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
May 12, 2020

VIDEO CONFERENCING of
STATUS CONFERENCE and SUMMARY of LAW and SCIENCE

BEFORE THE HONORABLE ROBIN L. ROSENBERG
UNITED STATES DISTRICT JUDGE and
THE HONORABLE BRUCE REINHART
UNITED STATES MAGISTRATE JUDGE

Official Court Reporter: Pauline A. Stipes
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THE COURT: Okay. Good morning, everyone. I hope that all of you are as excited as I am this morning to listen and learn throughout the day. There are many participants with us today on the Zoom call/video session and for the record, everyone is appearing by Zoom due to COVID-19. Leveraging the benefit of the delay from COVID-19 and the time the parties have had to develop their understanding of the case, I have asked that today and tomorrow the parties provide a road map of the litigation, a summary of the law, the science, their vision for case management, as well as the more traditional updates on where they are in discovery and developing proposed orders for the Court to review.

While I intend that this will be a helpful launch pad for me in accelerating my thinking about the case, you will quickly glean that my goal is for you to have a chance to educate the others within the court who will assist me in this case, and equally important, those on each side who may not be involved in the day-to-day negotiations that have been occurring, such that this is their first opportunity to hear directly from the other side about their view of the case.

Having reviewed the PowerPoints that our presenters submitted to me in advance, I want to thank you for taking the time to put together such thorough presentations. I can see the great effort that has gone into this endeavor. Equally, I want to thank you on behalf of all of those joining our

conference today for that work, which I believe will help all of our attendees greatly appreciate and advance their understanding of this litigation.

Now, while we had two full days last week of interviews from very, very talented applicants and many of those applicants, in answer to some of my questions, shared with me their vision of the case generally and/or specific issues related to this litigation. I want everyone here to know that I start today with a clean slate. I have not prejudged the case in any way, or any of the issues, and I come with a completely open mind in learning about both the substantive areas of law and science and about how best to manage this case.

While I have issued a number of pretrial orders, I think we are up to 20 or so, and much progress has already been made to date, there is no doubt that this is a very important day for me as it is the first time that I can hear directly from the parties about the issues you have outlined on the agenda and I have very much waited for today to start to form my opinions about the litigation.

I value and appreciate everyone's perspective and, as one who prior to joining the bench, has had a varied career serving as a Plaintiffs' lawyer, serving as Defense counsel in a major firm, serving as general counsel, and owning my own firm and a Government attorney as well, I know how important it

is to be heard and to be able to communicate your own unique perspectives.

This is the day where the Plaintiffs' leadership and the Defense leadership teams will educate me, Judge Reinhart, and the many other attorneys, parties, and other persons who are interested in this litigation.

I want to point out how much I appreciated hearing at the interviews that there was a widespread sense that not only have the two sets of co-leads worked diligently, but they have worked to productively resolve the differences that have arisen over the past several months.

While the Court is always available to hear any dispute or motion, I very much appreciate that the parties and special master have worked to narrow those areas of disagreement and reached agreement where possible and I want to applaud them for that work and how well they have worked together so far.

I know that the special master has conveyed my expectations and sentiments in that regard, but I felt it was important for you to hear that from me today directly.

I find Special Master Dodge's insights to be helpful in my thinking, and I hope that you have as well, and she has been a helpful sounding board in your own thinking as she seems to have a very informed and at times almost intuition about this very complex litigation.

I believe she will not just be a great resource for all of us, but also very helpful in helping make this MDL much more efficient and in turn cost effective for all parties, so I encourage you to continue to take advantage of her as a very helpful resource.

I want to take this opportunity to introduce someone whom you have not yet had the opportunity to meet yet, Judge Reinhart, the magistrate judge with whom I am paired. If I could ask Judge Reinhart to turn his video on for a moment while I brag about him. He might need a cohost to turn his video on. There you go. And his audio is muted for a moment.

Let me say a few things about Judge Reinhart and see if there is anything he wants to say. Judge Reinhart is the magistrate assigned to the case, I am paired with him. I have another magistrate judge whom I am paired with in Ft. Pierce. I hear matters in Ft. Pierce and West Palm Beach. Judge Reinhart and I work closely together.

So you are aware, he watched all of the interviews last week, has read all of the submissions, and has been closely watching the case and educating himself. Judge Reinhart and I work very closely together on all cases with which we are paired. We truly have a working partnership and together we try to offer the best of our time, our knowledge, and respective roles to the parties and attorneys in the case.

We do share similar goals, values, and vision for how

to manage our cases, while recognizing that every case is different and does call upon different tools and different approaches.

Judge Reinhart brings a wealth of experience to the bench from his prior career in both the criminal and civil arena and, as a magistrate judge, he has become immersed in civil litigation, including complex discovery matters. He has spoken at various conferences and is as knowledgeable as anyone I've met as to the nuances of discovery and the tools that come along with complex discovery matters.

He is so well regarded and liked that he has a very high consent rate, meaning he has taken cases away from me. Many of the parties consent to his full jurisdiction, not only discovery matters, motion, but trial, all the way to final judgment, and he is accessible, extremely bright, hard working, curious and creative in working with parties to manage tough discovery issues.

Tomorrow Judge Reinhart and I will be appearing by Zoom together. I wanted you to meet him today. And I don't know if you want to say a brief hello.

MAGISTRATE JUDGE REINHART: I am not sure I should add anything to that. I go nowhere but down.

I want to tell the parties, I do look forward to working with you and Judge Rosenberg in this fascinating litigation. I have been starting to learn about this case. I

was able to watch all of the Plaintiffs' interviews, and I read the submission by the Defense and it bodes well for me and Judge Rosenberg that we have such good lawyers in the case, the expectation we will have excellent briefing and argument and issues that we need to have decided will be framed out well.

I share Judge Rosenberg's commitment to the values in Federal civil procedure, one to bring this case to as just, expedient and inexpensive litigation as we can. I have no background in MDL pharma courts. I do manage a lot of discovery, and we can talk about this tomorrow.

I am fully committed to working with you on any creative or innovative ideas you may have to frame the issues and get the information exchanged as fast as we can so the parties can do the legal work in this case.

With that, I thank Judge Rosenberg for giving me a few minutes, and look forward to working with you.

THE COURT: Thank you very much.

So, too, my law clerks are joining us, although they are not appearing by video, but they are on, rest assured.

I have let all of them and Judge Reinhart know that if they have any questions, they can submit them to me. As you can see, I am looking off to the right, I have various electronic tools for people to communicate with me during the presentation today, but they can submit them to me, and I will try to ask them during the Q and A portion if I think it is

appropriate.

I say that as you may see me taking notes or typing during your presentation, and it may simply be that I am coordinating with them, so you should not read too much into that. Please know, as I mentioned at the interviews, you have my undivided attention at all times. Even though my eyes are looking to the right, I am listening, I am not multitasking. Everything you are doing today, I am listening to.

I believe through their questions, we may get at issues that are important for our Leadership Development lawyers on the Plaintiffs' side, for retained counsel who may not be familiar with MDLs, or for the third parties who have asked to join us today who are not affiliated with either the Plaintiffs or Defense. To that end, my clerks may have question that I may know the answer to after years on the bench, but which I believe would be useful to others watching these proceedings to hear the answer to, and so I may ask those question in the question and answer session.

That, in turn, means you should not assume I am not familiar with the law of Daubert and the Eleventh Circuit, with choice of law in MDLs, or whatever other topic our presenters may raise. Rather, I see today as not just educating me, and I have certainly a lot to be educated about, make no mistake about that, but all of the stakeholders in this litigation. I will ask questions to the extent that I see those gaps in the

presentations by either side today.

Having been in your roles before, I know that at a first hearing there is always an instinct to try to "read" the judge, and with the stakes in this litigation, I can imagine that it would be more so. I therefore wanted to be transparent with you that the questions I ask are not the result of any ideas that I have, and instead are truly geared toward making sure that all of the stakeholders in this litigation are as well informed as possible, so that you are not drawing any mistaken inferences.

With that, I am excited to hear from you for the first time in person about your views of the case.

I would like to recognize Mr. Gilbert and McGlamry, who I believe are going to be opening up, but let me just say for the benefit of not only me, but our court reporter who is transcribing the proceedings, that if each presenter, upon the first time that you are presenting, if you would just introduce yourselves with your full name so Mrs. Stipes can take that down.

And with that, I will turn it over.

MR. GILBERT: May it please the Court, good morning, your Honor.

THE COURT: Good morning.

MR. GILBERT: Is my audio okay?

THE COURT: Perfect.

MR. GILBERT: Let me just get set here. May it please the Court, good morning, Judge Rosenberg and Judge Reinhart, and the entire court staff who have made today possible.

First, on behalf of the co-leads, Plaintiffs' Steering Committee -- excuse me, Judge, I ran afoul of your first request. This is Robert Gilbert speaking on behalf of the Plaintiffs. Let me start over.

Good morning to you, Judge Reinhart, and the entire court staff. First, on behalf of the co-leads, Plaintiffs Steering Committee, committee chairs and Leadership Development Committee, we express our gratitude and appreciation for the confidence the Court has entrusted in us. We pledge to zealously represent and advance the interests of all Plaintiffs and claimants in this MDL to the very best of our ability, to work with our Defense colleagues with professionalism and civility and to conduct ourselves before this Court with integrity, honor, and respect.

Second, we extend our thanks to Special Master Dodge who, as you noted, has worked tirelessly with both sides since the first days of this litigation, including fashioning today's presentations. The parties are fortunate to have Special Master Dodge involved in this MDL, and we look forward to her continued service.

Third, we extend our thanks to our Defense colleagues with whom we have worked over the past few months. While we

have extremely different views of the facts and law that will lead to the ultimate outcome of this litigation, our civil justice system cannot work without civility, collaboration, and mutual dialogue. The past few months have proven that even during one of the most disruptive periods in our nation's modern history. Lawyers on both sides of the aisle can indeed work together. We are confident the relationships we have already established with our Defense colleagues will set the stage and tone for the remainder of this litigation.

Your Honor, multi-district litigation holds a unique place in our civil justice system. MDLs bring together before one Federal District Court for coordinated and sometimes consolidated pretrial proceedings the claims of hundreds, thousands, or millions of people whose claims share common facts. Given the substantial number of claimants, as well as the scope and magnitude of the claims and defenses that are asserted, MDL proceedings generally look and operate differently than most civil cases, but at their core MDL proceedings share the same foundation as all civil cases, indeed all cases. Like all cases in our judicial system, MDL proceedings involve a search for the truth, albeit in a larger and more complex setting.

Today marks the official beginning of the search for the truth for what may ultimately be hundreds of thousands of people who were diagnosed with cancer following their use of a

drug marketed as a safe and efficient treatment for heartburn and stomach ulcers prior to its sudden withdrawal from the shelves a few months ago, many, many years after it was first marketed to the public.

Today also marks the beginning of the search for the truth for what may ultimately be several million more people who purchased and/or used this drug and have not yet been diagnosed with cancer, but who now live with the knowledge that they face an increased risk of developing cancer after taking this drug.

Today marks the beginning of the search for the truth for how and why we are here, how and why this drug was developed, how the companies that developed and manufactured it got the FDA to approve that it was safe, how the ingredients in this drug affect -- excuse me, how the ingredients in this drug affect humans and why thousands of people have developed cancer after taking this drug, how and why it took more than 35 years before someone other than the Defendants brought this public health crisis to the FDA's attention, and why the drug was withdrawn from the market.

These are just some of the questions we expect to answer in our search for the truth in this MDL.

I've heard judges sometimes say that civil litigation is more like a marathon than a sprint. That analogy is especially appropriate here. Today is the start of the Zantac

MDL marathon. The Plaintiffs leadership team has been training for months preparing to embark on what may be a 26-month or longer marathon until we reach the finish line. At the start, a gaggle of lawyers will be bunched up trying to set the pace, some wanting to push it faster than others. Others understand that it is a long race and it's not about who has the best time in the first few miles, but who has the staying power to reach the finish line.

I will try to make my point with a brief look back in MDL history. In 1999, American consumers began buying and using a drug approved by the FDA and marketed as a safe and revolutionary non-narcotic painkiller.

For years millions of people purchased and used Vioxx without fear of serious consequences, but in September 2004 Vioxx was suddenly pulled from the shelves of every pharmacy in this country based on revelations that it caused heart attacks. Within days lawyers across the country began filing lawsuits seeking damages on behalf of Vioxx victims.

In February 2005, the JPML created the Vioxx MDL and assigned it to District Judge Eldon Fallon to preside over coordinated and consolidated pretrial proceedings. Two weeks later, Judge Fallon appointed Plaintiffs leadership and the Vioxx marathon began to move forward in earnest. In November 2007, approximately 30 months after the start of the Vioxx MDL, following fulsome discovery that uncovered evidence that had

never before seen the light of day, extensive motion practice and bellwether trials, the parties announced a $4.8 billion settlement for the victims of Vioxx.

Like Vioxx, Zantac was approved by the FDA. Like Vioxx, for years Zantac was marketed and sold to millions of people as a safe and effective drug to treat heartburn and GERD. No sane person would have taken on the risk of cancer and a possible death sentence in exchange for treating their heartburn. Like Vioxx, the makers and sellers of Zantac suddenly pulled it off the shelves in late 2019 following FDA concerns that it was unsafe.

Like Vioxx, civil lawsuits were filed in the days and weeks thereafter, ultimately leading the JPML in February of this year to create the Zantac MDL and transfer all cases filed in Federal Courts across the country to this Court for coordinated and consolidated pretrial proceedings.

Last Friday, as you noted, this Court appointed Plaintiffs leadership to prosecute the claims of all Plaintiffs and claimants for personal injury, wrongful death, medical monitoring, and economic loss arising from their purchase and/or use of Zantac.

Today marks the opening bell of the Zantac MDL marathon. As you noted in PTO 16, this Court directed both sides to make presentations on foundational topics and key concepts in this case to assist the Court in learning about

some of the factual, legal, and scientific issues the parties anticipate will be developed during the course of this MDL. Over the past weeks, as both sides prepared for today, we were reminded time and again that today is not the trial, it is merely the beginning of the Zantac MDL marathon.

We were directed to present opening statements, but both sides understand that these are not opening statements we will present to the people who sit in the jury box in your courtroom toward the end of the marathon. We were directed to make presentations about some of the over arching legal issues, but both sides understand that today is not about arguing motions for summary judgment, which will come much later in this legal marathon.

We were directed to prepare foundational science presentations, but both sides recognize that this is not the general or special causation hearings, which will come much later in this legal marathon.

For the next few hours, your Honors will hear both sides make these presentations on foundational topics and key concepts in this case. In just a moment my colleague, Mr. McGlamry, will help frame the Plaintiffs' position. He will present an overview of the facts, themes, and likely sources and categories of evidence from the Plaintiffs' standpoint, and touch on the personal injury and wrongful death claims we'll prosecute on behalf of individuals diagnosed with cancer as a

result of their usage of Zantac and Ranitidine drugs. After Mr. McGlamry, I will retake the screen to give an overview of the class claims and complete the Plaintiffs' opening statement. Then you will hear presentations from our Defense colleagues.

In part two you will hear about some of the over arching legal issues both sides expect to arise in this litigation. In part three, after lunch, you will hear some foundational science presentations relating to the science of Ranitidine causing cancer that both sides expect to develop during the course of this litigation.

Later today we will address some of the case management issues the parties have been discussing and working on over the past couple of months.

At this point, I will turn it over to my colleague, Mr. McGlamry.

THE COURT: Thank you.

MR. McGLAMRY: Thank you, Mr. Gilbert. While I wait for the PowerPoint to come up, your Honor, I want to thank you both this morning and Special Master Dodge and counsel for the Defendants.

I would like to say that MDL 2924 -- here we go -- and as I was standing here listening to Mr. Gilbert, I realized that if you added those numbers up, you get to 17, which I guess means 17 and 0 in honor of Coach Shula and the Miami

Dolphins.

Let me start. Making an opening statement at the beginning of a case is somewhat ironic and premature without discovery because we don't know all that we need to know, but it is undisputed that we do know this: That last fall we saw a dramatic turn of events that led to April 1, 2020, when the FDA announced a recall in the form of a market withdrawal of all Ranitidine containing products, or Zantac. Zantac and Ranitidine are synonymous, and for purposes of this presentation, I will generally refer to them both as Zantac. The recall covered all Zantac, prescription, over the counter, brand, generic, injection, syrup, granules, pills and capsules.

That was unprecedented for the FDA to issue a recall, and you have to know that with the multibillion dollar a year drug at issue and the liability that could follow, that all the lobbying industry organization pressure and scientific resources were marshaled to stop it, not just here, but worldwide.

On September 9, 2019, Valisure, Inc., after months of informal efforts to move the FDA to act, filed a citizen's petition calling for a recall due to their testing which confirmed exceedingly high levels of NDMA in pills. Then, less than four months later another lab, Emery Pharma, also filed a citizen's petition showing that NDMA accumulates at unsafe rates when exposed to heat during transport and storage.

In the meantime, the cards began to fall. Brand and generic manufacturers and retailers started recalling these products over their concerns of NDMA found in the medicine, out of a concern that it might contain a carcinogen, and because unacceptable levels of NDMA were discovered in Zantac.

Between September 9, 2019 and April 1, 2020, based on additional testing, studies, and reports, 43 countries and jurisdictions acted to restrict or ban Zantac products.

So, on April 1, 2020, the FDA acted saying that a recall was an effective method of removing or correcting defective FDA regulated products, particularly when those products present a danger to health. The FDA acted to protect the public health from products that present a risk of injury and because, quote, "the product being recalled presents a serious health risk."

By the end of the month, April 30th, the EMA, the European Medicines Agency, also recalled all Ranitidine medicines due to the presence of NDMA.

So let's think about this, Zantac -- Ranitidine is the molecule with the brand name Zantac, and it has been on the market for nearly 40 years. The FDA said it was safe and effective, now it says it is not. Now, after allowing Zantac to be sold for 40 years, the FDA has had to essentially take it back and make a monumental decision rarely seen absent an extraordinary risk.

So let's go back to the beginning.

In the late 1970's, Glaxo, a relatively small pharmaceutical company, came up with the Ranitidine molecule and branded it as Zantac. It was an effort to respond to Cimetidine, which was a molecule branded as Tagamet by SmithKline, which was then the leading product in this class of drugs.

Glaxo made the molecule on a computer and, boom, Glaxo was on the map. Zantac made Glaxo and so now they have everything to lose. Ultimately, and as the result of the money generated by the sale of Zantac, Glaxo bought SmithKline and now, as you know, your Honors, we have GSK.

Essentially, Glaxo took the Cimetidine molecule and reconstructed it by adding two compounds, nitrose, which gives us the N, and dimethylamine, which gives us the DMA. In the body they break off and join to form NDMA. Our science group will later show you this molecular design.

So, what is this NDMA?

It is a potent human carcinogen discovered as a byproduct of manufacturing jet fuel in the early 1900's. Today its only use is to induce cancerous tumors in animals as part of laboratory experiments. Its only function is to cause cancer. It has no business being in the human body, but it gets in through Zantac. It is not unlike a Trojan horse with the gift offering, the Zantac pill, but secretly exposing the

body to an unacceptable cancer threat.

Now, NDMA is found in cigarette smoke, too, at levels that have been measured between five and 43 nanograms per cigarette, which is an unquestionably small amount compared to the NDMA in one Zantac pill, and everybody knows the carcinogenic effect of cigarette smoke.

So, over this 40-year period, based on the information and science provided by these manufacturing Defendants, the FDA accepted an allowable daily limit of 96 nanograms of NDMA in a single dose, but now researchers have discovered over 3 million nanograms being introduced into the human body after ingestion of a single Zantac pill.

GSK knew about the NDMA problem long before Zantac came on the market. In 1981, in a well-known journal, The Lancet, researchers found that when Ranitidine was exposed to human gastric fluid in combination with nitrates, think red meat, the results were toxic and mutagenic effects. GSK knew at the time and indeed admitted that Ranitidine could react with nitrates in the stomach to form NDMA and that long-term use of Ranitidine could lead to elevated levels of NDMA in the human stomach.

Now, this is going to be a long story. It starts with Glaxo, now GSK, it passes through Pfizer, Johnson and Johnson, Boehringer Ingelheim, or BI, Sanofi, the generics, the active pharmaceutical ingredient companies, or API's, distributors and

retailers. We know that over most of this time GSK has had a history of malfeasance. Think of Ambien, Paxil, the Department of Justice, the FBI or the FDA. There is not enough time to go into all of that today, but we believe that this will be the latest chapter in that story, and that will come to the light of day.

Which leads me to emphasize where we go in this MDL, and that is to where Mr. Gilbert referenced earlier, a search for the truth. What we know now is only the very tip of the iceberg. We will be doing the discovery of the four brand manufacturers, the generic manufacturers, the API's, the distributors and the retailers, and these are the types of information and documents that will be produced by the Defendants.

As you can see on the screen, there are pre-clinical and nonclinical studies, animals, in vitro and vivo, you will hear more about that later, clinical trials, observational studies, post marketing reports, pharmacability vigilance, which is why I put PV in there so I don't have to pronounce it, case reports and adverse event reports.

In addition, and sort of more generally with regard to Defendants, we will also be looking at these categories of evidence: Company admissions, emails, memos, minutes, labeling documents, risk management documents, sales and marketing. We'll look at what they advertise, what their social media

looked like, their market share projections. We'll look at storage and transport and exportation. We'll look at their studies, their training manuals, their SOP's and audits and investigations.

We'll look at manufacturing, fabrication and production materials and documents, and we'll look at the recall. We'll look at the communications to the FDA. We'll look at the communications within the companies, and between the companies about the recall, and their studies and analysis in the investigation.

We will not only be looking at the parties, but third parties as well. The reason for that is pretty simple, because over time groups affiliated with the Defendants, groups that interact with the Defendants, and groups that work to support the Defendants have been involved with testing, studying, investigating, auditing, marketing, advertising, and promoting Zantac.

The following is an exemplar listing of these entities and individuals. You have the Governmental entities, the FDA, Department of Justice, elsewhere, looking at the recall, the regulatory issues, investigations. We'll look at Valisure and Emery Pharma. We'll look at industry groups. There are multiple industry groups that support these Defendants and support the defense of this drug. We'll look at the lobbyists. Each of these Defendants have paid lobbying firms in Washington

and elsewhere that are dealing with these issues, and dealing with them, I am sure, as we speak.

We'll look at marketing and advertising. Again, each of these companies have paid marketing and advertising firms that are working and have worked with regard to the Zantac issues, and ghost writers, those companies that write medical articles and then allow these companies to put their key opinion leaders or paid consultants as the authors of those articles. We'll look at all of that.

In addition, we'll look at educational and non-profit organizations, research universities, cancer institutes, as I mentioned before, key opinion leaders and consultants, journals and publications.

We'll also look at Johnson and Johnson because just recently in their annual report they have identified a notice of indemnification that they have received from BI and Sanofi as a result of this Zantac litigation. We'll also look at nonparty distributors, API's, wholesalers and retailers, and the industry as a whole.

Your Honors will hear from both sides soon enough about the legal theories, causes of action, defenses, the FDA, and science, but suffice it to say this is fundamentally a pharma products liability action on behalf of individuals who have sustained personal injuries or suffered a wrongful death as a result of having been diagnosed with cancer following

their use of Zantac.

Essentially, the personal injury and wrongful death claims will be for the defective design, manufacturing, transport, and storage of Zantac, including claims that the Defendants failed to warn of the danger and risk of NDMA and cancer. For starters, we know that none of these Defendants have ever warned of NDMA or cancer.

I am confident that the Court is aware from the initial census data that claims have been submitted involving multiple cancers. Why is that? That is fairly unusual. Typically in an MDL you will find that a device or a product is associated with a particular injury. So, why the numbers of cancers?

You will hear more in depth during the science presentations, but it is because the NDMA molecule is frighteningly small and there is nowhere in the human body it does not go. It passes through cells, the placenta, it rams into DNA, it links in with the DNA and causes mutations as it reproduces, and it causes cancers throughout the body, and causes cancers to metastasize, and it goes everywhere in the body very quickly, within just a few minutes of the pills or the drug being taken.

Some organs are more resilient than others. For example, the brain is a very resilient organ where the bladder is not so, and so you will see this and you will see cancers at

various locations in the body. With an average duration of usage among census participants of 14 years, there is a lot of exposure that we will be looking at.

You might wonder why from a statistical perspective that if cancer rates have, generally speaking, gone down rather than up while the Defendants have flooded the market with astronomical levels of NDMA, what is the connection? That is the red herring. We will talk about that in the science part, too. The fact is that some of these cancers have increased since Zantac was introduced into the population specifically.

There are other reasons why some cancer rates are down, and that has nothing to do with reducing the known carcinogens. In fact, what we think is the better question is, why don't we eliminate as a society the known carcinogens?

We expect at the end of the day, your Honors, when we get through the fact and expert discovery and have our general causation Daubert hearing that the Court will see the overwhelming evidence that support our claims and the cancers we will then have identified. We look forward to that day as it will lead us into the bellwether trials we need and our clients need.

Thank you for your consideration and your attention.

THE COURT: Thank you.

MR. McGLAMRY: Now back to Mr. Gilbert.

MR. GILBERT: Your Honor, I would like to spend just a

couple of minutes talking about the class claims in the Zantac MDL. Class claims are another tool in our legal tool box to help pursue justice on behalf of the Zantac victims.

Next slide, please.

While the class claims we pursue will largely be based on the same core body -- slide number 15, please. Slide number 15, please.

THE COURT: Mr. Gilbert, there is a slight lag, I noticed that previously. There is a little bit of a lag. I think it is just maybe because so many people are on the system.

MR. GILBERT: Thank you. While the class claims we will pursue will largely be based on the same core body of evidence that Mr. McGlamry discussed a few moments minute ago, the Zantac victims on whose behalf we'll advance these class claims are separate and distinct from the individuals represented in the personal injury and wrongful death claims. There are two categories of claimants on whose behalf we will advance class claims.

First, we will advance class claims for those seeking economic losses only. These include consumers who purchased Zantac and third parties who reimbursed their members for a percentage of the cost of these purchases. Both classes will essentially seek the same relief, damages equal to the amount paid or reimbursed based on the sale of the defective product.

Second, we'll advance class claims on behalf of individuals seeking medical monitoring relief. These class claims will be brought on behalf of individuals who used Zantac, but have not yet been diagnosed with cancer. The relief we will seek here will be the creation of a fund to help alert these individuals to their increased risk of cancer and cover proactive medical screening and monitoring.

Next slide, please.

In a little while our colleagues, Mr. Longer and Mr. Keller, will discuss the legal claims we'll advance in these class actions. Please close the PowerPoint.

Your Honors, as the Court hears today's presentations, please keep in mind that the bell has just sounded and we are all just crossing the starting line of this MDL marathon. There are many miles to go.

Pleadings at miles one and two, document production and fact witness depositions for the next 15 to 18 miles, expert witness reports and expert depositions at miles 15 through 18, general Daubert and class certification motion practice and briefing at miles 18 to 22, bellwether case selection, final pretrial discovery, and dispositive motions at miles 22 to 25, and as we turn the corner and see the finish line, bellwether trials and class trials right around mile 26.

Each of these points in the marathon are mutually dependent on each other. We can't reach general Daubert and

class classification without fulsome discovery, including a streamlined expedited process for resolution of discovery disputes. All the pieces have to compliment each other in order to enable the parties to compete fairly and finish this MDL marathon. That is part of what makes MDL litigation so interesting, there are many moving parts and they all have to fit together to make it work in the search for the truth.

Your Honors, we are excited to officially launch the Zantac MDL with today's initial conference. We appreciate the opportunity to give the Court a preview of what is to come as we all journey together on this MDL marathon. Thank you.

THE COURT: Thank you, Mr. Gilbert.

Mr. Agneshwar and Ms. Sharpe, good morning.

MR. AGNESHWAR: Good morning, your Honor. I am just sharing my screen. Hopefully it will go well. Does everyone see that?

THE COURT: We do.

MR. AGNESHWAR: Awesome. Step one accomplished.

Good morning, your Honor, good morning, Magistrate Judge Reinhart. It is my honor to be able to present the opening statement on behalf of the Defendants today. I represent the Sanofi Defendants in this litigation. I want to give a shout out to Special Master Dodge. I don't feel like I am at mile zero, with all the work that she has had us doing over the past few months I feel I am more at mile 10 or 12.

THE COURT: Good, I love that, so fewer more miles to go. I was going to say I don't know if I could do 26 miles anymore, it has been awhile since I ran my last marathon.

MR. AGNESHWAR: It's been seven years for me.

Your Honor, you have also emphasized the importance of mentoring and I really appreciate that. It is also my honor and privilege to be privileged to be copresenting this opening statement with my mentee of 12 years and my partner for four years, Paige Sharpe, who you will hear from after I talk for a little bit.

These are unusual circumstances and I am going to do the best I can over Zoom. My kids are safely in Zoom school, I have a homemade podium and Girl Scout cookies, and there is no one in the bathroom so hopefully there won't be a flush heard round the world.

THE COURT: You may need your kids at any point.

MR. AGNESHWAR: I already used them for the Zoom setup. Hopefully, they don't know as much about Zantac as I do.

With that, your Honor, I am going to launch in. We have heard a lot about what the FDA did, we have heard a lot about what Europe did. We've heard words like recall thrown around, even though it wasn't really a recall, it was a market withdrawal. We have heard a lot about NDMA, but, your Honor, my bold statement that I am going to begin with from the

Defendants' point of view is, in the real world there is no foundation for this litigation. There, in fact, is data on whether Zantac as used by real people in the real world creates a risk of cancer, and the answer to that, your Honor, is no.

What the Plaintiffs have here, and what they emphasize, is speculation built on speculation about laboratory tests involving NDMA that have resulted in inconclusive results. A litigation cannot be based on that type of speculation, your Honor.

Beyond that general causation issue, each Plaintiff is going to face insurmountable hurdles establishing their own case. Cancer is not a monolithic disease, so the Plaintiffs will have to have evidence on the particular cancer that they claim, and they will have to be faced with the unfortunate prevalence of cancer and the numerous other reasons why people get those diseases.

On top of that, your Honor, this product has been on the market nearly 40 years, it's been marketed by a number of companies over those 40 years. It is now generic and it has been generic for a long time. That is going to give Plaintiff hurdles not just on proof of use, but also on product ID, because if they can't establish that they used the branded product then they are out of court. We also have strong class action defenses that I will get into a little bit later.

So, let's go back to what I started with, Zantac in

the real word. This case is not about laboratory tests, it is about whether the use of Zantac, the way people use it gives rise to cancer. Zantac has been on the market for nearly 40 years, it's been one of the first medications to treat heartburn and GERD and other ulcerative conditions.

What I have here is over-the-counter Zantac. What the label says is that Zantac is typically used for short term. In fact, the label says stop and ask a doctor if you need to take this product for more than 14 days or your heartburn continues to worsen.

That is very important, your Honor, as you look at the data because, as the label also said, heartburn can be a sign of a more serious condition. In other words, there is a big chicken and egg issue here. The very symptoms that cause people to go to the pharmacy and pick up a Zantac are also symptoms that could be early signs of stomach cancer and other GI track cancers, and that comes into play when we look at the science and you will hear about that a little later.

All of these regulatory authorities that you have heard about that have supposedly taken the drug off the market, why are they saying this? The European Medicines Agency which regulates pharmaceuticals in 28 European countries has said that based on comprehensive review of clinical safety data currently available, it can be concluded that there is no evidence of a causal association between Ranitidine and the

development of cancer in patients, no evidence of a causal association. The Food and Drug Administration, on April 1st, the same day that they announced the market withdrawal, they said, overall, the risk to individual patients potentially exposed to NDMA remains very small.

So, why have these agencies that have asked the companies to withdraw this drug from the market given these reassuring statements that there is no causation here? Your Honor, that is because they wear two hats. On the one hand, they wear a public health hat where they are taking action in an abundance of caution to protect the public health. On the other hand, they are scientists that also dig into the data and do it the same way that scientists do in laboratories, look at the epidemiology, look at the studies, and look at the actual risk as demonstrated to real patients. It is that lab exercise that happens in laboratories and that the FDA and EMA did in making these statements that needs to happen in the courtroom, too.

Your Honor said earlier today that you are very familiar with Eleventh Circuit law on Daubert and, in fact, the Eleventh Circuit law emphasizes human epidemiology as the touchstone of proving general causation. It is the most important aspect of the science in proving general causation, and that is because epidemiology looks at real people being exposed to products, or being exposed to something, and

comparing them to a control group. In fact, what you didn't hear from the Plaintiffs, but there is, is epidemiology on the use of Zantac in the real world and various types of cancer.

In fact, one study that was released just last week concluded that Ranitidine is not associated with an increased risk of GI cancers, and several cancers were studied in this one, including colorectal, liver, pancreatic, and gastric cancers, many of the types of cancers that are alleged here. Now, this is an abstract, it has not been peer reviewed and published yet, but typically abstracts, when they are presented at conferences, give rise to studies a few months or several months later, but the fact that these authors who are scientists in Cleveland saw fit to present these findings which was over a ten-year period of time is really important.

The other thing that is important about this new epidemiology, this brand new epidemiology, is that it confirms what we have been seeing in the real world over the past 20 years in the studies that have been done.

As you will hear from my colleague, Mark Cheffo, later in the science presentation, there is other epidemiology on the relationship between Ranitidine and particular cancers, and it largely says no. There were also studies on the relationship between Zantac's class of drugs, H2RAs, and various cancers, and by and large the epidemiology says no.

There are a few positive results, but by the authors'

own admissions, typically those findings reflect confounding or chance or other methodological issues.

Here is a case in point, this was another study that came out just last week, a week ago today, where these scientists published in the British Journal of Cancer showed a modest association between PPIs and H2RAs like Zantac and gastric cancer, but they saw that risk decline the longer you took the drug, which is contrary to anything you'd expect. What they said is the chicken and egg issue. This is reverse causations. Our results revealed a marked increase in the prescription of acid suppression medications immediately before a gastric cancer diagnosis, suggesting role of reverse causation.

In other words, you get heartburn, for most people it is just heartburn, for some unfortunate few it is a sign of stomach cancer, but you immediately think it is heartburn and go take a Zantac and shortly thereafter end up being diagnosed with cancer. That is called reverse causation and that is what you are going to hear about later.

By and large, the epidemiology does not support a relationship between Ranitidine and any kind of cancer. Your Honor, that is really the end of the story on general causation, but what Plaintiffs have done is focused on NDMA, so let's talk about NDMA.

The NDMA theory that you heard about from the

Plaintiffs is really speculation built on speculation. Speculation number one is why NDMA is classified as a human carcinogen. It is actually classified as a probable human carcinogen for practical purposes only based on animal studies. There is not epidemiology on the relationship between NDMA in human beings and cancers, it is a probable, not a definite causation. So, that is one level of speculation the Plaintiffs have to get around.

Now, you would think from hearing the Plaintiffs' presentation that Zantac is the only thing that contains NDMA, and other than Zantac, we would not be exposed to it at all. That is not true, your Honor. NDMA is ubiquitous, it is found everywhere. It is in workplaces, the environment, in the water we drink, even in Florida water. It is in the vegetables we eat, it is in fruit, it is in mushrooms. So, you can get NDMA from a lot of different things.

What is also the speculation number two is, how much NDMA exposure do we need to have before we increase our cancer risk? Candidly, your Honor, nobody knows. There is speculation about that, but it is a big unknown, but the FDA set what is called an acceptable daily intake of 96 nanograms.

So, what are they saying when they say that is the acceptable daily intake?

Let me start with what they are not saying. What they are not saying is that acceptable daily intake equals a real

world risk. What this is, is a calculation extrapolated from animal studies that answers the following question: At what level of NDMA would a 110-pound person need to be exposed to on a daily basis for nearly their whole lives, for 70 years, in order to increase their cancer risk by one in a hundred thousand at a theoretical level? The FDA said even that one in a hundred thousand is probably understated -- I mean overstated.

Your Honor, when you contrast that theoretical risk to Zantac as Plaintiffs use it in the real world, you could not get any more different. Zantac has been on the market for only 35 years, it has not even been on the market close to 70 years, and the longest approved OTC course without a doctor's supervision is 14 days, again, very different.

But even if you give Plaintiffs every benefit of the doubt and say, okay, NDMA is a human carcinogen, it is proven; okay, 96 is the level at which above that there is risk, still, when you compare that to the risks of cancer, it is apples and oranges.

Cancer is a terrible disease, and all of us have faced it in our own lives, either ourselves, people we are close to, family and friends, and the reason for that, your Honor, is because it is all too common. The lifetime risk of bladder cancer is two and a half percent. The lifetime risk of colon cancer is four and a half percent. Even stomach cancer is one

percent. And the lifetime risk of prostate cancer is 13 percent in Caucasians and nearly 30 percent in African-Americans. These are high numbers, whereas the theoretical risk of being exposed to the acceptable daily intake of NDMA is one in a hundred thousand. It is a difference in magnitude of risk, your Honor.

Even beyond that, your Honor, the level of NDMA that is being alleged to be in Zantac has been a moving target and is still a moving target. This whole litigation started when a company called Valisure, which is an online pharmacy, submitted a citizen's petition to the FDA requesting that they withdraw Zantac from the market.

On the same day that Valisure filed the citizen's petition cases against these companies, my client and others, began to be filed, the very same day, suggesting some link between Valisure and the Plaintiffs Bar. Valisure purported to find levels in the millions of nanograms in tablets of Zantac, as you see on the left, and as my colleague, Mr. McGlamry, alluded to.

All of the complaints filed to date, as well as Plaintiffs' position statement, rely on Valisure, but Valisure and its testing methodology has been debunked, it has been debunked by the FDA. The FDA scolded Valisure that "we found that the test method you used in sampling Ranitidine for NDMA was inappropriate and contributed to or caused the levels of

NDMA to be artificially high."

What Valisure did was they exposed these products to like temperatures above the boiling point and created NDMA and then said, aha, look what we found, and the FDA said, no, that is not how you do it. We have a different better test.

Valisure also did another test to see if there was NDMA formed in the body as it interacts with gastric fluid, and, your Honor, here they succeeded, too, but they succeeded only when they pumped enough nitric acid into this gastric fluid, which is a compound found in smoked meats that is known to cause NDMA, in a quantity equivalent to 33 pounds of bacon and a half glass of water in a single sitting.

Now, I am a vegetarian so I don't eat bacon, but I doubt most people who take Zantac eat that much bacon in a single sitting to give rise to these elevated levels of NDMA.

So, fast forward a few months later. Mr. McGlamry also pointed to Emery Pharma, but now, months after this litigation is filed comes a different theory. Emery files a citizen's petition and says, no, no, we are not talking in the millions of nanograms, we are talking slightly above acceptable limits. We are talking like 100 to 150, and that is when it is exposed to heat.

So, what Emery did was they took these three samples of Zantac, some were generic and one was branded, and they exposed them to a temperature of 25 degrees Celsius, which is

about 80 degrees Fahrenheit, and 70 degrees Celsius, which is over 150 degrees Fahrenheit. What they found is that when you expose it to this really high temperature NDMA forms at a gradual level.

What Emery did was they expressed concern that maybe the product can reach these temperatures in high heat conditions, but in fact, your Honor, they cited no data on shipping conditions to make that point clear or to base it on any evidence. So, again, it is another speculation that is vastly different in magnitude and degree from what Valisure said.

So, what about the FDA? Well, the FDA did ask the companies to withdraw the product from the market. They did not do a recall and they specifically said they were not recalling the product.

What the FDA said in its press release and in its Q and A with the media was that some Zantac contained some unspecified, but elevated levels of NDMA under some conditions. But note what else the FDA said, your Honor, in this same press release. They did not find levels above acceptable daily limit in, quote unquote, "many of the samples that we tested." In another place, your Honor, they said most of the samples that they tested did not have elevated levels of NDMA. They requested withdrawal from the market, and this is a quote, "out of an abundance of caution."

That is a critical point, your Honor, because the Plaintiffs are basing a lot of their arguments on what the FDA did. The FDA specifically said it, your Honor, that it is not a recall because technically the products are okay, they have met all their specs and so forth. It is only when they are subjected generally to heat stress do they manifest higher levels, and that isn't what we'd expect that these products would be stored under those higher temperatures.

The FDA has never said Zantac causes cancer. The FDA has never said that intake above the acceptable daily intake means a real world risk of cancer. The FDA has never said that most or all of Zantac tablets contain levels above the acceptable daily intake, and certainly the FDA has never said that any particular product, any particular brand on any particular shelf contains NDMA.

At the end of the day, your Honor, in terms of the science of this case, which you will hear more about later, the Plaintiffs' case is based on a series of mights and maybes. There is no epidemiology now, but maybe there will be in the future.

Going to NDMA, do we know which packages contain NDMA? We don't. Do we know how much NDMA is in any particular package? We don't. Do we know whether any particular Plaintiff took a package with elevated levels of NDMA? We don't. Do we know what levels of NDMA can even theoretically

cause cancer in humans? We don't even know that, your Honor.

Your Honor, it is settled law that law is supposed to lag science, it's not supposed to lead it. When the science is not there, there shouldn't be a litigation. It's only if the science is there that law should then come. Your Honor, it is our position that the science is simply not there, your Honor, to link Zantac to cancer.

With that, I am going to turn it over to my colleague, Paige Sharpe, to pick it up.

THE COURT: Okay. Thank you very much. Welcome, Ms. Sharpe.

MS. SHARPE: Good morning, your Honors. My name is Paige Sharpe and it is a privilege to appear before you both this morning.

Your Honor, in my part of the presentation I am going to focus on the challenges that individual Plaintiffs are going to be facing in this litigation, challenges that we think are going to be insurmountable.

The first challenge has to do with a simple but fundamental fact about cancer. It is not a monolithic disease. Cancer is actually an umbrella term that encompasses all different types of cancers, each of which has its own risks and each of which has its own potential causes. As the Journal article quoted in this slide states, "It is inconceivable that a pharmaceutical agent should act as a universal carcinogen."

In other words, there is no single agent, no matter how carcinogenic, that can cause all types of cancer.

That is enormously important here because Plaintiffs haven't differentiated among types of cancers at all.

Thank you. This slide shows the types of cancers that are claimed just in the Complaints to date, there are some 18 different types, and they claim dozens more in the census. And you will see they're claiming just about every type of cancer imaginable, not just cancers associated with the same body system as Zantac, that is the gastrointestinal tract. No, they are claiming brain cancer, breast cancer, lymphoma and myeloma. The census includes claims for thyroid cancers, for skin cancers. There is simply no limiting principles to the types of cancers that are being claimed.

Plaintiffs are not going to be able to bypass Daubert with these undifferentiated claims. They can't use Epi from stomach cancer, for example, to show causation in a pancreatic cancer case. They can't use Epi from a pancreatic cancer case to prove causation in a breast cancer case. They are going to need evidence for each type of cancer.

That is just the beginning with respect to the challenges the individual Plaintiffs will face because even if the Plaintiff could show that Zantac can cause their particular type of cancer, you are, of course, still going to have to show that Zantac actually caused their individual cancer. That is a

very high hurdle. First of all, they don't have Epi to show that Zantac can cause cancer at all, much less any specific cancers.

This isn't a case where there is a signature injury where they can say that for this particular type of cancer we know what the cause is. To the contrary, I think we all know that there are risk factors for cancer that are out there and that we are all exposed to. Some we can control, like smoking, like alcohol intake, and our diet, but others we simply can't, like our genetic makeup, and the fact that the risk of cancer increases with age.

Let's also not forget that Zantac, to the extent that it even contains NDMA, is far from the only source out there.

Now, we have been focusing on the science and causation issues, but those, of course, are not the only defenses that the Defendants are going to have in this litigation, and I want to talk about a couple of those defenses because they are going to be so important in a case like this in particular. One of those defenses concerns proof of use and product identification issues.

This isn't a typical product liability case or even a typical product liability MDL where you have a single product that is made by a single manufacturer. We all know, I think, that it is much more complicated than that here. The fact that you have multiple products and multiple manufacturers is

important for two different reasons.

First of all, Plaintiffs are going to have the additional burden of proving not just that they took Zantac or Ranitidine, but which Zantac or Ranitidine they took and who made it. That is a tall order for a product that has been available over the counter for so many years, where prescription records are going to be unlikely to be had, and where there have been so many generic versions available as well, as many as 75 different generics over time.

Second, the difference between branded use and generic use can make the difference between having a cause of action or not having one at all, and that really matters here because since it went generic -- I'm sorry, since it went over the counter several decades ago, sales of generic Ranitidine have far outstripped those of branded Zantac. That makes sense, right? Generics cost a lot less than branded. Many consumers, when they go into a drugstore, are naturally going to reach for the cheaper option.

Now, I understand that the census data does not comport with the data that we have on sales. The census data suggests that the majority of claimants took branded Zantac or a combination, but that is a discrepancy that Plaintiffs are going to have to grapple with over the course of this litigation because the numbers on the slide do reflect hard sales.

Now, I mentioned that the issue of generic use is particularly important here in determining whether a Plaintiff has a claim, and that is because of the broad rejection of the theory of innovator liability.

That theory of liability that a branded manufacturer can be liable for injuries caused by a generic product has been almost universally rejected by State high courts, by every Federal Court of Appeals that has considered the issue, and it has never been applied in a case like this involving an over-the-counter product.

So, those Plaintiffs who took generic Ranitidine are not going to have claims against the branded manufacturers, and they are also going to have problems with their claims against the generics as well because of Supreme Court precedent saying that those claims are not viable either because the generic does not control the design of the product and it doesn't control the labeling.

With that, your Honors, I am going to turn the presentation back to Mr. Agneshwar for final points. Thank you very much.

THE COURT: Thank you very much.

MR. AGNESHWAR: Thank you, your Honor. Just a brief note about class actions. The Plaintiffs, as Mr. Gilbert said, are going to be filing Master Complaints in class actions, they are going to be pursuing medical monitoring, they are going to

be pursuing consumer class actions basically saying we paid too much for this product because we didn't understand the cancer risk, and they are going to be filing what seems to be third party payor claims.

Just so you know, there is consistent law going back years that says that in cases like this, pharmaceutical, essentially product liability cases, classes are simply not viable, and there are good reasons for that, your Honor.

If you look at Rule 23, virtually none of these are satisfied, going from ascertainability all the way to superiority. Just one after another Courts have rejected this and it is no surprise why. All the defenses that we have been talking about today apply equally in class actions.

There is going to be myriad differences in the laws of 50 states. It is going to be impossible to verify who took the drug and who is in the class. There's too many products over too much period of time, too many Defendants, there's retailers, there's branded, there's generics. There's too many cancers, each with individual proof, too many risk factors, too much individual variability. Medical monitoring itself is not accepted in the majority of states, and economic loss claims involving over-the-counter products are preempted, your Honor.

So, I don't see these class act allegations going far in this litigation.

Your Honor, we heard in the opening statements some

very personal allegations against some of the companies as to what they did in this case and another case, and the notice the companies supposedly had. We are confident that there is no way anybody could have known of a risk, and even today I think that is borne out by the fact that, as I have tried to demonstrate, your Honor, that the risk has not materialized even today. There just isn't such a risk.

Your Honor, thank you for listening. It is a pleasure to appear before you. I hope one day to do this in person. I have enjoyed working with Special Master Dodge, the Defense team, the Plaintiffs' team. I think we will work very collaboratively over this litigation and we look forward to be vindicated at the end when it comes. And there was no toilet flush, I hope.

THE COURT: No. Everything went perfectly. Thank you very much, Mr. Agneshwar and Ms. Sharpe.

I know on the agenda you have a break built in, and I would like to honor that agenda for the benefit of everyone, including our court reporter who is taking everything down. So, you had it from 10:30 to 10:45, and it is 10:20 now. Why don't we take a 15-minute break and we will be back at 10:35.

Please don't leave the meeting, it does put a great strain on those of our cohosts whom I want to thank again for helping in the administration of admitting everybody in, the liaisons and others, our special master.

So, don't leave the meeting, just keep yourself muted and your video off, which I will do as well. We will see everybody back at 10:35 and we will pick up with the law presentation at that point. Thank you so much.

(Thereupon, a short recess was taken.)

(Thereupon, trial reconvened after recess.)

THE COURT: Okay, welcome back, and I'm happy to move into the next item on the agenda, which is the law presentation.

So, I know we have Mr. Longer, Mr. Keller, Mr. Petrosinelli and Mr. Bayman, and I turn it over to you to proceed.

MR. PETROSINELLI: Good morning, Your Honor, Joe Petrosinelli here. Your Honor, the way we have divided this, I think we provided the Court with an outline of the topics, but it is a little different format than the openings where we are going to go back and forth a little bit, give it a little collaborative feel, because the four of us did put this presentation together. Ms. Zousmer, one of our colleagues, is going to run the slides for everyone hopefully to avoid any hiccups, but if there are hiccups, we apologize in advance.

We have it divided into five sections of law organized in a way that we thought made sense, so unless your Honor has any questions, I will just jump right in with the first topic.

THE COURT: Perfect.

MR. PETROSINELLI: Your Honor, the first section of law we wanted to cover for the Court was the law relating --

THE COURT: Mr. Petrosinelli, just hold on one moment. I'm sorry. Just a gentle reminder, our court reporter has asked each time you go back and forth if each speaker would just, again, state your name for the record so it clearly reflects on the transcript. Okay?

MR. PETROSINELLI: Of course, we will do so.

Your Honor, the first topic of law is the law relating to the FDA regulatory framework that governs this case and the way we have divided this is, I will cover the pre-approval of a new drug period, and Mr. Longer, on behalf of the Plaintiffs, I'll turn it over to him and he will cover sort of the post-approval period.

So, let's start with just what is the source of law that relates to the approval of a new drug product in the United States, and there are really sort of two sources. One is the statutory source, which is the Federal Food Drug and Cosmetic Act. Your Honor, I think in pharmaceutic litigation you will find you are going to be inundated with acronyms and this is the first one. You will hear reference to the FDCA, and when you hear that, this is the act that folks are talking about. You see the sections there that relate to -- the portion of that act that relate to drugs and medical devices.

I think probably more commonly you will hear talk

about during the litigation the second source of law, which are the implementing regulations under the statute which are found in Title 21 of the Code of Federal Regulations. Those are the FDA implementing regulations that describe what the FDA requires to get a new drug approved, and other things, in this country.

And then just a final introductory acronym is the acronym CDER, C-D-E-R, that you will hear. This is the portion of the FDA, the Center for Drug Evaluation and Research that deals with and evaluates medications as opposed to, for example, there are divisions that deal with food, there are divisions that deal with medical devices. This is the division that deals with medications. So, when you hear the term CDER, that is what it is referring to.

The question is, what is the legal basis or the legal framework for a new medication to get approved in the United States?

The start of the process on the FDA side is called an investigational new drug application. If we could go to the next slide, please.

The so-called IND, another acronym, that is the formal way in which a manufacturer or an applicant who wants to start the process the usual way -- there are some exceptions, emergency use and so forth, but this is the usual way and certainly was the way with Zantac that a sponsor seeks approval

for the FDA to start the process of testing a new drug in human beings.

Now, importantly, it is not the start of the process from the manufacturer's side. Before you submit an IND, you will have done typically two major things; one is the discovery of the molecule. Bench scientists who are employed at pharmaceutical companies and dedicate their careers to discovering new medications that target certain diseases or cells will do what you would think of as lab experiments in test tubes and petri dishes, the kinds of things we all did in high school science class.

And you'll hear the term "preclinical tests," you will hear that a lot in this litigation. When you hear that term it really means two things; it means the lab tests that I have just described in test tubes and petri dishes, often referred to by the term "in vitro". So, in vitro tests, that is what those are.

Then, the second piece that a company will have done, and has to do before submitting an IND, is tests in animals. So, those are often called in vivo tests because they are in a live organism. And the way it will work is a company will, if it finds a molecule that seems to have efficacy in test tubes or petri dishes on a target compound, protein, enzyme, whatever is being targeted, then the company will do tests in animals, live organisms, and they will do all sorts of tests screening

for, among other things, efficacy and adverse events that would occur. Those data, the results of those tests have to be presented to the FDA in the IND.

That is one thing and it is -- one of the reasons why I point it out here is, those include carcinogenicity tests, which I will talk about in a second, but obviously that has relevance to this litigation.

The second thing, the main thing an IND is, you have to tell the FDA what clinical trials, meaning trials in human beings as opposed to preclinical trials, what you propose to do, how you propose to do it, and describe how you intend to do it into three phases, phase one, phase two and phase three clinical trials that I will describe in just a moment, what the difference is between those.

The final thing that I highlight here because it is relevant to this case based on the theories we have heard from Mr. McGlamry, for example, is you have to describe to the FDA in the IND the chemistry and manufacturing of the drug, including what methods are used to manufacture the compound to make sure that its purity and stability, two concepts that you will hear a lot about in this litigation, are true, and that the drug doesn't have impurities and doesn't have instability. You have to explain to the FDA how you have assured that and the FDA has to approve that. So, that is part of the IND package that would be submitted.

Once you submit an IND and the FDA gets an opportunity to review it and they approve it, you now are authorized to conduct -- by law, authorized to conduct clinical trials in actual human beings. So if we can go to the next slide.

This is from another part of the CFR, this is 21 CFR, Section 312.21. This is a graphic illustration of what it says in that section. These are the three types of clinical trials a company must conduct in human beings before it can get a drug approved. You see -- I won't read through it all, but generally speaking, as would make sense, it is a gradual progression. You start with smaller studies, mainly to -- usually in healthy patients and mainly to figure out dose levels, like safe dose levels.

Then you move to what are called phase two trials, which are we are treating people with the active disease you are trying to treat. There are typically hundreds of patients, there could be more, but usually hundreds, and that takes anywhere between some months to a couple of years.

And then you get to -- if you see no adverse events of concern and there is efficacy, you get to the phase three trials. These are much larger trials, up to thousands of patients, take much longer time to do, typically several years, and the key thing about these trials is that they are typically -- not all of them have to be, but there at least several that are randomized double blind placebo-controlled

clinical trials, I think everyone would agree the gold standard in assessing whether or not a pharmaceutical agent causes adverse health effects in human beings.

And because those trials happen, and because they take a long time, they help define the warnings that would be provided in the labeling for a product because during the trial, as adverse events happen in human beings, and they happen ranging from minor to serious, they are recorded, and there is a discussion with the FDA about which of those are significant enough or prevalent enough to be put in labeling.

Those are the three trials that are done and, your Honor, we are talking about a many years long process, but when you get to the stage where you have done these clinical trials and all the other things, pre-clinical testing, chemical and manufacturing testing, your next stop and the sort of final stop to get a drug approved is the so-called new drug application, or NDA.

If we could go to the next slide, please.

You will hear this acronym, I am confident, quite often in this litigation. The NDA is a massive -- I remember many years ago when we didn't have electronics and you had to produce NDAs in litigation, I remember being a young associate, and it filled an entire conference room of documents, and I thought this is going to be a painful document review, but this is a massive document because it contains all of these things

and more. I have picked out some highlights here. It must contain by law all of these things you see on the screen, including, I mentioned this earlier, in the pre-clinical test results, particularly toxicology studies on animals, there must be carcinogenicity studies. And so, the details of how that is done is sort of beyond the scope of this presentation on the law, but actually you will hear a little bit about it in the science presentations.

These were, of course, done on Zantac. GSK, the inventor of the drug, when it submitted its NDA had submissions on carcinogenicity tests that it had done and the FDA reviewed those and you will see what the results were those when my colleague, Mr. Cheffo, presents the science piece.

Of course, the results of the clinical trial, again, the information about stability and purity, and the applicant submits its own analysis, overall analysis of the summary of the data on safety and effectiveness.

And then, of particular note in this case because it relates to preemption -- several of these things relate to preemption issues that you will hear Mr. Bayman talk about in a second, but the sponsor or the applicant submits its proposed labeling for the drug. When I say labeling, in a prescription drug context that is typically referring to the label that goes to the prescribing doctor who can then advise his or her patient about risks and so on. In an over-the-counter context

it is a little different, obviously, and I will talk about that in a moment.

But the NDA is submitted and the FDA then gets an opportunity to review it.

If you could go to the next slide, please.

Labeling is governed very carefully and specifically and strictly by a number of provisions in the CFR. Here are three of them that relate to prescription medications, and all of these things have to -- are sections that are mandated to be in the label and, as I say, the applicant will submit its proposed wording for all these things, including warnings, precautions, adverse reactions, and the FDA will then, having had all the data now in the NDA, will then review the draft that the sponsor or applicant submits to see if they agree.

And that gets us to the last piece, which is the actual process of approval. If we could go to the next slide.

Again, there are laws in the CFR cited here that govern what the FDA does with a new drug application, and you will see, not surprisingly, the sort of standard is if the drug meets the statutory requirements for safety and effectiveness, manufacturing and controls, and labeling, the FDA will approve it.

Of note, you see in other sections of the CFR there are all sorts of reasons why the FDA could reject an application, to include all of the things we just talked about.

If they think that the data submitted about manufacturing in terms of how to ensure purity and stability is inadequate, if the clinical trial and pre-clinical trial results show some concern about safety, or if they don't like the labeling that has been proposed, they can reject the application.

What you will see, and certainly with Zantac, is at the end of the day, if the FDA is going to approve, there is a document called the Summary Basis of Approval in which the FDA summarizes why it is approving the product. Importantly, your Honor, when I say the FDA, CDER, the division we talked about, has itself a bunch of different offices with different medical professionals and scientists that each review sort of pieces of the application.

So, what do I mean by that? They have medical doctors, toxicologists, epidemiologists, biostatisticians, all sorts of scientific disciplines that are relevant to the various pieces of the application. They each do their own memo recommending whether or not they would approve based on their piece of the scientific world, and those get funneled to the leadership of CDER ultimately which then issues this Summary Basis of Approval document.

Your Honor, that is on the prescription drug side. So, when Zantac was originally approved as a prescription drug, that is a summary of the process. It is a little different for over the counter and generic.

If we could go to the next slide.

For an over-the-counter product, which is typically, and it certainly was in this case, a product that is a prescription product, but the manufacturer seeks over-the-counter status, that is generally done -- there are some details here that I don't think are particular relevant now, but it's generally done through a new NDA submission or what is called an abbreviated NDA or ANDA. That's another abbreviation you will hear. As you might imagine, for conversion from a prescription status to an over-the-counter status the FDA requires a large margin of safety because you are going to have consumers buying the product without -- perhaps without consultation with a doctor.

Secondly, and importantly here, there is a very specific provision in the CFR about what exactly must be in an over-the-counter product label that sort of standardizes, no matter what you are manufacturing, if it is a drug and it's over the counter, it is going to follow the format of what is laid out in the CFR. That has all sorts of sections, like a section called stop use and ask your doctor if.

So, if he we go to the next slide.

Your Honor, just to show you, this is the sort of most recent over-the-counter labeling for Zantac 150 milligrams, and you can see on the left that format that is shown is the format that is set forth in the CFR provision I just told you about

that everyone has to follow.

And then we just highlighted -- you heard, I think, Mr. Agneshwar talk about a couple of these, like the stop use and ask your doctor if, and the issue about if you need to take the product more than 14 days. That language is talked about and negotiated with the FDA.

In other words, everything that is in both the prescription version label and this label will have been discussed with the FDA, gone back and forth between the company and the FDA, and the FDA will have agreed that, based on the data, that is the appropriate language to be in the label.

If we could go to the next slide.

The final thing is generic products. You have heard that in the 1990's, I think mid to late 1990's, the patent expired on Ranitidine that GSK held and that allowed generic products to enter the market. Two things to note about generic approval; it is a different pathway, it's through this ANDA, abbreviated new drug application process, where the generic has to -- the generic doesn't have to do its own clinical trials or pre-clinical testing like we saw in the brand space, but it has to show chemical equivalence and it has to show bio equivalence of a medication that has already been approved. That is one thing. It is a much more compact application.

Secondly, there is the so-called Doctrine of Sameness in the law, in the FDA regulatory law, which is that the

generic has to basically have the same of everything about the medication that has already been approved, so the same API, active pharmaceutical ingredient, Ranitidine here, strength, and so on.

And of special note, as you will hear in the preemption section later, the generic's labeling must be the same as the labeling that was approved by the FDA for the branded product, whether it is a prescription label or an over-the-counter label, and that the generic has no obligation -- has no ability to unilaterally change the composition of the product or the labeling of the product, it has to be the same. That, as you will hear, has implications in the case law about preemption.

So, your Honor, that is a broad overview of the law that relates to pre-approval of an FDA approved product, and I am going to turn it over now to my colleague for the Plaintiffs, Mr. Longer, who is going to cover the post-approval period.

THE COURT: Okay, thank you very much.

Good morning, Mr. Longer.

MR. LONGER: Good morning, your Honor. I am just getting myself set up.

My name is Frederick Longer. This is my first appearance before the Court apart from my interview. I would just like to extend my thanks to your Honor, Magistrate Judge

Reinhart, and Special Master Dodge for your efforts and attention while I give my presentation.

I intend to address three subjects related to the post-approval period of a pharmaceutical drug. I will cover an overview of the regulatory requirements dealing with the how and why of adverse event reporting, the obligations to update the label with new safety information, and the third is FDA information about recalls or withdrawals.

While Mr. Petrosinelli had a number of slides to address the pre-approval process, I will do mine a little old school and just briefly explain to the Court branded and generic drug manufacturers' obligations to continue to monitor the safety of their products once they are on the market.

These standards are baked into the FDCA and the CFR, the Code of Federal Regulations. It is well recognized that simply because a drug has received FDA approval, the obligation to continue to study the safety of the drug does not end. Approval of marketing really is just a new beginning in drug safety. Both the act and the regulations put the obligation on the manufacturer to ensure that its product is safe and the label adequately warns of the risk of the drug, and the reason for that is simple.

The manufacturer is the expert about the drug it makes. The manufacturer has studied the drug and knows or should know more about its product's safety profile than any

other entity, including the FDA, which is why by law the manufacturer is always responsible for the drug even after it has been approved for marketing. This is true under Federal law and it is equally true under State common law.

The reason that the parties are addressing both the pre-market and post-market regulations is, just as Mr. Petrosinelli was mentioning, because these Federal standards could impact on whether preemption of state law duties would apply.

So, my brief discussion about post-marketing duties in a sense sets the stage for the next discussion to follow about preemption.

Since I am doing this a little old school, I would ask Ms. Zousmer if she could take down the PowerPoint because -- oh, very good, thank you.

So, the first topic I wanted to cover, your Honor, was about regulatory requirements.

As your Honor saw from the presentation by Mr. Petrosinelli, pretrial clinical studies are confined to a limited population of study subjects. Some studies include less than a hundred patients. As a consequence, risk assessment during product development makes it impossible to identify all the safety concerns during the clinical trial period. Once a product is approved for marketing, however, the number of persons exposed to the agent increase significantly.

In the case of a very popular drug the numbers could be in the millions of persons exposed to the agent. Plus, that population now includes persons with co-morbid conditions and the potential for use of other drugs.

Consequently, the need for post-marketing safety data collection and risk assessment are critical to understand the product's risk profile, and what I have just described to you, your Honor, is the driving force behind pharmaco vigilance. FDA guidance defines pharmaco vigilance as all scientific and data gathering activities related to the detection, assessment, and understanding of adverse events.

What are adverse events? Congress defined them in the context of adverse drug experience, which means any adverse event associated with the drug -- I am sorry, with the use of a drug in humans whether or not considered drug related.

That covers the gamut of issues, including adverse events occurring in the use of the drug in professional practice, an adverse event occurring from an overdose of the drug, whether it's accidental or intentional, an adverse event occurring from abuse of the drug and other matters.

So, under the FDCA, Congress requires marketed drugs to be subject to rigorous reporting requirements. This post-marketing reporting obligation also applies equally to the ANDA holders, the generic drug manufacturer.

Indeed, the CFR is chock full of regulations

pertaining to post-marketing reporting, the contents of those reports and where the information can be observed.

For example, alert reports for adverse event reports must be reported as soon as possible, but no later than 15 days after the event. Also, periodic and annual adverse drug experience reports are required, mandated by the FDA.

This information, your Honor, is posted in what is called the FDA's Medwatch where spontaneous and voluntary reporting of cases are presented. Medwatch is the FDA's database that anyone can tap into to see if there are adverse event reports being reported for any particular drug.

So, that is the general picture for adverse event reporting.

Technical difficulties, your Honor. I am working from a new podium.

So, the second topic I wanted to cover, your Honor, addresses label updates. Federal law requires a manufacturer to update the label of an approved brand drug to warn of emerging risks. The Supreme Court recently stated in Albrecht, the case involving Merck and Fosamax just last year, "we also observed that through many amendments to the FDCA and to FDA regulations it has remained a central premise of Federal drug regulation that the manufacturer bears responsibility for the content of its label at all times."

We also learned from Wyeth that a drug manufacturer is

charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market. "Thus, when risks to a particular drug become apparent, the manufacturer has a duty to provide a warning that adequately describes that risk."

So, how does a manufacturer alter its label if it finds a new risk? There are two ways. One, through the changes being effective, or CBE process; and two, through a prior approval supplement, which, as its name suggests, requires prior approval of the agency. A CBE, however, permits the manufacturer to make changes in the labeling to reflect newly acquired information without prior FDA approval when the change is to add or strengthen a contra indication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the label.

For example, in the case of warnings and precaution, the regulations recognize the need to get out important safety data fast, so, for clinically significant adverse reactions the CFR provides that the label must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with the drug, but a causal relationship need not have been definitively established.

The post-marketing reporting obligation again becomes

relevant in the context of preemption which my colleague, Mr. Keller, will address as well as Mr. Bayman.

So, a couple of other related points, your Honor. The FDA now has authority to initiate a process to mandate label changes. Specifically, if FDA becomes aware of new safety information that FDA believes should be included in the labeling of the drug, it now has statutory authority to require new labeling, but when Congress granted FDA this authority to require new labeling it kept the responsibility of making the labeling changes on the manufacturer, which included the obligation to update the label under a CBE.

My second related point addresses generic manufacturers and non-prescription drugs, the ANDA holders. They have the obligation to report safety data to the FDA so that the agency can address updating the label to accurately reflect new safety data, and as Mr. Petrosinelli mentioned the duty of sameness, FDA recognized that as a result of the so-called duty of sameness, if a generic manufacturer believes that new safety information should be added to its drug's labeling, it must provide adequate supporting information to the FDA and the FDA will determine whether the labeling for the generic and the brand name drug should be revised.

Last, your Honor, I wanted to briefly talk about recalls and withdrawals. We heard mention of this in the opening statements of Defense counsel and I just wanted to

cover them as well. This is my third point.

Recalls and withdrawals are covered in 21 CFR, part 7. FDA's recall policy provides for removing or correcting consumer products that are in violation of laws administered by the Food and Drug Administration. The FDA prefers voluntary action by manufacturers and distributors so that they can carry out their responsibility to protect the public health and well-being from products that present a risk of injury or gross deception or are otherwise defective. Voluntary recalls are reserved for urgent situations.

Now, in addition to recalls, your Honor, FDA may also institute a market withdrawal, which again calls on the manufacturer who is ultimately responsible for the safety of the drug to take appropriate action and is liable for taking any actions that are inappropriate.

FDA recognizes that some market withdrawals may present a health hazard and can treat a market withdrawal in the same manner as a recall. The proof of that pudding is that FDA published a press release and put the recall of the Ranitidine products into the recall enterprise system that FDA uses to track recalls.

Last, your Honor, in this regard, FDA has enforcement authority to prevent interstate distribution of any drug that is adulterated or misbranded. In other words, if its labeling is false or misleading in any particular the FDA can prohibit

the sale of the drug through either recall, withdrawal, or other enforcement mechanisms.

So, those are the points I wanted to cover about post-marketing regulations, your Honor. With that, I yield back to Mr. Petrosinelli or Mr. Bayman for the next discussion.

I will put myself on stop video.

MR. PETROSINELLI: Thank you, your Honor. This is Joe Petrosinelli again for the Defendants.

Just one brief comment in response to Mr. Longer just to clarify one thing, and then I will turn it over to Mr. Bayman who will lead off the discussion on preemption, and that has to do with what Mr. Longer was saying right at the end about recall versus withdrawal.

This is important in the context of this case. When the FDA -- its action on April 1st of 2020, when it -- it asked for a withdrawal, not a recall, and that is significant, and your Honor can review the document, and it went through what the standard is for recall and what it is for withdrawal. It is significant because the standard -- as Mr. Agneshwar I think said in his opening, the standard for withdrawal is a removal or correction of a distributed product which involves a minor violation or no violation at all of FDA law.

So, that is the way in which the FDA chose to proceed with respect to Zantac, and I am sure there will be argument later about why they chose that as opposed to the recall

avenue, but I wanted to make that clear.

With that, I have no other comments on Mr. Longer's presentation, and I will turn it over to Mr. Bayman who is going to address preemption.

THE COURT: Thank you. Good morning, Mr. Bayman.

MR. BAYMAN: Good morning, your Honor. I am Andrew Bayman with the law firm King and Spalding and I'm counsel for Boehringer Ingelheim, or BI.

I am going to give the Court an overview of the Doctrine of Federal Preemption which the Defendants believe is a critically important issue in this litigation.

Could I have the first slide, please.

The Doctrine of Preemption is grounded in the supremacy clause of the Constitution, and under Supreme Court jurisprudence, this means that where state law conflicts or interferes with Federal law or standards, Federal law overrides State law. In the pharmaceutical drug context, the FDA has regulatory authority over all aspects of drug approval and sale. So, that means the FDA must approve the design of the product, the manufacture, and the labeling of the drug as part of the approval process.

Once the FDA approves, the manufacturers cannot change the drug itself without prior FDA approval. Once approved, manufacturers cannot make major changes to the manufacture or labeling of a drug without FDA pre-approval.

Preemption in this context attaches when Federal requirements conflict with what the Plaintiffs through their state law claims allege that State law requires. It is impossible to comply simultaneously with both State and Federal law.

The Supreme Court has recognized that Federal law can conflict with State law under different circumstances which give rise to preemption. The first is what is called express preemption. That occurs when Congress enacts a statutory provision expressly stating that the State law claims are preempted.

Another is the doctrine of implied preemption. Claims that are not expressly preempted can still be impliedly preempted. This occurs when State and Federal law directly conflict making it impossible to comply with both State and Federal law, but also where operation of State law poses an obstacle to achieving Congress' objectives or where Congress has taken exclusive control over an entire regulatory subject displacing impliedly all State law in that field.

Various Courts have recognized that claims involving pharmaceutical drugs can be preempted under a number of different circumstances. I am going to briefly address those now, your Honor.

Next slide.

I will start with express preemption. There is no

express preemption, your Honor, for prescription drugs. Over-the-counter drugs, however, are governed by the express preemption provision 21 U.S.C. 379r, which expressly preempts all State requirements applicable to over-the-counter manufacturers that are different, in addition to, or otherwise not identical with Federal requirements.

Now, 21 U.S.C. 379r contains a savings clause which does not preempt product liability claims. However, under subsection e of that same regulation, claims that are not traditional product liability claims such as claims solely for economic loss are preempted, and the Kanter case which we cite here is one example. Although there is no express preemption provision for prescription drugs, State law claims involving prescription drugs can still be preempted under the doctrine of implied preemption.

Because the FDA has regulatory authority over all aspects of the approval and the sale of drugs where State law -- from a State law lawsuit, or other State law cause of action, where that State law irreconcilably conflicts with the FDA's regulations and decisions preemption will attach.

The Courts recognize a number of specific situations where irreconcilable conflicts exist between State and Federal law with respect to claims against pharmaceutical manufacturers.

Next slide, please.

Two U.S. Supreme Court cases have held that Federal law broadly preempts claims against generic manufacturers. The first case, what is known as the Mensing case, held that warning defect claims against a generic manufacturer were preempted. In that case, the Plaintiff alleged failure to warn and claimed a generic pharmaceutical product's label was inadequate and it should have had a different warning.

The Supreme Court held that Federal law imposes a duty of sameness on generic drug manufacturers by requiring that the generic drug's labeling be the same as the brand name pharmaceutical product. Therefore, to adopt the Plaintiff's proposed warning the generic manufacturer could not simultaneously comply with the Federal duty of sameness and provide labeling State law allegedly demanded. The generic label, as pointed out previously, must be identical to the branded labeling. Therefore, failure to warn claims against generic manufacturers are preempted.

The second case from the Supreme Court, the Bartlett case, held that design defect claims against generic drug manufacturers are also preempted. Generic drugs must have the same active ingredient, the same route of administration, the same dosage form, the same strength and the same labeling as brand name pharmaceutical products. So, State law design defect claims that conflict with Federal law prohibiting a generic manufacturer from altering a drug composition are

preempted. Generic manufacturers cannot legally make generic drugs in another composition. The result is State law product liability claims are broadly preempted against generic manufacturers.

Next slide, please.

Certain state law claims against branded manufacturers are also impliedly preempted. Mr. Longer mentioned the changes being effected were CBE regulations which permits a manufacturer to make changes to a drug's label based on "newly acquired information" which provides reasonable evidence of a causal association of a clinically significant adverse reaction linked to a drug.

The regulations provide the newly acquired information must be evidence and data that was not previously submitted to the FDA or new analyses of previously submitted data if the new analyses reveal risks of a different type or a greater severity or frequency than previously included in the submissions to the FDA.

There are two leading cases from the United States Supreme Court, your Honor, with respect to implied preemption against branded manufacturers. They are the Wyeth versus Levine case and the Albrecht versus Merck case, which Mr. Longer briefly mentioned.

In Wyeth versus Levine the Court addressed whether State law failure to warn claims against brand name

manufacturers are preempted, it's a case from 2009, and in that case the Court held that claims in the case were not preempted because the manufacturer could have unilaterally added through the CBE regulation that you see on the screen stronger warnings about the drug in the label under the CBE regulations as allegedly required under State law without violating Federal law.

However, the Supreme Court did note that the FDA retains the ultimate authority to reject labeling changes made pursuant to the CBE regulation in its review of a manufacturer's supplemental application. The Supreme Court said, absent clear evidence that the FDA would not have approved the change to a drug's label, the fact that the FDA could have rejected the label change did not mean it was impossible to comply with Federal and State law from submitting a CBE supplement.

The second case, your Honor, Merck versus Albrecht, was decided last year, in 2019. The Court made some notable findings. First, the Court held that the question of preemption is one for the Court and not for a jury to decide.

The Court also in Albrecht tried to explain what the Levine clear evidence standard means. It stated, clear evidence is evidence that shows the Court the drug manufacturer fully informed the FDA of the justifications for the warning required by State law and that the FDA, in turn, informed the

drug manufacturer that the FDA would not approve a change to the drug's label to include the warning.

These cases typically arise, your Honor, in which the Plaintiff contends in his or her State law claim the warning should somehow have been different or changed and the Defendant contends that the FDA would not have approved that label change.

Next slide, please.

The next topic is preemption of State law design defect claims. Once a drug is approved, manufacturers are prohibited from making any major changes, and that would include modifying the qualitative or quantitative formulation of the drug product, without obtaining FDA's prior approval.

Therefore, although we have not seen the Plaintiffs' Master Complaint in this case, to the extent Plaintiffs' claims in this case will be that any changes to Zantac's design, formulation, or specifications, those would represent a major change requiring the FDA's pre-approval.

Any State law duty requiring unilateral action by a manufacturer that conflicts with FDA's regulations requiring FDA pre-approval results in preemption. The Court in Mensing held that the relevant inquiry for implied conflict preemption is whether a private party could independently do under Federal law what State law requires. If FDA pre-approval is required, then the claim is preempted, your Honor.

The Yates case recently, from 2015, in the Sixth Circuit similarly held that any claims the Defendant should have altered the formulation of the prescription medication in some way is preempted.

Importantly, your Honor, in the Bartlett case, which I had presented on the previous slide, which is a case involving a generic product, the Court in that case held that design defect claims are preempted as a matter of both Federal law and basic chemistry as the manufacturer could not unilaterally change the drug's composition without first obtaining the FDA's approval whether that drug was a generic or a brand name drug. So, Bartlett applies to design defect claims both for generic and brand name drugs.

To the extent Plaintiffs' design defect claims in this litigation are premised on a theory that Zantac should have been altered in some way to make it safer by changing its formulation, changing its manufacturing specifications, any other changes that would allegedly reduce high levels of NDMA, those claims are preempted.

Before concluding, your Honor, I want to briefly address two other important aspects of preemption. The first is the so-called stop selling or never sell claims.

In the Bartlett case, the First Circuit, before the case went to the Supreme Court, reasoned the manufacturer could comply with both Federal and State law by choosing not to make

the drug at all. The Supreme Court expressly rejected this logic and said that its preemption cases presume that an actor seeking to satisfy both his or her Federal and State law obligations is not required to cease acting altogether in order to avoid liability.

Similarly, in the Yates case from the Sixth Circuit, the Court rejected both an argument the manufacturer should have stopped selling the drug or should have never sold the drug in the first place under the same logic as Bartlett. The never selling, or never start selling rationale was rejected under the Bartlett Court's reasoning.

Second are claims that are so-called fraud on the FDA claims. These claims were addressed by the Supreme Court in the Buckman versus Plaintiff's Legal Committee case in 2001. The Food Drug and Cosmetic Act, which Mr. Petrosinelli described, contains no private right of action to enforce its provisions. Because of this, the Supreme Court found that certain claims seeking to enforce directly provisions of the act are impliedly preempted. In that case specifically the Court held that claims seeking to punish the alleged fraud committed on the FDA for not disclosing information during the approval process are impliedly preempted.

Next slide, please.

In sum, your Honor, depending on the way the claims are pled and developed in this case, the Defendants would

expect to argue that most, if not all of the claims are preempted in some way depending on the legal theory, and here you can see a summary of what I just covered in my presentation.

At this point, your Honor, I am going to turn it over to Mr. Keller for a rebuttal from the Plaintiffs.

THE COURT: Thank you, Mr. Bayman.

MR. KELLER: Good morning, your Honor. I will ask the obligatory questions, can you see me and hear me okay?

THE COURT: I can, thank you. Good morning.

MR. KELLER: For the court reporter, I am Ashley Keller from Keller and Lenkner. It is a great privilege to be with you this morning. I want to thank the Court and all of its staff and Special Master Dodge for doing such a superlative job of putting together the electronic means by which we are communicating today of 186 some odd participants. That cannot be easy logistically to do.

I am excited to talk about preemption, but before I do, I also want to thank my new friend and colleague, Ms. Zousmer, for taking over all of our screens and running the technology and shouldering that responsibility. It is a great relief for me that she has agreed to do that because that is not my area of expertise.

By agreement of the parties, we didn't put together rebuttal slides, so I am perfectly happy to use the Defendants'

slides on preemption for my remarks, so I'd ask Ms. Zousmer to go back to the first substantive slide and I will run through it from there.

Finally, let me offer my thanks to Mr. Bayman whose learned and cogent presentation covered a lot of the black letter law principles of preemption with which, of course, we agree, but there are some important areas of disagreement that I think are going to control all of the issues that are coming down the pike in this case. So, I do want to spend some time on those points of disagreement.

And I guess I will start not with a point of disagreement, but with an addition in response to an omission, which is that it is black letter law that preemption is an affirmative defense. The Supreme Court has said that multiple times, most recently in the Merck versus Albrecht case that Mr. Bayman referred to. And so always the burden of proof is relevant in a civil dispute. It is the other side's burden to carry both the factual and legal predicates of establishing preemption.

It is particularly important to focus on the burden with respect to implied conflict preemption and possibility preemption because the Supreme Court has said, starting in Wyeth, and again reaffirmed in Merck, that it is a demanding defense, it is quite difficult to establish.

The second point that I would make is a different

level of emphasis on the language of the supremacy clause, your Honor. Mr. Bayman focused, appropriately from his perspective, on the "shall be the supreme law of the land" language of the supremacy clause of Article 6, Paragraph 2, which is, of course, what establishes the preemptive of fact. We want to focus on a different word.

The supremacy clause says the Constitution and the laws, "laws of the United States which shall be made in pursuant thereof are the supreme law of the land."

The reason I put the accent on the word "laws" is because we are dealing here, of course, with the FDA and an agency and a regulatory body, and not all agency action carries the force of law. The Supreme Court has reiterated that the supremacy clause means what it says, it grants supreme status only to laws and agencies, in order to carry the force of law, have to go through certain hoops that administrative law principles establish. As Justice Thomas noted in his concurrence in Albrecht, hypothetical agency action or mere agency musings do not qualify as laws of the United States.

So, I hope the Court will indulge me for a moment while I go through some basic principles, a primer, if you will, on some agency law precedent from the Supreme Court which I think is eventually going to be important for the issues that the parties disagree with each other on in this case.

So, I will start with the seminal case of Chevron

versus NRDC. I think that it still claims the status as one of the five most cited Supreme Court precedents of all time. What Chevron says is -- in the wake of the New Deal Congress wanted to entrust expert agencies and regulatory bodies with the authority to make policy, and so they have wide latitude to interpret the statutes they administer.

And so the famous statement from Chevron is that if Congress has spoken to the precise question at issue in the statute in question, here the Food Drug and Cosmetic Act, then Courts don't have any latitude to defer to the agency, they have to enforce the statute according to its terms; however, if there is more than one reasonable interpretation of a statute, the agency gets leeway to decide which interpretation to embrace, and under certain circumstances, that interpretation, through the CFR, through the regulations, can carry the force of law and thus trigger the supremacy clause and preemption if there is a conflict with State law.

Since Chevron was decided the Supreme Court has added some important provisos that I want to flag for the Court. The first is a case called United States versus Mead, 533 U.S. 218, where the Supreme Court said, look, if Congress is going to delegate lawmaking power to an agency, which is still with experts, but they're unelected, they have to jump through certain formal procedural hoops before Courts are going to afford their pronouncements the force of law.

For example, if an agency like the FDA promulgates rules through notice and comment rule making which allows all the different stakeholders to provide their perspective and then considers those different points and promulgates a reasonable interpretation of the statute through regulation, that will carry the force of law.

If an agency engages in formal adjudication, acting very much like a court with a trial, with cross-examination, with witnesses, with evidence, and then issues a reasoned opinion interpreting statutory language which is susceptible to more than one interpretation, that can carry the force of law.

But mere informal action, publishing something on a website, a letter, a statement, an email from a regulator at the FDA, Courts can look at that, they can take into account that there are experts at the agency who chose to make that informal statement, but those do not carry the force of law under United States versus Mead.

Another important concept is when an agency is not issuing a rule, but is interpreting a prior rule that the agency promulgated, and there is a case called Hour (phon) that says agency interpretations of its own rules do not carry the force of law, but they are entitled to deference under certain circumstances. And importantly, the Supreme Court clarified just last term in a case called Wilkie, 139 Supreme Court 2400, where the question presented was, should the Court overturn

Hour deference altogether, the Court narrowly, in a five to four decision, said no, we are going to retain Hour deference, and agencies still can receive deference when they are interpreting their own regulations, but the office of the Hour doctrine was constricted by Wilkie.

What the Supreme Court said was, first, a regulation has to be genuinely ambiguous before we are going to give the agency any deference in interpreting it. The Supreme Court even said, "when we say ambiguous, we mean it." Courts are not allowed to just fly the white flag of surrender and say this regulation is kind of impenetrable, it's really tough to read, we are just going to let the expert agency decide what it means and move along. No. Courts have to conduct a much more thorough analysis when they interpret their regulations if they are going to get deference. There must be legitimate ambiguity.

Moreover, even if there is legitimate ambiguity, if the policy rationale behind the implementing statute that Congress passed doesn't support deference, Courts don't have to give deference. So, Hour deference still exists, but it exists in a much more narrow sphere in the wake of Wilkie from just last term.

The final administrative law point that I want to make to your Honor, which is important and I think stems directly from the logic of Chevron, comes from a case called Brand X,

545 U.S. 981, where the Supreme Court said agencies are allowed to and frequently do change their minds. If they change their mind by moving from one reasonable interpretation of a statute or a regulation to another reasonable interpretation of a statute or regulation, that choice must be respected. And indeed, Chevron itself was a case where the agency was moving from a previous interpretation with a new administration to a different interpretation of the statute, and Brand X makes clear that agencies are entitled to do that.

One of the things that Brand X flags as a reason to no longer necessarily afford the same level of deference to a prior interpretation of a statute or regulation is a change of administration. A different FDA is entitled to view the complete corpus of its regulations in a different way with different expertise and different reasonable interpretations brought to bear on that entire body of regulatory law.

So, with those basic principles firmly in view, let me move on in the order that Mr. Bayman did just talking about preemption for over-the-counter, generic, and then branded pharmaceutical manufacturers.

Ms. Zousmer, if you could move to the next slide, please. Sorry, one previously. There we go. The OTC manufacturers.

So, I am not sure whether there is disagreement here, your Honor, but I just wanted to state our position for

completeness because there might be.

We, of course, agree that Section 379r is an express preemption provision that applies to OTC manufacturers, and we, of course, agree that subsection e creates a savings clause that says the preemptive effect of 379r will not have any application to products liability cases.

Where there may be some disagreement is with respect to the Kanter case that is cited in this slide, and I think the proposition of law that Mr. Bayman articulated was that the product liability law exception to preemption does not allow any recovery of economic losses.

We agree that that is what the Kanter case says, but we do not agree that that applies across the board. What Kanter was saying -- it's an intermediate California Court of Appeals case and it says that, under California law, products liability law does not allow recovery for economic losses.

So, to the extent that your Honor, in considering California cases in the future where California law applies, believes that Kanter is a good prediction of what the California Supreme Court would say, we agree that that is relevant authority that you could consult, but Kanter does not purport to speak for the law of the other 49 sovereign states who have every right to define the metes and bounds of their own products liability law, and have every right to say that products liability law can allow recovery for economic losses.

For that proposition of law, in a case that actually cites Kanter, I would commend to the Court's attention Carter versus Novartis, 582 F.Supp.2d 1271, from the Central District of California in 2008. That is a case that actually goes against us on preemption, but it very clearly notes that Kanter is only speaking for California and that the law of every other state is entitled to encompass whatever it wants with respect to products liability and recovery.

So, the other point of disagreement that may exist between us here is about the express preemption clause. We agree again that subsection e allows products liability claims, but the express preemption clause doesn't foreclose every other type of State law claim. What it forecloses are claims that are different, or in addition to, or not identical with the Federal requirements. If there is a State regime that doesn't sound in products liability law, but exactly mirrors the Federal statute or regulations that are entitled to the force of law, those claims are also not preempted, and for that proposition of law I cite to your Honor Canale versus Colgate Palmolive, 258 F.Supp.3d 312, from the Southern District of New York, 2017.

We will, of course, have many more citations when we get to the briefing on these issues, but I at least wanted to give your Honor a couple of cases that you could look to that we think clearly establish the principles I have just

articulated.

So, that, I think, covers the scope of our potential respectful disagreements with respect to the OTC manufacturers.

Now let's turn, please, Ms. Zousmer, to the next slide on the generic manufacturers. And this is going to be, as your Honor could no doubt predict, an important point of focus between the parties. It is going to control a lot of the claims for a lot of Plaintiffs and certain Defendant manufacturers, so it is worth spending a few moments on this slide. I am going to focus most on the left most part of the slide in Mensing because I don't think that Bartlett adds that much other than to simply apply Mensing faithfully. So, Mensing is, I think, where the action is and it's the seminal case with respect to generic manufacturers.

We agree with a lot of what Mr. Bayman said about the case, but there are some important differences that I will get into now.

So, Mensing rests on two basic principles, first, as already articulated, the duty of sameness. The FDA regulations do indeed require that ANDA holders have the same label as the branded manufacturer.

The second principle of Mensing, though, which is more controversial and I think, in light of the principles I previously articulated, more open to question is that ANDA holders are not allowed to invoke the CBE process, the change

being effected process, that the branded manufacturers are to change their label unilaterally and then see if the FDA chooses to pull them back.

The reason that's more controversial, your Honor, is that in Mensing the Supreme Court, through Justice Thomas, gave deference under Hour to the FDA's then interpretation of its own regulations. There is not a regulation that says that the ANDA holders are not allowed to implement a change unilaterally through the CBE process. It was the FDA's interpretation of its own regulations that led the Court under Hour to that conclusion.

Obviously, we have a different FDA today, and your Honor will be allowed at the appropriate time to solicit the opinion of the FDA to see if they still adhere to the view that the previous FDA did, and I believe your Honor is going to be obligated under the Wilkie precedent to do a more searching analysis of whether the regulations are genuinely ambiguous. The Court in Mensing did not do that, it simply cited Hour and moved on. Interestingly, Justice Thomas now believes that Hour should be overturned, so the lineup of the Court on this question is different. But let's put a pin in that.

I believe that even if you take Mensing on its own terms, Mr. Bayman's statement of the law is a little bit too broad. Mensing does not say that generic manufacturers cannot be held liable for their storage conditions, for the

manufacturing conditions, if they store the drugs at too high a temperature and that produces NDMA, if the manufacturing API partners that they have selected are introducing NDMA in the manufacturing process. There is no regulation in Mensing or that anybody has pointed to that would preclude Plaintiffs from recovering under those sorts of theories. So, Mensing does not speak to that.

Similarly, I don't even think that Mensing speaks to a broad prohibition on duty to warn claims. Quite to the contrary, Mensing embraces the FDA's position that there can be duty to warn claims, it just can't be duty to warn through the label. So, let me unpack that for a moment, your Honor.

There are many states, including California, that have said our common law duty to warn includes the duty to warn third parties such as the FDA if that is the most effective means of disseminating important safety and efficacy information to doctors, consumers, and patients. And through a case called Coleman versus Medtronic, 223 Cal.F4th 413, the California intermediate Court of Appeals expressly said parties subject to the FDCA have a duty to warn the FDA if they become aware of no risks.

So, in this context, under California law, and the law of other states when we get to the area analysis that we will present to your Honor, there can be a duty by the generic to inform the FDA of adverse events, of new risks that they have

discovered, and invite the FDA to change the label. You don't have to look any further than Mensing itself and the FDA's own position in that case to see that this is true.

What the FDA told the Court in Mensing was there is no preemption because the generics have an obligation to come to us with new information so that we can try and change the product label, and they were quoting 57 Federal Regulation 17950-01, paragraph 40, and the Supreme Court agreed with that. They said, we'll agree that the FDA is right that the generics have a duty to come to us so that we, the FDA, can change the label, but the problem in that case was the theory of recovery for the Plaintiff was failure to change the label. The Federal regulations prohibited the generic from unilaterally changing the label so there could be no recovery.

If the theory of recovery under the State common law is, you didn't warn, generics, the FDA to allow the FDA to implement the label change, that is not preempted, and there is a persuasive authority from the Ninth Circuit in a case called Stengel versus Medtronic, 704 F.3d aa 1224, it was an en banc decision by Judge Fletcher that embraces this theory of recovery and says that if that is what the State common law warning regime requires, there is no preemption under the FDCA or any FDA regulations that are entitled to the force of law.

Let me just briefly cover Bartlett on this slide, your Honor, because, as I mentioned, I don't think it adds very much

to the Mensing analysis. The warning defect claim, as the top bullet under Mensing, and the design defect claim under Bartlett makes it seem like all sorts of different types of claims are preempted, but it was basically the same theory of recovery. Under New Hampshire law in Bartlett, it is a design defect if you don't have a proper warning on your product. So, the Plaintiffs were trying to just shift from one theory of recovery to another, and the Supreme Court said, no, I don't care what you style the theory, what you name the tort, if you are trying to make the generic unilaterally change the label, Mensing says you can't do that, and so it is preempted.

We agree with Mr. Bayman that Bartlett clearly held that a stop selling theory is not actionable, and so that is, I think, the gloss that Bartlett provides for Mensing.

Could you turn to the next slide, please. Thank you.

I am going to be very brief with respect to the branded manufacturers because, very respectfully to my learned colleagues on the other side, I don't think that this is really a close call. The Wyeth case, I would commend it to the Court, it is crystal clear that it is extremely difficult for a branded manufacturer to invoke implied impossibility preemption because of the CBE regulations.

The only thing that I would point out on the slide, your Honor, that I believe is -- I won't say misleading, but incomplete is the Celexa case, which essentially makes it seem

like if you already have the data in your possession when you first went to the FDA that can't be a basis for invoking the CBE process. That was roundly rejected in Wyeth, 555 U.S. at 569, and I'll just read directly from the opinion.

"Newly acquired information is not limited, not limited to new data. The rule accounts for the fact" -- the FDA rule that is. "The rule accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments."

And so, the notion that the data has to be new is again squarely at odds with the Supreme Court's binding pronouncement in Wyeth. So, the only way that the branded manufacturers are going to be able to invoke the very difficult defense of preemption in this case is to say that they presented everything that the Plaintiffs are eventually going to present to you, your Honor, and ultimately on remand to the jury, about what happened here, what the risks were associated with these drugs. They are going to have to say that they presented that to the FDA, and had they done so, the FDA would have said, no, we are reversing your label change. You invoked the CBE process improperly, you have to go back to the old label.

I think it is going to be exceedingly difficult for the brands to meet that heavy burden given that we don't have

to deal in the realm of hypotheticals. We know what the FDA actually did here when presented with a scintilla of the information that we are ultimately going to present at trial, it took the products off the market entirely. It didn't say change the label; it just said stop taking these drugs. So, I think that the affirmative defense of preemption for the branded manufacturers is going to be a very tough one to surmount, very respectfully.

If we can go to the last slide -- you can skip this slide and go to the last slide, please.

I will conclude where I began, which is that preemption is an affirmative defense and a very difficult one to surmount when it comes to implied impossibility preemption. I think this concluding chart makes it seem like we have a tightrope to walk in order to succeed on preemption, but it is actually the other way around.

I would just conclude by saying that the final two points, the stop selling point and the fraud on the FDA point, we agree with that, but I would characterize those bullets as truthful irrelevancies. No Plaintiff is bringing a stop selling or fraud on the FDA claim. So, while those are correct propositions of law, I am not sure that they have any salience with respect to the claims that the Plaintiffs are bringing.

With that, your Honor, unless you have any questions at this time, I am happy to turn the Zoom presentation back

over to my friend, Mr. Longer.

THE COURT: Okay, thank you. Thank you, Mr. Keller. We are going to have Mr. Longer come back on.

There you are.

MR. LONGER: Thank you, your Honor. I tried to get over my technical difficulty before. Fred Longer for the record.

I was asked to explain the theories of the case as we anticipate filing of a Master Complaint. While we were, and still are, investigating matters without the benefit of formal discovery, we have learned a great deal about Zantac and Ranitidine containing products. Obviously, our investigation is ongoing, but I hope this discussion provides the framework within which Plaintiffs perceive our theories of the case.

What I will describe is that there are basically three components to the framework. Those include, one, the responsible Defendants; the second is the mechanism by which injury occurs; and the third are the legal theories we will likely be pursuing in the Master Complaint against any particular Defendant.

So, as you see on the screen, your Honor, the first tier there is the identification of the different types of Defendants. So, I would like to begin in the middle actually with the active pharmaceutical ingredient manufacturers, we call them API manufacturers for short. They sell API to finish

dose manufacturers, who then sell the Ranitidine containing products to distributors who then distribute it and sell the product to retailers, including but not limited to pharmacies, drug stores, grocery stores, etc. to dispense them to patients who are our Plaintiffs. The API Defendants have not been named, but our investigation suggests they may be responsible parties, and their liability is noted in this flow chart.

Just as an example, your Honor, Dr. Reddy, which is an India -- an Indian company, has subsidiaries here in the United States and would be an example of an active pharmaceutical ingredient manufacturer.

The next type of Defendant is the brand manufacturer, they are the finish dose manufacturer. These include the GSK Defendants, the Boehringer Ingelheim Defendants, Pfizer, the Sanofi Defendants.

Next is the generic manufacturer, generic manufacturers are also finish dose manufacturers. These include current and former and abbreviated new drug application holders, and examples of them, you may recognize the Apotex Corporation which is situated in Weston, Florida, there are others.

The next type of Defendant is the distributor, this will include the big three, which is Cardinal Health, AmerisourceBergen and McKesson.

Finally, there are retailers, pharmacies like CVS,

Walgreens. Some of these companies actually are involved in distribution as well, but generically, those are the types of Defendants -- I'm sorry, retailers that will be named.

So, if we could advance the slide, thank you, to the next level, which is the method of injury. And by the way, I owe a debt of gratitude to Ms. Zousmer as well because this is terrific to have the assistance.

The method of injury is the overarching contentions in this litigation which my co-counsel will later explain in the science presentation about Ranitidine being an unstable molecule. It's susceptible of forming NDMA in three discrete ways. So, the first way we describe is that NDMA forms in the body. The way the human body digests Ranitidine results in the molecule breaking down into NDMA.

The next concern is that NDMA increases through the manufacturing process. So, through the manufacturing process, use of solvents and other procedures, NDMA is created in the Ranitidine product itself.

The last, as we found out from many of the studies that have been done by the FDA, NDMA increases through storage and transport. This method was confirmed by the FDA and other independent laboratories who found extraordinarily high quantities of NDMA in Ranitidine products which was associated with storage and transport and exacerbated by heat and time.

So, following up, if we could advance the slide once

more, please. Thank you.

So, from those theories the claims being asserted against the various Defendants flow. We are going to have strict liability failure to warn claims, we will have strict liability design defect claims, and we will have strict liability manufacturing defect claims against the various Defendants as identified here.

We will also have negligence claims, we will have fraud based claims like negligent misrepresentation. We will have supply chain defect claims which address the liability for heat and time. We will have warranty claims, express and implied warranty claims. We will also be asserting equitable remedies, such as unjust enrichment.

Now, as these cases present themselves in this court through diversity jurisdiction choice of law determinations will result in different state laws being applied depending on the citizenship of each Plaintiff and other factors.

That, in essence, describes the theories of the case and where we intend for the litigation to proceed.

The next point of discussion, your Honor, is related to a procedural point regarding Lexecon, which is an issue that is unique to multi-district litigation.

In the Lexecon case, the Supreme Court curtailed the longstanding practice of transferee Courts to self transfer within the MDL in order to preside over a trial of foreign or a

transferred action.

The Supreme Court's ruling was based on a literal interpretation of Section 1407, which requires that any action transferred for consolidated proceedings shall be remanded by the panel at or before the conclusion of such pretrial proceeding to the District Court from which it was transferred unless it shall have been previously terminated.

Following the Supreme Court's ruling, MDL Courts have observed different practices to obtain the end of preserving their ability to conduct representative trials that remain within their authority. Either the MDL Court tries cases that were originally filed in the transferee forum, or the Court evokes a waiver of each party's right to a Lexecon remand so that the trial may occur in the MDL court.

The conduct of bellwether trials, your Honor, is essential to afford the parties and the Court information and jury feedback regarding both the merits of the claims and defenses and the efficacy of witness testimony and evidence presentation. Such trials also require a commitment of both judicial and litigant resources.

For those reasons, it is recognized in MDL proceedings that the results of bellwether trials are only valuable to the extent they are instructive, and every effort should be made to select and try bellwether cases which are truly representative of the entire census of cases filed in the MDL.

In some instances, one or both parties refused to provide a Lexecon waiver. Typically, a Plaintiff who prefers the convenience and availability of local witnesses, doctors, for example, refused to waive their right to a trial in the transfer order forum.

However, there are occasions where Defendants, for tactical purposes, refused to waive their Lexecon rights. Whereas there are a multitude of Plaintiffs in MDLs who are willing to waive their Lexecon rights and participate in the bellwether process, there are a more finite number of Defendants, and should the Defendants refuse to waive their Lexecon rights here, we believe the Court -- the Court and Plaintiffs' leadership should be informed early on in the litigation to permit the development of alternative bellwether trial plans.

Just by way of example, Your Honor, this was a recent experience of mine in the Xarelto litigation where we were -- Judge Fallon presided over that MDL, and he sits, of course, in New Orleans, in the Eastern District of Louisiana, and the Defendants in that case refused to waive their Lexecon rights, so the Court was restricted to trying cases that were basically filed in Louisiana or Mississippi because there were no Texas Plaintiffs that Plaintiffs could try.

So, it became very restrictive, and obviously not very representative of all of the different claims across the United

States because we were limited to Louisiana or Mississippi law to determine Plaintiffs' rights.

So, that refusal to waive Lexecon in that instance was known early on, and it directed and channeled the parties regarding how they proceeded through the bellwether process, but it is certainly something that we think we should know early on in the litigation so that we, when we get to the bellwether selection process, are very prepared as to how to proceed.

Unless the Court has any further questions, that is my conclusion and I would turn it over to counsel opposite.

THE COURT: Okay. No, no questions at this time. I want to make sure everyone has an opportunity.

Who are we going to next?

MR. PETROSINELLI: Your Honor, this is Joe Petrosinelli. I think we have fallen a little behind in time after that rebuttal on preemption, so let me just save some time here and say, in terms of what Mr. Longer just said, I don't have much to say about the Plaintiffs' claims. Those arrows made me a little dizzy, but I think whenever we see the master complaint we will be able to talk about what claims there actually are.

With respect to Lexecon waivers, in my experience, we are way, way too early in this litigation to be talking about that. I am sure we will have that discussion somewhere down

the road. In my experience, just as often Plaintiffs don't waive as Defendants, but whatever it is, when we get the census data and so on I think we will be able to have an intelligent discussion about that, so I don't have any particular comment about that right now.

To keep us going, I will turn it over to Mr. Keller who is going to speak on the innovator liability theory.

THE COURT: Okay. Let me just let you know that I am willing to forego the 15 minutes I had allotted for Q and A before we break for lunch. I don't want you to feel rushed, Mr. Petrosinelli, so if you had something more you wanted to say now, feel free to say it and then you'll have an opportunity to respond to Mr. Keller afterwards.

I do want to just, obviously, remind everyone that there is going to be ample time throughout this litigation to have full briefing. I am very mindful that this is broad strokes, this is an overview, and I don't want anyone to feel concerned in not being able to present everything that you might otherwise do when it is time for a full briefing.

MR. PETROSINELLI: Thank you, your Honor. I don't have any further comments. I will turn it over to Mr. Keller who is going to explain Plaintiffs' innovator liability theory.

THE COURT: Okay. Mr. Keller, so coming up on the lunch hour.

MR. KELLER: Thank you, your Honor. Ashley Keller

again for the Plaintiffs. I will now adhere to Polonius' maxim that brevity is the soul of wit and move through innovator liability much more quickly.

So, let me confess that I allowed innovator liability to be the title of this slide because it is commonly referred to that way, but with a little bit of reluctance because innovator liability is not the name of the tort in any state, it is just common law negligence that is being applied, and the office of this tort of common law negligence and this theory really only applies with respect to folks who only took an exclusively generic version of the drug.

The theory of liability here, again applying common law negligence principles under the law of certain states, is that the branded manufacturer can be held liable because the label for the brand is being put on the generic product for generic sales. This stems from the regulatory environments that we were talking about previously with the duty of sameness and the fact that the generic and the holder has to use the brand's label.

What certain State Supreme Courts have said is that the brand thus foresees that if they don't take their responsibility seriously and use the CBE process appropriately to change their labels that any generic sales are going to also fail to warn. So, it is appropriate as a matter of state public policy to hold the brand accountable for those generic

sales.

So, the leading case in this regard comes from the California Supreme Court, it's TH versus Novartis, 4 Cal.5th 145. To very quickly talk about the policy rationale behind this theory of recovery, after going through the common law negligence principles, it's the same elements of negligence, duty, breach, causation, and damages. What the California Supreme Court said is that as a matter of public policy, if the brands are not held accountable for the generic sales when there is a failure to warn it will actually encourage consumers to buy only the branded product because that is the only way they will get to recover for a failure to warn.

On the margin, as an economic proposition, that runs directly counter to the policies of California and to the policies of the United States which is to lower prescription drug prices by encouraging consumers to take a generic version of the product after a brand loses brand exclusivity and patents expire or what have you. So, once they are no longer charging the monopoly price we want consumers to buy the cheaper version of a drug, and this is a good way to ensure that they do so, by imposing a duty on the brand that they should foresee given their responsibilities and the unique regulatory framework of prescription drugs.

Just very quickly, there are some variations on the California version of this theory. For example, Massachusetts,

in Rafferty versus Merck, 479 Mass. 141, from 2018, said we want to balance the policy considerations. On the one hand we agree the brands should be held accountable when they really misbehave, but on the other, it is a big thing to hold them accountable for a different manufacturer of sales, so we're going to raise the level of misconduct to gross negligence as opposed to mere negligence.

There are some State Supreme Courts, admittedly, that have rejected the theory. The West Virginia Supreme Court did so last year. Different Federal Courts have made different predictions of what State Supreme Courts would do under the Erie Doctrine, and your Honor is going to have to engage with that issue as well because most states have not said one way or the other certainly through their state highest court whether they would embrace this common law theory of negligence, but that is the theory in a nutshell.

Unless you have questions, I am happy to leave it there.

THE COURT: Okay, thank you.

MR. BAYMAN: Your Honor, Andy Bayman again. Just in the interest of time, I am not going to do a rebuttal other than to say Ms. Sharpe pointed out some of our contentions in her opening. I would note that every Federal Circuit Court of Appeals that has considered this question has rejected innovator liability, as well as the highest Courts of the State

Legislatures in four states, and Florida has also, as well as the Eleventh Circuit rejected it. I have nothing further in the interest of time, your Honor.

THE COURT: Okay. Were there any other presenters in the law presentation?

MR. PETROSINELLI: Yes, your Honor, the next thing is that Mr. Longer will present on the medical monitoring cause of action of the Plaintiffs.

MR. LONGER: Back again, your Honor, thank you. Fred Longer for the record.

Because so many people were exposed to NDMA in the Zantac or Ranitidine containing products they consumed, they are now at risk of contracting a latent disease of cancer. For every harm there is a remedy and medical monitoring fits that maxim, your Honor.

The theory of the claim itself, the thinking behind the monitoring, I think is best explained in a case just around the corner here from where I used to live in Paoli, the Paoli Railroad Yard case, Judge Becker. In that opinion the Court said that medical monitoring is a legal theory by which Plaintiffs seek to recover the costs of periodic medical examinations that they contend are medically necessary to protect against the exacerbation of latent diseases brought about by exposure to a harmful substance.

So, that is the essence of the claim. There are

choice of law concerns that arise in that because there are so many Plaintiffs in this litigation.

Since the seminal case of Friends For All Children, which was out of the D.C. Circuit, a large number of Courts around the country recognize the validity of approving some form of medical monitoring to persons seeking equitable or legal relief. State Supreme Courts recognize that medical monitoring claims are available in Arizona, California, Florida, Maryland, Massachusetts, Nevada, Pennsylvania, Utah, and West Virginia.

Now, Mr. Agneshwar earlier said that medical monitoring is not accepted in the majority of the states. We disagree, in fact, we see it just the opposite, but that issue will present itself at a more appropriate time.

Meanwhile, we submit that most jurisdictions authorize medical monitoring theories of recovery.

There are differences in how states treat medical monitoring theories, they exist, but the variances are often minor and groupings of claims can be employed to manage any differences amongst those variations.

Finally, how do Courts treat medical monitoring? Some Courts, depending on the jurisdiction, recognize medical monitoring as a distinct cause of action for which damages are recoverable. That is certainly the case here where I live, in Pennsylvania. The Supreme Court here in the Redland Soccer

case found that to be the case. Other Courts simply find medical monitoring is available as a form of damages. That is the case in California, Potter versus Firestone. And still even other Courts recognize medical monitoring in the form of an equitable trust. That goes back to the Friends For All Children case.

This theory is particularly apt for the class actions which we will be discussing, but it is a widely recognized theory of recovery either in tort or in damages.

I believe Mr. Petrosinelli may have some comments based upon what I said, but I will leave it up to him.

THE COURT: Thank you, Mr. Longer.

MR. PETROSINELLI: Thank you, your Honor, Joe Petrosinelli again for the Defendants. I have the next two sections which will be quick. We're coming up near to the end here.

One of my sort of rebuttal on medical monitoring is, your Honor will just have to see the case law and if you want, we can submit you the states, but by our count there are 16 states out of the 50 that recognize medical monitoring either as a cause of action, that is seven states, Florida happens to be one, and then, or as a remedy for a traditional tort claim like a negligence claim, that is nine. We think it is 16 states, which is important because, as Mr. Longer says, when we talk about the class actions related to medical monitoring it

presents a problem, we think, for class certification, the difference in state law. Anyway, that is all I will say about medical monitoring. I'm sure, as we get into it, we can talk to the Court about our respective views on which states recognize it and which states don't.

The next section we have is a few selected defenses that the Court is likely to encounter in the case beyond preemption. The first one is Statutes of Repose. Because this product was on the market for so long, many states have -- 19 by our count have a Statute of Repose, Florida included, that applies in products liability actions.

Typically -- there's a little variation in the state laws, but typically from the point at which the Defendant sold and delivered the product until -- and then you count the years forward, most states it's ten years, some states it's 12, some states it's 20, but those are the states, the 14 states that have statutes that bar product liability claims a set number of years, as I say, typically ten after the product is sold or delivered.

There is an asterisk next to Alabama because that actually is not a statute, but it's common law in Alabama.

Then there are five states listed there where it doesn't create an absolute bar, like a traditional Statute of Repose normally does, but a rebuttal of presumption that the product was not defective if the injury took place that much

longer after the Defendant sold and delivered the product.

So, that is a defense that will be -- you see a lot of big large states in there where I expect we are going to have a lot of claimants from the census. That will be in play. There are obviously exceptions under certain state statutes that will have to be dealt with, but just in terms of a core defense, that is one of them.

The next one I was going to talk about before I turn it over to Mr. Bayman is -- next slide, please.

There are also a number of states, Florida also included, that create statutory defenses for products that comply with Government standards. Some of them, like the Florida law, are general to all Government standards, or some states, like Michigan you see there, for example, it is actually specific to FDA approved products, and again, depending on the state -- and these are only three states, there are other states that have statutes like this -- either it is a bar to recovery, or it is more commonly a rebuttal of presumption of non-defectiveness, or you see New Jersey, that the label is adequate.

Those are two defenses that you are likely to see come up in the context of this litigation, and I will turn it to Mr. Bayman to talk about one or two more.

THE COURT: All right. Thank you.

MR. BAYMAN: Thank you, your Honor. I will be quick

with the lunch hour coming up, and Ms. Sharpe covered this briefly in her opening.

But Plaintiffs have the burden of proof in this litigation to demonstrate the particular claimant consumed Ranitidine, whether branded or generic, that the Plaintiff also has the burden of identifying which manufacturer's Ranitidine was consumed, and the Plaintiff also has the burden of demonstrating that harmful levels of Ranitidine were consumed.

In Levine versus Wyeth, not the same case as the Supreme Court case we talked about, and I would commend that decision to your Honor, the Court dismissed claims against branded manufacturers where the Plaintiff's testimony was that he ingested only a generic form of the drug and the Court does an analysis about the need for proof of use and for product identification because a manufacturer does not owe a duty to a Plaintiff who did not consume its product.

This is a key issue in this litigation, your Honor, because, according to the initial census data, more than half the claimants have reported using more than one medication.

Finally, your Honor, for me, there are issues of personal jurisdiction in the case. I just want to highlight for your Honor, I am not going to get into those in any detail, but several cases in this MDL have named the foreign, that is non U.S. parent companies of GlaxoSmithKline and Sanofi, these companies never held the NDA for Zantac, and for manufacture or

distributor promoted Zantac in the United States and they will be asserting personal jurisdictional claims. Because of their foreign status, general jurisdiction does not apply, and the analysis would be a specific jurisdiction analysis.

Next slide, please, Ms. Zousmer.

The test in the Eleventh Circuit is the Waite case. You see that the Plaintiffs have to establish the first two elements, that their claims arise out of or relate to at least one of the Defendant's contacts with the forum, and that, importantly, that the Defendants purposely availed themselves of the privilege of conducting activities in the forum.

The Takata case, which was an MDL also in the Southern District of Florida, holds that generalized and conclusory allegations that a foreign Defendant designed, developed, manufactured, marketed, sold, or advertised the product are insufficient to confer jurisdiction.

I just wanted to highlight that for your Honor. These defenses are going to be asserted in much more detail by some of the Defendants in the litigation.

Thank you, your Honor.

THE COURT: Thank you.

MR. LONGER: Fred Longer. My thought was I would turn on my video now, but I do believe that Mr. Keller will address the earlier arguments by Mr. Petrosinelli and some by Mr. Bayman, and then I was just going to address the last dealing

with personal jurisdiction.

THE COURT: Okay.

MR. KELLER: If that pleases the Court, Ashley Keller again for the Plaintiffs. I will be extremely brief.

We are in agreement with the Defendants that of course they get to raise their affirmative defenses, whether it is Statute of Repose or otherwise. Most of those issues are questions of fact. I'm sure I could cite to your Honor chapter and verse and you have read already chapter and verse that that is true. And so, there are going to be factual issues associated with that. There are going to be choice of law issues associated with that.

Imagine a Plaintiff who took a drug starting in Tennessee, and then moves to Florida and continued taking the drug, and then moved to West Virginia and discovered her injuries there. Each state might have a competing interest in having its own law applied, so that is going to be a thorny question. Obviously, they get to raise these issues and they may apply in certain fact specific circumstances. And similarly, with respect to evidence, of course we have to establish causation. To the extent that they are trying to say that the normal rules of evidence don't apply, we don't agree with that.

A Plaintiff who has taken a pharmaceutical product for, on average, 14 years is competent to testify as to which

product they took as the way to identify it and establish causation, and they can put in place whatever rebuttal or challenge the memory that they want, but again, those will be fact specific issues. We have no quibble, of course, with their ability to raise the panoply of defenses that they mentioned in the previous slides, and I will close my remarks there.

THE COURT: Thank you.

MR. LONGER: Your honor, I just wanted to address the personal jurisdiction presentation. I heard about Polonius just a moment ago, brevity being the soul of wit. Let me try to keep it very short.

Personal jurisdiction, to the extent it is a defense, it raises a lot of factual questions and there is no discovery yet. Typically, within the Eleventh Circuit case law recognizes that where discovery would be appropriate, it should be granted so that the defense can be met. That would be my one position as to the personal jurisdiction.

And the last is, whether or not the Defendants intended to raise it or not, it is possible that they meant to include a BMS argument as addressed to class actions which you have on the screen right here, and there is ample authority to suggest that, under Federalism, Rule 23 has not yet been superseded, and that a national class action can still be permitted absent -- or despite the BMS ruling.

So, to the extent that is at issue, I don't know that it was intended in Mr. Bayman's argument, but to the extent it was embedded therein, we will have an opposition to that position.

If you have no further questions on that, your Honor, I would speak to you very briefly about class actions. I know that the lunch hour is coming up and we are into your Q and A period.

So, as Mr. Gilbert started out our discussion earlier this morning, we are going to be presenting consumer class actions and third party payor class actions. The consumer class actions will involve individual Plaintiffs and putative class members who purchased Zantac or Ranitidine containing products based on representations of the Defendants that their products were safe and effective when in fact they were exposed to products that contained dangerously unsafe levels of the known carcinogen NDMA.

Had the Plaintiffs and putative class members known of these risks posed by these products, they would not have used the products. That is the essence of the theory. There is going to be a whole host of claims presented to address those issues. Mr. Gilbert alluded to them earlier in consumer claims. We are going to have nationwide and state classes, presenting Federal RICO claims, Magnus and Moss Warranty Act claims, unjust enrichment claims, fraudulent and negligent

misrepresentations and omissions, negligence and negligence per se claims, state consumer protection statute claims, express and implied warranty, fraudulent concealment, and as we just talked about a moment ago, medical monitoring claims, and theories of recovery which will address those states where the theory is recognized and available.

So, that is all that I wanted to say about where we are going with class actions in the brief amount of time that I have, your Honor, unless you have other questions.

THE COURT: No, no questions. Thank you.

MR. PETROSINELLI: Your Honor, this is Joe Petrosinelli. We'll just make our 12:30 deadline.

I think all I will say on the class action piece is, I will echo what you might remember Mr. Agneshwar said in the opening, which is the fact of the matter is in pharmaceutical litigation consumer classes, proposed consumer classes and proposed third party payor classes are -- almost always certification is denied. You can look at all sorts of cases, MDL cases, non-MDL cases, but generally on predominance grounds, or lack of predominance grounds because there are so many individual issues with respect to -- you heard Mr. Longer describe the claims.

They are sort of grounded in fraud type claims, warranty and fraud claims, and those cases in the pharmaceutical context almost always result in certification

being denied. I looked for the last couple of pharmaceutical MDL opinions on this. In the testosterone replacement therapy litigation, Judge Kenelli (phon) in Illinois recently denied class certification of a third party payor class in that litigation.

There are many, many MDL opinions where, because of differences in state law, individual questions that predominate over common ones, and ascertainability questions, one issue -- your Honor may not deal with a lot of class actions, but in over-the-counter cases, not so much prescription cases, trying to define or ascertain what the class is, there's a bunch of Eleventh Circuit and Southern District of Florida case law denying class certification of proposed classes relating to over-the-counter products because of inability to ascertain the class in a reasonable manner.

So, we are a ways away from a class certification motion, but there are plenty of cases that repeatedly -- the cases repeatedly reject class certification in the pharmaceutical context for those reasons, so I won't say more than that now.

That is the last piece of our law presentation and I look at my clock and it is 12:30.

THE COURT: Perfect. Okay. So, we are right on schedule. We just excised the Q and A out, but the presentations were so thorough I don't need to utilize those 15

minutes and certainly not now. Thank you, everyone, this morning for giving such a comprehensive, collaborative and informative presentation. I can't tell you how much I appreciate it.

The technology worked beautifully. You crystallized the issues for the Court, and I recognize you are just scratching the surface, but it is incredibly helpful for the Court and for all of the other participants to just sort of hear the highlights of the legal issues that will be presented in this case, so I can't thank you enough.

With that, I am going to call a lunch break until 1:30, one hour, just as we have on the agenda. We will pick up with the science presentation. Again I ask, if you intend to be here this afternoon, not to leave the meeting, just keep your video off, your mute on, so our cohosts don't need to readmit you and it saves time.

We will begin as promptly as possible at 1:30. Have a nice lunch, and we will see you back.

(Thereupon, a luncheon recess was taken.)

THE COURT: Welcome back, everybody. I hope you had a nice lunch. I did want to say from the outset that I am going to give up my Q and A session at 2:45. I hope that that gives the presenters a little more latitude. I don't want anyone to feel rushed, and I think that is all I really wanted to say. I will put everybody at ease so you don't feel rushed.

With that, if we could have our science presenters.

MS. FINKEN: Good afternoon, your Honor. Can you hear me okay?

THE COURT: Yes. Good afternoon.

MS. LEONE: Before we get started, could I just ask that my colleague, Jonathan Tam, be able to screen share since he is running a number of these slides for us.

THE COURT: Absolutely. There is a slide on the screen right now, so maybe he has already begun.

MS. LEONE: Perfect. Are we ready?

THE COURT: Yes. For the benefit of our court reporter, if you are all going to be on together, the first time you speak if you would say your name for the record so it is very clear who is speaking.

MS. LEONE: Good morning, your Honors, Judge Rosenberg, Judge Reinhart. My name is Judy Leone and I represent GSK.

To start off the science section of the presentations I will be speaking on behalf of the Defendants and Daniel Nigh on behalf of the Plaintiffs, but this is intended to be a joint presentation, one on which we will be collaborating and passing the baton back and forth to cover our slides.

We are going to present for you a brief timeline of, one, the regulatory approvals for Ranitidine and the indications for which it was approved; two, the changes in

ownership for OTC Zantac over time; and three, the timeline for the arrival of generic forms of Ranitidine, both prescription and OTC, over the counter. Sorry.

To begin with, Glaxo first discovered Ranitidine in 1976, and in 1977 the first tests on Ranitidine began. Following extensive toxicity tests in animals, clinical trials began in 1978, and in 1979, GSK submitted the initial IND for Zantac tablets to the U.S. FDA, and that is the investigational new drug application that Mr. Petrosinelli spoke about this morning.

We can move to the next slide.

Zantac was first approved late in June of 1981, and GSK began marketing the product in that country. Shortly thereafter, in 1982, GSK submitted the original NDA for prescription Zantac tablets to the U.S. Food and Drug Administration.

Following numerous discussions with GSK, the FDA approved Zantac for prescription use as a histamine 2H2 blocker in June of 1983. At this time, Zantac was a prescription medication indicated for the short-term treatment of active duodenal ulcers and the treatment of pathological hypersecretory conditions such as Zollinger-Ellison syndrome, which is a condition in which gastric tumors cause the stomach to produce too much acid. The recommended adult dosage at that time was two 150-milligram tablets daily.

Go to the next one.

The FDA reviewed this medication frequently over the ensuing years, approving Zantac for a number of additional indications. In 1985, the FDA approved Zantac for short-term treatment of active benign gastric ulcers, and then later that year, FDA approved Zantac 300-milligram tablets for duodenal ulcers.

In 1986, FDA approved Zantac for maintenance therapy of duodenal ulcers as well as for gastroesophageal reflux disease, which most of us know as GERD. So, Zantac for duodenal ulcers for maintenance therapy, Zantac could now be given for maintenance therapy for duodenal secretions at a reduced dosage after the healing of the acute ulcers.

In 1992, the FDA approved Zantac for the treatment of endoscopically diagnosed erosive esophagitis, and that was a recommended adult dosage of 150 milligrams four times a day. Then in 1994, FDA approved Zantac for maintenance therapy for the healing of erosive esophagitis.

Finally, in 1995, the FDA approved Zantac for maintenance therapy for the healing of gastric ulcers. For this condition Zantac could be prescribed at a reduced dosage after the acute ulcers had healed.

Now I am going to turn the microphone over to Daniel for the over-the-counter discussion.

MR. NIGH: Good afternoon, your Honors, Daniel Nigh

for the Plaintiffs. I am going to talk about when over-the-counter Zantac became available. This would obviously be the time at which you could purchase Zantac over the counter and not need a physician's prescription.

First, it starts in approximately July of 1993, GSK and Warner Lambert entered into a partnership contract under which GSK and its affiliates would manufacture over-the-counter Zantac products for the partnership. GSK submitted the original NDA for over-the-counter approval of Zantac 75-milligram tablets in September of 1994. In December of 1995, the FDA approved over-the-counter Zantac for the treatment of heartburn, acid indigestion, and sour stomach. Over-the-counter Zantac launched in April of 1996, and was first available in 75-milligram dosage.

Next slide, please.

On December 18, 1998, the partnership between GSK and Warner Lambert formally dissolved. Warner Lambert retained the exclusive rights to sell over-the-counter Zantac 75-milligram in the U.S. GSK retained the rights to sell prescription Zantac in the U.S. In 2000, Pfizer acquired Warner Lambert and became the NDA holder for over-the-counter Zantac 75 milligrams.

In August 2004, FDA approved over-the-counter Zantac 150-milligram tablets. In 2006, Boehringer Ingelheim acquired rights to over-the-counter Zantac and became the NDA holder.

In 2017, Sanofi acquired the rights to over-the-counter Zantac and became the NDA holder.

MS. LEONE: This is Judy Leone again.

As you will see, the FDA approved several different forms of Zantac over the years, including injection and injection pre-mixed which were used in hospital settings, syrup, GELdose, which are gel capsules, and EFFERdose tablets and granules which are dissolvable. As you see on the slide, these different forms of Zantac were transferred to other companies or discontinued, the first two transferred to Covis Pharma in 2011, and the next group, syrup and EFFERdose, discontinued at various times from 1994 up through, for syrup, 2013.

Although the generic version of prescription Ranitidine came on the market in 1997, GSK continued to sell prescription Zantac 150-milligram tablets until 2017, and 300-milligram tablets until 2018. The very last batch of prescription Zantac expired in early 2019.

MR. NIGH: Next slide, please. This is Daniel Nigh for the Plaintiffs.

In terms of generic Ranitidine -- again, Ranitidine is the generic form name of the medication Zantac. In 1997, prescription generic Ranitidine became available. Generic over-the-counter Ranitidine manufacturers were able to seek FDA approval for their products beginning in June of 1998. Ms.

Leone and I have been trying to figure out exactly when the first generic over-the-counter Ranitidine was sold, but we believe it was sometime in 1998, 1999, and then approximately 75 companies have likely sold generic prescription or generic over the counter. That concludes our joint presentation.

THE COURT: Thank you very much. As I understand it, you are going to divide up 30 minutes for each side. As I said, I am going to give up the Q and A, so you have a little latitude there to make sure everybody has enough time to say what you want to say.

MS. FINKEN: Thank you. Good afternoon, your Honors. This is Tracy Finken on behalf of Plaintiff, and I am going to be joined by Daniel Nigh and Brent Wisner to provide a basic primer on the preliminary science that is involved in this case. We are going to be moving at a very quick pace so if you need us to slow down at all, please let us know. Thank you.

THE COURT: Everyone feel free to just take your time, especially with some of the terminology and this and that. I have a perfectionist of a court reporter. And Pauline, just feel free to put your hand up if you want me to have something repeated. Thank you.

MS. FINKEN: If we are moving too quickly and you need me to slow down, please just let me know, but we have a lot to cover in a short period of time so we are going to try to move through it as quickly as we can.

To get started, Mr. McGlamry talked a bit about the timeline of regulatory action that has occurred from September 2019 until the recent FDA product recall request. I have a timeline up on the screen for your Honor.

As you are aware, the story began with the Citizen's Petition that was filed by Valisure in September 2019, putting the FDA on notice that they had tested batches of Zantac and found extremely high levels of NDMA, a known carcinogen. Subsequently, the FDA did its own testing and also found NDMA in all test samples, many of which had unacceptable levels.

In December, and this is an important point, the FDA notified consumers that there was evidence that when ingested Zantac could form NDMA if nitrates were also present in the human body. The FDA advised Zantac users to limit the intake of nitrate containing foods such as processed meats to reduce the risk of NDMA forming when Zantac reacted with nitrates in the stomach. Next slide, please.

In January 2020, Emery Pharma filed a Citizen's Petition requesting a full Zantac product recall, and raising the concern that Zantac generates a significant amount of NDMA under elevated temperatures such that could occur during storage or transport.

If you fast forward then to April 1st, the FDA responds to Emery, and in the response cites to 1978 International Agency for Research and Cancer Guidelines that

NDMA should be regarded as carcinogenic to humans. These same guidelines from 1978 noted that NDMA is carcinogenic in all animal species tested, that it induces tumors in various organs in various species, including the liver, kidneys, and respiratory tract, and that a dose response relationship had been established, meaning that the more exposure, the higher the risk of developing cancer. So, as of 1978, it had already been well established within the international medical community that NDMA was a toxin. Next slide.

The FDA then requested that all U.S. Ranitidine containing products be recalled and all consumers should stop taking it, and the FDA noted that its testing demonstrated three things that I would like to point out.

One, that NDMA levels in Zantac increased to unacceptable levels even stored at room temperature; two, that elevated levels of NDMA were found in all products after two weeks; and three, that the agency was no longer confident that any Ranitidine product would remain stable or free of NDMA through its label expiration date.

The FDA recalls were followed by multiple foreign regulatory bodies removing all Ranitidine products from the global markets, and with that being said, your Honor, I am going to turn the floor over to Brent Wisner, who is going to talk to you a little bit about the science.

THE COURT: Thank you.

MR. WISNER: Good morning -- good afternoon, your Honor. It's morning for me. Can you see me?

THE COURT: I can.

MR. WISNER: Great. I am going to be talking to you about cancer and specifically what causes it. Now, before you can talk about what is a carcinogen, you first have to understand what cancer is. Cancer is a particularly vicious disease, it does not operate the way traditional diseases work with a pathogen or an underlying medical condition, but it's actually turning one's own cells against you to become lethal.

To get to that point there are a lot of steps in the process. You first have a healthy human cell, it gets initiated by exposure either to a carcinogen or to a natural genetic predisposition. Once that cell is initiated, it then can be promoted and then proliferated, ultimately leading to what we consider a tumor or a malignancy.

Now, each one of these steps, your Honor, actually is part of the causal chain in causing cancer, so any substance that affects any aspect of this chain is considered a carcinogen.

For example, substances that may not initiate a cell, but ultimately promote cancer toward the latter end of a person's treatment or condition, they are considered carcinogens just as much because they play a substantial role in contributing to the development of a malignancy.

What is really underlying this, your Honor, is fundamentally an understanding that cancer is multi factoid. Right? People have certain predispositions and other people don't. Somebody can smoke three packs of cigarettes every day for 30 years and not get lung cancer, and another person can smoke half a pack for five years and get lung cancer. Those differences are what we call sort of genetic (inaudible) -- there are various predispositions that make them more or less vulnerable to a particular carcinogen.

What this case is trying to focus on and what --

THE COURT: Hold on one second, Mr. Wisner. Mr. Wisner, do you have a volume button you can turn up? You do fade out.

MR. WISNER: Sure. I can speak up, too. Is that better?

THE COURT: Yes. Start that last point again so we get the full thought.

MR. WISNER: Sure. So, what this litigation is ultimately about is the interplay of the genetics or predisposition of an individual and their exposures to various aspects of carcinogens in the environment. The overlapping form of cancer, that is really where this case derives. This is really important in understanding concepts like dose response, right, because what dose is needed to cause an individual's cancer is going to vary by definition by

individual. Now, there are studies that look at these issues and we are going to go over that --

THE COURT: I'm sorry. I just put the volume up on my computer. Maybe that will help.

MR. WISNER: I just changed microphones. Is that better?

THE COURT: Much better, yes.

MR. WISNER: I will use this one. I am sorry, your Honor.

THE COURT: That's okay. Just maybe say that last thought because we cut you off.

MR. WISNER: Thank you, your Honor. So, when it comes to issues of dose response, this is really important because the dose that might affect one individual may change based upon their particular medical conditions and underlying genetics. There are studies that go into this. We will get into that, obviously, as part of our scientific analysis in the process of developing this case, but I think it is really important to understand that the dose issue is largely how it affects a specific individual. We will get into that a little later towards the end of the presentation.

In the realm of cancer science there are really three pillars, and these three pillars are well recognized in every scientific regulatory agency and every scientific body. These various aspects of the cancer science pillars, as we like to

call them, reflect the various types of data that we have.

To say that one of these is more important than the other I think is very problematic. Indeed, a lot of substances are deemed carcinogens just based on animal studies, a lot of substances are called carcinogens based on cell studies, and, of course, many are based on epidemiology.

At the end of the day, it is really important not to itemize the science. You have to look at all of the data, and look at it holistically, and that is something that I will bring together at the end of this presentation when we talk about general causation.

Animal studies have a benefit over, for example, epidemiology studies. They are highly controlled. The exact dose, temperature, food, everything is controlled in a sort of hermetically sealed environment, so you can really tease out just what effect is being caused by the compound, the agent here, versus what is being caused by the natural background rate. You are looking for replication of tumors, rare tumors, seeing it across species. For example, your Honor, when it comes to NDMA, it has caused tumors in every animal it has ever been tested in. Hard stop.

Similarly, cell studies are very informative as well. They take us down to the cellular level and see what is happening with a chemical compound on a homogenic level. You can actually see it causing genetic damage in these types of

experiments. Now, they are done, obviously, in living creatures, in vivo, as well as in vitro, but this data, combined with the animal data and the epidemiology, help us create a picture both relating to what causes cancer, but also how it causes cancer and the way it goes about affecting individuals.

These types of studies are really important in understanding what sort of genes are being impacted by a chemical.

That leads us to epidemiology. Obviously your Honor is going to hear more about epidemiology from my colleagues and you are going to hear more about it from the Defendants. I have a feeling it is going to be an important story in this litigation as it unfolds. I am not going to get into too much detail about what epidemiology is, it's a broad subject, but basically there are two broad types of studies that we're really interested in. Right?

One study follows individuals --

(Background conversation.)

THE COURT: I am not sure if that is somebody on the screen -- do you have something going on in the background?

MR. WISNER: Not me.

THE COURT: If any participants have their audio on inadvertently, just go ahead and turn it off.

You are being tested, Mr. Wisner. All of our

technological challenges are revealing themselves, so we will see how you navigate them. You have navigated them very well. So, carry on.

MR. WISNER: All right, your Honor. So, we have two types of epidemiology studies that we're primarily interested in. One follows different groups of people, those exposed and unexposed over time, to see how their cancer outcomes are. The other one takes people who have cancer today and compares them with people who don't have cancer today and makes sure they're similar enough, and then looks back in time to see, okay, who of those individuals were exposed to the agent at issue.

Now, I can get into the nuances of epidemiology, we don't have time for that. I could do a two-hour presentation of just the facts and ways to do epidemiology. I think what is really important for this presentation, really to set the stage, is how to read epidemiology.

Typically epidemiology is represented this way. You have a point estimate which tells you what the data shows. So here 2.2 would mean that twice, or 2.2 times as many individuals in the exposed group are getting the cancer from people who are unexposed. Another way of saying this is it is more than doubling the risk, 2.2 odds ratio, or relative risk, or it multiplies the risk by 220 percent. All of those sort of capture that same idea.

But that number is just what that data shows, and what

you are trying to find out is, is that data, that point estimate a fair representation of the rest of the world, and that is where statistical significance tries to come in, tries to tell us is that result that we are seeing just the product of statistical anomalies or is it a real risk, okay, and that is what the confidence interval is. It is often expressed as a 95 percent confidence interval.

Now, it is very common for certain scientists who want to see a result to just disregard non-statistically significant results, but this has largely been rejected in the scientific community as just bad science. Just last year 800 epidemiologists published an article in Nature condemning the use of significance testing altogether because it can obscure risks.

But what this number actually shows -- and this is typically, by the way, your Honor, how we plot out an odds ratio on a graph. Right? We have an increased risk to the right of one, and the decreased risk to the left of one. Anything to the right of the blue line is considered elevated, and anything to the left of it is considered protected, and the question is, what is the range? Does that range cross one?

What that is really reflecting here, your Honor, is a probability curve. So, we know based on our data that the most likely probabilistic outcome is 2.2. Now, we want to be confident that 95 percent of those probable outcomes are

captured, that is what is under the curve. Those are the probabilistic possibilities of what the risk is outside of our data set, and this confidence interval is supposed to capture that. We're leaving two and a half percent on each side of the curve out saying we are not concerned about those outliers, we are just focusing on 95 percent. Draw a line between them and that gives us what we call a confidence interval. Most of the time odds ratios are represented this way.

Now, it is really important that you consider this also in the context of non-statistically significant results. So here we have a 1.3, so it's an elevated risk, the data is showing a 30 percent increased risk, but the confidence interval spans from .8 to 2.3. Now, if you draw the curve underneath it, just like we did above, you will see that over 90 percent of the area under the curve falls to the right of 1, only a small percentage falls to the left of 1.

So, if you were to disregard this result and say, well, it doesn't tell us anything, then you would be disregarding 90 percent of what this is telling you, which is one of the reasons why epidemiologists like to look at everything and consider is there a holistic trend in the data we're seeing, specifically, are they all basically to the right of 1, because you can change the width of a confidence interval with sheer data. Just add more numbers and it will decrease it as the function of statistical laws.

This, your Honor, is interesting, and I want to pass it over now to Mr. Nigh, who is going to talk about NDMA, but you know, earlier in the presentation Defense counsel said to you that there was no epidemiology related to morbidity, and that is just not true.

These results are actually real data. This is the risks of invasive breast cancer for women. For current Ranitidine users, that's 2.2, statistically significant result, and the 1.3 shows for invasive breast cancers for users who used Ranitidine for longer than two years.

With that, I hand it off to Mr. Nigh.

THE COURT: Thank you very much. Mr. Nigh.

MR. NIGH: Thank you, your Honor. This is David Nigh for the Plaintiffs. I am going to be discussing a few things during my topic. I am going to talk about how NDMA causes cancer and then I'm going to talk -- NDMA, the carcinogen itself. Then I'm going to discuss how Zantac breaks down into high amounts of NDMA and the multiple ways that it does so, and ergo, therefore Zantac causes cancer. But after me, Ms. Finken is going to discuss the different ways -- or the epidemiology that shows Ranitidine itself, Zantac, causes cancer.

Next slide.

I am just going to hit some of the highlights here because we have talked about some of it already, but every health authority that has looked at this issue, or nearly every

health authority that has looked at this issue, they all agree that NDMA is likely a carcinogen.

Next slide.

A few things I want to point out here, I won't get into all of this because Mr. McGlamry touched on it in his opening statement.

I want to point out first that NDMA is in the family of nitrosamines, but it has been pointed out that NDMA is the most potent in that family. When trace amounts of NDMA are found in the water Governmental agencies can spend hundreds of millions of dollars to minimize the amounts of NDMA in drinking water. NDMA is found in foods like bacon, cured meats, and salted fish, but these industries have spent lots of money to try to minimize the amount of NDMA in those foods because they have recognized, and they have done many studies that shows just low levels of NDMA in these foods can cause a significant increase in the risk of multiple types of cancers.

Next slide, please.

Next, NDMA is a genotoxic carcinogen. What that means is the toxicity of genotoxic carcinogens is referred to as being "non-threshold," meaning there is essentially no level of exposure that does not pose some probability of producing a carcinogenic response. Therefore, no dose of NDMA can be considered to be risk free.

Now, the EPA had calculated an oral slope factor for

the risk, and they have shown it 51 milligrams per kilogram per day, converted here into the U.S., as you heard earlier, that would be 96 nanograms for somebody who weighs 110 pounds.

Now, I will tell you the risk and that association would mean you have one in 100,000 people at that weight who would get cancer. I can tell you that slope factor at 110 pounds, that is not indicative of me, clearly, because I obviously weigh more than 110 pounds, and a lot of people weigh more than that, especially in the American population as compared to the European population.

Another thing that is important to understand is that the dietary studies showed that with higher concentrations of NDMA the oral slope factor increases significantly. So, this slope factor is calculated at 96 nanograms per day to get you to 100,000, but as your concentration increases, this slope factor is not linear, it is exponential. So, the slope as to your cancer risk as its concentration increases will increase significantly as well.

Also, this slope factor is based on animal studies. In vivo studies in human s have shown that NDMA is much more reactive in the human tissue compared to the animal tissue.

Next slide, please.

NDMA's only practical purpose today is to induce tumors in laboratory animals for the purpose of studying cancer and the treatments of cancer. NDMA, when they want to study

cancer and the treatments of cancer, is often the toxin ala choice that scientists will use because they recognize they can induce a tumor at any cancer site unlike most carcinogens. Substances that induce tumors in animals are considered as presumed or suspected human carcinogens until convincing evidence to the contrary is presented. This is a basic toxicological principle.

Next slide.

I am not going to go into a lot of detail on mechanistically how NDMA causes cancer. Mr. Wisner showed you some of the different steps. I will advise that NDMA can initiate a cancer from a single cell. It can also promote a cancer once the initial cell has formed.

Next slide.

But I think most importantly, and something that is important to understand when it comes to latency, is that NDMA and a lot of the cutting research over the last ten years on tumors themselves is that the introduction of NDMA can cause clinical cancer diagnoses very quickly.

To describe this, a lot of the new literature shows that most of the people in the population, that we actually have tumors inside of us. So, what that means -- it sounds very odd to just hear that, that most of us have tumors, probably most of us in this panel have tumors at multiple organ sites. The reason we know this is that when people pass away

in a car accident they will do autopsies, people that have donated their body to science, they will do autopsies of them and they will see that for people who were never diagnosed with cancer, weren't aware of it at all, they will see tumors at multiple sites, often times smaller tumors, and those tumors have become dormant in multiple different ways, as the slide previously shows. They have been dormant as a result of our immune response. They have been dormant as a -- because of cellular dormancy, and multiple of these different ways.

What happens with NDMA, and what is important, is that NDMA can disturb every single one of these types of dormancies. The important key is now, in terms of cancer, when does it go from subclinical to a clinical manifestation of the tumors? And so we can see that NDMA very often times will initiate a subclinical dormant tumor that may have never been a problem in that person's life to a clinical manifestation of those tumors.

This has been discussed in multiple other litigations, these -- and those reports have occurred also in other litigations.

Next slide.

Now, I want to talk about how we know that cancer is caused by NDMA in humans. There are multiple different things that we can rely upon. As I said before, Ms. Finken is going to talk about the Zantac Ranitidine specific episodes.

The other things that we look at, though, are dietary

NDMA studies. We have heard multiple times that, yes, bacon, salted foods, those types of things do have NDMA, but what we have found is that actually diets are very explanatory of many of the cancers that people have here in the U.S., absolutely. It has been pointed out numerous times that a person's diet can be one of the most indicative things as to why they got cancer. People have become aware that red meats can be bad for you, your doctor tells you that. Your doctor does not tell you that your medication that you are taking for GERD can give you cancer.

Now, in terms of dietary studies, diets that consist of 79 nanograms of NDMA per day, 79 nanograms of NDMA per day, can lead to a 66 percent increase in stomach cancer. There are dietary studies that show that just those low levels can have a very significant increase in your cancer risk.

There are many NDMA dietary studies that show that your diet, at these type of low levels, can lead to a significant risk of stomach cancer, pancreatic cancer, breast cancer, prostate cancer, liver cancer, and I am not surprised, as you saw in that graph of the cases that are filed, that most of the cases that are filed are precisely those kinds of cases.

The other thing I will talk about is occupational exposure studies. The dye industry is one of these types of occupational exposure studies where people have been exposed to low levels of NDMA for a long period of time. Those studies

have also shown that they have an increased risk of those same cancers, stomach cancer, pancreatic cancer, breast cancer, prostate cancer, liver cancer, and many other types of cancers. We talked about animal studies and in vitro studies. I won't go further into that other than to say there is a plethora of data in terms of NDMA causing cancer.

Next slide.

Next I want to show you the Ranitidine molecule and the NDMA molecule, and explain how Ranitidine breaks down in NDMA. You can see the entire Ranitidine molecule on the left side and you can see the entire NDMA molecule on the right side.

The odd thing is that every piece of ingredient that you need to get NDMA is wholly contained in the Ranitidine molecule, and this is precisely what makes the Ranitidine molecule so unstable, is that the two edges of the molecule are sheared off the molecule to formulate NDMA.

Next slide.

Now, because Ranitidine is so unstable, it breaks down in NDMA in multiple ways, not just one or the other, and every one of these ways is additive and/or multiplicative in terms of the amount of NDMA that a person is going to get.

The first way that people will formulate NDMA, as shown by the Valisure study, is that if you have a high nitrite diet in your stomach at the same time that you are taking

Zantac or Ranitidine it is going to formulate high levels of NDMA that are going to be broken off or sheared off because the nitrites in the stomach will shear off the NDMA -- or the Ranitidine molecule will shear off the parts of the NDMA and they will form in the stomach.

Second, shipping and storage. We have seen from the Emery Pharma that when you ship or you store, even at room temperatures, but obviously the higher the heat, the higher the amount of NDMA that is going to break down, that is in addition to what is breaking down in the body.

Finally, and really the base level, is the API manufacturing because we have seen in Valsartan, and we will see it here again, we can tell by the numbers already, that when they are manufacturing the active pharmaceutical ingredient over in India and China they get sloppy. They reuse solvents and their manufacturing process makes an unstable Ranitidine molecule very susceptible to NDMA.

We can already see it in the results and I will show how we can see a base line of NDMA that is already in each one of these products just in the API manufacturing alone.

Next slide.

Finally, I will show the amounts of NDMA. First, this is the Valisure study, I won't go into details again other than to show Valisure started this out by testing it under the standard FDA testing protocol, that protocol involved using

heat, and they found about 2.6 million nanograms of NDMA per pill. We certainly don't need those kinds of levels to establish a cancer being caused by NDMA.

The most important thing about this testing is to show that while this is the standard protocol testing for every other drug, it couldn't be for Zantac or Ranitidine where it created this high level of NDMA because the molecule is so unstable.

Next slide.

Let's go ahead and highlight it in red. This is early on, this is several months ago that this testing was done by the FDA. This is before the April 1st announcement by the FDA withdrawing all medications. This testing, all of these in red have excessive amounts of NDMA, and they were recalled by each of the manufacturers numerous months ago. These levels likely represent the underlying amount of NDMA being introduced as a result of the API manufacturing process, and some of the negligence that was done during those processes.

We know that by the varying levels of NDMA, for example Sanofi. Now, how do we calculate NDMA? We simply multiply the 2.38 times the 150 milligrams and that will give us the amount in nanograms. That leads to 357 nanograms, significantly higher than the 96 nanogram level threshold set by the FDA and EPA. You can also take a look at the Navidea, 855 nanograms, significantly higher than the 96 nanograms.

That is just the starting point. That is the base line.

From there, it becomes additive as a result of shipping and storage, and as a result of breaking down inside of the body.

Next slide.

We can see this additive multiplicative process in the Emery study. Emery is another fully accredited laboratory. Let's take a look at the results on the next slide.

This is a petition that was filed in January to the FDA where Emery looked at what is the effect of heat on Ranitidine, and they chose 70 degrees Celsius because they actually were informed that this is the temperature that a lot of these products were stored and a lot of these products were shipped.

So, just in looking at 70 degrees, all they wanted to do is go for two weeks and see how much NDMA is established. At less than 12 days 150 nanograms had broken down from a Ranitidine product that at zero days that you see on the graph there for that red line, at zero days its baseline level was approximately only 20 nanograms.

The FDA agreed with Emery Pharma that these drugs break down over time and form significant levels of NDMA. This is in addition for multiplicity to the NDMA created during the API manufacturing process and in addition to the NDMA broken down in the stomach.

You can see just in this process in 12 days the amount of NDMA that has formed at this temperature has been multiplied sixfold when it only started with 20. So, imagine how much NDMA is going to build that starts at 855 nanograms and then is multiplied sixfold under heat conditions.

Finally, I want to talk about the mixed study because several years ago Stanford investigators designed a simple study that gave multiple volunteers Zantac. After only 24 hours they compared the NDMA levels in the urine for the volunteers that ingested Zantac versus the volunteers who did not ingest Zantac. Stanford investigators found astonishingly significantly higher levels of NDMA in the urine of the volunteers who ingested Zantac. This study cannot be replicated now as it would be inhumane to give humans Zantac, a known carcinogen now.

What this shows is that the Ranitidine product clearly breaks down into significantly high levels of NDMA in the human body.

With that, Ms. Finken is going to discuss the epidemiology of a few cancers.

THE COURT: Thank you, Mr. Nigh. Ms. Finken.

MS. FINKEN: Thank you. Your Honor, I am going to now go over a very brief sampling of epidemiological data showing an increased risk of certain cancers associated with Zantac. This is not exhaustive, but just meant to give your Honor a

glimpse of the available data that we already have before Zantac -- before discovery has even begun that demonstrates a doubling of the risk of certain types of cancers with Zantac and which also demonstrates evidence of a dose response relationship with exposure to NDMA and these same types of cancers.

I can only assume, based upon the opening statements, that counsel for Sanofi, Mr. Agneshwar and Ms. Sharpe, do not have these studies, but I am happy to provide them with copies of these studies after the conclusion of these conferences.

Looking at the first slide, this is a study from a 2019 meta analysis conducted that looked at the link between H2RAs as a class and pancreatic cancer. H2RAs is the class of medication that Zantac is in and it includes Tagamet, Pepcid, and others. A meta analysis is a statistical analysis that combines the results of multiple scientific studies.

None of the studies contained in this meta analysis looked at Zantac specifically, but they looked at the class of medications as a whole and found that there was a combined overall odds ratio of 1.26. That was statistically significant. This means that there was a 26 percent increased odds of developing pancreatic cancer after exposure to H2RAs.

Next slide.

However, when looking at Zantac specifically in a cohort study from 2000 comparing Zantac to Tagamet, which is

another medication in the class, as well as compared against non H2RA users, it was found that Zantac specifically had a relative risk of 2.6. That was a statistically significant, more than doubling of the risk of pancreatic cancer with ingestion of Zantac compared to nonusers. Tagamet did not demonstrate an increased risk of pancreatic cancer.

This data that you're looking at on the screen now is from a study looking at a population with occupational exposure to NDMA and the risk of pancreatic cancer. That is one of the types of studies that Mr. Nigh just discussed.

This study demonstrated a statistically significant increased risk of death from pancreatic cancer in people who were exposed to NDMA in the workplace which ranged from 1.59 to 2.6. These findings are similar to the risk of pancreatic cancer found in the Zantac exposed population and they show consistent findings between NDMA epidemiological studies and Zantac specific epidemiological studies.

Last, this study also shows a dose response relationship, meaning that the greater the exposure was associated with the higher risk of pancreatic cancer.

Okay, this next slide, this is data from a study looking at dietary exposure and the risk of pancreatic cancer. As you may recall, Mr. Nigh pointed out that dietary exposure to NDMA can occur through items like red meat, tobacco smoke, beer, and smoked meats, and as you can see here, consumption of

red meat was associated with a relative risk of pancreatic cancer ranging from 1.1 to 2.4. Again, this is showing a similar risk as the prior occupational exposure and Zantac exposure studies, which were 2.6, 2.6, and now we are at 2.4.

Next slide.

This is from the same dietary study and shows more than a doubling of the risk and sometimes more than a tripling of the risk of pancreatic cancer associated with exposure to cigarette smoke or beer, both known to contain NDMA. Again, this is showing consistency among the studies and the dose response relationship in that the risk increased as the exposure increased.

As you can see, your Honor, all three studies demonstrate more than a doubling of the risk of pancreatic cancer when exposed to NDMA whether the Trojan horse that was carrying the NDMA was Zantac, or tobacco smoke, or dietary consumption, or workplace exposure, so it is consistent.

Now I am going to show you a similar analysis with prostate cancer. So, we have a Zantac specific study that demonstrated a statistically significant increased risk of prostate cancer in Zantac users compared to Tagamet users, which showed no association. The overall relative risk was 1.57. However, this study also demonstrated a statistically significant and a substantial risk, over five times the risk of prostate cancer for Zantac users who were 59 or younger. The

relative risk was 5.33.

This study also demonstrated more than a doubling of the risk of prostate cancer in Zantac users between the ages of 60 and 69, and this was compared against the general population as well as against Tagamet users.

Again, this is the same occupational exposure study that I went over previously. This time it shows a risk of death from prostate cancer after exposure to NDMA in the workplace. The hazard ratio ranges from 2.32 in the lower quartile to 5.36 in the higher quartile. Again, the risk was statistically significant and demonstrated a dose response relationship, as well as consistency between the studies whether the exposure was from NDMA in Zantac or from NDMA exposure in the workplace.

The data that I just presented is a small snapshot of the science that is out there. The science in this case is still developing, but epidemiological evidence already exists demonstrating more than a doubling of the risk of certain types of cancers with Zantac use and a dose response relationship.

In addition, there is unanimous consensus in the scientific and medical communities that NDMA is toxic and a carcinogen that causes cancer in multiple organs. This statement holds true whether the Trojan horse delivering the NDMA is Zantac or tobacco smoke or through occupational exposure.

When you look at the weight of the evidence thus far you can see a picture beginning to appear even though we are only seeing the tip of the iceberg. We believe discovery will only add to the weight of the evidence demonstrating that the NDMA in Zantac causes certain cancers within the human body.

In fact, you can see how much it has changed in the last few weeks with the national recall. Last week a study was published in the British Journal of Cancer, the study that Mr. Agneshwar discussed in his opening. This study evaluated the class of H2RAs and gastric cancer and the authors stated that they found some evidence of the associations between PPI and H2RA use and gastric cancer risk. Those authors recognize the possibility of reverse causality, which Mr. Agneshwar noted, but what he did not tell you was that they adjusted for this possibility when they analyzed the study results.

When they examined the data in relation to Zantac specifically there was an increased risk of gastric cancer compared to non-Zantac users with fully adjusted odds ratios ranging from 1.42 to 1.17 with varying statistical significance. So, it was simply incorrect to state that the authors found no increased risk.

In addition, two posters were published at an industry sponsored convention last week regarding Zantac and cancer. We don't have the complete data or the full publications, but one poster indicated that the overall incidence of cancer was 26.4

percent in the Zantac exposed population compared to 13 percent in the general population, again a doubling of the percentage of incidents of cancer found in Zantac exposed population compared to the general population.

And the second poster was the Kim poster which Mr. Agneshwar also discussed in his opening. Kim noted that NDMA is a carcinogen and known to cause various malignancies. Again, I will preface this by saying we do not have the underlying data or the full publication, but the poster indicated that the authors only examined the risk of gastric cancer with Zantac versus two other drugs. Zantac was not evaluated against the general population.

The authors further noted that there was no increased risk compared to the other two drugs, but that the Zantac group had less risk factors for gastric cancer overall compared to the other two groups, and that may have affected the results.

Again, I bring these points up to demonstrate that the science is still developing and I suspect as we get into full discovery we will find further scientific evidence to support that the NDMA in Zantac leads to an increased risk of certain types of cancers.

Next slide.

Last, your Honor, this slide is a visual aid to show the increase in cancer incident rates over the ten years after Zantac was approved in the U.S. This data demonstrates the

incident rates when you plug in the top ten cancers that the Plaintiffs listed in the registry census data. As you can see, taking the ten most commonly listed cancers in the census and plugging them into the National Cancer Institute's database to track incident rates over time, it shows a very dramatic increase from 1983, when Zantac was approved, onward, and so the red line represents when Zantac was approved.

This next slide that just came up is a graph that is similar to the last graph, however, this time we plugged in the six types of cancers where there is epidemiological data showing an increased risk of cancer with Zantac. Again, you can see a rather dramatic increase in these cancer incident rates during the ten years after Zantac entered the market.

The last slide, we did the same analysis, but we only plugged in the breast cancer. As you recall, your Honor, Mr. Wisner mentioned the Mathes study from 2008, which demonstrated a 2.2 to 2.4 statistically significant relative risk of ductal carcinoma breast cancer in Zantac users compared to Cimetidine, which is Tagamet, Tagamet users. Again, you can see a really dramatic increase in the ten years after the product was approved for use in 1983. You see bumps up -- it spikes up again when Zantac over-the-counter 75 milligrams became available in 1995, and again when Zantac over-the-counter 150 milligrams became available in 2004, you can see the trends going up.

You start to see a drop right after the time that Prilosec goes generic and Nexium hits the market at right around 2001, and both of those products -- that situation that occurred in 2001 significantly affected the Zantac market share. They were direct competitors of Zantac, a different class of medications not associated with breast cancer, and you can see there is a little bit of a leveling out of the big spike in breast cancer rates that had occurred.

Your Honor, with that, I will conclude. I thank you for your time and consideration. I am going to turn the floor over to Mr. Wisner to conclude our science presentation for today. Thank you.

THE COURT: Thank you.

I just want to assure the Defense that you will be given ample time because, again, I am not going to be going with my Q and A from 2:45 to 3:00 because I do see we are at 2:30.

MR. WISNER: Thank you, your Honor. I apologize for us taking so long. We have a big burden of proof in this case and we are trying to lay out the basics as much as we can early on in the case.

What I am going to talk to you about for the last next few minutes here is, okay, look at all of this stuff we have seen about science, how the heck do you actually prove that in a court of law? That is sort of what I have done in my work as

a trial lawyer and working on how to prove cancer, and I kind of want to walk you through that process.

We obviously start with the jury instructions. I pulled the Florida jury instruction as well as the California jury instruction. Many states, not all, but many states follow a similar standard of causation. It is not that it has to be the only cause, that the substance has to be the only cause of the cancer, but a substantial contributing factor.

Well, what does that mean? I think the way you do that is you look at the process through which oncologists and physicians actually go about examining this question. They do something called a differential etiology or often referred to as a differential diagnosis.

The first thing you do is you make a list of known risk factors. For here I will give a hypothetical example, we'll say prostate cancer. I am not saying these are the risk factors for prostate cancer, but just for purposes of this exercise I am going to walk you through that.

You list all those risk factors. As you can see there at the bottom, NDMA exposure is one of the risk factors for prostate cancer. Determining that list of risk factors requires examining genealogy and science, and very often these risk factors are largely agreed to in the scientific community. For example, we know HIV is a known risk factor for lymphoma. There is no dispute about that.

Once you have the list of known risk factors, you then have to look at the individual client and ask yourself which of these known risk factors actually apply to this person, the person in front of you, the patient. You go through them all and you cross out the ones that just don't apply, and you move over the ones that do. For example, this hypothetical individual, their age was a potential contributor, they also had some Agent Orange exposure back in Vietnam, and they had NDMA exposure. Now you have gone through the known risk factors, the potential contributors for this specific individual.

Now comes the last step. That last step actually examines -- has you look at the specific potential contributors and decide which ones of them were substantial. And how you define "substantial" means more probably -- it's a probabilistic determination, it's similar to the weight of evidence that we have in a court of law, to show was it is a substantial contributing causal factor in that person's cancer.

So here, for example, the person's age, they were very elderly, and it's a disease highly associated with age, so age ends up then being a substantial contributing factor. The Agent Orange exposure that we identified originally, it turns out he was exposed only once back 45 years ago, there's no way that that itself could have caused it.

Then, of course, we have NDMA exposure. Here we have

a significant amount of NDMA exposure so they both are substantial contributors. Now, at this point, your Honor, we have actually proven our case because we have now shown maybe it wasn't the only cause, but it was a substantial contributing cause, and that is what is required by the law.

There is also an instance, your Honor, where you get to the end of it, and you have nothing left on the list. You crossed out all the potential contributors, and there are just no substantial contributing factors. Well, that's called idiopathic.

Something caused the cancer, we just don't know what it was. So, when you can't figure it out, we call it idiopathic. I think it's really important to keep that in context because very often someone will say, well, you haven't ruled out idiopathic causes. Well, the phrase idiopathic cause is itself incoherent because idiopathic means an unknown cause.

In any event, I think as we look at the general context of what we are doing here in discovery, first list, the known risk factors, that's general causation. The question you are trying to answer is: Is NDMA found in or created by Ranitidine capable of causing a particular type of cancer? We fully agree with the Defendants that we are going to have to do it on a cancer-by-cancer basis, but this is the question we are trying to resolve for the most part.

And then you go to the specific causation: Did the

NDMA exposure caused by ingesting Ranitidine substantially contribute to the development of that Plaintiff's cancer?

These two questions are what get you ultimately to a conclusion by a jury one way or the other whether or not Ranitidine caused that person's cancer.

Your Honor, I know we are way over time here and I apologize, I am trying to rush through this. The last point, it is really important, and that is how we untangle association and causation.

This is one of the core problematic things that we deal with in the science area, particularly epidemiologists deal with. This exact point was addressed by Sir Bradford Hill. He was a researcher, in 1965 he published an article titled The Environment and Disease: Association or Causation.

What he did is he outlined the various factors that you should consider when you see an association to determine if that association is in fact causal. These Bradford Hill factors are uniformly accepted in every regulatory agency, it's accepted in every scientific institution like IARC, part of the World Health Organization, and it is what Courts routinely consider in assessing whether or not general causation exists.

These are the factors, I will not get into them today, your Honor, this will be the subject of significant Daubert briefings and discussions later on, but I just wanted to give this as sort of template, the factors that we are going to go

through about the associations we're seeing that NDMA cancer are in fact causal.

Finally, the reference manual discusses this at length, I'm sure your Honor has studied this, and it says very clearly that this analysis, this Bradford Hill analysis, this is a function of judgment, that you have to look at it, consider it, is it realistic. And although these factors, none of them by themselves get you there, not having one of them also doesn't get you there. So, they are just things to consider and whether or not that methodology, which is reliable and acceptable, an appropriate way of doing it.

With that, thank you, your Honors, for your time. I know it has been a marathon and we turn it over to the Defendants.

THE COURT: Thank you from the Plaintiffs' team, and I look forward to hearing from the Defense team.

MR. CHEFFO: Good morning, your Honor, Mark Cheffo. For this presentation it is a team of one. Mr. Tam actually was good enough to get it up for me.

So, I am Mark Cheffo, your Honor, and I represent GlaxoSmithKline, and I am going to be doing the presentation on behalf of GSK as well as Boehringer Ingelheim, BI, Sanofi and Pfizer.

Let me first start by echoing what you have heard a lot of the last day or so, which is thank you. Thank you for

all of the work that you have done and the magistrate judge, special master, your staff and your team in getting us to this point and it's certainly well noticed.

The other thing that has really been impressive is that, notwithstanding all the challenges that we've faced, we have been so collegial about how you encouraged us to move forward, and we thank you for that, and also certainly thank you for the opportunity to present this science because not only is this my first Zoom Federal Court science presentation, it is probably the first time that I've actually had an opportunity, on behalf of my colleagues, to speak with a Federal Court Judge, probably any judge, this early in the litigation about the science issues. So we really do appreciate that.

We spent a lot of time, frankly, cutting down our presentation trying to get within -- I will tell you, I think we are going to keep it within what we understood we were supposed to be doing, but I also heard your Honor saying that if I need a few minutes, that you are not going to --

THE COURT: I just want to be clear, I want you to take the time that you need. I really have been liberal with time, but it was not intended to be to the detriment of any party. When we have more formal proceedings and trials, you know, I am very time sensitive because there are a lot of moving parts, including jurors and witnesses, and things of

that nature, but I feel my time -- I am available to hear everything you have to say, so I don't want you to feel that you have to stick within your time limit.

If we have to go over a little bit and it encroaches -- I know we have a break coming up -- we are fine. So, don't feel pressure to stick within. I've tried to afford a little bit of leniency here today with everyone.

MR. CHEFFO: And I appreciate that. Thank you, your Honor.

With that, let me just see if I can jump into it. Irrespective of time, today is not the day to cover every single issue we have, or address every single allegation, but certainly we would like to highlight for your Honor the main themes and issues that we think are important for your Honor to consider, and obviously, we will try to address many of the Plaintiffs' points that they have raised to the extent that we think it is appropriate at this point.

Just to give your Honor a quick road map of where we are going to go, there are maybe five themes that I think you will hear in this presentation today.

First, and I don't think this is controversial, is that we believe that well-established scientific principles and methods should be applied by your Honor, just like they would be by scientists and experts and researches outside the Court. As I said, I don't think that is controversial.

Second, general causation is a threshold issue, and we will talk a little bit about that.

Third, and this is very important, particularly based on what you have heard for the last 50, 60 minutes, Ranitidine is not NDMA. Data and science about Ranitidine, not NDMA or other products, or red meat or other exposures, are what we respectfully submit should actually drive the Court's inquiry. As you will hear, that is not hard to do because this is a product that's been on the market for a long time, and there actually is epidemiological data, even though I'm not sure that you heard that much about it from the Plaintiffs' perspective.

Fourth is that cancer is not a monolithic disease. I think there is actually some fair agreement on this one. It is a heterogenous disease, it's not homogenous, and I think we need to kind of evaluate the different types of cancers just as they would be evaluated in the real world.

Finally, we believe that when you look at the reliable scientific epidemiological and other data, there really is no causal connection between Zantac and any of the cancer disease end points that the Plaintiffs have alleged in this lawsuit.

That is particularly highlighted when you look at the regulatory actions of both the FDA and EMA, which is essentially the European FDA, because what their actions actually involved were not a determination of causality in any regard and we will talk a little bit about that.

So, that is kind of a broad road map. With that, your Honor, I am going to jump right into the slides here.

So, again, you have heard that Zantac is the brand name for a medication that is generically known as Ranitidine. It is in a class of medications called H2RAs, and what they do is they reduce stomach acid and they are effective in treating ulcers, reflux, and damage caused to the esophagus that is caused by reflux.

What you may not have heard or been aware of before is, we have all probably heard of Zantac in our normal lives, and think of it as a heartburn medicine, and in fact it is used for heartburn, but what I think is also important is that at the time that Zantac was actually approved it was a very important medicine because it was only the second nonsurgical treatment for ulcers at the time. So, obviously that gave patients and physicians a much broader range of optionality in terms of how to treat what could be potentially very serious ulcers that required surgery prior to that.

So, again, with the caveats, your Honor, that you certainly have probably dealt with causation, you have probably dealt with that as a practitioner, so I am going to only gently or generally touch upon these.

You will see a few things. One is, what we tried -- if you look on the bottom of our slides, we sourced, where it is appropriate, the actual citations, and you will also see

many of our the citations come from things like the reference manual. So, hopefully that will make it easier for your Honor if you care to kind of check any of the sources or followup, if you will. With that, general causation and specific causation, two important points.

One is, it is the Plaintiffs' burden, I don't think there is any dispute about this, to prove both general, and if they get there, specific causation. It is not our burden to disprove any of them.

General causation, the way I think about it is examining whether an agent can cause an illness or injury in the general population, can it cause the injury. And then specific is, to the extent you determine that it can as a general matter, did it or does it in a particular individual. That is specific causation.

I said earlier, your Honor, that general causation is a threshold issue. The reason why I said that, one, it is from the manual, but it is also important that to the extent that the Court determines as we, again, respectfully submit that it can and should, that there is no -- the Plaintiffs have not met their burden on general causation, essentially it is do not pass go, full stop, we do not get to specific causation. In that regard, if it can't cause it from a population based perspective, then it certainly can't cause disease in any individual.

So, we've tried to, I think, objectively identify kind of what the question is that your Honor might ask yourself or might ask us to answer, really, at the general causation stage, and that is: Does the scientific evidence reliably demonstrate that therapeutic doses of Ranitidine, the actual medicine here, cause the specific cancers alleged?

There are a few components to this particular question, but I would like to first focus on the specificity of the exposure, and by that I mean Ranitidine and Zantac, because this case is about -- this MDL is not about red meat or occupational exposures to NDMA or anything else; it is about Ranitidine and about Zantac.

The Plaintiffs have kind of classified the, you know, the medicine as a pernicious carcinogen, and I don't think the Court should be left with the misinterpretation or misapprehension that, in fact, Ranitidine is some rare toxin with a signature injury. In fact, it is really just the opposite.

You have seen a similar slide to this, and I actually ask your Honor to look at a few points of this.

Before we kind of get there, we've heard a number of things. I think earlier in the opening we heard from Mr. McGlamry that NDMA has no business in the body. I think we heard a few times that this is a Trojan horse. We have seen that Trojan horse slide. This is like all the Trojans are

outside the horse because, in fact, this is levels in kind of everyday food at 3.5 ounces.

So, just taking beer that many of us might have a beer a day, or whenever it is, if you look at 3.5 ounces, it is 202, that translates to about a 12-ounce beer being 700 nanograms per day, which is seven times more than the actual FDA limitations that you heard about earlier today and I will talk a little bit about. Combine that with a sausage sandwich and some other things and you are obviously well over these daily limits.

There is a study that we cite here also that talks about dietary intakes, a recent study reporting up to 600 nanograms a day for human beings.

So, let's talk about this 96 nanogram per day kind of FDA daily living. Mr. Agneshwar talked a little bit about this earlier, but I think it's worth highlighting just what this is and really how it -- it can't be overstated or oversold.

So, let me start from the beginning. It is not our point on any of this that this should be ignored, or the FDA does not have any right to set regulatory limits, of course not. The other side of this is that this is not a causation standard, this is not if you go -- if you have 97 nanograms a day somehow it is going to cause cancer. In fact, what the FDA has said is if you use this limit and you take it for 70 years, it is not expected to have an increased risk of cancer.

They characterize this as a theoretical calculated level. We know that this was used in, I believe, rat or mice studies, not human beings. So, this is a guide point, this is a regulatory limit that obviously the FDA has every right to set, but it is not a causation standard.

We also know that the FDA recently did some testing of samples of Zantac and determined that some of them actually exceeded the 96 nanogram per day limit, but others didn't, and what I don't think you saw in the Plaintiffs' presentation is the ultimate conclusion from this market withdrawal, which is that overall the risks to individual patients potentially exposed to nitrosamines in any drug product remain very small.

Again, the FDA has a right to do that, all the companies, to my knowledge, involved in this litigation have withdrawn their products, but the FDA did not come out and say that there is a causation between these issues, between cancers and Zantac, just the opposite.

Similarly, the EMA, again, the European FDA, said in probably even stronger language, available safety data do not show that Ranitidine increases the risk of cancer and any possible risk is likely to be very low.

We have heard a lot about the recent action, but I think it is hard to not focus on the actual statements and conclusions by the agencies that are instigating those actions, and just without taking that context of really what the

agencies have told us.

Your Honor, we know -- I think we have seen this, the Rider case cited perhaps by both sides, but I think it is important. As I said, what the FDA has done, it is a risk utility analysis and they are fully within their rights to do it. But I think many Courts, including the Eleventh Circuit, have said that the FDA's risk utility analysis involves a much lower standard than that which is demanded by a court of law. A regulatory agency such as the FDA may choose to err on the side of caution.

We believe that is what they did. Again, appropriate for them to do that, but as you read on in this, it basically says the standard that you are ultimately going to be judging general and specific causation under Daubert are very different in both the real world and before your Honor's courtroom.

So, if all of those things that I have been talking about are not ways to determine causation, how is it that we should look at the question of causation?

I apologize, this slide is a little bit busy, but let me see if it hopefully helps your Honor in thinking about some of these issues.

So, I would say that these are -- there are methodologies that are absolutely generally accepted and procedures and ways that scientists both, frankly, inside and outside the courtroom look at the questions of causation, and

it is largely a four-step process.

The first is possible association, is there association.

I will turn in a few minutes to the question of whether people look at Epi data or not, but I would submit that the vast majority, if not everyone other than outliers, would suggest that determining a possible association requires human epidemiological data that shows some type of positive association. So, that is the first.

But like most things in the world, and certainly in science, scientists don't take just a specific point estimate or a confidence interval or a dot on a chart at face value and just say, ah-hah, this causes cancer, this doesn't cause cancer. Frankly, if that was the way it worked, any of us could do it.

What they do is they use possible association data from epidemiology studies and then they go a few steps further. They then say, okay, is it possible that that finding is the result of what is called chance, bias, or confounding, because we have to rule out each of those. And these are very common concepts among scientists and researchers and peer review studies.

Then if, and only if, you actually get past the association, step one, chance, bias, and confounding, step two, do you then move to the Bradford Hill factors. Mr. Wisner

talked a little bit about those, and I agree that those are standard factors. I think if you were to read the literature on it, what it would tell us is that you don't have to apply -- every one of them doesn't have to be a check the box, but typically the strength of the association must be kind of satisfied in terms of Bradford Hill, and then once you apply all the Bradford Hill factors, then you could actually make a considered decision based on causation or lack of causation.

So, there is absolutely a hierarchy of evidence, of scientific evidence. I think this might be an area where we kind of agree and respectfully disagree. We agree that there is human data, there's in vivo, animal data, and there's test tube data, but certainly having three pillars and kind of representing that they are all the same level of importance and hierarchy, we would kind of strenuously disagree. I think that is inconsistent with what you would find kind of in the real world with respect to scientific evidence.

Human Epi data is kind of the gold standard. It is at the top of the food chain, if you will, the hierarchy. I am going to talk about animal and test tube data. We are not suggesting that they are useless or that they don't have a point or they should be ignored, just the opposite.

Typically, what in vitro and in vivo data are used for are hypothesis generating to find out is there something potentially there, can you rule it out, and typically the way

science works and medicine and even the formation and approval of medicines require human epidemiological data to make sure that these findings can be replicated and are consistent in human beings.

So, remember in my little chart, the first is, is there association, right? And again, this is from the manual, your Honor. An association is the degree of statistical relationship between two or more events or variables, but because there are steps two, three, and four, association does not necessarily imply causation.

Then in step two we talked about, based on what the science tells us, and obviously this is validated by the manual -- let's take a step back.

I think a lot of what the point estimates -- and not being critical, I know there was a limited amount of time, but you saw a lot in the Plaintiffs' presentation just about charts and about all the point estimates and kind of trends. I think it would be helpful for the Court to also know that the story actually continues.

You have to then look at is there chance, bias, and confounding, because just because you have a positive association doesn't necessarily mean that it is a true or valid association; it could be false.

So, this is such a mockup of -- you probably heard a little bit about this, and you'll forgive me, your Honor, if it

is something that you are very familiar with, but I am going to spend a minute or two just to give some background.

This is a forest plot and we took some kind of hypothetical end points to just show the role of chance. That is one of the first, the chance, bias, and confounding.

The way scientists typically look at whether there is chance is that they look at whether there is statistical significance. I always hate to kind of overstate it, but the idea that you could have all these non-statistically significant findings and actually get a drug approved, that would probably be surprising. In other words, in the real world, statistical significance is very important, it is what epidemiology looks at, and it is what statisticians look at.

What this end point first shows is that you have a positive association. You can see that little purple circle to the right, and I agree with Mr. Wisner, he said that there was proof of an elevated risk or a protected risk. So, you have a positive association, but because the purple line, the confidence interval, crosses one, which is the center line, that means it is not statistically significant.

The second is a negative association, which again is not statistically significant. You can't rule out chance.

The third and fourth show findings that are statistically significant, right? One is a positive association, the other is a negative. That is statistically

significant because neither one of those in the confidence intervals -- if you look, it's CI, on the last one it's 0.9 to 0.32. It doesn't include the number one, so that means that it is statistically significant. But even if you have a statistically significant finding it doesn't mean you have ruled out chance, but more importantly, it doesn't mean game over because you now have to kind of -- oops, sorry, I think I dropped here.

Excuse me, your Honor, technical problems.

THE COURT: Take your time, that is fine.

MR. CHEFFO: Your Honor, I apologize, this is a problem I never had in a courtroom before, place a screen behind a book.

So, let me just give you kind of an example. The way I typically think about this is, is something else going on? There's obviously scientific explanations for it. Confounding occurs when other causal factors confuse the relationship between the agent of interest and the outcome of interest. I wonder why my team picked this example from the manual, but for example, researchers may conduct a study that finds individuals with gray hair have a higher rate of death than those with hair of another color. Instead of hair color having an impact on death, the result might be explained by the confounding factor of age.

Again, in the real world, if you were to do a study

and you were to say we are going to look at people who have gray hair and then do a point estimate and determine that, in fact, it showed that it was relatively high that gray hair was a factor or caused death, it would be confounded by age. That's why you can't just look at the specific numbers, you have to actually look at is something else going on, essentially.

We talked about bias as well, this is protopathic bias, and for ease of memory, and certainly for me not to butcher the word, most people talk about this as reverse causation. I think you may have heard about this earlier, but let me just give you an example why this is so important, because not only do I think it is something your Honor will be presented with throughout this litigation, but in the real world studies that I am going to be talking about in a few minutes, the authors explain some of their findings, not me, in terms of reverse causation.

So, kind of a perfect example of this is that if someone were, unfortunately, to have stomach cancer that had not been diagnosed, they would likely have or they may have heartburn, right, and they don't know why they have heartburn, and then they go and they might take Zantac for the heartburn.

If someone were then to say, oh, within four months later that person went to the doctor and got diagnosed with stomach cancer, there would be a finding that they were taking

Zantac and they were diagnosed with stomach cancer, but clearly that is reverse causation because it's not that the Zantac caused the stomach cancer, it is that there was an underlying cancer that actually had a symptom that was treated by the medicine, so that is reverse causation. As you can imagine, in this kind of forum and these types of medicines and these diseases this is kind of a very common issue.

Now, the manual also tells us that you need replication and consistency and often, as things with science and, frankly, the law, things make sense, so you want to have replication and consistency. In order to do that, if we are going to say that something is a toxin or a carcinogen, we want to make sure that we actually can replicate the findings, that we have looked at it under similar situations, that the findings, the procedures are consistent, so we don't have the bias, and confounding, and the chance issues.

I would respectfully submit that picking a finding from occupational exposure, or red meat, or NDMA, or H2RAs, that is not what the science or the manual is talking about when they talk about replication or consistency.

If you have an actual disease causing agent and you look at a forest plot, you see multiple studies on the positive side with statistical significance with meta analyses. That's how you determine causation, when you have replication and consistency. As I am going to show your Honor in a few

minutes, when you actually look at the actual data for Ranitidine you do not see that.

So, taking our same question, your Honor, and just focusing briefly on another component, which is the specific cancers alleged -- you know, in some regards, many of us have been doing this for a pretty long time, your Honor, but having said that, we are always a little surprised, and I think many of us were surprised to see the panoply of cancers that were alleged. It seems every body system above the thigh, the Plaintiffs are alleging that Zantac caused those cancers. And, you know, again, respectfully, we don't think that that is the way, you know, carcinogens or toxins work.

Cancer is not a monolithic disease, it's not heterogenous. It has different biology, as your Honor can see on the screen, prognosis and progressions, different inductions and latency periods, different symptoms, etiologies, causes and risk factors. I won't belabor the point because, as Anand said earlier, unfortunately, probably all of us have been impacted one way or the other with cancer. I should have said at the beginning no one is minimizing, obviously, any of these diseases, they are very serious. The question here today is, is there a causal connection.

The fact is, if you went into a doctor's office and said, I have cancer, that really wouldn't tell anyone very much. You would have to know how you treat it, what the cause

is, what the risk factors, what the potential for spread is. All of those would depend on all the different factors and the differences between how the cancer spread, was caused, and how you treat it. So, they are very different, and that is why even within oncology we know doctors and specialists will often focus on very specific cancer end points.

And we also know, not from us, but from the American Cancer Society that even the strongest carcinogens don't raise the risk of all types of cancer.

If you looked at -- our colleagues on the other side are great lawyers, right, and they are going to be zealous advocates, and they already are, but what I would say is, if you looked at a lot of the discussion about even NDMA, it is a possible carcinogen, it is maybe, or it is linked, or we should make an assumption.

So, again, this case is not about whether NDMA causes cancer -- or Zantac, but even with respect to NDMA, it is certainly not the strongest carcinogen. Even if it was, the American Cancer Society tells us we would not expect it to be a complete body system cancer pill.

Now, the scientific evidence, your Honor, that is what we're going to focus on, the Zantac, Ranitidine specific data, and just a few words on that. You will see some actual human data.

In many regards this is unlike a lot of different

substances where we don't have a track record or there is no data, but here there actually is, and as you've heard, this product has been on the market, this medicine, for almost 40 years. I am going to talk about the human data and I'm also going to talk about the others. You shouldn't be left with, hopefully, the implication or the impression that we are in any way trying to kind of run from or hide from the animal or test tube data, just the opposite.

We are trying to essentially be honest with ourselves and your Honor about how science works and focus on what scientists do, which is to look at the human data, but of course we will also talk briefly about the animal and test tube data.

So, this is that -- again, a little bit of an eye chart, we recognize that, your Honor, but this is a forest plot. We wanted to be super clear with our colleagues on the other side and with your Honor, this is a forest plot that has the main top level findings of specific cancers. There are other sub group analyses and smaller studies, and for a number of reasons, including time, but also, frankly, the reliability of those data, if we were to look at some of these sub group analyses, we would see findings from positive or negative.

But looking at kind of the reported out top level findings, what you see is a picture that does not say causation. In fact, if we kind of group these, and you look at

these different -- even within breast cancer, you heard a little bit about that earlier, if you look at the top, that is a non-statistically significant finding which trends negative, then you have non-statistically significant findings -- you have heard about the Mathes study, but in his overall study it is basically not a statistically significant finding with a minor positive trend and the same thing from the second breast cancer finding.

As you can see when you go down -- and we are not ignoring, your Honor, the three that are not highlighted now, but I just wanted to highlight these first.

You see, basically, the vast majority of the actual human Ranitidine data, which we think your Honor should be focusing on, and the Plaintiffs have not, is actually what tells the story here, that this is not a picture of a causal agent, much less the cancer pill that the Plaintiffs seem to be alleging in this litigation.

So, let's talk about the two findings. You will see that these are nominally statistically significant, meaning that they are positive findings, and that they are to the right of the axis.

Actually, can we go back for a minute to the last slide. Just a quick point I wanted to raise, your Honor, I am sorry about that.

You heard that, you know, we should be looking at the

data, even if the end point, that little dot, is to the right, we should -- you know, it could send us information or send signals, and I don't think any of us are suggesting that you just ignore data, that is not the point.

Could you imagine if you looked at all the dots on the left-hand side and we were saying, well, because it is trending negative, we think we should treat people with colorectal cancer, or esophageal cancer, or lymphoma, melanoma, ovarian cancer and uterine cancer with Ranitidine because there is a negative association, meaning you are less likely if you are using according to those studies? The answer would be absolutely not. That is not the way science works.

No doctor would look at that, or scientist, and say, oh, because it is trending negative, but it is not a statistically significant finding that this is somehow a cure for it. Similarly, if it is a positive association that is not statistically significant where you can't rule out chance or other factors, that also doesn't establish causation.

So, back to these, your Honor, apologies.

You have these three findings, and these authors, we are going to show you in a minute, they did exactly what you would expect because that is what happens when you go and you have a peer review study.

This is what Habel, the author -- I can't read the small print, I believe it is a she. Basically what she

found -- remember, there is only three in that whole study -- that elevation of cancer risk might reflect the use of Ranitidine for early symptoms of cancer. In other words, we are seeing people diagnosed with cancer, but we think they actually had the underlying disease and were taking the medicine for that.

And she also, and her colleagues, also said that information was not available on known factors other than age and gender for specific cancers and our estimates may be confounded, meaning we really couldn't rule out here whether there were other things going on that also could have and perhaps likely contributed to those issues. You don't see the author saying, ah-hah, we think that this causes cancer, actually just the opposite.

And Habel basically, that same author, your Honor, published a textbook or was an author in a textbook and continued even eight years later to say that looking back at 11 observational studies that looked at PPI and H2RAs for more than five years, what the author determined was that this review could not exclude reverse causation, and no data were available on underlying gastric conditions.

The same author that had those one or two findings basically says reverse causation, confounding, both then and eight years later.

You heard a lot about this, your Honor, but I think

this is a pretty interesting study in a lot of ways. One is, if we want to know what the author thinks the data said, not what the lawyers think, you have to look at what the author said. What the author said was these associations were sensitive to the duration of lag time used in the analysis. "Our results revealed a marked increase in the prescription of acid-suppression medications immediately before gastric cancer diagnosis suggesting the role of reverse causation."

Let me just see if I can break that down because I have had the benefit of reading that five times and the first time I read it, it wasn't a hundred percent clear to me.

What the author said, if you look back at that forest plot you would see three separate findings under Liu. One of them was statistically significant, the second two were not statistically significant. The first one that was statistically significant actually was within a year -- they looked at people who were a year of discontinuing Zantac, and they had a statistically significant elevated association between the cancer, I think it was stomach in that case and esophageal, and the Zantac.

The author said, well, that doesn't really make sense because the more -- you have heard about dose response. Cancers take a long time to develop, and it should be the more you actually take a medicine if it is actually a carcinogen, the greater the likelihood would be that you actually would

develop it.

What happened here is the people who only took it for a short period of time, there was a statistical association. When they looked at years two and three, that statistical significant association went away. So the authors, not us, concluded that there is confounding here, and this is the thing we talked about, the people actually had the cancer to begin with, took the medicine and then there was a finding, as opposed to the medicine causing the cancer.

Very briefly, your Honor, you saw the -- I think there was a fair amount of time spent by the Plaintiffs, or some time on the Mathes study. I showed you the top level findings on the forest plot, but what I think is important to understand also, in the concept of chance I think the numbers are, if you run -- in these studies, if you run 20 separate tests, for every 20, one of them will likely be the result of chance, either positive or negative. That is why when you see some of these studies that have 300 or 400, nothing is wrong with authors looking at it or doing it, but what they also recognize is that the more studies you run, the more likely from a statistical perspective you are likely to get certain findings of chance.

What this author said is that he recognized that -- he ran multiple testing, 82, and four of them would be subject to chance alone. So, we can look at the point estimate that you

were shown earlier, but when you actually look at what the author said, he said we cannot rule out that this observed increase risk in breast cancer among Ranitidine users "is a chance finding due to the number of statistical tests we did." That is what the author said, not what we are saying.

And again for completeness, but hopefully some level of brevity, as I said with the animal and test data, your Honor, we are not running away from it because we think it is not helpful. In fact, we don't think it really changes the equation. It is just a matter if you really want to find out if Zantac causes a cancer, you don't need look at red meat, and occupational exposure, and H2RAs, you look at the data from Ranitidine. But if you were to look at the H2RA class data, what you would find is that it does not actually support a finding of causation.

So, La Vecchia concluded that epidemiological data are consistent with the absence, with the absence -- you see that underlined -- of the causal association. Ahn could not rule out protopathic bias for reverse causation. Liu that we talked about just told us that the data suggests reverse causation because Liu actually dealt with H2RA data.

And then there is a very recent study, you know, you saw some information on pancreatic cancer in one of the slides, and obviously people talked about how that was a confounding and bias issue, but also this study looking at meta-analyses,

recent study, said "H2RAs were not associated with an increased risk of pancreatic cancer after the exclusion of a study with extreme results. In conclusion, there is no strong association between PPI and H2RA and the risk of pancreatic cancer."

So, while the data are actually evolving, they are not evolving in a way that shows causation.

Very briefly, your Honor, I am just going to talk about the animal data and test tube data, and then I will rap it up for you and your court reporter who has been so gracious.

To the extent that there was a question of the animal data, it is one of these examples of kind of hidden in plain sight. This is from the label, and in fact there was animal testing as you might imagine. You heard Mr. Petrosinelli talk about there was a truckload of information for MDAs. All of that was looked at. They didn't see any tumorgenic or carcinogenic effects when they were looking at this. They didn't see any mutagenic effects, which is an impact on mutations of the DNA. So, all of that was studied early on, it is in the label. The FDA approved it.

In terms of the bench science, just briefly, Mr. McGlamry talked about a Lancet article in his initial comments, and basically, I think the implication was that the study came out and that Glaxo either ignored it or was on notice.

Let me just put some color as to what actually happened. What Glaxo did was they analyzed that study. If it

was published in Lancet, it is obviously very well known, so it is hard to believe any regulatory agency would not have seen an article published in Lancet, but nonetheless, they looked at it. They shared the underlying studies and Glaxo's actions with the FDA. That study used NDMA at 20,000 times the dose of a fasting human gastric fluid and then they wrote to the FDA basically saying they have evaluated, they didn't think that there was any issues based on what they have done in this study.

What did the FDA do after that, having the study, having the data? They actually approved the product, Ranitidine, Zantac then for sale.

So, your Honor, everything we have talked about at every level of the hierarchy, there really is no reliable evidence of causation when you look at it the way, respectfully, we think scientists and your Honor will both inside and outside the courtroom.

Now, this was covered a little bit, but just very briefly in terms of specific causation, you know, it is obviously a differential diagnosis, and we agree that that would be the way to look at this to the extent your Honor got this far.

Also, we agree -- I think Paige talked about this a little bit earlier -- that in order to rule out all of these other -- you have heard about them even from the Plaintiffs,

how complicated this is with genetics, environmental factors, idiopathic, occupational exposures. A doctor would have to, he or she, if she got past the general causation, determine that it was Zantac that was a fact substantial contributing factor, whatever the specific law might be in that case.

I think, your Honor, that kind of brings me to the end. If you will indulge me maybe 30 more seconds, I would be remiss if I didn't kind of conclude with one quick point because I have been tasked to do the science today.

There were a number of claims and somewhat colorful rhetoric about the companies, and I think there will be a time and a place to address that and now is probably not that time, but I would just also suggest that we have people and companies who work pretty hard and they are trying to develop things like cures for COVID and get us all back to work, people who mean well, just like the Plaintiffs, and I would just suggest, just as I think there is a level of cordiality and collegiality and professionalism between the lawyers, as there is, I would suggest that we make sure that also extends to the clients on both sides, your Honor.

THE COURT: Okay, thank you very much, Mr. Cheffo.

Are you the last presenter for the science session?

MR. CHEFFO: Mercifully, yes, your Honor.

THE COURT: Okay. Thank you so much, I really appreciate it.

MR. CHEFFO: Thank you, your Honor.

THE COURT: So, we are going to take a little break. I recognize we are just off, but I would say we are doing pretty well given there is a lot of information packed into the day. If we are off by a few minutes it doesn't bother me. I hope it doesn't bother any of you.

It is 3:20, we are going to take a 15-minute break and we will be back at 3:35, and at that point, we will pick up with the case management issues, and I know you have allotted an hour for that, so let's try to keep that within an hour. We'll look to conclude by 4:30ish as opposed to 4:15. Quite frankly, actually I had us concluding at 4:30, so I think we are right on the mark. Without taking any more of our break time, we will see you back at 3:35.

(Thereupon, a short recess was taken.)

THE COURT: Okay, we are back and now we are moving into the case management issues, agreed case scheduling proposal, and I turn it over to our presenters for this session.

MR. AGNESHWAR: Good afternoon, your Honor. I am Anand Agneshwar from Arnold & Porter on behalf of Sanofi. Welcome to the home stretch, at least for today.

THE COURT: What mile are we at? I want to know.

MR. AGNESHWAR: I think we are at about 26.1, because as long as your Honor likes what I am going to tell you, and

what we're all going to tell you, I think this should be a relatively short session that might even get us out of here a little bit early tonight.

THE COURT: Okay.

MR. AGNESHWAR: As your Honor has heard throughout the day, I think one thing that is clear from today is that the parties have diametrically different views about this case, about the science in the case, about culpability in the case, about really the whole shebang. Candidly, your Honor, that is where negotiations on how a case is going to be litigated often break down in an MDL, and that is structural, what is going to go first, what is going to go second, what is going to go third, how are things going to be organized. So, in this case, I mean, it is no different.

Because of these different views, back to the marathon analogy, it is clear from today we see this, general cause, as being the big issue in this case, and we see that as really the be all and end all, so we kind of see it as maybe a 5K or even a sprint in the litigation. Plaintiffs, obviously they are goading to get to trial, they want to go the whole shebang, they see general cause as kind of a nuisance along the way, and they are looking at it more as a marathon.

Notwithstanding those differences, over the past several weeks Joe Petrosinelli and I and Bobby and Mike on the other side -- I hope it is okay that I refer to them by first

names, we have been spending a lot of time together over these last couple of months -- have rolled up our sleeves to see if we can break through that and figure out a way to minimize the work on your Honor and on the Magistrate Judge and present to you a structure that we think is going to work for this case.

After all these meetings, after a lot of internal stuff we have had to do on our side and with our clients, and I am sure there has been a lot of sheep herding on the other side as well to sort of get all the ducks in a row, I am pleased to report that, with the assistance of Special Master Dodge, we have an agreement for a framework of this case.

THE COURT: Wonderful.

MR. AGNESHWAR: We haven't put it to writing yet, but we will do that, but right now I will let you know what the outline of that is.

THE COURT: Okay.

MR. AGNESHWAR: Basically, in a nutshell it is this: General causation, Daubert briefing, and that decision on general causation is going to precede the selection of bellwether and individual case workup.

The agreement is that we will file our Daubert motions 18 months from June 1st, which will be about December 1st, 2021. Hopefully we will be out of quarantine by then. That will be the first brief that we file and will trigger opposition briefs, replies, ultimately a hearing on this issue.

Between now and then, we will engage in non-bifurcated discovery. In other words, we, the Defendants, have agreed not to insist on case discovery or bifurcated discovery such that only general causation discovery will go first. We will agree that all discovery against the Defendants will happen within that 18-month period. That was important to the Plaintiffs because for them, if they prevail on some or all of the general causation hearing, they want to get right to it in working up individual cases for trial.

We have also agreed that, depending on how things shake out over the next 18 months and in the Daubert hearing, then we will at a later time, particularly when your Honor rules on general causation and we know if there is anything left in this case, or if it is one cancer or if it is two cancers and how that matches up with the census, we will have a better idea what the case workup is going to be like, are these all going to be people that have a 30-year history or is it going to be shorter term use, and that is going to inform what the time frame will be if the Plaintiffs survive general causation for case specific discovery and trial.

We have agreed to revisit that at that point in time.

In the meantime, we have also agreed that class certification will be done on the same track as Daubert so that first briefs to -- motions to certify class, however many classes the Plaintiffs feel they want, those motions will also

be filed on December 1st, 2021.

So what that means is, your Honor, that we have a lot of work to do over the next 18 months, but we know your Honor wants to keep things going, so there will be a Master Complaint that will be filed in the personal injury cases, there will be Master Complaints that will be filed in the class cases. There will be motions, I'm sure, but there will also be negotiations on discovery. You have a lot of companies here, so the Plaintiffs will have to tell us what they want and we will be negotiating things like search terms, custodians, how many depositions.

Similar on the class side, I think the Plaintiffs have told us that there is going to be approximately a hundred class representatives, so that is going to give rise to medical record collection and depositions of some number, if not all of them.

We think -- because we have been working collaboratively and we have come this far, I think this is kind of the big enchilada, reaching an agreement on the structure. We believe that if we start right now and roll up our sleeves and start negotiating that we will be able to do that.

That's essentially how we see the case going forward.

I think Mr. Gilbert wanted to talk a little bit about our vision for the next case management conference and what the immediate next steps will be with your Honor. With that,

unless your Honor has any questions about the schedule, I can turn it over to him.

THE COURT: No. I just want to reiterate my great appreciation for the hard work and the collaboration. I can only imagine that was not necessarily an easy consensus to reach on such critical issues in the case to both sides for different reasons.

Did you have to negotiate that you were the one able to actually make that announcement to the Court? I think that would have --

MR. AGNESHWAR: We talked about that at about 8:00 o'clock last night, and that was the consensus decision as well.

THE COURT: Good. That is terrific. I want to express my gratitude, thank you.

MR. AGNESHWAR: Thank you, your Honor.

THE COURT: Okay. Mr. Gilbert, you wanted to address some other issues.

MR. GILBERT: Yes, I would like to just respond to my colleague, Mr. Agneshwar. Before I do so, let me, on behalf of all of us, and I know I speak on his behalf and on behalf of our Defense colleagues, but specifically on behalf of the Plaintiffs' leadership, I thank the Court, thank your Honor, thank Judge Reinhart, thank your staff and the Court Reporter for your attention today.

I'm sure you recognize how much work went into putting this day on from our standpoint, and we in turn recognize how much time and effort it took on the Court's part to get ready for it and to hold it, and we are all very appreciative. That is number one.

Number two, with regard to what my colleague, Mr. Agneshwar, just announced, in principle we have the same understanding. There are a couple of tweaks that, maybe just in hearing it, I didn't hear it exactly the way I understood it, but I don't think it is going to be an issue.

There are four orders that we discussed yesterday that are foundational, what we call foundational discovery orders, that we need to have in order to make a schedule like this work. In order to start discovery on day one and finish it by month 18 so that those motions can be filed everything has to be set and ready to go on the day the discovery date opens.

There are four orders that Mr. McGlamry and I discussed with Mr. Agneshwar and Mr. Petrosinelli yesterday that have been the subject of ongoing negotiations, and we hope will be resolved very shortly, that need to be in place on the day discovery opens, and that is the preservation order, the privilege order, the confidentiality order, and the ESI order.

You will hear more about those tomorrow. I am cautiously optimistic, as the Court knows I generally am, that we are going to reach agreement on either all or most of those

orders shortly.

What we discussed yesterday with our colleagues on the Defense side is that in the event we are unable to reach agreement and submit them to the Court by June 1st, which is our projected start date for discovery, and if any of those orders have not yet been resolved, that the unresolved orders, we notify the Court about those, and the Court can schedule a followup case management conference for sometime in the middle of June, and hear from both sides about our respective differences with respect to whichever of those orders haven't been resolved, and then make a decision and decide, okay, I am entering the ESI order based on this or based on that.

When the fourth of those orders are entered, that would become the official start date, the opening gate of discovery.

That was the only small nit, if you will, that I heard, a slight difference with my colleague, Mr. Agneshwar, about, but in principle, yes, from the start date of discovery we would go 18 months on full discovery, no bifurcation, no phasing. At the end of that 18-month period, they would file their general causation motions on Daubert in the PI cases, we file our motions for class certification.

The four of us expect to be able to put the dates and details on the key events and deadlines that need to take place between the opening of the discovery gate and the briefing on

those motions and be able to submit that comprehensive scheduling order to your Honor by June 1st as well, and we discussed that yesterday.

The last thing that is a joint issue that we discussed is that we plan to file our Master Personal Injury Complaint and our Master Class Complaints no later than 45 days from the date of the leadership appointment, which would come out on Monday, June 22nd. If we can get them filed sooner than that, we would love to, but we don't want to ask the Court for more time, so we have settled on the idea of 45 days, which comes out to Monday, June 22nd. And it is my understanding from our prior discussions that our colleagues on the Defense side have no objection to that as well.

So, that is where we are and I am hoping that Mr. Agneshwar will confirm that my slight tweak to his presentation is accurate, and assuming he does, we have one more Plaintiff side issue to discuss and I believe the Defense, Mr. Petrosinelli, has one more side issue to discuss.

MR. AGNESHWAR: Yes, your Honor, that is right. I did not mention that June 15th date because that is a date that happens only if we don't reach agreement on these initial orders. It was my understanding that Mr. Gilbert was going to handle that. I didn't view that as my responsibility to raise that issue, but all of that is correct. It is also correct, if this sounds acceptable to your Honor, then we will try to fill

in these dates over the next couple of weeks and hopefully submit yet another agreed upon order.

THE COURT: Okay. No, that sounds good.

Did I hear you, Mr. Gilbert, propose that there be a scheduled date for a conference, or shall we wait and see if you work things out so that I don't set it and then have to cancel it?

You all have worked so well together, I am like 99.9 percent sure you are going to work it out because you have done that with a hundred percent of everything so far.

MR. GILBERT: We are in agreement that we don't want you to set it and have to cancel it if we work it out.

I confirmed to my friends on the other side that if we are unable to reach agreement and submit all the agreed orders by June 1st to the Court, we'll notify the Court that we need the conference, and then we'd ask the Court to set it sometime at the Court's convenience in the middle of June.

THE COURT: I will make myself available, so I think, consistent with the theme we heard last week and today, in many ways things are much more difficult because we are dealing with things remotely, but then again, in many cases things are easier. I can send you a Zoom link, and we could meet tomorrow.

And, you know, to be quite honest, there is a lot that is not happening in the courthouses these days because of COVID

and other things can go on. Fortunately, at this stage of the MDL right now, we can go on.

I guess that is a long way of saying I am available, so I don't want you to work out of fear that if we don't get to her and we don't work it out -- I do want you to work it out, or at least try to, so I take that back, but I am available, and with the ease of Zoom, we are like pros now after all of these sessions we've had. I am very accessible.

MR. GILBERT: We appreciate that. We can all tell our kids we are pros now even if they don't believe that.

Yes, obviously lawyers work well with deadlines. We don't need to have the Court set a hearing yet. We've agreed internally between our two sides that June 1st is that deadline, if you will, to get these agreed orders submitted or to say we couldn't reach agreement on one of them or two of them, and to so advise the Court.

So we have agreed on the deadline of June 22nd, subject to the Court's approval of it, for the filing of the Master PI Complaint and the Master Class Complaints, and we have agreed that we are going to submit the proposed scheduling order to the Court that Mr. Agneshwar announced. It will take us through Daubert, general causation Daubert, and to class certification by June 1st as well. With the cooperative spirit that has already developed and that you have recognized, I am extremely confident that we will be able to accomplish all

those goals and hopefully won't even need a mid June hearing.

The one last thing I actually forgot to say is that, assuming we don't need the mid June hearing, Mr. Agneshwar and Mr. Petrosinelli suggested that it would be a good idea to get a case management conference on the books for about -- I think they said about a week or ten days after the filing of the Master PI and Master Class Complaints, and that would give everyone an opportunity to have looked at them, reviewed them preliminarily, and there might be some peripheral discussion with the Court at that time to talk about how we are dealing with those particular matters.

THE COURT: I think that makes sense if Defense agrees. I had thought, short of there being issues that couldn't be resolved that you needed the Court for, and anticipating that you were going to propose a filing date of the Master Complaint that was within a very reasonable period of time -- okay so it's not 30 days, but we will take 45 -- that it would seem to make sense to have the status conference following that.

So, I am very amenable to the week to ten days. What if I do this? What if I speak with Special Master Dodge, and she can coordinate with you to make sure your calendars are free, maybe you are not as available as I am, but coordinate so that we don't interfere with any outstanding obligations and we will set a date and a time consistent with that seven days to

ten days following the filing of the Master Complaints.

MR. GILBERT: That sounds great from our perspective, Judge.

MR. AGNESHWAR: And ours, your Honor, and I think at that case management conference we will also have a recommendation to your Honor as to how often we should have these management conferences over the next 18 months of this litigation.

THE COURT: That would be great. I had thought about do we want to lock ourselves in today or even tomorrow. I have looked at a lot of case management orders from many judges, and it would be easy to sort of pull one and say, okay, we are going to meet every month on the first Thursday of the month, but let's think about it and what makes the most sense, and at least for right now, I'm very available.

You have the time to mull that over and see how often you want to meet on a regular basis, but nothing precludes the parties from reaching out and saying we need something out of the ordinary, something has come up and we want to get off schedule for this month, and that is fine, too.

MR. AGNESHWAR: Understood, your Honor, we appreciate that and thank you.

MR. GILBERT: Thank you, your Honor. Do we need to submit anything to you now with respect to the June 22nd date or will the Court memorialize it --

THE COURT: Sorry to interrupt.

I think it would be -- again, we can develop what our approach -- mutual approach will be that works best for everyone. On a going forward basis, as you know, I like to be prepared and plan, so certainly before conferences having proposed agendas would be highly helpful. So we can maybe start thinking about how far in advance, how you want to submit them, what has worked well in other MDLs for you. It is not to say that an unexpected issue that may come up between the time you submit the agenda and the status conference is off limits, although I don't want to unfairly prejudice the other side by not having notice, so it is as long as everybody is okay with it.

But I would like as much advance planning, I am not a seat of the pants kind of person, although I recognize in some instances you need to be, but I do like to be prepared.

That's a long way of answering your question that before case management conferences I would like to have proposed agendas and you can think about how far in advance you are comfortable doing that, and then following each status conference I think it would behoove the parties and it would be helpful to the Court if the parties could submit a proposed order that memorializes that which we accomplished during the status conference.

If there is disagreement between the parties about

that, I can ultimately be the one -- obviously I will be the one to enter the final order, but I think that that -- you know, you can put the wording that you think works best.

So, to that end, if you would submit a proposed order following the status conference that memorializes, even if it is just these few points, I would be prepared to enter it.

Any time you do that, I would like it in Word format. You submit it to the Zantac email. I would like the other side to be copied and there be a representation in the email that leadership on both sides have reviewed and agreed with this order.

MR. GILBERT: Of course. We will work with Mr. Agneshwar and we will prepare it and get it in to the Court in the next couple of days.

THE COURT: For little things, you are spending so much time on big issues, not every order has to be taking a lot of your time. So far, Master Complaints on June 22nd and proposed scheduling order on June 1st, and any other dates, projected start date for discovery, June 1st, things of that nature, so it can be very short and simple, because there will be plenty of times when we will have more detailed orders that will require much more time on everyone's part.

MR. GILBERT: Of course. Thank you.

MR. YOO: Your Honor, this is Thomas Yoo. May I be heard for a moment on behalf of the generics?

THE COURT: Yes, absolutely. Do you want to put your video on so you can be seen as well?

MR. YOO: I am trying, but I am being blocked.

THE COURT: I think one of the cohosts will let you in. Let's just be patient a moment. I know that has happened in the past where it takes a moment for the video.

There you are. With you on, Mr. Yoo -- and I was going to -- actually when Mr. Petrosinelli was going to address, I think, the next section, I was going to call upon you, and also Ms. Johnston. If she wants to come on as well now, that is fine.

MR. YOO: Than you, your Honor. I don't want to cause any friction with how smoothly today has gone, and on behalf of the generics, we do appreciate all of the presentations. As your Honor knows, Mr. Petrosinelli has worked with me and my colleague, Rick Barnes, on behalf of the generics, and he has done a very diligent job of keeping us in the loop, but there are a lot of different cooks in the kitchen cooking up a lot of different things.

We felt it was necessary for us to just make one point with regard to the last agenda item regarding the case management plan as it relates to discovery.

This is the first the generics are hearing about this particular plan. We wanted to note for your Honor, and for everyone else on the call, the generics have not had an

opportunity to consider things like a start date, June 1st, for discovery, I heard the expression full discovery. We have not had a chance to speak with Plaintiffs about any specific proposal or what else they may have in mind with regard to the generics concerning the discovery.

I will also add on behalf of the generics that, as your Honor saw in the presentations today, preemption is going to be a particularly important issue for the generics. We as a group believe that preemption is a totally dispositive issue for our group.

So, we would like, certainly, to be considered on appropriate motions to dismiss once we see the Master Complaint, but we would also like an opportunity to speak with your Honor, Special Master Dodge, and the Plaintiffs, we have not had a meet and confer with the Plaintiffs yet, about holding discovery in abeyance as to the generics until the preemption issue is decided, or otherwise limiting initial discovery, but the idea of full discovery starting on June 1 is both a foreign concept to us and one that we think raises some important issues for our group.

MR. PETROSINELLI: May I respond, your Honor?

THE COURT: Yes. And did Ms. Johnston want to come on the video as well for the retailers? There she is.

Let me just ask, Ms. Johnston, did you want to say anything at this time before I turn it over to Mr. Gilbert?

MS. JOHNSTON: No, your Honor. Thank you.

THE COURT: There you are.

MR. GILBERT: My colleague, Mr. McGlamry, is on as well as you can see.

I am a little surprised to hear the presentation on behalf of generics only because it was my understanding that the Defense had been coordinating the discussions that we were having regarding the opening of discovery gates and the 18-month plan with all of the different buckets of Defendants. Perhaps I misunderstood, but I will ask my colleague, Mr. McGlamry, to chime in here.

Obviously, discovery is discovery is discovery. If we are going to move forward in this case with discovery along the lines that we discussed, we intend to move forward with this discovery against all the buckets of Defendants, not select buckets of Defendants.

So, I'd ask Mr. McGlamry just to chime in to make sure that I didn't mishear what I thought the representation that had been made to us was, and let's see where it takes us.

THE COURT: What I will say is tomorrow is called the discovery conference, so this is the centerpiece of tomorrow's conference, and so, while I don't think that it is a bad idea that perhaps there are some -- there is some alert now to maybe some possible -- I don't want to say misunderstanding, but need to further clarify among the group that has worked so well

together, I will let Mr. McGlamry respond.

I am not going to make any ruling, I can tell you right now, about holding any kind of discovery in abeyance for any party at this very moment.

Now, while I appreciate hearing from Mr. Yoo, I do think that the issues for discovery are better suited for tomorrow. I would just say that, in light of Mr. Yoo's comment, that perhaps there can be some more discussions following the conference today as we move into tomorrow and certainly we can flush some of these issues out in greater detail.

MR. McGLAMRY: Thank you, your Honor. I feel like Joe and I are seconds at a duel and we are here to make sure that Bobby and Anand are doing this correctly. Let me respond, your Honor, because you are correct, tomorrow is our discovery day, and we will go through most of this tomorrow, but I will say this:

It is my understanding as we work through these various discovery orders, ESI, confidentiality, privilege, preservation, all of that has been on behalf of all Defendants, not just the four brand manufacturers, and they have included the generics and the retailers in that.

So, I find it hard to kind of appreciate that the generics would not understand that discovery would start like everybody else as the result of the work with these orders.

I do believe that we have had discussions, I have not personally, but others in our group with retailers, with Ms. Johnston about discovery beginning here as we get started, and so, obviously, we can talk about all of that tomorrow. Our goal, as it has been in our discussions with Joe and with Anand over the past several weeks with regard to this issue, that it is a full open discovery with all hands on deck from all parties. Thank you, your Honor.

THE COURT: Why don't I hear from Mr. Petrosinelli.

MR. PETROSINELLI: Yes, your Honor, I just was going to echo what you said, which is the issue that Mr. Yoo raises is really an issue for tomorrow.

One of the things I think your Honor has asked us is to consider a leadership structure on the Defense side. One of the things that relates to that is -- as Mr. Yoo said, I have been keeping the generics and the retailers, we have had weekly calls, up to date, and generally we have been able to submit a unified position to Mr. Gilbert, Mr. McGlamry, and the Plaintiffs, for example, on discovery orders we have and have been circulating those to the generics and retailers, but there are times when the generics and retailers raise issues that are, quite properly, unique to them. I can't speak for them on behalf of those and they are entitled to speak for themselves on behalf of those.

If they have an issue, as Mr. Yoo said, about

discovery or wanting to hold it in abeyance upon filing of preemption motions, that is their right to raise, in my view. It is not my right to say anything about that. But that is a tomorrow issue, I think, not a today issue.

THE COURT: Just following up on your point about leadership structure, can you speak as to what structure you believe has worked well, would work well on a going forward basis? I know that in one of my prior PTOs the Defense leadership team was put in place on an interim basis, and then we have the liaison counsel as well on an interim basis.

What process might you suggest for converting interim to permanent?

MR. PETROSINELLI: Yes, your Honor, we have to address that. We have -- since your Honor entered interim leadership appointments and liaison appointments, we have talked about this subject, talked about it with Mr. Yoo, Ms. Johnston, Mr. Barnes, and we actually have a consensus, and obviously they can speak for themselves, that the current structure has worked well, and at least at this stage of the litigation, given the Defendants, meaning the buckets of Defendants now are the brand Defendants, the generic Defendants and the retailers, we think that the way it has worked so far with the interim lead appointments essentially of the lead counsel for the four brands, then Mr. Yoo and Mr. Barnes as the liaison counsel for the generics, and Ms. Johnston as the liaison counsel for the

retailers, seems to have worked well.

We considered alternative structures, but we thought, given how well things have been working and given the current state of the litigation, that we would ask the Court to make those appointments permanent. They are always subject to being revisited if the nature and shape of the litigation changes, for example, if more Defendants in different categories are added, and so on. At least at this point, we thought we would ask your Honor to make these appointments permanent.

In terms of the process for that, I take guidance from the Court, but I assume that the Court would -- it is sort of an agreed slate in a sense, so it's a little bit different than the Plaintiffs' side, but if your Honor wanted short applications and conflict disclosures as you did on the Plaintiffs' side, because it is sort of an agreed slate, I feel confident we could do that in relatively short order.

THE COURT: Okay. What do you mean by short order?

MR. PETROSINELLI: Maybe about a week.

THE COURT: Okay. May I turn to Mr. Yoo and Ms. Johnston to see whether you are in agreement or have a different idea about leadership structure for the Defense.

MR. YOO: I am in agreement, your Honor, and I know Mr. Barnes is as well on behalf of the generics.

MS. JOHNSTON: Yes, your Honor, I am also in agreement for the retailers. It is something that we discussed as a

group and I think the structure as it seems works well.

THE COURT: Thank you so much.

Were there other issues, Mr. Petrosinelli, that you wanted to discuss other than leadership structure?

MR. PETROSINELLI: Just one other issue on the defense case management side. I think your Honor asked us particularly with respect to the census to consider and propose a cost sharing order. I don't have anything to report on that other than we are having productive discussions about that. I don't think there is anything to talk about today. There are no costs that have been incurred yet from the census vendors, and so we will continue to talk about that on our side and hopefully come to an agreed order on that.

THE COURT: Okay. Let me just ask as to everyone, as perhaps a final issue, or close to final issue, thus far between the Special Master and the Magistrate Judge, who will play a more active role tomorrow, Judge Reinhart, do you feel that you have adequate resources available to you, whether it be from the Court or from Special Master Dodge, or is there anything else that you need?

MR. PETROSINELLI: I was going to say, I think I speak for Anand as well, not at all. The help that we have gotten from Special Master Dodge, who seems to have boundless energy and has been able to really facilitate discussions on case management issues and the census, for sure, I think has been

incredibly helpful to us, and I don't think -- in fact, I think it might be even worse if we added another resource at this time because I think she has been so involved in the back and forth. So, from our perspective, it has been working perfectly well and we would like it to continue.

MR. AGNESHWAR: If I could say, your Honor, I don't want to jinx things, but I am amazed at how seamlessly this process has gone over the past month or two and I do believe that Special Master Dodge has done a great job in facilitating that and the parties have worked well together. We have now gone about seven and a half hours on a Zoom call and it has gone much more seamlessly than I thought it would, so I am finding the whole thing very impressive.

THE COURT: That is probably a good note to end on lest we do jinx something.

MR. GILBERT: From our perspective, your Honor, we completely agree. Special Master Dodge, as Anand and Joe have said, is just an incredible resource to both sides and we very much hope that she will continue in this role. Between her continued service and being able to have the opportunity to work with Judge Reinhart on the areas of his expertise starting tomorrow, we don't see any need right now for an additional appointment.

We have one small housekeeping thing. I meant to bring it up before.

THE COURT: Okay.

MR. GILBERT: We had previously submitted to you a proposed common benefit order. It was not -- now that we have formal leadership appointed, we would like to update that order and submit a final proposed common benefit order to you. It probably won't take us until June 1st, but since we have set June 1st as the deadline for everything else, I would just as soon set that and keep the deadline the same, but if we can get that in sooner, we certainly will, so the Court can enter it, assuming the Court is in agreement, and then we can move forward in that regard as well.

THE COURT: Yes, I am aware that I have been sitting on that insofar as you submitted it, it was intentional, it wasn't an oversight. I felt it was appropriate that leadership be put in place before an order of that nature be entered. It sounds like that was wise because you may want to update it or change it, or at least get the benefit of others who are now part of the leadership team.

You can include that in the deadlines that we have discussed here today, and June 1st would be acceptable.

I suspect coming out of tomorrow's hearing there may be other matters, so whether it is one combined order that includes what we just discussed today -- and I know Mr. Yoo still wants to have some discussions with Defense. And again, no order is going to be entered until I know that there is

agreement from everybody or I feel that there needs to be further discussion on the issue.

I look forward to seeing everybody tomorrow, tomorrow morning at nine o'clock, and following the agenda that you have laid out for me. It looks like it is a bit of a shorter day tomorrow, so that should maybe be a welcome relief for everybody.

MR. PETROSINELLI: Yes, thank you, your Honor.

THE COURT: With that, thank you so much, everybody, our presenters and all of the participants who are hiding behind the video. I can't see you, but I appreciate your attentiveness and wanting to learn more about the case. I hope you did. I certainly did, and wish everybody a nice evening and see you tomorrow morning.

MR. GILBERT: Thank you, Judge.

MR. PETROSINELLI: Thank you, your Honor.

(Thereupon, the hearing was concluded.)

* * *

I certify that the foregoing is a correct transcript from the record of proceedings in the above matter.

Date: May 24, 2020

/s/ Pauline A. Stipes, Official Federal Reporter

Signature of Court Reporter