actually did testing using LC/MS-MS as well, and we can see the difference in what the chromatographs look like.

Next slide, please.

Here is another report about a month later. This is from October 17, 2019, where the FDA set forth its protocols and its methodology for using LC/MS-MS of Ranitidine drug products. Let's look at what those chromatographs look like.

Next slide, please.

This is a chromatograph using LC/MS-MS just for water, nothing else. You can see that the line is squiggly, there is a lot of noise, and the reason is because the methodology of LC/MS-MS is extremely effective at picking up small variations in the signal. That is the advantage of LC/MS-MS.

Let's look at what the FDA found when it applied LC/MS-MS methodology to an NDMA sample.

Next slide.

Here is what it looks like, and you can again see that there is a lot of noise in here because the methodology is highly effective at picking up small variations in the signal.

If we compare this chromatograph back to the ones that the Defendants represented was somehow unreliable -- next slide -- we can see, well, actually, it is not that different from the one on the right, there are squiggles, but there is also a clearly defined spike.

That just undermines the comparison that the Defendants are trying to make here between the FDA's chromatograph using a different methodology of a pristine API as opposed to the actual drug product.

Now, there are other problems in the comparison as well. What we find in these types of chromatographs and LC/MS-MS are these squiggles are called baseline imperfections, and they are absolutely routine in the science. The question is: How big are they and how does the analyst deal with them? The answer of how big they are really matters.

Next slide.

THE COURT: That is five minutes.

MR. SELIGMAN: I will wrap up in a second.

THE COURT: Okay.

MR. SELIGMAN: Here we have two different chromatographs from two different samples. We can see the top one where the NDMA was about 100, and the bottom one where the NDMA was about 16,000. The baseline imperfections are about the same absolute magnitude always. What that means is that the very high values that you see in some of Emery's sample testing isn't explained by these alleged baseline imperfections.

Instead, it is only extraordinarily small variations that you find from the inherent sensitivity of the LC/MS-MS process and only for small readings of NDMA.

Thank you.

THE COURT: Okay, thank you very much.

Let's go into the last, the Wang presentation, which is a total of 15 minutes, and then we will take a break after that.

We are going to hear from Defense first on that one.

MR. PETROSINELLI: We have to retrieve Mr. Cheffo.

THE COURT: I didn't give notice. Is he nearby? Otherwise, one of you can just jump in.

You're busted, the one time the Court goes out of order. We were going to take a break, but we will do the 15 minutes, you get ten, Plaintiffs have five, and then we will have some questions and then closing and make sure everyone gets out on time.

MR. CHEFFO: Thank you, your Honor, Mark Cheffo for the Defendants. Good to see your Honor.

We asked for an opportunity, so thanks for a chance to do that. I understand you may have some questions about our stipulation, but I am going to address where we are on this right now, in ten minutes.

This study was just published. The Plaintiffs have submitted some supplemental reports, so we wanted an opportunity to share some initial thoughts and observations about the study so you are not kind of left without that.

As I was listening today, a few things, I was thinking situational science, maybe I am nerding out and also cherry picking. It also felt a little bit like I was watching a tennis match because on the one hand, we have heard so much about, prior to today, active comparators and all the problems, and we really shouldn't pay much attention to it, but yet, today when we see the Wang study, lots of slides, active comparators, maybe they're not so bad.

In the Wang study there is actually a statistically significant protective finding for liver for PPIs, but we have also heard a lot of stuff about maybe that is kind of confounding because of PPIs.

Si, I think as we go through some of the slides you will see that it is kind of like which way is it? Because the Plaintiffs can't have it both ways. I think they said early

on -- there are two things. Ms. Finken said this supports an increased risk for all of the cancers at issue here, and Mr. Snidow said this is a real problem for our experts.

I think it is just the opposite, and we will talk about the one finding, the statistically significant liver cancer finding, but when you look at everything else in the study, it is absolutely consistent with everything that we, but more importantly our experts have said to you literally since the beginning of this litigation.

Next slide, please.

So, you know, it is important to look at kind of what the authors say and what they don't say, what they do and what they don't do.

The authors -- this came out last week. Previous studies, including studies on NDMA and studies looking at Ranitidine were contradictory. The data were not sufficient to reach definite conclusions. The conflicting results of studies underlie the lack of concrete evidence supporting the role of Ranitidine in cancer development.

That is kind of stunning, that essentially the Plaintiffs have gone all in on this study. I am not going to talk about the specifics other than to say lots of paper, ink spilled on this. This basically says exactly what we are saying, it feeds into the law lag, science, and everything else, which is this study says, as of last week there is

contradictory and there is a lack of concrete evidence.

That is exactly the point here, that the world's community has looked at this, they are submitting a study that says there is no there there with respect to causation.

Next slide, please.

How much time have we heard about followup? I think you may recall from Dr. McTiernan, they made the same kind of argument, well, the followup is a problem, but then we showed you that her own studies were right in the middle, but again, you can't have it both ways.

This study is followup right in the middle of the other active comparator studies, so if it's a problem for all of them, certainly it would be a problem for Wang that their experts are saying you should rely on it.

Next slide, please.

We saw this slide today. Well, the really good studies are the ones that address confounding for smoking. The ones that get time out, the X, they are the ones that don't address it.

What is missing from this? Wang. It would be on the left hand, the time out side with the X boxes. So, again, situational science, is it good to do it, is it not good to address confounding? Can't have it both ways.

Next slide, please.

I want to take a minute on this because you have seen

snippets, unfortunately, today. I think maybe twice we saw a finding for bladder cancer from Cardwell and then you saw it kind of switched quickly, and then there was this assumption that this study and these studies kind of -- don't look over here because they show causation for all of the cancers, but this is what this study does.

When the Plaintiffs say it is actually supportive of them or gives our experts a problem, it is hard to understand that when you look at the data.

They looked at a number of different cancer end points, but I obviously put up the five because those are the five that are at issue here.

You heard a little bit about this earlier, Mr. Boehm mentioned this. When they looked at bladder and esophagus, there is no statistically significant finding, zero. That was their big focus two weeks ago, but we didn't hear anything about bladder from the Wang case.

If anything, this completely undercuts everything they have been saying about bladder and esophagus just on its face from statistically significant findings. We are trying to give you all the information, so you see gastric, pancreatic, and liver, there are statistically significant findings. This is nonuse, but we want to present all to be fair to the Court.

Then you go to the next column, the dose response. They didn't do a dose response for esophagus and bladder

because essentially it was supposed to be confirmatory, more information reliability, but they didn't pass go with respect to those, so they didn't do a dose response.

They did do a dose response for gastric and pancreatic, and when they did the dose response, which you have seen charts from the Plaintiffs today and before that that is really important, what they find is no dose response, their study for these four cancers, and this is in nonuse.

They do find it -- obviously I am not ignoring liver, there's checks right below, but they kind of do pass go on these four guideposts with respect to liver, but I also think it is important that we kind of understand what this study says and what it doesn't say.

Then, when they look at the active comparators, which we have heard a lot about and certainly the most reliable type of analysis, you see again no association, no statistically significant association other than liver, so that is compelling.

Then, there was also a PPI finding, and again, it was only statistically significant with respect to liver, and the point again there is what I raised earlier, when you look at the PPI finding from this study, it is statistically significant protective, so that is at odds with a lot of what we have heard about from the tension.

Next slide, please.

So, you know, context is everything. You have heard probably more than you will ever want to in your next litigations consistency and replication, it is going to start rolling off your tongue like it does with us, but again, we didn't come in a few weeks ago, or before the Wang study, and say, look at this, it is protective, and these are data points that answer the question.

What we said and would say now is, when you look at Kim, Yoon, and Iwagami, Wang is not the only study out there, this shows, at best, no association. There is protection here in the Kim study, but when you look at Wang you can't just ignore everything else that is in the world's literature.

At best, this says one positive finding, one protective finding, and the other two that on the left side, but they certainly don't show any causation. They aren't like, ah-ha, mission accomplished on this.

Next slide, please.

This idea of consistency, right, is -- I won't repeat this much more, but this is from Dr. Moorman, right, that judgments on causality by epidemiologists typically are not based on a single study or even a few results. We agree with that.

Where does this take us? This takes us to the point which I think is fully consistent with, frankly -- to the extent good lawyers on both sides try to have themes or have a

thematic approach to this, our thematic approach is you can't cherry pick, right. If you like active comparators and you think they are compelling and important, then you have to take the good with the bad.

If you basically want to look at a particular study, you can't basically say, oh, just look at the liver cancer finding and that supports everything that we say, and will give their experts a lot of problems when in the same ten -- 18-page study it also shows data points that are at odds, fully inconsistent with everything the Plaintiffs have told you with respect to the other four cancers.

And as I said, with respect to the liver cancer findings, and maybe our experts will have more to say on the validity of that, but for today's purpose, taking it as a valid point, even if it were accurate, even if it were true, it doesn't change anything because, at most, we have one over here, one over here, two in the middle, and that is not causation, your Honor.

THE COURT: Thank you. And from the Plaintiffs, you have asked for five minutes.

MR. SNIDOW: Could I have the Defendants' slide 4 up again for a second. I won't get to it for a moment.

Before I dive in, I think it is worth taking a pause and clarifying what actually happened in Wang because it is easy to get lost in the distractions.

That study, which included 99 percent of the population of the entire country of Taiwan, which although it is a small island, it's one that is pretty dense, about the size of Florida, they went back in the registry and matched cohorts of 50,000 people. This is exactly the kind of study design the Defense said is the most reliable. We heard it last week, we heard it again today, gold standard, most like a randomized control trial, top of the line, the list goes on.

What they did, and this is so critical, is they looked at these matched cohorts, which were designed to be as identical as possible across a variety of characteristics, and they compared which group got more cancer. They did it for Ranitidine versus non-Ranitidine, and the answer was that the people who took Ranitidine got more cancer.

They did it with a comparator to a heartburn medication, and the answer again was the people who took Ranitidine got more cancer. That is powerful evidence that what our expert has been saying is reliable, and is powerful evidence to what the Defendants answered in their expert reports really wasn't the right general causation question at all.

I want to be clear on one thing, we can talk about statistical significance, but I don't want this to get lost in the weeds because it is just true. When they looked at those 50,000 cohorts in that study, the cohort who took Ranitidine

got more cancer for every single type of designated cancer in this litigation. Those are the numbers. We can talk about significance, but those are the numbers.

A few other points. Primary methodologies. As the Court knows, the Eleventh Circuit has this three primary methodology thing. On background risk, if the Court looks at Table 2 you will see that the Wang study authors quote the background risk for each of the designated cancers as well as the risk for people using Ranitidine.

Dose response, that's Table 3, I talked about it this morning, but it is true, at least for liver and for stomach cancer the dose response there is clear, and for pancreatic, our experts get into it, but there is a dose response as well.

Epidemiology is the third primary methodology, and if the Court looks at the conclusion section of Wang, it is, of course, an epidemiology study, and what those study authors conclude is that in their real-world study their results suggest a real link between Ranitidine and cancer.

Next, Wang looks at and confirms all of the criticisms of the Defendants' studies that we have been lodging all along.

I showed a slide -- Ms. Finken showed a slide of it this morning, they looked at the Iwagami and the Yoon study. Defense counsel earlier tried to make it seem like, well, look, they noted that there were inconsistencies, they were going against the grain.

What actually happened was good science. The Wang study authors said, huh, we showed a real result here, in past studies they got a null, no signal emerged. What happened? What the Wang study author said was that in those two studies, the ones it looked at, Iwagami and Yoon, it was the low followup, and they identified the low number of subjects. That is exactly what our experts have been saying.

Similarly, I showed you that chart in my earlier presentation with the lines diverging. If the Court is interested in knowing why we have been saying all along, well, I know you have these active comparator studies, but how much Zantac did those people take, the reason is because the lower the dose of Zantac that people took in Wang, the lower their cancer rate and the harder it is to distinguish a real association.

The same with for lag time. If you look at that same chart, if you go out 18 years the risk is very clear. If you look at only three years the risk is not so clear, and that is critical given that the Defendants' studies that they say are the gold standard and that you have to laser like focus on are very, very short.

Just to be clear, we are not cherry picking. I said it before, but I will say it again in case you thought maybe I misspoke, in the abstract active comparator studies is a good thing. It absolutely does reduce the risk of confounding by

indication.

But when you look at an active comparator study, you have to evaluate it on its own merits. You have to look at not just did it do an active comparison, whether it was structured in a way that is going to detect the actual risk that you are looking for.

I did want to say two bars on smoking.

THE COURT: Well, I know you all negotiated your time, so why don't we keep it to what you all agreed to.

Okay, all right. So, we will take a ten-minute break. So it is 3:13, we will be back at 3:23, and I will ask a few questions and then we will do the closing. I will try to get you out by 4:30 so nobody is stressing about their flights. Be back at 3:23.

(Thereupon, a short recess was taken.)

THE COURT: Okay, I have a few questions and then I have some more questions, so try to give quick answers to the best that you can so we can get through this, and then I will turn it over to counsel for closing, which I will do no later than 4:10, maybe even sooner, and you have allotted 20 minutes for your closing.

So, question -- this goes back to epidemiology for the Plaintiffs. In your omnibus motion in support of your argument that Defendants' experts failed to apply the Bradford Hill criteria, you state "the Defense experts disregard the

associations that have been found in multiple observational studies and ignore the conclusions of the study authors themselves."

Can you explain the importance of your assertion that the Defendants' experts ignored the conclusions of the study authors as succinctly as you can?

State your name before you respond.

MR. SNIDOW: If memory serves, that was the situation where the study authors themselves said the study is not long enough for them to predict the risk, to the extent it is there, and the witness in question said, I disagree with that, I think it is long enough.

Our view is that that indicates that particular expert didn't review the literature in a way that is proper. Frankly, I don't think standing by itself that is probably grounds for exclusion under Daubert, but -- sorry, the other one, Tracy is reminding me.

In Cardwell the study authors noted there was an association, which there was, and the expert said that the association was invalid. So our view is that it is an indication that that particular expert didn't conduct the kind of review that is required under Daubert.

I am not sure standing by itself that one thing would be enough, but that is how it is played into our argument.

THE COURT: Okay. On a more general level, what is

the problem, I guess not with any particular -- the Cardwell or -- just generally, the Plaintiffs' position on an expert disagreeing with the conclusions of the study authors.

MR. SNIDOW: I think it depends on the situation. It is hard to answer in the abstract, Judge. For example, to the extent that the study actually reports an association numerically, and one epidemiologist is looking at all of the associations, the fact that the study authors didn't call out an association in that study, if you look at it in context with the other studies, it could still be evidence of association.

If it is something where the expert is just wrong about a fact in the study and one of the study authors is saying something contrary to the expert, then I think that is grounds to be concerned.

I feel like I am not answering the Court's question, but it is hard to answer in the abstract.

THE COURT: Okay. Response from the Defense.

MR. TOBEY: Danny Tobey, your Honor. I think that is a reference to Dr. Witte, and what he said was he disagreed with that conclusion, but in his analysis he only applied it in as far as that author reached in his own conclusion, so he stayed within that boundary for his application.

THE COURT: Okay. Defendants' position generally on if an expert is disagreeing with the conclusions of a study author.

MR. PETROSINELLI: Your Honor, we think that is a critical factor under Daubert. The McClain case is probably the leading case in the Eleventh Circuit on this issue where it pointed out that when the Plaintiffs' experts were reaching general causation opinions based on studies where the authors not only had not reached causation opinions, but also had explained the results of their studies and why they thought the point estimates were this or that, and that Plaintiffs' experts disregarded it, that was grounds for exclusion.

It indicates a methodological defect, and as we pointed out two weeks ago, that is a main problem with the Plaintiffs' experts.

THE COURT: Okay. Thank you.

MR. SNIDOW: Your Honor, Ms. Finken just reminded me of something that I think is important.

I believe the case law is that experts shouldn't disagree with the conclusions of the study authors without explaining why in a way that is reliable under Daubert. So, we argue, and correctly, that the things that we deemed their experts were ignoring were things that they hadn't adequately explained for ours. This goes back to the general point I was making all morning, they do a much more fulsome analysis and explain exactly why they are saying what they are saying.

THE COURT: Thank you. For Plaintiffs, in your omnibus motion, Docket Entry 5841, you state that the

Defendants' experts asked the following question, "Assuming each Plaintiff is typical of the subjects in the human epidemiological Ranitidine studies did Ranitidine cause her cancer?" Docket Entry 5841, at 9 through 10.

You state that Defendants answer the question with no, and state the answer is "unsatisfying" because "many Plaintiffs are not like the typical ones in the human epidemiological studies and those studies do not measure the long-term effects of Ranitidine use."

Can you clarify why many of the Plaintiffs are not "like the typical ones in the human epidemiological studies?" Is there any additional reason apart from your assertion that epidemiology does not measure the long-term effects of Ranitidine use?

MR. SNIDOW: Can I give you the second one first? One large one is dose, or exposure as it is sometimes referred to in the literature. It is true that a lot of the Plaintiffs in the MDL took Ranitidine for much longer than were measured in the studies that the Defendants' experts rely on.

As I said, in our registry 60 percent of the Plaintiffs took Ranitidine for more than ten years. That is just not true for a lot of the subjects that were in the studies that the Defendants rely upon.

Sorry, your Honor, would you remind me of the first part of your question?

THE COURT: Why many of the Plaintiffs are not like the typical ones in the human epidemiology studies.

MR. SNIDOW: That is hard to say. It depends on the study, how it is designed, where the study was located in the world, what data set they were relying upon. I will give one concrete example, your Honor, it is not a complete answer, there are lots of reasons.

Some of the studies included age cutoffs that make the cohorted issue more like the Plaintiffs in others. In Wang I think the cutoff was 40. They excluded patients under 40 because people under 40 are not likely to get cancer. In some of the studies the Plaintiffs relied on, I showed you the data, the median age was 54, 56, which is a patient population that is not likely to get cancer.

If the Court is asking why that is, I am not sure I can answer that. It really just depends on the study and how they pick their cohort, but the fact remains is, in a general causation case where you have to consider the highest possible dose taken, and the longest followup time that is possible, you do need a study that mimics those parameters and all the other ones we point out in the brief.

Their studies don't for whatever reason, and I am not criticizing them, but it is just they don't.

THE COURT: Is there any brief response?

MR. PETROSINELLI: It would not be very brief, but I

will give this brief response. What you heard at the end about this whole issue of for general causation you must look at what the highest dose of Plaintiff in this MDL could be is completely wrong, totally inconsistent with Eleventh Circuit case law. I was going to address that in closing, but I can do that now.

THE COURT: Okay. Plaintiffs, in your omnibus motion you state, "Even despite the significant flaws and limitations in the designs of the Ranitidine human epidemiological studies, there still exists evidence of an increased risk of bladder, liver, pancreatic, esophageal, and stomach cancer with exposure to Ranitidine," at page 69.

I understand your position to be that the human epidemiological studies are unreliable for a number of reasons, including that they did not, as you state, have enough followup time; however in your motion you state that despite the reasons why they cannot be relied upon, that they provide evidence that supports your experts' opinions.

Can you explain how you reconcile these two ideas?

MR. SNIDOW: Yes. That is one of the things I was going to get into on Wang. Do you remember in the Defendants chart they said Wang was the same length of time -- I think this is one of the things you are getting at.

So, if you want to know whether a substance causes especially a long-term disease like cancer, and you study it

for 30 years and you don't see anything, that won't tell you -- that might tell you something very important.

If you are followup time is low, and you don't see anything, that can be for one of two reasons, either there is really no association, or there is an association and you didn't wait long enough for it to show up.

Both sides have used cigarettes all day, it's an easy one. If you imagine a study that looked at people who smoked a lot of cigarettes, but then you waited one year to see if they got cancer, you might not see anything. If you waited three years, you might not see anything. If you waited five years, given cigarettes, you actually might see something, and that would be really, really powerful evidence of association, but the fact that Wang is the same -- given that Wang did show an association, the fact that Wang was the same length as some of the Defendants' studies doesn't undermine our general point that ideally you want to wait for 30 years.

THE COURT: Putting aside Wang, just more generally how your experts can rely on studies that they deem unreliable.

MR. SNIDOW: They are unreliable in one direction, and i know it might sound like gerrymandering, but it is true for this particular point. It is not that they are unreliable, you throw them in the waste bin. It's that if you are using them for the proposition that we have definitively shown that there is no cancer risk, which is what Defendants want to use it

for -- they want to say, look, the questions have been answered, we looked, it is unreliable for that purpose.

But to the extent there is an increased risk in those studies, that is particularly powerful evidence that something is going on given that you didn't even wait very long to start looking for that risk.

Is that helpful? I am trying to explain it in a couple of different ways.

THE COURT: If you find a study unreliable and presumably the methodology is unreliable, so how do you rely upon it in part, but not for other things, calling it in part unreliable, but otherwise not?

MR. SNIDOW: Because it is unreliable for a particular purpose. We are not saying it is unreliable for any use you might want to have for it. I get what the Court is asking, you said it is unreliable, throw it away. That is not what we are saying.

What we are saying is, to the extent you want to use it to say there is no risk of cancer, you really do need to wait for 30 years. That is what the IARC preamble says. If you do actually end up seeing a risk at a shorter time period, that is telling evidence that something is going on.

THE COURT: Is their case law that you are aware of that speaks about reliability related to particular purpose, such like in the case law where it can depend on purpose?

MR. HEINZ: I can't think of case law addressing reliability in particular in that way. I will say I think the word reliability kind of has strong Daubert connotations and the meaning in the brief was bias toward the null, and that is what Dr. McTiernan explains at length in her report.

It's the concept that we discuss using a colorful analogy on page 76 of our opposition brief, that's at DE 5915, where we say if you imagine someone getting ready to do a race, and they get sick the day before, maybe they have a sprained ankle or something like that, if the person wins the race that tells you something remarkable about that runner. If the person who loses the race it really doesn't tell you that much because they were sick and had a sprained ankle.

That is sort of the point with a lot of these studies, there is bias toward the null. So, given that bias, if you still find a signal, that is extraordinary evidence that can be relied upon to find an association.

If you don't find a signal, it doesn't necessarily mean that much on the other side because it is bias toward the null, bit it doesn't mean it is unreliable in the sense that it is completely useless. It simply means that you need to take the conclusions, you know, in light of the study design to see how to evaluate it overall.

THE COURT: Response.

MR. PETROSINELLI: Your Honor, what you have just

heard is the argument that their experts made, that the Ranitidine epidemiology is unreliable if it doesn't show an effect, but it is reliable if it shows an effect. That is the antithesis of sound science.

There is no case that says anything like what they just said the reference manual says nothing of the sort. You cannot -- it's what Mr. Cheffo was saying earlier, you can't have it both ways. To say that we are going to find a study reliable if it shows an effect, but not reliable if it doesn't is grounds for exclusion under Daubert.

THE COURT: Okay thank you. Plaintiff, in your omnibus motion you state that numerous in vitro and in vivo studies have attempted to analyze nitrate levels in the stomach and the most are not reflective of real world conditions for Ranitidine use because, based upon the label instructions for Zantac it should be taken 30 to 60 minutes before or after meals or at bedtime.

In this section are you referring to Florian as one of the studies that was not reflective of real-world conditions due to the timing of when Zantac was administered, the researchers in Florian having administered Ranitidine one minute after starting a meal, which falls squarely within the window of Zantac's label instructions of a 60-minute window either before or after meals?

MS. FINKEN: Your Honor, Tracy Finken. So, to answer

your question, yes, we are including Florian in that analysis, and Florian gave Zantac immediately upon waking after a 12-hour fast. There was no water taken with it, nothing in the stomach contents, and then they were directed to start eating and eat during a 25-minute window.

The Zantac label, and it depends on the indication, because how it is labeled for people to take the drug is based on the indication they are taking it for, and it differs between prescription use versus over-the-counter use.

The prescription use, how Zantac is labeled, there are multiple different ways based upon the conditions they are taking it for. For example, if they are taking it for maintenance of healing ulcers, the label recommendation is to take it once at bedtime. If they are taking it for GERD or gastroesophageal reflux disease, the label indication is to take 150 milligrams twice a day, and if they are taking it for erosive esophagitis, they are supposed to take it four times a day.

This very different from what was done in the Florian.

THE COURT: What about the part of the label that says 30 to 60 minutes before or after the meal?

MS. FINKEN: That is referring to the over-the-counter use, your Honor, that is a different label than the prescription use. For over-the-counter use it is recommended for twice daily with water 30 to 60 minutes before eating food

or drinking beverages that cause heartburn.

Typically, what we have seen and what our experts have said, and what I believe I referred to your Honor the last time we were here, was the White article, which is referenced on page 55 of Dr. Marletta's report.

They criticize Florian for this very reason, because taking the pill and then immediately eating first thing in the morning is not typically how people take this. You are taking it later, taking it with the evening meal when the stomach is not entirely empty. People have been drinking and eating all day, so that affects pH, which is this whole multi factorial analysis that Ms. Luhana did. I don't know if you remember her very lovely slides that she put up last week, but it is multi factorial.

It affects the pH, it also affects the nitrite levels in the stomach, the bacteria in the stomach. All those change throughout the course of the day when you are taking Zantac, and Florian doesn't measure those types of variables because of the timing when it was taken.

Your Honor, you don't have to believe me on Zantac affecting those different variables, Defendants' own clinical studies show this point, and I can point your Honor to one of the publications, which is the Thomas publication, and I will get the cite for to you.

THE COURT: I have to limit it because I have to move

on.

MS. FINKEN: Thomas is a publication based on a clinical trial that GSK did, and what Thomas shows is that the pH is affected, the nitrate levels are affected, and the nitrosamine in the stomach is affected for people who are taking Zantac. That is in the published literature, and I can get you the cite if your Honor wants it, but it is cited in our briefing.

THE COURT: Okay. Any brief response from Defense?

Ms. RYDSTROM: As your Honor knows, the reason the Florian researchers designed the study the way they did was to maximize -- to see if they could maximize the amount of endogenous formation of NDMA that they could see in Ranitidine users, and they did that by putting fasting -- giving the Ranitidine to fasted users when the stomach is very highly acidic, and then asking them to eat because that decreases the acidity, so capturing the spectrum that Ms. Finken was talking about.

When they did that, as your Honor is well aware, what those researchers found is there was not the increase that Plaintiffs are attempting to tell the Court exists with respect to endogenous formation of NDMA from Ranitidine.

THE COURT: Okay. Thank you all very much.

I am going to shift gears here. A couple of days ago the Court received Docket Entry 6041, Plaintiffs' expedited

motion to submit supplemental expert reports and incorporated memorandum of law, Docket Entry 6046, the brand Defendants' response to the Plaintiffs' expedited motion to submit supplemental expert reports, and then at Docket Entry 6047, the joint stipulation regarding supplemental expert reports.

I communicated through our special master that for purposes of the hearing today you could talk about the Wang -- just to be clear, the Wang C-H-U-N, hyphen, H-S-I-N-G, that is the first name, study, and you all did that, but I precluded there being any discussion about the supplemental reports because the Court hasn't ruled on the motion yet.

I have a couple questions about your stipulation, so whoever you want to designate for each of your sides is fine.

As I see it, there are two aspects of the stipulation that I wanted to address. One is that there is no depositions on the general causation amendments or supplements and the other is that there would be limitations on what the experts could discuss in their supplements or their amendments.

The Court has some concern about a lack of depositions insofar as -- as you know, the experts haven't been here because you all didn't feel that you needed them, and the Court didn't either at the Daubert hearings. In large part it is because I have every study and every deposition transcript, which have been very helpful, particularly the deposition transcripts, and the deposition transcripts do allow the Court

to see how the experts defend their opinions under scrutiny of questioning from the other side.

So, I believe the transcripts to these depositions have been important to the Court's ability to understand the Daubert issues. It's not to say you haven't done a good job summarizing the study, it is not that the Court has difficulty in understanding the study, but what the Court needs to understand is the study in the context of the expert opinion and then how that fits in with other opinions, which dovetails into the other issue, which is, you know, limitations on what experts may be able to say should the Court permit any amendments or supplements.

I [read the stipulation that you are not saying, you know, it is open season to alter prior opinions, but rather to -- or to defend prior opinions, but rather to -- because certainly those opinions have been out there for ten months, so we really don't want that happening, but rather, that the agreed upon stipulation is contending that the parties will be permitted to render an opinion on Wang, the new study.

Really what I want to hear your input on is the notion of the deposition and the degree to which, if the Court is going to allow this, we supplement. I already see in the Defendants response you have some objections to certain areas in which the Plaintiffs have gone, you argue, outside of the Plaintiffs' supplemental reports in going beyond just

discussing Wang.

But the reality is that there probably does need to be a little leeway for, I would imagine, for example, the Defendant, if you were going to depose one -- if we were going to have depositions and you were going to depose one of the Plaintiffs' experts again you are not just going to be asking about Wang, but if the expert said something about Wang and you think it is inconsistent with something that expert said about something else, I would think you would want to ask about that something else.

So, you know, I am interested in what you have to say. If there is truly a desire to supplement, and if the Court is telling you that the Court believes it is helpful to the Court to have the depositions, I would think you would need and be ready and have available those experts from the Plaintiff.

We can just focus on the Plaintiffs' experts now because we can look at this -- we can stage it, but look at it first from the standpoint of the Defendants' motions which we heard two weeks ago challenging the Plaintiffs' experts, now the Plaintiffs want to come forward with some supplemental reports, that the Plaintiffs' experts should be made available immediately for deposition.

One of my first questions is, are the Plaintiffs' experts whom Plaintiffs seek to supplement their report, and maybe that is consistent with all the supplements you have

attached, which include pretty much all your epidemiology experts -- you have McTiernan, Moorman, you know who you have, Salmon, I believe, and -- are they all available on a moment's notice to subject themselves to a deposition by the Defendants strictly on their supplement -- Michaels you have -- on their supplemental report -- you have Le as well -- on Wang only? But to the extent that the answer to the question leads the Defense to ask another question that may relate to another opinion.

It's not that the Plaintiffs' experts can change their opinion at all, at all. They have been deposed, they have written reports, they have written rebuttal reports, we have had hearings, but to be subject to cross-examination.

So let's start with that question, I guess, from the Plaintiffs. Have you conferred -- they certainly got the supplemental reports done quickly, so they must have some time on their hands. I mean over the next two weeks?

MS. FINKEN: Tracy Finken for Plaintiffs, your Honor. I can certainly discuss it with them. I have not because we had an agreement with the Defense that we didn't want to take further depositions at this point in time, but at the point that we would get to a bellwether trial we would have limited depositions on this specific supplement for both sides, the Plaintiffs and the Defendants.

THE COURT: Do you want the Wang supplements to be

considered for general or specific only? If it is for specific only it seems like I don't need to address the issue today.

MS. FINKEN: No, we have stipulated that they would be for part of general causation. Just to be clear, your Honor, the supplements don't change our experts' opinions. It's a piece of evidence that they evaluate and may use to bolster the opinions that they already gave.

So, the methodology that they used when they evaluated this study is the same methodology that hey used to evaluate all the other myriad of studies that they evaluated to reach their conclusions.

I don't know that a deposition is going to give that much more information other than what has already been established through the depositions, the reports, and argument and all the briefing that we have done, but certainly if your Honor requires it, we can speak to the experts and get their availability for testimony.

We certainly would be willing -- if you we decide to have another hearing, we can talk to them about whether or not they could be available to answer your questions via Zoom on the particular supplement if that is more helpful to your Honor than another lengthy deposition taken by Defendants.

THE COURT: I wouldn't imagine the depositions should be lengthy, like the ones that were initially taken, they should be limited. I am making the point that we could all

reasonably anticipate that you are going to have to mention another study or another opinion, it is not going to be so narrowly tailored to just Wang.

What the Court wants to understand again, as I said before, is not just the experts' opinion about Wang in isolation, but how that also comports or, arguably, doesn't comport with their overall expert opinion on the myriad of other things we have heard about.

What about from the Defense? I know you have reached a stipulation that you don't think depositions are necessary. What I am suggesting to you is that I have found them to be helpful to me. Can I say whether these will have am added degree of helpfulness? I don't know. I just know what has been helpful to me so far has included the scrutiny by which all of the experts, Plaintiffs and Defense, come under when they have to answer the questions of the very talented lawyers.

MR. CHEFFO: Your Honor, this is an easy one. I will say this is consistent, Ms. Finken and I had the opportunity to negotiate a lot of these things, but what we always say, frankly, is yes, but this is subject to what the judge wants and what is helpful to the Court. It doesn't really matter what we think is best, ultimately it is what is best for you.

From our perspective, yes. The answer is if we can do this in a few weeks -- I will tell you one of the reasons -- there were two reasons, I think you have addressed it, at least

from the Defense perspective, we were concerned. Your Honor has taken Herculean efforts to get us here to today and we didn't want this to be like, well, this person is away, then it's Thanksgiving, and we are talking about this in January, February.

THE COURT: No, we are not going to be talking about this in January, February, or even November.

MR. CHEFFO: Then you have given us a lot of comfort. Then there is always kind of the back fill, what is your name, and let's talk about this study. You are going to be the arbiter of reading it, so that is why we put in the language that, to the extent people went beyond Wang -- but to get back to where I started, we will work with the Plaintiffs. If we can do this expeditiously in a few weeks, and frankly, if someone is unable to do it, I suppose the remedy could be there is no supplemental report.

THE COURT: That's my thinking, that if you want the supplemental report you make the expert available for the deposition. You can't have one without the other, and I feel that if they were that available to write the report, they should be -- they have some time on their hands and counsel would be cautioned that you should be very measured and reasonable in the taking and defending of the depositions.

It is for a very specific purpose, it is how are they considering this new study, what does it mean to them, and then

anything they say about it, if that triggers, well, wait a minute that doesn't jive with what you said about this other study, then sure, you ask that question, but it emanates from the original question, which is about the Wang study.

To repeat myself, there will be no review, no one is changing their opinions, and no one is bolstering a prior opinion or elaborating on a prior opinion. It is explaining what Wang means to the expert, and if on cross-examination they need to explain how that is consistent with another opinion about and another study that would be the extent of going outside a discussion of Wang.

That seems pretty straightforward to me. There should not be many objections in the deposition, and I would say that if there is an objection, you just object and save it so it is in the transcript and keep going. When I read it, I know these depositions, not as well as you do, but I know them well, and I will realize when I feel somebody is going astray and trying to do a redo as opposed to just answering a question.

It would be a lot easier on me to not have to read a ton of pages of objections and going back and forth, and just sticking with the mission. I want to make sure there is clarity on the mission. Is it abundantly clear to everybody what would be the purpose of these depositions?

MS. FINKEN: Yes, your Honor, it would be. I think what would be helpful, a couple of things if you will indulge

me for a minute.

Typically when we take depositions of our experts we have the benefit of the rebuttal expert reports before those depositions go forward. The Defendants negotiated with us the ability to serve their rebuttal supplemental reports by October 14th, so we would ask the Court's indulgence so that we can get the rebuttal reports before we provide our experts for deposition. That's one.

THE COURT: Let me stop you there. So Defense is agreeing that each one of your experts who will speak to the supplemental reports shall issue a rebuttal report by the 14th?

MR. CHEFFO: That's right, your Honor. This may change so I may get booted off the island, but I think our plan was to have one, maybe two, so we are not going to have a ton. We can get them ready for the Plaintiffs.

THE COURT: Those will be available by the 14th.

MS. FINKEN: Our experts?

THE COURT: The Defense will have the rebuttal reports by the 14th.

MS. FINKEN: Yes. The second point I was going to make is that we would request the ability to depose their experts on their supplemental reports as well, in a limited scope, of course, and --

THE COURT: Let's stop there. If I want to stage this so that I want to look at it in the context of the Plaintiffs'

motions -- the Defendants' motions to the Plaintiffs' experts, is there any reason why the Plaintiffs would have to take the Defendants' experts' depositions in the context of the Defendants' motions? Just like I have staged the hearings, if we are trying to --

MR. SNIDOW: Yes, your Honor, if we are going to have -- if this is going to be what the Court understands is the expert's view of what Wang is, we of course want their experts on the record to confirm where possible whether they agree with our experts, whether they disagree with our experts. That is critical.

THE COURT: That is presuming you will have additional briefing. Are you contemplating additional briefing?

MR. CHEFFO: No. Your Honor, there are two things on this. One is, and let's not lose sight, this is a motion -- the Plaintiffs could have just submitted this -- we didn't object to the study. We've told you law lags science, we didn't say law ignores science. We could have said here is a study to read, but they have gone further. They said we have these, some are 25 pages, some are five pages. They want to at the 11th hour submit this.

So, for that privilege and your discretion, you are basically saying, okay, and then we are going to have a deposition of them. It doesn't go further -- this is what I'm concerned about, it's never ending, then there is going to be a

supplemental brief.

They are asking for something that is discretionary at this point. Last week you specifically asked them, are you relying on this study? Now, in fairness they said something like, well, it hasn't been published, but they also said, no, no, we are just showing you, it's for another purpose. Now they are saying we want to supplement and talk about it.

I think a fair resolution here would be if they want to do that, then they should be deposed. We have agreed we will give them the rebuttal reports so they will have the perspective, but going two more steps, to briefing and deposing our experts, seems far afield for the privilege of an 11th hour supplementation of the record.

THE COURT: Why not let the Court receive the supplemental reports, the rebuttal reports, the depositions of the Plaintiffs' experts based on their supplemental reports, so I am really receiving the study, the supplemental reports, and however many persons you choose to have deposed, and I will decide whether I need more briefing and a hearing or anything of that nature. I will know whether I need anything more than that.

MR. GILBERT: Judge, may it please the Court. We will do whatever the Court directs, but I rose because I think it is fundamentally unfair to allow Defense experts to serve supplemental reports in response to ours. They can say

whatever they want.

THE COURT: I'm sorry, what is unfair?

MR. GILBERT: What is unfair is to allow the Defendants' experts to serve rebuttal reports to say whatever they want.

THE COURT: You all just asked for that, to have that before the depositions.

MR. GILBERT: If I may finish. To allow the Defendants -- the stipulation we submitted provides that the Defendants, by October 14th, would submit supplemental rebuttal reports in response to what we served and attached to our motion. That is in the stipulation. The stipulation also provided for no depositions, but the Court would like depositions, and you suggested that --

THE COURT: I haven't accepted the stipulation yet. I had you file it so it would be part of the record so we could talk about it, but I haven't adopted it because I had a lot of questions.

Let me ask you this: What if the Defendants didn't -- I am not sure it is okay or not okay with them, but what if you just did your supplemental reports and the experts were subject to a deposition?

MR. GILBERT: Without a supplements Defense report --

THE COURT: I am asking, what is the Plaintiffs' view on that?

MR. GILBERT: If that is how it was limited, that would be better as long -- in keeping with your prior discussion about a very narrow targeted deposition.

THE COURT: What about the Defendants view on that?

MR. CHEFFO: Coming back to the principle here, which is the Plaintiffs are asking for something extraordinary, for all these reports, and it is true, getting back to we didn't agree in the stipulation, I am referring to that because we are hearing right now -- Mr. Gilbert is saying, you know, we can't just have an expert report from the Defendants without taking deposition, but that is what the stipulation was. They did agree to that. We were going to submit it by next week and that would be the record.

Now you are saying, which is fully fair, that you want to have depositions of the experts. I think where you were going is, we should have an opportunity to submit one or two expert reports, right, because that is fair, and then we should take their depositions. If you need more, then obviously you will get it.

The flip side is that is conditional upon -- they want to submit and supplement the record. If they don't want to have the records and they just want to say here is the Wang study, here is the citation, rely on it, then that is fine, too. If they are asking for things they should also have some efficiency here so we can get on with your Honor being able to

rule here.

THE COURT: Okay. What is the problem with the original stipulation plus the depositions?

MR. GILBERT: My friend, Mr. Cheffo, always talks about the goose, gander rule. The problem with it is, if your Honor is going to accept the supplemental rebuttal reports from Defense experts responding to ours, without allowing us to cross-examine them as to what they put in them, that is fundamentally unfair.

THE COURT: So the ability to cross-examine them on their report.

MR. GILBERT: Correct.

THE COURT: What would be the Defense's choice, no rebuttal or rebuttal and have your one or two experts deposed?

MR. CHEFFO: I am trying to answer your questions directly I have a bit of a constituency, so could I talk to them about that choice?

THE COURT: I know two of you are making closing and probably want to be involved in the discussion, but we still have time, but I would like to get this resolved before you leave. Maybe somebody else can get on the phone with the experts and find out what their schedule looks like over the next couple of weeks. There are a lot of people here.

This is all conditional on this happening very quickly, very quickly.

MR. CHEFFO: I can give you an answer in five minutes, your Honor.

THE COURT: Your experts are available?

MR. CHEFFO: What we are going to do, what our choice is.

THE COURT: What answer are you giving?

MR. CHEFFO: Whether we take a deposition with the supplemental or not.

THE COURT: If you have one or two, it is less of an issue, scheduling two depositions as opposed to five. So the questions out there, depos and reports from the Defense, and then for both sides, availability of your experts. So maybe someone can be making phone calls to find out. Then we can go into closing and wrap it up with what we have learned from our research over the next 20 minutes.

MS. FINKEN: As far as our experts' availability, and we can certainly reach out to them, that is fine, whatever your Honor wishes, but it would be helpful to know if there was going to be a time limitation on the deposition. For example, in the past when there was a supplement with Adami, they asked for additional time to depose Dr. McTiernan and that was limited bu Judge Reinhart to 47 minutes I believe.

THE COURT: Why don't you talk about that. I think they should be limited. I think you all should be reasonable, you don't want to waste money and time. It is narrow, and

there shouldn't be a bunch of objections. You can make them for the record, but you should keep going and I will sift through what I find helpful and what I don't. Why don't you include that as part of your conversation.

MS. FINKEN: I can, your Honor. Just to be clear, it is a lot easier for us to get our experts' availability. If it is going to be a 30, 45-minute deposition, we can find that time.

MR. CHEFFO: There was a 25-page supplement.

MS. FINKEN: On one study, though, it shouldn't take that long for them to be able to question her the same way as it was for the Adami supplement and it was very lengthy as well.

To the extent that your Honor will limit the deposition in time, I do not foresee a problem and we can make our experts available over the next two weeks for a very limited deposition.

THE COURT: If you are not getting the rebuttal until the 14th, you are looking at the week of the 17th and the week of the 24th.

Why don't you see, and I think they should be limited. Counsel could talk while we hear the closing, and if you can't agree, tell me what your respective proposals are and I will make a decision. I will surprise you and rule from the bench on the amount of time for the deposition. I am confident you

can work it out. You all have worked out most everything.

Okay, let's move into our concluding remarks.

MR. GILBERT: Would you be kind enough to give me a warning when I have a minute left?

THE COURT: You have ten minutes. Do you want me to give you a nine minute warning?

MR. GILBERT: Please.

THE COURT: Okay.

MR. GILBERT: Thank you, your Honor.

May it please the Court, Robert Gilbert for the Plaintiffs. Once again our thanks to the Court and your staff for your extraordinary engagement in this very important matter and a special shout out and our gratitude to Ms. Stipes for your dedication to providing us with the most accurate record of these proceedings.

Your Honor, throughout these proceedings we have consistently said this Court's gatekeeping role is limited to reviewing expert methodologies, which includes examining each experts' explanation for their conclusions. That is why the Seventh Circuit in Schultz and Judge Rodgers in Abilify instructed that Daubert does not permit a Court to pick and choose which studies are better or worse in answering the general causation inquiry.

Conclusions are off limits, reasonably explained judgment calls are off limits, and weighting some studies

differently from the experts' weightings is also off limits.

Two weeks ago we promised you we would faithfully apply this the black letter law when we got to our motions challenging the Defense experts and we made good on that promise today. We are not attacking their experts' conclusions.

While we believe the best evidence shows that exposure to NDMA in Zantac can cause all five designated cancers, we recognize that competing evidence would allow a reasonable scientist to reach a contrary conclusion. That is why, at this stage, the focus must only be on methodology, and it is methodology where we focused our motions.

The first point I want to hammer home is that Defendants are inviting the Court to reach its own conclusions. Two weeks ago, the Defendants paid lip service to the relevant law and tried to mask their attacks on legal conclusions as attacks on methodology.

Today their approach was exposed for what it really is, an invitation for the Court to move from the role of gatekeeper to the role of fact finder. Once again, the legal question, as we have talked about ad nauseam for the past three days for general causation is whether the highest realistic exposure to NDMA from Ranitidine could have caused any MDL Plaintiffs cancer, but rather than defending their own experts' methods or attacking our experts' approach for answering those

questions, what did the Defendants do?

They insist on the answer they like and they attack the answers they don't. If that is not arguing conclusions in contravention of Daubert, I really don't know what is.

Mr. Boehm said this when he told you Florian proved, quote, "there is no consistent signal," unquote, essentially arguing that the Court must accept this one sentence from Florian as a matter of law.

The way they justify asking the Court to reach that conclusion is by asking your Honor to pick and choose how to weigh the studies, ignoring the teachings of Schultz, Roundup, Valsartan, and countless other Daubert decisions, pay no heed to Hidajat, dietary studies, or the broad consensus on NDMA's carcinogenicity. Only active comparator studies of Ranitidine are relevant.

Plaintiffs' experts noted serious limitation with these studies for evaluating the general causation question, short followup times, short periods of use, misclassification bias, and confounders in the patient populations. In many cases those critiques mirror the confessions made by the authors of the studies themselves.

How do the Defendants respond? Not by disagreeing with our experts and the study authors, but by pounding the table and saying that no reasonable scientist could rely on those limitations when deciding how much weight to give the

studies.

That is pure argument by lawyers. There is no authority to support the proposition that our experts were not allowed to discount flawed active comparator studies. There is no authority that allows a gatekeeper to make these sort of scientific judgment calls.

On the subject of active comparator studies, the new Wang study, as we have all discussed, shows an increased risk of each of the five designated cancers. Our experts say this study fortifies their conclusions. What do Defendants say?

After previously telling the Court that active comparator studies are the only game in town, they wave their hands and claim that Wang now actually supports them, its findings are just noise, and you must view Wang in context with studies they like. Apparently the sands are shifting. You are only allowed to look at active comparator studies and now you can't positively weight one that is bad for them if there are others they like.

That is not the law. Abilify called an epidemiological study showing an association, plus an expert opinion that the association is causal, quite, and I quote, "powerful evidence of general causation." And that is Abilify at page 1307.

It is obvious they want you to reach the general causation conclusion rather than evaluate the merits of the

experts' methodology, and we respectfully suggest that the Court should decline that invitation.

I have to correct opposing counsel for mischaracterizing Judge Kugler. They claim he admitted that Dr. Panigraphy based only -- they claim he admitted Dr. Panigraphy based only on internal Defendant documents and FDA determinations. They claim Judge Kugler found an association based only on a regulatory finding and internal admissions. They claim because that that is because the Third Circuit law is different, but none of that is true.

The record from Valsartan specifically reflects what Judge Kugler said, and I don't have time to read it aloud, but the record speaks for itself.

The second concluding point is that Defendants' experts had unreliable methods because they answered the wrong question, didn't weigh all the evidence to answer it, and didn't consider it carefully.

The general causation question is a simple one, and it is one we entrust to juries: Could the exposure to NDMA in Zantac have caused any MDL Plaintiffs' cancer. Plaintiffs theory, as we told you last time, is not and has never been that a short period of Zantac use with very few pills ingested is sufficient to cause cancer. NDMA is undeniably dangerous to humans, but it takes more than a little to measurably increase the risk of the five designated cancers, and even after

exposure to enough NDMA, cancer takes time to form.

Every single expert in cancer knows about this latency period, and even Defendant's experts, when they are being honest, acknowledge that undeniable fact.

In light of our theory of the case, it is obviously not helpful to evaluate whether short-term use of Ranitidine causes cancer after short followup period, but that is precisely the question Defendants' experts answer. They focus on studies with short followup times and limited exposure.

For example, the Adami study, which the Defendants love and was done by a Sanofi consultant, looks at users with only ten Zantac prescriptions. In fact, two-thirds of that study are patients with one prescription. Our experts point out that a serious flaw of Adami is it focused on short-term users because one or even ten prescriptions do not equate to years or decades of use that match the MDL registry population.

Defendants' experts don't even have to agree with ours. Perhaps they could have come up with a scientifically valid explanation for why someone who filled at least ten prescriptions would be highly likely to continue taking Zantac year after year to match the registry.

If they had done that, both Plaintiffs' and Defendants' experts could testify.

THE COURT: That's nine minutes.

MR. GILBERT: Thank you. If they had done that, even

though our experts would vigorously disagree, at least they would be attempting to use Adami to answer the right question.

By focusing on the wrong question it is no surprise that Defendants reached their conclusions without considering all the relevant evidence, running afoul of Abilify.

Your Honor, in summary, as you consider Plaintiffs' Daubert motions, we ask that you ask yourself the following questions:

One, which set of experts were intellectually honest?

Two, which experts candidly acknowledged the evidence that cut against their client's position and explained it?

Three, which undertook the rigorous and complete scientific inquiry that Daubert demands?

We submit that the only answer to those questions is that Plaintiffs' experts did and Defendants experts did not. For that reason you should exclude the Defendants' experts.

Thank you.

THE COURT: Thank you. That was about ten minutes and 19 seconds.

From Defense.

MR. PETROSINELLI: Thank you, your Honor, Joe Petrosinelli here. If I could get a one minute warning, too, that would be great.

THE COURT: Yes.

MR. PETROSINELLI: Your Honor, I am here to talk about

some legal principles to bring us home here. I want to pick up on a couple things we just heard form Mr. Gilbert. He said conclusions are off limits. Of course that is an inaccurate statement of the law. Chapman, all the Eleventh Circuit cases quote Joiner that said, conclusions and methodology are not entirely different. Chapman in particular says that the Court should go on and judge whether there is too great an analytical gap between the conclusions and the methods, and that is a lot of what our position has been.

I want to talk about the issue of dose because that has been a huge focus two weeks ago and today.

Mr. Gilbert just cited Schultz, a Seventh Circuit case, Roundup, a Ninth Circuit case, and Valsartan, a District of New Jersey case.

As I said to you earlier, they have said two weeks ago, and then they are all in today, that in an MDL, to get past general causation in a toxic tort case all you have to do is show a dose that -- the highest level of exposure, duration and dose that anyone in the MDL had, and then everyone in the MDL, even the lowest dose people, pass general causation. That is completely contrary to Eleventh Circuit law and, frankly, MDL practice.

Next slide, please.

I showed you this slide two weeks ago. These are the quotes from McClain and Chapman, and the Plaintiffs said today,

well, those were single Plaintiff cases, they were not an MDL.

Number one, that is not true actually. McClain had four Plaintiffs in it, and of course Chapman was part of an MDL, it was a single Plaintiff case, but Judge Altonaga had the MDL. So that is number one.

Number two, nothing in these cases say this only applies when it is only a single Plaintiff, this wouldn't apply in an MDL. Of course it does apply in MDLs. When I hear the suggestion that you only look at general causation with the highest doses, and if we can show a study that has that dose we pass everything, I know a lot of MDL judges would be shocked to hear that statement.

Judge Gergel, in the Lipitor MDL, Judge Bryer, one of the most experienced MDL judges in the country, in the Celebrex MDL, these are pharmaceutical MDLs where they said, Plaintiffs, you have to show us the dose, and what they found was at the highest dose you can get past general causation, but at these lower doses, no, there is not reliable evidence.

Under the Plaintiff's logic, if that were true, if their standard were true, those cases would have said, oh, you get past the highest dose, so everyone comes in, that is not the way the law works, in the Eleventh Circuit for sure, and certainly in pharmaceutical MDLs.

Next slide, please.

What have we learned? Remember two weeks ago the

Plaintiffs made this statement, and you asked them, could you rely on this, and they said yes. Their general causation theory is many years of regular use, and you might remember some frustration two weeks ago because you and we kept asking, what is the reliable evidence, how many years, what does regular use mean, and they really couldn't answer it two weeks ago.

We saw about 25 slides today where they tried to answer it finally. What did we see?

Let's look at the next slide.

These are Plaintiffs' slides you saw today, and I heard Mr. Snidow begrudgingly finally admit, albeit in his rebuttal argument, that threshold dose matters, because he said, using this slide, well, you could have a dose that is above the dose that anyone in the Plaintiff pool could have.

Number one is, I said that is not the standard, it is not what the highest dose a person has, but the point that we have made is that they have no reliable evidence of what the threshold dose is. What is the dose at which human beings generally who use Ranitidine can have an increased risk of cancer? That is what they have to show.

By the way, I should say, of course our motions as to their experts and their motions as to our experts highlighted the issue of they have no reliable evidence of an association between Ranitidine use and any cancer at any dose. So it is

sort of like if that question is decided in our favor, it doesn't really matter what the threshold dose is. They don't even have that.

If we were going to get to this -- next slide, please -- this is what they told you today their dose is. They say they have identified numerous doses shown to cause cancer, and they have six doses along the side there.

Now, number one, they have five cancers here, they have to say what is the dose from a general causation standpoint that could cause each of these five cancers separately. It is not the same dose, it couldn't possibly be because of the different cancers and different organs involved.

So, these numbers here are from all different cancers, number one.

Number two, this is nothing more than what we talked about two weeks ago. You see the numbers 3.8, and above that, 6.6, 7.5, that is Dr. Salmon and Dr. Panigraphy's charts, we talked about that two weeks ago, that were based on the Hidajat study and NDMA dietary studies, not Ranitidine epidemiology. So that is those four numbers.

Then the three years is from Cardwell, the bladder cancer finding, which I will talk about in a second, and the one year is the new Wang study. Now they say we have -- at least we have three years and one year for bladder cancer and liver cancer, not the other three.

They have no -- this chart shows you, they have no dose testimony, minimum threshold dose, which they have to show in the Eleventh Circuit, based on Ranitidine epidemiology for three of the five cancers, so those are gone under the Eleventh Circuit law.

Now let's look at these two.

Next slide, please.

They showed you this to support their three years for bladder cancer. This is what Cardwell shows, and this is in fact data from Cardwell. It is the comparison with the nonuse population. Mr. Snidow, I am sure he misspoke, said that this was data comparing Ranitidine to the active comparator from Cardwell. That is inaccurate.

This is comparing Ranitidine use to nonusers. What Cardwell then did, as you know, is compared Ranitidine users with active comparator groups and the association went away. There was no dose response, there was no association at any dose. So they have nothing on bladder cancer.

And then finally -- next slide, please -- the latest is on Wang, and this is a chart that Mr. Tobey showed earlier today. Yes, in the active comparator study Wang, that study showed a dose response relationship in the active comparator group. Of course Adami, which did it for liver cancer, a dose response analysis, showed no dose response relationship.

So, you have one study that did and one that didn't.

No reliable scientist would conclude, even if Wang was the only study, would conclude that this is reliable evidence of dose response, but surely not when you have Adami which has longer followup than Wang, that that would be a reliable finding.

Next slide, please.

What you saw today moreover is lawyer argument. Dr. Moorman and Dr. McTiernan, they don't say any of this, they say none of this. Dr. Salmon and Dr. Panigraphy had the charts that we talked about. But on the Ranitidine epidemiology they were asked, "they" meaning Dr. Moorman and Dr. McTiernan, point blank in their depositions, tell us what the dose response curve is for Ranitidine use in any of the five cancers.

This is what Dr. Moorman said about the Ranitidine studies: You really can't describe anything about dose response, other than she notes the Cardwell finding on nonuse.

This is lawyer argument that they are sort of flailing for an answer on this. They didn't have one two weeks ago, they had one today. It is no better than they were two weeks ago. They have no reliable evidence on dose or dose response for any of the five cancers.

THE COURT: That's nine minutes.

MR. PETROSINELLI: This is my last slide.

Your Honor, I leave you with the fundamental methodological point here, both as it relates to our motions and as it relates to their motions, which is the law lags

science point.

In all these cases, and I told you this two weeks ago -- I don't know if you remember i showed you the slide with all the pharmaceutical MDLs that have excluded general causation opinions, and all of these judges make the same points that the Eleventh Circuit has made, which is that we are not saying this is junk science, quote unquote.

We are not saying these experts aren't qualified. We are not saying these experts don't honestly believe that the evidence is good enough for them, but they can't -- you can't get ahead of the science, and the science here has not concluded, no one outside this courtroom has concluded that there is a causal relationship.

Look at what has happened, Wang now comes out. We can fight about what it means and what it doesn't mean. The science, maybe it will develop more, maybe it will develop in their favor. I don't think so based on what you see in Wang and other studies. But, as the Eleventh Circuit says, you have to accept the state of the science as it is, and methodologically the state of the science as it is does not show reliable evidence of a causal association.

Thank you, your Honor.

THE COURT: All right. Thank you. It looks like everybody came back in to report on hopefully an agreement on how you see a path forward for the supplemental reports and

depositions.

If there is anyone who needs to catch a flight, you should feel free to leave. Don't worry that I would be judging you if you left.

MR. MADERAL: Good afternoon, your Honor, Frank Maderal for the Plaintiffs. There was a back and forth that Plaintiffs wanted to clarify that we had with your Honor a moment ago. When Ms. Finken was speaking of the purpose of the supplements she said the experts are not changing methodologies, they are not changing their conclusions, they are bolstering their opinion with this additional piece of evidence that has just come out.

After a few back and forths after that, what we are not doing with the new expert reports -- I don't know if this was intentional or not, but one of the things your Honor mentions was you said we are not bolstering the opinions, and Ms. Finken agreed.

So, I think we have an inconsistency there, and I do think it is important for the Plaintiffs, our position is that we are indeed bolstering for the purpose of the 702 analysis the opinions with the supplement of the Wang report, if that is clear.

THE COURT: Maybe I shouldn't have used that word.

You can't redo your opinions, but you have a new study and you want to tell the Court how your experts have included

this study in their opinion, and so that is what I want to know.

MR. MADERAL: That is correct, your Honor. Thank you.

THE COURT: Okay. That was the easy part.

MS. FINKEN: He just felt left out.

MR. MADERAL: That was the easy part.

MR. CHEFFO: We have some good news and maybe some not good news. We did talk.

THE COURT: That is good.

MR. CHEFFO: That is good news. I wanted to tell you the good news. In terms of timing, and Ms. Finken will tell me, we could probably agree on timing of when it should occur. Like by the 14th we would submit our supplement. The next week, to the extent there are depositions of Plaintiffs, it would be that next week, and then the following week would be the depositions. So we know kind of by the 28th or 29th of October at the latest that it was all done.

THE COURT: Defense rebuttal report on the 14th, and depositions on the week of the 17th and 24th?

MR. CHEFFO: Yes, a week after that.

THE COURT: 14th to the 21st?

MR. CHEFFO: Realistically probably the following week, like you said.

THE COURT: So by the 21st?

MR. CHEFFO: Right, before we put it in stone, we have

a fundamental disagreement on the amount of time that we would take.

THE COURT: Okay. First of all, who would be deposed?

MR. CHEFFO: Anybody who wants to continue to have their report considered.

THE COURT: Anyone who wants to do a supplemental report based on Wang will be deposed.

MR. CHEFFO: It wouldn't be any more than the five who have already done it, but if somebody said I check out, then we wouldn't depose them.

THE COURT: No more than five. The Plaintiffs, right, no more than five?

MS. FINKEN: Of the Plaintiffs' experts, yes, your Honor.

THE COURT: Did we decide for Defense?

MR. CHEFFO: We are in that process, but as I said to you, I don't think it will be more than two, it could be one. Either one or two.

THE COURT: We have agreed on that. We can't agree on how long the depos will take?

MR. CHEFFO: I basically proposed -- and again, beauty is in the eye of the beholder. We thought that of the five experts, because some are longer than not, we would have -- for three of the experts we would have no more than three hours, and two of the experts we would have no more than two hours to

take these, and that seems to be the way these depositions go, you can't do too much more than that.

The Plaintiffs were thinking 45 minutes to an hour, which I said was completely unacceptable, and I said we would oppose the motion because you can't really do that.

THE COURT: What was the Plaintiffs' position on how long the depos should take?

MS. FINKEN: Your Honor, what we offered up was similar to what Judge Reinhart had ordered previously with the other supplement on the Adami study, which is a 45 minute to one hour deposition. This is a limited deposition regarding one study. Four out of the five expert reports that were served were six pages or less, your Honor. It certainly does not require two to three hours of cross-examination, especially given the fact that most of these experts have already sat through a ten to 12-hour deposition. Dr. McTiernan has already sat for 13 hours of cross-examination on her report and her supplemental reports.

An additional three hours on top of that we believe is unnecessary for purposes of asking about one study and one supplement.

MR. CHEFFO: First of all, it is not just one study. Dr. McTiernan's report is 27 pages, and going back to principle number one, this is something that is discretionary.

The idea that we are quibbling about a little bit of

time when the Plaintiff are asking for 45 minutes to an hour when they were able to mobilize all these people on three days and essentially work around the clock seems not consistent with that.

MS. FINKEN: Your Honor, as of an hour ago Defendants didn't feel it was necessary to take a single deposition of any of these experts on the supplement. Now they are saying they require three hours, and it is excessive, your Honor. They have already sat for 12 to 13 hours. This is a single study that you are requesting that they be cross-examined about, and they should not be subjected to one to three hours of cross-examination. Thank you.

MS. CANAAN: Your Honor, may I say a couple of words about Dr. McTiernan's deposition? One of the first questions I asked her -- she submitted a supplemental report on the Adami study because she was not able to answer any question about the Adami study previously. The first question I asked, are you relying on the Adami study for your opinions? She took literally 15 minutes, we counted, to answer that question. That is why we, respectfully, are asking for three hours. Thank you.

MS. FINKEN: Your Honor, I would like to add, we know that the Court wants these depositions and that the Court feels they are necessary, and to the extent the questions are asked of our experts they will be responsive. They can do that

within an hour time frame.

I would suspect that if the Defendants do not believe they are responsive to those questions they will be back in front of the Court with their complaint. That is something that has happened, it has been denied by Judge Reinhart multiple times that they have brought a request for additional time because they believed Dr. McTiernan was unresponsive, and Judge Reinhart disagreed on the record. He said he did not agree with Ms. Canaan's position, and that he believed Dr. McTiernan was responsive during that deposition.

THE COURT: When you are talking about your overall time, how have you discussed direct and cross?

MR. CHEFFO: Well, there are a few little things in our stipulation, and you raise a good question, your Honor. Two issues we raised, if this drags on your Honor is addressing that. Second, this is back filling. I don't think the suggestion here is that there is clarifying recross, but this shouldn't be an opportunity for a full trial type of thing.

So I think within that, it would be -- we would get the three hours, and if they wanted to ask some clarification questions that were fair, just like we would, then that would be outside, and that should be limited to 15 minutes, 20 minutes, whatever it is.

THE COURT: Whatever time you are agreeing to, that is for the Defense and then the Plaintiff would take --

MS. FINKEN: We have addressed this previously with Judge Reinhart and how we addressed it is, if the Defendants have a one hour block of time to take the deposition, they can reserve from that time rebuttal, and then Plaintiffs have an equal amount of time, whether it is the one hour, we would have an equal amount of time to do a direct of our witness after the fact, and they can reserve their rebuttal.

This has happened with every deposition we have taken in this case so far. To limit us being able to rehab witnesses to ten minutes when they are requesting a three hour deposition is patently unfair, your Honor.

THE COURT: Other than not agreeing on how long the deposition should take, what else -- we talked about 10/14 for the Defendants' supplemental reports, depos completed by 10/24. When would the Defendants be?

MR. CHEFFO: The following week.

THE COURT: You should try to get this done by the end of October. Maybe we say Plaintiffs deposition -- if you want to look at the calendar, we have the week of the 17th, the week of the 24th, and October 31st, and that goes into November.

MS. FINKEN: Respectfully, your Honor, we would be able to schedule this much quicker if you gave us a deadline for all of them, instead of staggering Plaintiffs and the Defense. To the extent that we can maneuver them -- if you want them all done, for example, by October 31st, and issue

that order, Plaintiffs and Defense, we can work among ourselves.

THE COURT: Isn't that when you had to get your depositions done last year? Are we having deja vu?

MR. CHEFFO: If we do on the 14th, a Friday, we provide our reports, we have the following week, until the 21st, to do the Plaintiffs' experts, and then we have until October 28th, before Thanksgiving, to finish. The first week is theirs, and then the week to do the one or two depositions of ours, and we are done by the 28th.

THE COURT: What other issues do you think need to be addressed?

MR. CHEFFO: There was something in the stip that maybe you can agree, I think we did, which is, if we don't -- we are trying not to pile on and have all of our experts file reports, but if the Court would allow the experts to pass, we would put a footnote that we would have an opportunity to submit a supplemental report after the fact. We would like to make sure we are not waiving that.

Rather than force us to do it all by the 14th, we would like to be more surgical about it.

MR. GILBERT: Your Honor, that is unacceptable to Plaintiffs. That was part of a negotiated stipulation which the Court has not accepted. As part of that stipulation the Defendants waived the right to take any depositions. We are

not agreeing to that any further unless -- any expert they want to put up for a supplemental report, they can put them up now on general causation.

MR. CHEFFO: It seems like we are trying to do what I thought we were doing, which is trying to string this out to December or January. Now they are going to force us to file reports that say the same thing and then subject them to depositions. I am not really sure what the ask here is.

THE COURT: Okay. Anyone else want to be heard on any other issue as it relates to this? No. Okay.

All right. Happy Friday, save travels, good to see everybody. Sorry to have to end on a little bit of a contentious note, but I appreciate everyone's presentation today. Thank you very much.

(Thereupon, the hearing concluded.)

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I certify that the foregoing is a correct transcript from the record of proceedings in the above matter.

Date: October 10, 2022

/s/ Pauline A. Stipes, Official Federal Reporter

Signature of Court Reporter