Case No. 17-30845

UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

IN RE: XARELTO (RIVAROXABAN) PRODUCTS LIABILITY LITIGATION

JOSEPH ORR, JR.; JOSEPH ORR, III; KELLI WALKER; KIM DEAGANO,

Plaintiffs - Appellants Cross-Appellees

v.

BAYER HEALTHCARE PHARMACEUTICALS, INCORPORATED; BAYER PHARMA AG, formerly known as Bayer Schering Pharma AG; JANSSEN PHARMACEUTICALS, INCORPORATED, formerly known as Janssen Pharmaceutica, Incorporated, formerly known as Ortho-McNeil-Janssen Pharmaceuticals, Incorporated; JANSSEN RESEARCH & DEVELOPMENT, L.L.C., formerly known as Johnson & Johnson Pharmaceutical Research & Development, L.L.C.,

Defendants - Appellees Cross-Appellants

JOSEPH J. BOUDREAUX, JR.; LORETTA BOUDREAUX,

Plaintiffs - Appellants Cross-Appellees

v.

BAYER HEALTHCARE PHARMACEUTICALS, INCORPORATED; BAYER PHARMA AG, formerly known as Bayer Schering Pharma AG; JANSSEN PHARMACEUTICALS, INCORPORATED, formerly known as Janssen Pharmaceutica, Incorporated, formerly known as Ortho-McNeil-Janssen Pharmaceuticals, Incorporated; JANSSEN RESEARCH & DEVELOPMENT,

L.L.C., formerly known as Johnson & Johnson Pharmaceutical Research & Development, L.L.C.,

Defendants - Appellees Cross-Appellants

consolidated with 18-30102

IN RE: XARELTO (RIVAROXABAN) PRODUCTS LIABILITY LITIGATION

DORA MINGO,

Plaintiff - Appellant Cross-Appellee

v.

JANSSEN RESEARCH & DEVELOPMENT, L.L.C.; JANSSEN PHARMACEUTICALS, INCORPORATED; BAYER PHARMA AG; BAYER HEALTHCARE PHARMACEUTICALS, INCORPORATED,

Defendants - Appellees Cross-Appellants

On Appeal from the United States District Court
for the Eastern District of Louisiana
Case Numbers 2:14-md-2592, 2:15-cv-3708, 2:14-cv-2720, 2:15-cv-3469

APPELLANTS' OPENING BRIEF

Frederick S. Longer
Levin Sedran & Berman
510 Walnut Street, Suite 500
Philadelphia, PA 19106
Telephone: (215) 592-1500

Attorney of record for Appellants

Case No. 17-30845

IN RE: XARELTO (RIVAROXABAN) PRODUCTS LIABILITY LITIGATION

CERTIFICATE OF INTERESTED PERSONS

The undersigned counsel of record certifies that the following listed persons and entities as described in the fourth sentence of Rule 28.2.1 have an interest in the outcome of this case. These representations are made in order that the judges of this court may evaluate possible disqualification or recusal:

1. Plaintiff/Appellant – Joseph Orr, Jr.
2. Plaintiff/Appellant – Joseph Orr, III
3. Plaintiff/Appellant – Kelli Walker
4. Plaintiff/Appellant – Kim Deagano
5. Plaintiff/Appellant – Joseph J. Boudreaux, Jr.
6. Plaintiff/Appellant – Loretta Boudreaux
7. Plaintiff/Appellant – Dora Mingo
8. Defendant/Appellee – Bayer Healthcare Pharmaceuticals, Inc. and its related entities, including Schering Berlin Inc., Bayer HealthCare Holdings LLC, Bayer Corporation, Bayer US Holding LP, Bayer World Investments B.V., Bayer Solution B.V., and Bayer AG
9. Defendant/Appellee – Bayer Pharma AG, formerly known as Bayer Schering Pharma AG, which is wholly owned by Bayer AG, which has no parent company and no publicly-held company which owns 10% or more of its stock

10. Defendant/Appellee – Janssen Pharmaceuticals, Inc., formerly known as Janssen Pharmaceutica, Inc., formerly known as Ortho-McNeil-Janssen Pharmaceuticals, Inc., which is wholly owned by Johnson & Johnson, which is a publicly-held corporation

11. Defendant/Appellee – Janssen Research & Development, L.L.C., which is wholly owned by Centocor Research & Development, Inc., which is not a publicly-held corporation

12. Counsel for Plaintiffs/Appellants – Fred Longer and Levin, Fishbein, Sedran, Berman

13. Counsel for Plaintiffs/Appellants – Leonard Arthur Davis and Herman & Katz, L.L.C.

14. Counsel for Plaintiffs/Appellants – Gerald Edward Meunier and Gainsburgh, Benjamin, David, Meunier & Warshauer, L.L.C.

15. Counsel for Defendants Bayer Healthcare Pharmaceuticals and Bayer Pharma AG – Lisa S. Blatt, Steven Glickstein, William Hoffman, Arnold Solow, Elisabeth Theodore, William Perdue, and Arnold & Porter Kaye Scholer, L.L.P.

16. Counsel for Defendants Bayer Healthcare Pharmaceuticals and Bayer Pharma AG – Stanley Blackmon, Lindsey C. Boney IV, and Bradley Arant Boult Cummings LLP

17. Counsel for Defendants Bayer Healthcare Pharmaceuticals and Bayer Pharma AG – Lyn P. Pruitt, Adria W. Conklin, Benjamin D. Brenner, Mary Catherine Way, and Mitchell, Williams, Selig, Gates & Woodyard P.L.L.C.

18. Counsel for Defendants Bayer Healthcare Pharmaceuticals and Bayer Pharma AG – Walter T. Johnson and Watkins & Eager, PLLC

19. Counsel for Defendants Bayer Healthcare Pharmaceuticals and Bayer Pharma AG – John F. Olinde and Chaffe McCall L.L.P

20. Counsel for Janssen Pharmaceuticals, Inc. and Janssen Research & Development, LLC – Rodney M. Hudson, Chanda A. Miller, Susan M. Sharko, Sherman Vance Wittie, and Drinker Biddle & Reath LLP

21. Counsel for Janssen Pharmaceuticals, Inc. and Janssen Research & Development, LLC – Richard E. Sarver, Celeste R. Coco-Ewing, and Barrasso Usdin Kupperman Freeman & Sarver, LLC

22. Counsel for Janssen Pharmaceuticals, Inc. and Janssen Research & Development, LLC – James B. Irwin and Irwin Fritchie Urquhart & Moore LLC

/s/ Frederick S. Longer
Frederick S. Longer

Attorney of record for Appellants

Case No. 17-30845

IN RE: XARELTO (RIVAROXABAN) PRODUCTS LIABILITY LITIGATION

REQUEST FOR ORAL ARGUMENT

Plaintiffs-Appellants (hereinafter "Plaintiffs") hereby request that the Court schedule these appeals for oral argument. While these appeals involve only three cases, their resolution could impact more than 20,000 individual cases pending in the Eastern District of Louisiana in the Multi-District Litigation proceeding, *In re: Xarelto (Rivaroxaban) Products Liability Litigation*, MDL No. 2:14-md-02592.

Some issues raised in these appeals likely will be raised again in most, if not all, subsequent trials, including: (1) whether evidence from foreign labels and foreign medical associations is admissible to establish a drug manufacturer's knowledge and notice of the inadequacy of their domestic warnings; and (2) whether juries should be instructed about federal regulations mandating instructions about helpful laboratory tests and about the ability to establish liability through a violation of those regulations. Since this Court's rulings could impact more than 20,000 cases, it is especially important for this Court to receive full presentations the facts and laws at issue. For this reason, Plaintiffs believe this Court would benefit from oral argument.

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JURISDICTIONAL STATEMENT

The district court had diversity jurisdiction over these three cases under 28 U.S.C. § 1332(a). Plaintiffs are citizens of Louisiana (*Boudreaux, Orr*) and Mississippi (*Mingo*). Defendants are residents of New Jersey (Janssen Research & Development LLC), Pennsylvania (Janssen Pharmaceuticals, Inc.), Delaware (Bayer Healthcare Pharmaceuticals, Inc.), and Germany (Bayer Pharma AG). Also, the matter in controversy exceeds the value of $75,000, exclusive of interest and costs.

In each case, the district court entered a final judgment based on the jury verdict in favor of Defendants, and within thirty days thereafter, Plaintiffs filed a timely Rule 59 Motion for a New Trial.[1] Within thirty days after each post-trial motion was denied in each case, Plaintiffs timely filed a Notice of Appeal.[2] This Court has jurisdiction over these three appeals under 28 U.S.C. § 1291 because the district court's final orders and judgments disposed of all parties' claims.

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[1] The dates of the final judgment orders and the Rule 59 motions are: (1) *Boudreaux*: May 15, 2017/May 16, 2017 and June 12, 2017 (ROA.17-30845.85714, 85926, 90112); (2) *Orr*: June 15, 2017 and July 13, 2017 (ROA.17-30845.90994, 92442), and (3) *Mingo*: August 31, 2017 and September 15, 2017 (ROA.18-30102.16540, 16559).

[2] The dates of the orders denying the Rule 59 motions and the Notices of Appeal are: (1) *Boudreaux*: September 20, 2017 and October 18, 2017 (ROA.17-30845.98478-98487, 103568-103569); (2) *Orr*: September 20, 2017 and October 18, 2017 (ROA 17-30845.98478-98487, 103566-103567); and (3) *Mingo* December 14, 2017 and January 12, 2018 (ROA.18-30102.16981-16987, 16988-16989).

STATEMENT OF ISSUES

1. Whether the district court erred in *Boudreaux* and *Orr* in precluding Defendants' instructions in foreign Xarelto labels as evidence of Defendants' knowledge and notice of information missing from the U.S. label about the value of using PT testing to assess the anticoagulant effect of Xarelto.

2. Whether the district court erred in *Boudreaux* in precluding peer-reviewed literature as evidence of Defendants' knowledge and notice of information missing from the U.S. label about the value of using PT testing to assess the anticoagulant effect of Xarelto.

3. Whether the district court erred in *Orr* in precluding Bayer's statements to Health Canada as evidence of Defendants' knowledge and notice of information missing from the U.S. label about the value of using PT testing or anti-Factor Xa assays to assess the anticoagulant effect of Xarelto.

4. Whether the district court erred in refusing to grant a new trial in *Mingo* despite discovery of a new Bayer study highlighting the clinical value of using PT testing and anti-Factor Xa assays to assess the anticoagulant effect of Xarelto, which was not publicly published or discoverable until the trial was concluding, and which probably would have changed the outcome of trial if it had been available for presentation to the jury before the evidence was closed.

5. Whether the district court erred in *Boudreaux* in admitting evidence from a defense witness about his wife's personal use of Xarelto.

6. Whether the district court erred in all three trials in refusing to charge the jury about federal labeling regulations mandating instructions about helpful laboratory tests and about the ability to establish liability through a violation of those regulations.

STATEMENT OF THE CASE

This appeal stems from three cases consolidated within MDL 2592 and assigned to the Honorable Eldon E. Fallon of the Eastern District of Louisiana. They were the only three cases to go to trial as part of the bellwether process in the MDL. All three cases involve personal injuries suffered as a result of using rivaroxaban, a prescription blood thinner marketed under the brand name Xarelto.

All three cases revolve around Defendants' failure to provide instructions in their Xarelto labeling about the availability and advisability of performing a routine laboratory test – a prothrombin time ("PT") test, preferably with the Neoplastin reagent[3] – to identify patients at a high risk of bleeding while on Xarelto. A higher PT level is associated with a higher bleeding risk.

[3] A PT test uses a reagent to measure the number of seconds it takes for the blood to coagulate. While the label for the Neoplastin reagent does not specifically state it can be used to measure the anticoagulant activity of Xarelto, it leaves open this possibility by stating: "The prothrombin time is a coagulation screening test.

Defendants not only failed to provide instructions about PT testing in their U.S. label; they affirmatively misled doctors to believe there were no standard laboratory tests available to assess the anticoagulation effect of Xarelto. Consequently, Plaintiffs suffered injuries that could have been avoided, or at least mitigated, if their doctors had been adequately instructed about PT testing and given the opportunity to assess risks and modify their treatment plans.

All three cases ended in defense verdicts, but those verdicts resulted from the improper admission or preclusion of certain evidence and the improper omission of essential jury instructions. Each error impaired the substantial rights of each Plaintiff. Given the significant and unfair prejudice which resulted from these errors, when considered either individually or cumulatively, the defense verdicts should be vacated, and the cases should be remanded for new trials, where the proper evidence is admitted (or precluded), and the juries are correctly instructed on the standards applicable to their decision-making process.

A new trial is further warranted in *Mingo* so newly-discovered and highly-relevant evidence demonstrating Defendants' acceptance and use of tests to assess

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It ***measures***, as a whole, the ***activity*** of the coagulation ***factors*** II, V, VII, ***X*** and I." Neoplastine Label at ¶ 2 (ROA.17-30845.85699) (emphasis added) (The trade names Neoplastin and Neoplastine are interchangeable; the name differences are attributable to international spelling conventions.) It is thus appropriate to use this generic coagulation test to measure the activity of factor X in a patient on a drug that acts on factor X, such as Xarelto.

the anticoagulant effect of Xarelto in the treatment of patients, which evidence probably would have changed the outcome of the trial, can be admitted and considered by the jury.

I. FACTUAL HISTORY OF PLAINTIFFS

A. *Boudreaux, et al. v. Bayer Healthcare Pharmaceuticals, Inc., et al.*, No. 2:14-cv-02720 (E.D. La.) ("*Boudreaux*")

The first bellwether trial involved the claims of Joseph Boudreaux Jr. and his wife, Loretta Boudreaux. Starting on February 3, 2014, Mr. Boudreaux was hospitalized for five days after taking Xarelto for less than a month to prevent the risk of stroke due to atrial fibrillation ("AFib"). During his hospitalization, Mr. Boudreaux received four units of blood to treat a gastrointestinal ("GI") bleed and anemia he suffered from his ingestion of Xarelto.[4]

As a result of this bleeding event, Mr. Boudreaux is now at a greater risk of bleeding, so he is no longer a candidate for any anticoagulant to reduce the risk of stroke from his AFib. Consequently, in May 2015, Mr. Boudreaux underwent a LARIAT procedure to close the left atrial appendage of his heart, as an alternate means of decreasing his risk.[5] Although the LARIAT procedure was successful, Mr.

[4] *Boudreaux* Trial at ROA.17-30845.113758:18-22, 114017:11-13.

[5] *Id.* at 113252:8-113253:16.

Boudreaux developed fluid around his heart, and had to undergo another invasive procedure to drain the fluid in September 2015.[6]

On the day Mr. Boudreaux was diagnosed with AFib, immediately prior to starting Xarelto, his PT was within normal range. Less than a month later, when Mr. Boudreaux presented to the hospital for his GI bleed, his PT was above normal range. When tested again, fifteen months after stopping Xarelto, his PT was within normal range. His only abnormal PT reading was from when he was taking Xarelto.[7]

In the pivotal study of Xarelto for the AFib indication (ROCKET AF), Defendants learned that the top quartile of subjects were at an excessive risk of bleeding based on their PT results, but Defendants never instructed physicians in the U.S. that patients with prolonged PT measurements are more likely than patients with normal PT results to experience a serious bleed on Xarelto, and that the risks of Xarelto therapy for these patients outweigh the benefits.[8]

Had a PT test been performed as soon as Mr. Boudreaux started taking Xarelto, the test would have confirmed that his bleeding risk was too great for him

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[6] *Id.* at 113253:17-113254:21.

[7] Before taking Xarelto, his level of 11.4 was within the normal range for the reagent used (9.0-12.5). While taking Xarelto, his level of 13.6 was above the normal range for the reagent used (9.0-12.5). After stopping Xarelto, his level of 13.2 was within the normal range for the reagent used (11.5-14.0). *Id.* at 113417:11-113419:3, 113428:8-113429:3, 114009:11-114010:18.

[8] *Id.* at ROA.17-30845.112852:24-112863:12.

to continue taking Xarelto, and his doctor would have been in a position to alter his treatment plan accordingly.[9] Mr. Boudreaux's doctor, however, did not know about the relevance and helpfulness of this screening test, and, as a result, he was unable to predict and prevent Mr. Boudreaux's GI bleed on Xarelto.

B. *Orr, et al. v. Bayer Healthcare Pharmaceuticals, Inc., et al.,* No. 15-cv-03708 (E.D. La.) ("*Orr*")

The second bellwether trial involved the ingestion of Xarelto by Sharyn Orr. Mrs. Orr died on May 4, 2015,[10] ten days after suffering an intracranial hemorrhage while taking Xarelto to reduce the risk of stroke from her AFib. Survival and wrongful death claims were brought by her husband (Joseph Orr Jr.) and their three children (Joseph Orr III, Kelli Orr Walker, Kim Orr Deagano).

Mrs. Orr started exhibiting symptoms while on a dinner date with her husband, around 6:30 PM on April 24, 2015. Those symptoms included a headache and vomiting, and progressed over the next few hours to diarrhea, physical instability, and lethargy.[11] This led to a call to EMS and transfer to the Ochsner Baptist Hospital ER, where CT brain imaging revealed the intracranial hemorrhage, likely originating

[9] *See id.* at ROA.17-30845.113660:15-113661:2.

[10] *Orr* Trial at ROA.17-30845.115045:14-17.

[11] *Id.* at ROA.17-30845.116216:22-116218:14, 116404:24-25, 116405:10-15.

from the brain's ventricular space.[12] Successful treatment required emergent intervention to relieve the pressure on her brain, so at 1:15 AM, she was transferred to Ochsner Main Campus, where neurosurgical coverage was available.[13]

Because of the risk of bleeding associated with Xarelto use, and the lack of an agent to reverse its effects, Mrs.'s Orr's use of Xarelto became a significant factor to consider.[14] She normally took her dose in the evening, but her family members and treating physicians did not know if she had taken it that evening, or, if she had, whether she was at peak dosage given her vomiting episodes.[15] Defendants had failed to instruct physicians to use PT testing to assess bleeding risks, and instead had said no standard laboratory test could measure Xarelto's anticoagulant effect. Consequently, the on-call neurosurgeon, Dr. Cuong Bui, had to assume Mrs. Orr was therapeutically anticoagulated on Xarelto, so he delayed surgical intervention by more than thirteen hours, until 2:10 PM, to give any Xarelto remaining in Mrs. Orr's body a chance to clear.[16]

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[12] *Id.* at ROA.17-30845.115371:12-115372:7, 115382:14-17, 115385:23-115387:12.

[13] *Id.* at ROA.17-30845.115205:18-22, 115401:13-115402:18, 115410:8-115411:25).

[14] *Id.* at ROA.17-30845.115180:9-14, 115381:17-115382:13.

[15] *Id.* at ROA.17-30845.115173:12-19, 116216:14-16, 116591:9-15.

[16] *Id.* at ROA.17-30845.115172:12-115174:4, 115180:21-115184:6, 115187:23-115188:2).

Over the nineteen hours that passed between the start of Mrs. Orr's symptoms and the time Dr. Bui placed two external ventricular drains ("EVDs") into her brain the next day, to try to drain the blood and relieve the pressure it was placing on her brain, it was too late to reverse the effects on her brain. The unrelenting pressure progressively lowered her chance at a favorable outcome, and ultimately deprived her of a chance at a meaningful recovery.[17]

Had Dr. Bui been instructed to use PT results to assess bleeding risks, he would have known that the information needed to clear Mrs. Orr for surgery was available by 11:16 PM – less than five hours after her symptoms began – when a routine panel revealed that her PT was 11.4, well within the normal range for the reagent used (9.0-12.5).[18] Mrs. Orr thus was at no increased risk for bleeding, but Dr. Bui did not know this, because he never had been told that a PT value could shed light on a patient's anticoagulation status.[19]

Dr. Bui testified that if he had known there was no drug on board, he would have placed the drains to remove the blood upon admission, giving Mrs. Orr a greater chance at a positive outcome.[20] Likewise, Plaintiffs' expert neurosurgeon, Dr. Peter

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[17] *Id.* at ROA.17-30845.115417:22-115438:3.

[18] *Id.* at ROA.17-30845.115377:5-115379:15.

[19] *Id.* at ROA.17-30845.115182:20-115184:6.

[20] *Id.* at ROA.17-30845.115189:12-115192:20.

Liechty, testified that Mrs. Orr would have had a substantial probability of a meaningful recovery had Dr. Bui been able to surgical intervene soon after she arrived at Ochsner Main Campus.[21]

C. *Mingo v. Janssen Research & Development, LLC, et al.*, No. 15-cv-03469 ("*Mingo*")

The third bellwether trial involved the claims of Dora Mingo. On February 13, 2015, three weeks after Mrs. Mingo started taking twice-daily Xarelto to treat a deep vein thrombosis ("DVT"), she was instructed by her primary care physician to go to the ER immediately, after routine blood testing revealed a dangerously low hemoglobin level.[22]

After presenting to the ER, Mrs. Mingo was diagnosed with a life-threatening GI bleed and admitted to the ICU, where she remained hospitalized for two days, while requiring transfusions of four units of red blood cells and two units of plasma.[23] She also underwent an EGD, which revealed an oozing ulcer that was ablated and clipped.[24]

On the day Mrs. Mingo was prescribed Xarelto, but prior to receiving her first dose of Xarelto, her PT was 12.5, well within the normal range (12.1-15.2). The next

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[21] *Id.* at ROA.17-30845.115434:7-115436:6.

[22] *Mingo* Trial at ROA.18-30102.18689:9-18690:8, 18693:6-15.

[23] *Id.* at ROA.18-30102.18698:6-18699:8.

[24] *Id.* at ROA.18-30102.18694:23-18696:6.

day, ten hours after her last dose of Xarelto, her PT level almost doubled to 23.6, significantly outside the normal range. Her level increased even more, to 26.2, when she presented to the ER three weeks later. Within a day of stopping Xarelto, her level decreased to 16.4, almost within the normal range.[25]

Mrs. Mingo's prescribing physician, Dr. Renie Jordan, said that if he had known about the correlation between PT levels and the anticoagulation effect of Xarelto, and the relevance of readings outside the normal range, he would have stopped the medication.[26] Defendants, however, failed to provide these instructions, and instead led doctors, including Dr. Jordan, to believe it was not necessary, or even possible, to measure the anticoagulant effect of Xarelto.[27] As a result, Mrs. Mingo's elevated PT level meant nothing to Dr. Jordan, leading him to allow her to continue taking Xarelto, resulting in her life-threatening GI bleed.

II. FACTUAL HISTORY OF XARELTO

Xarelto is an anticoagulant approved by the FDA in July 2011 for the indication of preventing deep-vein thrombosis ("DVT") and pulmonary embolism ("PE") in patients undergoing hip or knee replacement surgeries.[28] In November

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[25] *Id.* at ROA.18-30102.18696:11-18697:12. The same reagent, with the same normal range, was used for all her tests.

[26] *Id.* at ROA.18-30102.18790:21-18791:16.

[27] *Id.* at ROA.18-30102.18781:22-18783:2.

[28] *Boudreaux* Trial at ROA.17-30845.113090:24-113091:2.

2011, Defendants obtained FDA approval for another indication addressing the risk of stroke and systemic embolism in patients with non-valvular AFib.[29] In November 2012, the FDA approved Xarelto for the additional indication of treating DVT or PE and reducing their recurrence after initial treatment.[30]

A. PT Screening Can Be Used to Identify Xarelto Users at a High Risk of Bleeding

Most patients who take Xarelto do not experience bleeding, but it can be life-threatening for those who do, because there is no reversal agent available to stop the bleeding.[31] Clinical studies showed significant variation in the way Xarelto is processed in each patient's body, and as a result, it is not possible to reliably predict the concentration of the drug in a patient's system or the associated bleeding risk based solely on the dose administered.[32]

1. FDA Reviewers Validated Defendants' Screening of Xarelto Subjects with Neoplastin PT in their Clinical Studies

It is, however, possible to assess bleeding risks while on Xarelto. Indeed, in their own clinical studies, Defendants assessed the bleeding risks of Xarelto subjects by performing PT tests with the Neoplastin reagent, which has been shown to be the

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[29] *Mingo* Trial at ROA. 18-30102.18056:13-16.

[30] *Id.* at ROA.17-30845.18056:17-20. Subsequent approvals for additional indications are not pertinent here.

[31] *Boudreaux* Trial at ROA.17-30845.113396:6-15.

[32] *Id.* at ROA.17-30845.113398:6-113406:5.

most sensitive and reliable PT reagent when used in conjunction with Xarelto.[33] This possibility was first established in the context of the ROCKET AF study – Defendants' pivotal Phase III randomized, double-blinded, multi-center, prospective, "gold standard" clinical trial performed to support the AFib indication.[34]

In the context of determining what to do about Xarelto in 2011, the FDA's clinical pharmacology reviewers analyzed this PT data from ROCKET AF and confirmed the existence of a linear correlation between Xarelto concentration, PT levels, and major bleeding risks, such that higher PT levels were associated with higher Xarelto concentrations and higher bleeding risk, without any reduction in stroke risk.[35] This data also revealed that the top quartile of Xarelto subjects (i.e., the 25% of Xarelto patients with the highest PT measurements) had more than twice as many major bleeds.[36] This, along with other concerns, led the primary clinical reviewers to recommend against approval of the drug, but the drug was nonetheless approved.[37]

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[33] *Id.* at ROA.17-30845.112865:6-20.

[34] *Id.* at ROA.17-30845.113806:19-113807:24.

[35] *Id.* at ROA.17-30845.112846:8-112849:20, 112867:22-112868:15, 113411:22-113416:12, 114000:4-11, 114002:6-16, 114118:18-114119:15.

[36] *Id.* at ROA.17-30845.112852:24-112863:12, 113412:16-113414:8.

[37] *Id.* at ROA.17-30845.114000:4-114002:5.

Thus, it was established through the ROCKET AF trial, in and of itself, that Xarelto increases a patient's risk of bleeding in a variable way, which can be evaluated in individual patients by using Neoplastin PT testing.

2. Defendants' Scientists Support Neoplastin PT Screening of Xarelto Patients

Additionally, Defendants' own scientists, when operating outside the context of litigation, identified Neoplastin PT as an appropriate tool to evaluate whether patients are proper candidates for Xarelto therapy.

For example, beginning in 2005, Dagmar Kubitza (Bayer's Clinical Pharmacology Lead for Xarelto and Head of Clinical Pharmacodynamics), has written in published, peer-reviewed medical literature that Neoplastin PT is a useful screening tool. In an article published that year, Dr. Kubitza said there was "a direct linear relationship between [Xarelto] concentration and PT," and suggested that "PT, a routinely used coagulation test, could be used clinically to monitor the anticoagulation effect of [Xarelto] if necessary."[38]

Almost a decade later, in 2014, Dr. Kubitza was listed on another peer-reviewed, published medical article with lead author, Wolfgang Mueck (Bayer's

[38] *Id.* at ROA.17-30845.113406:21-113410:1, 113410:14-24; *see also Orr* Trial at ROA.17-30845.116346:7-15; *Mingo* Trial at ROA.18-30102.18470:2-18471:12, 18653:13-18655:16; Kubitza Multiple Dose Article at 779-780 (ROA.17-30845.75176-75184).

Head of Clinical Pharmacokinetics, Cardiovascular), which was published online in 2015. This article confirmed the existence of a strong correlation between PT levels and bleeding risk; higher PT levels were associated with higher bleeding risks.[39] A year earlier, in 2013, Dr. Mueck published another article noting the correlation, and recommending that Neoplastin PT testing be used in emergency situations, so doctors can get an idea of how much Xarelto is in the patient's system and changing the patient's clotting.[40]

Bayer's scientists continue to maintain this stance outside the context of litigation. For example, an August 14, 2017 peer-reviewed medical article co-authored by Dr. Kubitza concluded that "[s]ensitive prothrombin time and activated partial thromboplastin time assays can be used to estimate the anticoagulant effects of rivaroxaban." The article further confirmed that "in some clinical situations (such as medical emergencies that require prompt decision-making) it may still be beneficial to assess the extent of drug exposure and how this relates to anticoagulant effect."[41] Thus, not only does the new evidence establish that Neoplastin PT can be

[39] *Boudreaux* Trial at ROA.17-30845.112842:4-112845:7.

[40] *Orr* Trial at ROA.17-30845.115954:19-115956:25; *see also* Mueck 2013 (ROA.17-30845.71849-71864).

[41] Kreutz Article at 3, 16 (ROA.17-30845.97925-97953).

used to assess Xarelto's anticoagulant effect, it also supports the position that it may be beneficial to do so in certain clinical settings.

Additionally, Defendant Janssen also agrees with these assessments outside of the litigation context. For example, if a physician actively searches for the information on the Xarelto website, this statement can be found: "If assessment of rivaroxaban plasma concentrations is necessary, the PT was reported to be an appropriate coagulation test. The relationship between PT and rivaroxaban plasma concentration when Neoplastin Plus … is used as the reagent is linear and closely correlated."[42]

3. Peer-Reviewed Literature Supports Neoplastin PT Screening of Xarelto Patients

There are multiple additional peer-reviewed publications that discuss the relationship between PT and Xarelto and/or the use of PT to evaluate the anticoagulant effect of Xarelto.

The most pertinent article, published in peer-reviewed literature, was from Giuseppe Lippi, entitled "Recent guidelines and recommendations for laboratory assessment of the direct oral anticoagulants (DOACs): is there a consensus?"

> The dogma that DOACs do not require monitoring is countered by ongoing recognition that laboratory testing for drug effects is needed in many situations.

[42] *Orr* Trial at ROA.17-30845.116489:12-:11695:14.

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> It was therefore concluded that the PT may be used for urgent measurements of rivaroxaban and as a screening tool to assess the risk of bleeding in the individual patient because it's available to all hospital laboratories, is prone to worldwide standardization, is relatively cheap compared with other tests, and is sufficiently sensitive to Xarelto, views in agreement with other expert opinions.
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> ***
>
> Regarding Factor Xa inhibitors, the PT was proposed as a reliable screening test in patients taking these drugs in six of seven guidelines.[43]

In essence, this article concluded – based on a systematic search using the three most accessed scientific databases (Medline, Scopus, Web of Science) and data gathered from around the world – that PT measurements may reliably be used to screen for the risk of bleeding in individual patients taking new oral anticoagulants such as Xarelto. [44]

4. Foreign Agencies and International Medical Societies Support Neoplastin PT Screening of Xarelto Patients

Numerous government agencies and international medical associations also support the use of Neoplastin PT testing to assess the anticoagulant effect of Xarelto:

- New Zealand Medicines and Medical Devices Safety Authority: "PT is influenced by Xarelto in a dose-

[43] *Id.* at ROA.17-30845.116329:2-116330:3, 116336:22-116337:8, 116340:6-9; *see also* Lippi Article (ROA.17-30845.85286-85298).

[44] *Id.* at ROA.17-30845.116335:14-116340:23.

> dependent manner if Neoplastin® is used for the assay."[45]
>
> - Health Canada: "The prothrombin time (PT), measured in seconds, is influenced by XARELTO in a dose-dependent way with a close correlation to plasma concentration if the Neoplastin® reagent is used. In patients who are bleeding, measuring the PT using the Neoplastin® reagent may be useful to assist in determining an excess of anticoagulant activity."[46]
> - British Committee for Standards in Haematology ("BCSH"): "The PT is useful as a readily available method for determining the relative degree of anticoagulation in patients taking rivaroxaban, if a reagent with known sensitivity is used."[47]
> - International Society on Thrombosis and Haemostasis ("ISTH"): "When a Quick-type PT reagent with known sensitivity is used, the PT is useful as a readily available method for determining the relative degree of anticoagulation in patients taking rivaroxaban."[48]

The FDA found the European label germane to its own investigation.[49] Additionally, Defendants made statements to foreign regulatory agencies, recognizing the potential utility of PT testing. For example, Defendants told the Canadian authorities:

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[45] New Zealand Xarelto Data Sheet at 7 (ROA.17-30845.85408-85439).

[46] Canadian Xarelto Product Monograph at 9 (ROA.17-30845.85329-85403).

[47] Baglin 2012 at 2 (ROA.17-30845.85319-85321).

[48] Baglin 2013 at 758 (ROA.17-30845.85323-85327).

[49] Prior to approving the U.S. label, the FDA requested a copy of the European label, received a summary report, and addressed foreign labeling questions. *See* Brief Description at M6, M12 (ROA.17-30845.85465-85478).

> Although there is no need to monitor clinical practice, in certain infrequent situations such as overdosage, acute bleeding, urgent surgery, in cases of suspected non-compliance, or in other unusual circumstances, assessment of the anticoagulant effect of rivaroxaban may be appropriate. Accordingly, measuring PT using the Neoplastin reagent . . . may be useful to inform clinical decisions in these circumstances."[50]

B. Defendants Did Not Instruct Medical Providers to Use Neoplastin PT Screening to Identify Xarelto Patients at a High Risk of Bleeding, Even Though Defendants Had the Ability to Unilaterally Change Their Labels to Add Those Instructions

As discussed above, there is no dispute that PT testing is a safe and effective way to identify patients at a higher risk for bleeding while taking Xarelto. Scientific and regulatory communities throughout the world have recognized the benefits of PT testing for Xarelto users, and Defendants themselves relied on Neoplastin PT to make reliable scientific findings about Xarelto concentrations in their studies.

The critical point is that Defendants did not include in the U.S. label any instructions to physicians about the ability to use PT testing to identify patients at a high risk of bleeding. To the contrary, Defendants led doctors and patients to believe that there was no ability to assess bleeding risks, by stating in their labels that the "anticoagulant effect of XARELTO cannot be monitored with standard laboratory

[50] *See* ROA.17-30845.116763:3-22 (during offer of proof).

testing."[51] Consequently, doctors generally, including the prescribing and treating doctors in the cases at issue, were not conducting PT tests or considering results of PT tests that were conducted in order to identify patients at a high risk for severe bleeding events while taking Xarelto. And, more to the point for present purposes, none of the juries in the cases at issue were allowed to consider the full extent to which Defendants, outside of the courtroom, acknowledged the clinical value of this testimony.

Federal regulations mandate that the warnings section of a prescription drug label "must identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions."[52] The regulations further require that "[i]f appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be performed before, during, and after therapy."[53] Brand-name drug manufacturers may use a Changes Being Effected ("CBE") supplement to unilaterally add such instructions to their label, without prior approval, if the change is to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or "an instruction about dosage and administration

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[51] *See, e.g.,* Xarelto Label at § 5.4 (ROA.17-30845.80432-80464).

[52] 21 C.F.R. § 201.57(c)(6)(iii).

[53] *Id.*

that is intended to increase the safe use of the drug product.[54] Defendants' deliberate choice not to identify PT testing as clinically "helpful" is in clear violation of this regulatory mandate, although the jury instructions in the cases at issue did not include reference to the regulation itself.

III. PROCEDURAL HISTORY

A. Plaintiffs were Precluded in the *Boudreaux* and *Orr* Trials from Presenting Defendants' Instructions in Foreign Xarelto Labels as Evidence of Defendants' Knowledge and Notice of the Inadequacy of their U.S. Label

Defendants sought to exclude all foreign labeling and regulatory evidence prior to the *Boudreaux* trial, positing that such evidence would not bear on the adequacy of the U.S. label, and would cause confusion, because different foreign regulatory standards apply in different jurisdictions.[55]

Because Defendants' prior knowledge and notice of the usefulness of PT testing is expressed in other labels across the globe, Plaintiffs opposed the motion.[56] At oral argument, Plaintiff's counsel confirmed his intent to present such evidence to refute Defendants' anticipated argument that nobody supports using PT testing to assess the anticoagulant effect of Xarelto.[57]

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[54] 21 C.F.R. § 314.70(c)(6)(iii)(A), (C); *Wyeth v. Levine,* 555 U.S. 555, 568 (2009).

[55] ROA.17-30845.80868-80883.

[56] ROA.17-30845.82305-82308, 85260-85271.

[57] 03/23/17 Argument (ROA.17-30845.112413:8-112414:4).

Following argument, the district court issued an opinion stating that foreign labeling and regulatory evidence was likely excludable under Federal Rules of Evidence 401 and 403, but reserved its ruling, stating that the evidence might need to be considered for context or rebuttal.[58]

Subsequently, as anticipated, throughout the *Boudreaux* trial, the jury was repeatedly told by defense experts and defense corporate witnesses that Neoplastin PT was useless and did not work. This false narrative was successfully reprised by defense counsel at summation:

> **Medical associations, you didn't hear them cite a single medical association that says this test should be used, or a peer-reviewed publication that says this test should be used.** Now, why is that? Because in the outside – outside of this courtroom, **nobody thinks this test works.** They don't think it helps. They want you to second-guess all the scientists out there, all the doctors you've heard, all the medical associations, all the medical literature, and they want you to believe that they're the only ones that understand this test and they're the only ones that want it in the label because nobody else understands what the company does. **Well, Dr. Johnson certainly understands.**[59]

In making such statements, defense counsel ignored that many foreign regulatory authorities and international medical societies think PT testing is useful

[58] ROA.17-30845.83093-83094.

[59] *Boudreaux* Trial at ROA.17-30845.114295:5-17.

in assessing the anticoagulation status of a Xarelto user, as summarized above from the labels in New Zealand and Canada, statements Defendants made to the Canadian authorities, and statements made by the BCSH and the ISTH.[60]

Plaintiffs, however, were precluded from presenting this evidence to refute defense counsel's false claim that "nobody thinks this test works." Plaintiffs tried to admit statements made in Bayer's Canadian label for Xarelto, through designations to deposition testimony from Dr. Scott Berkowitz, Vice-President at Bayer Pharmaceutical, but the district court sustained objections to the testimony under Federal Rules of Evidence 401 and 403, opining that it was irrelevant and confusing because different standards are applied by the FDA and Canadian authorities.[61]

As discussed in the following section, at trial the district court also precluded evidence from the peer-reviewed, published Lippi article, which summarized PT guidelines from medical associations around the globe, reasoning that the jury might be confused by evidence involving foreign regulatory standards. Since the issue of foreign evidence had been raised and ruled upon at least three times, it was clear that Plaintiffs would not be permitted to present any of this evidence, so they were not

[60] *See* pages 17-19, *supra.*

[61] ROA.17-30845.83709-83712.

required to present further, futile, objections or explanations to preserve this issue for appeal.[62]

Plaintiffs raised this prejudicial error in their motion for new trial,[63] which was denied.[64] After the *Boudreaux* trial was completed, the district court appears to have realized the importance of at least some of this evidence, because in ruling on a motion *in limine* filed by Plaintiffs in *Orr,*[65] it broadened the scope of permitted foreign evidence:

> This Court finds that anything the Defendants have said to anyone, even foreign regulatory bodies, should be admissible. What is not admissible, however, is what the Defendants did or what they put on Xarelto's label in other countries in order to comply with foreign regulatory bodies or agencies."[66]

When the issue was raised again during the *Orr* trial, the district court ruled that Defendants' statement to the Canadian authorities was admissible as a prior statement under Federal Rules of Evidence 613 and 801(d)(2) to show Defendants'

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[62] Federal Rule of Evidence 103(b) provides that once there is a ruling on the record, even if entered before trial, there is no need to renew the objection or make a subsequent offer of proof. Additionally, the Fifth Circuit has confirmed that no formal offer of proof is required at trial if the substance of the proposed testimony is otherwise known. *U.S. v. Ballis,* 28 F.3d 1399, 1406 (5th Cir. 1994).

[63] ROA.17-30845.90120-90124, 93718-93719.

[64] ROA.17-30845.98484.

[65] ROA.17-30845.85243-85494.

[66] ROA.17-30845.87188.

knowledge.[67] However, the district court continued to preclude any evidence about the actual label.[68] Strict adherence to this distinction prevented Plaintiffs from being able to present material evidence.

For example, Defendants' electrophysiology expert, Dr. Sammy Khatib, testified on direct examination that based on his extensive study of PT measurements, it would have been "inappropriate" and "reckless" to include the following labeling language proposed by Plaintiffs' regulatory expert: "Accordingly, measuring PT may be useful to inform clinical decisions in this circumstance."[69] *This purportedly "inappropriate" and "reckless" language actually came from Bayer's own label in Canada.*

Nonetheless, the district court would not allow the witness to be cross-examined by citing the language from the Canadian label, and in turn prevented the jury from learning that this defense expert was condemning language actually used by Defendant Bayer in the Canadian label for Xarelto, simply because the language happened to be contained within a foreign label.[70] Consequently, Dr. Khatib, was able to testify – effectively unchallenged – that Bayer had not used that language

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[67] *Orr* Trial at ROA.17-30845.115623:1-115624:7.

[68] *Id.* at ROA.17-30845.115624:8-115625:11, 115677:20-115680:23, 115683:9-24.

[69] *Id.* at ROA.17-30845.116295:10-116296:25, 116297:12-17.

[70] *Id.* at ROA.17-30845.116378:20-116379:19, 116380:24-116382:2-7.

with doctors outside of the United States, even though Bayer had used that language in its Canadian label. This was tantamount to the jury being allowed to believe a demonstrable untruth.

Likewise, Defendants' neurosurgical expert, Dr. Najeeb Thomas, testified that the same proposed labeling language was "dangerous." This testimony, like that of Dr. Khatib, remained effectively unchallenged, because Plaintiffs were forbidden from challenging Dr. Thomas with **the same purportedly "dangerous" language from Bayer's own label in Canada,** simply because the language happened to be contained within a foreign label.[71]

Plaintiffs raised this prejudicial error in their motion for new trial,[72] but the motion was denied.[73] The district court issued a similar order in *Mingo,*[74] when ruling on a motion *in limine* opposed by Plaintiffs.[75] At the *Mingo* trial, Plaintiffs were permitted, with a limiting instruction, to present testimony about Bayer's statements in the Xarelto labels in Canada and Europe, to establish Defendants'

[71] *Id.* at ROA.17-30845.116585:9-116586:19.

[72] ROA.17-30845.92445-92448, 98132-98136.

[73] ROA.17-30845.98485-98486.

[74] ROA.17-30845.94707-94708.

[75] ROA.17-30845.93973-93978.

knowledge and notice of the value of PT testing, but were precluded from admitting the actual labels.[76]

B. Plaintiffs were Precluded in the *Boudreaux* Trial from Presenting Peer-Reviewed Literature as Evidence of Defendants' Knowledge and Notice of the Inadequacy of their U.S. Label

As discussed above, Defendants' theme throughout the *Boudreaux* trial was that "nobody" thinks Neoplastin PT testing works. Plaintiffs attempted to refute this not only with statements from Defendants' own foreign labels, but also with statements from peer-reviewed literature, but, again, they were precluded from doing so.

For example, defense expert Dr. Colleen Johnson repeatedly told the jury that Neoplastin PT was not a helpful test.[77] During Dr. Johnson's cross-examination, Plaintiffs' counsel attempted to question her about her failure to consider the peer-reviewed Lippi article, discussing the fact that numerous medical associations have recommended PT in their medical guidelines as a reliable screening test in patients taking an anti-Factor Xa inhibitor, including Xarelto. The district court prohibited the presentation of that evidence simply because it happened to involve foreign

[76] *Mingo* Trial at ROA.18-30102.18078:4-18079:18, 18366:1-18370:12, 18846:10-18847:4.

[77] *Boudreaux* Trial at ROA.17-30845.113905:6-24, 113934:22-113935:7, 113950:4-11, 113958:21-113959:1.

medical associations, reasoning that the jury might be confused by evidence involving foreign regulatory standards.[78]

This ruling was based on a false premise, in that no foreign regulatory standards were addressed in the article in question. Only science-based global testing recommendations from independent medical associations were addressed. Independent of that fact, the science *per se* behind Xarelto's linear relation to bleeding risk as measured by Neoplastin PT does not vary from country to country, and is utterly untethered to the regulatory standards in a given country.

Table 3 of the Lippi article showed that six medical associations determined that PT was a reliable screening test for patients taking anti-FXa inhibitors, including Xarelto: (1) the ISTH; (2) the European Society of Cardiology ("ESC"); (3) the European Heart Rhythm Association ("EHRA"); (4) the Australasian Society of Thrombosis and Haemostasis ("ASTH"); (5) the Federation of Centers for Surveillance of Anticoagulation, the Italian Society of Laboratory Medicine, the Italian Society of Clinical Biochemistry and Laboratory Medicine, and the Italian Committee for Standardization of Hematological and Laboratory Methods ("FCSA,

[78] *Id.* at ROA.17-30845.113987:8-113989:14.

SiMeL, SiBioC, and CISMEL"); and (6) the BCSH.[79] Similar statements from these medical associations have been referenced in additional peer-reviewed publications.[80]

Each of these six medical associations are independent, non-profit, membership organizations. Their stated goals are not to analyze the regulatory requirements of particular jurisdictions and outline what should or should not be submitted to the regulatory agencies in those jurisdictions. Their goals instead are to assess the best clinical treatments for patients, regardless of where those patients are treated. For example, the ISTH's Mission Statement states:

> The International Society on Thrombosis and Haemostasis (ISTH) is a **global not-for-profit membership organization** advancing the understanding, prevention, diagnosis and treatment of thrombotic bleeding disorders.
>
> The Society is dedicated to transformative scientific discoveries and clinical practices, the development of young professionals and the education of physicians, scientists and applied health professionals **wherever they may live.**
>
> At the ISTH, we initiate and promote education and outreach initiatives, research activities, scientific meetings, peer-reviewed publications, expert committees

[79] Lippi Article at 8 (ROA.17-30845.85286-85296). One additional medical association (the American College of Chest Physicians, or "ACCP") concluded that no screening was reliable. *Id.*

[80] Baglin 2012 at 2 (ROA.17-30845.85319-85321) (BCSH); Baglin 2013 at 758 (ROA.17-30845.85323-85327) (ISTH).

> and **the development of standards allowing a common language and approach to basic and clinical science all over the world**."[81]

The ISTH has over 100 related societies, including three of the six medical associations that believe PT is a reliable screening test for Xarelto users: ESC; ASTH; and BCSH.[82] One of those (ESC) says it is "**a world leader** in the discovery and dissemination of best practices in cardiovascular medicine," clarifies that it "has European roots, **but a global scope,"** and highlights its global focus:

> We are a **not-for-profit medical society led by expert volunteers**. We unite Member National Cardiac Societies, cardiovascular ESC sub-specialty communities, Affiliated Cardiac Societies, distinguished Fellows of the ESC and individual members **from around the world**. This network allows us to reach out to **the global cardiology community** and keep our finger on the pulse of cardiology. **Diversity is our strength**.[83]

Given the independent, non-profit, nature of these membership organizations, and their global focus, the district court was in error to infer that their opinions with regard to the reliability of PT testing are based on foreign regulatory standards or foreign labels that have no applicability to patients in the United States. Their

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[81] ISTH Webpage at 1 (emphasis added) (ROA.17-30845.90205-90206).

[82] ISTH Resources and Partners at 6, 7, 10 (ROA.17-30845.90208-90228).

[83] ESC Webpage at 1, 3 (emphasis added) (ROA.17-30845.90230-90232). The EHRA is a branch of the ESC. EHRA Constitution at 1 (ROA.17-30845.90234-90250).

statements instead have applicability to patients throughout the world, in every country, including the U.S.

Plaintiffs raised this prejudicial error in their motion for new trial,[84] but the motion was denied.[85] This critically important scientific evidence, rather than being withheld from the jurors, should have been admitted, with Defendants having the right to diminish the weight of the evidence based on their argument that the societies themselves were from other countries.

C. Plaintiffs were Precluded in the *Orr* Trial from Presenting Bayer's Statements in a Draft Response to Health Canada as Evidence of Defendants' Knowledge and Notice of the Inadequacy of their U.S. Label

During the *Orr* trial, the district court precluded the admission of an email with an attached draft response from Bayer to Health Canada addressing the benefits of PT testing and the ability to run anti-Factor Xa assays to assess the anticoagulant effect of Xarelto. Janssen's Senior Director of Global Affairs, Sanjay Jalota, confirmed that he had received these materials during the ordinary course of business, but the district court forbade any questions about them, simply because the

[84] ROA.17-30845.90115-90120, 93715-93718.

[85] ROA.17-30845.98483-98484.

witness said he had not read them.[86] Counsel was forbidden from even asking questions to challenge the witness's claims that he had not read the materials.[87]

In a later offer of proof, Mr. Jalota admitted he might have read the email,[88] but the preclusion still stood, out of concern for the potential for confusion since they involved foreign labeling, even though Bayer's statements to regulators were previously deemed admissible.[89] Consequently, Mr. Jalota was able to testify – unchallenged – that he was not aware of company statements made about the benefits of PT testing.[90] Plaintiffs raised this prejudicial error in their motion for new trial,[91] but the motion was denied.[92]

D. The District Court Refused to Grant a New Trial in *Mingo* Even Though Newly Discovered Evidence Generated at the Conclusion of Trial Probably Would Have Changed the Outcome of Trial

A new study conducted by leading Bayer scientists that was not published until the *Mingo* trial was reaching its conclusion contains striking new evidence

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[86] *Orr* Trial at ROA.17-30845.115741:11-115745:19.

[87] *Id.* at ROA.17-30845.115743:2-115745:19.

[88] *Id.* at ROA.17-30845.116752:21-116753:7.

[89] *Id.* at 1343:13-1347:2 (ROA.17-30845.115746:13-115750:2).

[90] *Id.* at 1347:7-1348:9 (ROA.17-30845.115750:7-115751:9.

[91] ROA.17-30845.92448-92449, 98136-98138.

[92] ROA.17-30845.98486.

regarding the use of Neoplastin PT and anti-Factor Xa assays to assess Xarelto's anticoagulant effect.[93]

The study, reported in the Kreutz article, compared the anticoagulant effects of rivaroxaban (Xarelto) and apixaban (Eliquis), with a secondary objective to "examine corresponding surrogate measures of the effectiveness of the drugs, namely anti-FXa activity … [and] PT … to explore their relationship with the plasma concentration of both drugs" to "help further inform physician decisions regarding DOACs and the appropriate dosing regimen."[94] The same Neoplastin reagent used to measure Ms. Mingo's PT was used for PT assessments in the study.[95]

The authors note that Figure 6 exhibits a clear prolongation of PT that is in agreement with other recently published data, including an article published by Plaintiff's expert Robert Gosselin, and further acknowledge the close relationship between the plasma concentration-time profiles and the anti-Factor Xa activity of rivaroxaban.[96] The article concludes that "[s]ensitive prothrombin time and activated partial thromboplastin time assays can be used to estimate the anticoagulant effects

[93] Kreutz Article (ROA.17-30845.97925-97953).

[94] ROA.17-30845.97929-97930.

[95] ROA.17-30845.97933.

[96] ROA.17-30845.97940, 97943.

of rivaroxaban."[97] The authors further state that "in some clinical situations (such as medical emergencies that require prompt decision-making) it may still be beneficial to assess the extent of drug exposure and how this relates to anticoagulant effect."[98]

The study findings and article statements directly contradict Xarelto's prescribing information and key representations made during the *Mingo* trial. The significance is underscored by the fact that six of the eight scientists who conducted the study and co-authored the article are Bayer scientists, and the two others worked as Bayer consultants.[99] Hence, the inability to present this new evidence, never disclosed by Defendants, but independently discovered by Plaintiffs' counsel literally as the *Mingo* trial was concluding, undermines the results of the *Mingo* trial. Its admission likely would have resulted in a different outcome if Plaintiff had the opportunity to investigate this matter further. Plaintiff requested a new trial on this basis,[100] but that motion was denied.[101]

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[97] ROA.17-30845.97927.

[98] ROA.17-30845.92940.

[99] ROA.17-30845.97942.

[100] ROA.17-30845.97909-97916.

[101] ROA.18-30102.16985.

E. Defendants were Permitted in the *Boudreaux* Trial to Elicit Irrelevant and Unduly Prejudicial Evidence from a Defense Witness About His Wife's Use of Xarelto

Prior to the *Boudreaux* trial, Plaintiffs sought to exclude evidence regarding the personal use of Xarelto on grounds of irrelevance and undue prejudice.[102] The district court sustained the motion, but reserved its ruling as to witnesses and experts, saying the issue might go to credibility.[103]

At trial, over Plaintiff's objections, the district court allowed the following testimony from Dr. Gary Peters, a Clinical Senior Director in the Cardiovascular Department at Janssen, about his wife's use of Xarelto, reasoning that Dr. Peters' credibility had been put at issue:

> Q. Dr. Peters, do you think that Xarelto is a safe and effective medicine?
>
> A. Yes, I do.
>
> Q. Is it effective at preventing strokes?
>
> A. Yes, it's very effective. As we mentioned, versus warfarin, it's very effective, and we were at least equal if not better. So it's a very effective medicine for preventing strokes.
>
> Q. And you told us about your wife early on. You've been married 39 years. I assume you like her.

[102] ROA.17-30845.80005-80062.

[103] ROA.17-30845.83084.

MR. BARR: Your Honor, if this is going where I think it's going, I have an objection.

MR. SARVER: Well, it is. Let's go up to the bench.

(WHEREUPON, the following proceedings were held at the bench.)

THE COURT: I assume she had –

MR. SARVER: She took it and she did fine and all that stuff.

MR. MEUNIER: Your Honor, this was the subject of a motion in limine as to which you reserved a ruling, and you said it would depend on credibility and other issues that may arise at the trial. There is no need to enhance this man's credibility by saying that his wife took Xarelto, and I think it has a prejudicial effect that outweighs the probative value and so we'd ask that it not be allowed.

MR. SARVER: This testimony has already come in through another witness, Your Honor, not for Dr. Peters' wife, but I believe it was a witness that was by deposition.

MR. MEUNIER: We were not able to properly screen that. It should have been objected to.

MR. SARVER: Okay. I thought this was resolved. That's fine.

THE COURT: It may not have been resolved. The issue really is only significant insofar as credibility is concerned. It has no relevance other than that, but it does have some relevance of credibility. This witness is testifying as the company representative. The plaintiffs take the position that the company did

> something – did not do something that they should have done, and there's also a suggestion that they did it for commercial reasons. This witness has been involved with the Xarelto, the development and design of Xarelto. So his credibility is significant to the whole case, it seems to me. The plaintiffs have attempted to take him on cross and to show that his credibility is a problem. That's obvious. Certainly, they take the position that the company's credibility is at issue. So I weigh the advantages, disadvantages, and it seems to me that the 403 analysis tips in favor of allowing it.
>
> MR. SARVER: Thank you, Your Honor.
>
> THE COURT: That's my ruling.
>
> MR. SARVER: Yes, sir.
>
> (WHEREUPON, the following proceedings were held in open court.)

MR. SARVER:
Q. We're back, Dr. Peters. Are you ready for us?

THE WITNESS: Okay.

BY MR. SARVER:
Q. Okay. So, Dr. Peters, you told us earlier that you've been married for 39 years.

A. Yes.

Q. I'm assuming you like your wife.

A. I didn't hear that –

Q. I don't know that I've ever asked this question in 35 years, but do you like your wife?

> A. Yes. Yes, I do.
>
> Q. And you want nothing but good things for her?
>
> A. Her birthday is tomorrow, actually.
>
> Q. All right. Do something good for her. So knowing that you like your wife, does your wife take Xarelto?
>
> A. Yes, she did. She had her right knee replaced a couple of months ago. Her orthopedic surgeon wanted us to use aspirin, and I asked him to use Xarelto. And he agreed to that.
>
> Q. How has she done?
>
> A. She's done very well. She actually had maybe her last therapy session this morning for rehabilitation.[104]

Defense counsel, however, counted on the jury viewing personal use evidence as probative of Xarelto's safety, rather than as evidence of credibility, as evidenced in her summation:

> Plaintiffs said to you at the beginning that this was a safety test. Again, why did he say that? Because he wanted you to think we were terrible people. We're actually the big pharmaceutical companies I think he called us, and we don't want to do a simple safety test. Think about what that said. **That all of the doctors who work on our companies who told you they were on Xarelto themselves or prescribe it for their mother, that they**

[104] *Boudreaux* Trial at ROA.17-30845.113814:13-113817:14. There was also testimony about personal use by a family member from another Janssen employee, Dr. Nauman Shah, but that consisted of only one sentence: "My own mother, you know, took it once." *Id.* at ROA.17-30845.113585:1-2.

> **don't care about safety.** They don't care. That's what he wants you to believe.[105]

Plaintiffs raised this prejudicial error in their motion for new trial,[106] but the motion was denied.[107] Plaintiffs filed a similar motion *in limine* in *Orr*.[108] Although too late for the *Boudreaux* plaintiffs, in its ruling on that motion, the district court implicitly acknowledged the above-mentioned prejudicial effect of its *Boudreaux* ruling by precluding evidence of Xarelto use by a witness's family member absent the provision of all the medical records of that family member to allow for cross examination, explaining:

> If one of Defendants' witnesses intends to discuss or refer to a family member's use of Xarelto, he or she must first produce all of the medical records of that family member to allow for cross examination. Each person who takes Xarelto is different, and the circumstances are different. In fairness, there ought to be some testing of the specific circumstances of *that* person if the Defendants wish to bring up this issue at trial. Accordingly, Defendants will not be permitted to elicit information about a witness' family member taking Xarelto without producing *their* medical records.[109]

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[105] *Id*. at ROA.17-30845.114291:14-22 (emphasis added).

[106] ROA.17-30845.90124-90130, 93719.

[107] ROA.17-30845.98484.

[108] ROA.17-30845.84883-84975, 86086-86093.

[109] ROA.17-30845.87176-87178.

F. The District Court Refused in All Three Trials to Charge the Jury about Federal Regulations Mandating Instructions about Helpful Laboratory Tests and the Ability to Establish Liability Through a Violation of Those Regulation

In the *Boudreaux* and *Orr* trials, Plaintiffs asked the district court to provide the following two instructions to the jury:

> You are instructed that certain federal regulations applicable to this case provide that the warnings section of a prescription drug label: … must identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be performed before, during, and after therapy.
>
> While a manufacturer's violation of one or more FDA regulations designed to protect consumers is not conclusive evidence that a product is unreasonably dangerous, violation of such standards may be considered as evidence of the appropriate standard when determining whether the instructions provided to the treating physician were inadequate.[110]

Plaintiffs proposed a similar instruction, essentially combining the two instructions with additional language, in *Mingo*.[111]

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[110] ROA.17-30845.84270-84271, 114231:18-114232:12 (*Boudreaux*); 85807-85808, 116619:23-116620:17 (*Orr*).

[111] ROA.17-30845.94192.

The district court declined to provide these instructions, not because they were improper, but because its preference was to address this issue with more general language. The language used by the court in *Boudreaux* and *Orr* is as follows:[112]

> AS I PREVIOUSLY MENTIONED, XARELTO IS A BRAND-NAME DRUG. THE FDA APPROVED BOTH XARELTO AND ITS LABEL. YOU MAY CONSIDER THIS FACT IN WEIGHING THE EVIDENCE IN THIS CASE IN DETERMINING THE LIABILITY OF THE DEFENDANTS.
>
> HOWEVER, FDA APPROVAL, ALTHOUGH RELEVANT, DOES NOT IN AND OF ITSELF ABSOLVE THE DEFENDANTS OF ALL LIABILITY, NOR DOES IT ESTABLISH THAT THE WARNINGS OR INSTRUCTIONS PROVIDED WITH THE DRUG WERE ADEQUATE UNDER THE STANDARDS OF LOUISIANA LAW. IN FACT, ANY ACTION OR INACTION ON THE PART OF THE FDA, THOUGH RELEVANT, DOES NOT FORECLOSE A CLAIM UNDER LOUISIANA LAW. THEREFORE, EVEN IF THE DEFENDANTS HAVE MET ALL THE APPROPRIATE MINIMUM STANDARDS FOR FDA APPROVAL AND GOVERNMENTAL REGULATIONS AND REQUIREMENTS TO OBTAIN

[112] *Boudreaux* Trial at ROA.17-30845.114232:13-23 ("I've taken that up. 22 and 23 of the charge deal with the fact that the FDA approval may be relevant, but it's not, in itself, dispositive of liability. I also take up the fact that whether the FDA did or did not do anything, that that's not sufficient and it's not conclusive. With regard to dealing with specific items of evidence that should be in, I don't think the jury charge should focus on specific items of evidence. I chose not to do that, but instead speak the law generally and let the jury decide on it. So I'll deny that motion."); *Orr* Trial at ROA.17-30845.116620:18-22 ("I think taken as a whole, the jury charges are accurate and they express what the Plaintiff has indicated. I don't think that zeroing in on something is even helpful to the jury or helpful to the parties. So that's the reason I deny it.").

> FDA APPROVAL, THIS COMPLIANCE AND APPROVAL, THOUGH RELEVANT, IS NOT SUFFICIENT TO CONCLUSIVELY ESTABLISH THAT THE DEFENDANTS HAVE TAKEN THE STEPS NECESSARY UNDER THE LAW WHICH APPLIES IN THIS CASE. MORE SPECIFICALLY, **IF YOU FIND THAT THE DEFENDANTS FAILED TO APPRISE TREATING PHYSICIANS OF APPROPRIATE TESTING TO ADDRESS RISKS THAT THEY KNEW OR SHOULD HAVE KNOWN PRIOR TO FDA APPROVAL OR BECAME KNOWN OR SHOULD HAVE BECOME KNOWN AFTER THE FDA APPROVAL XARELTO'S LABEL, THEN FDA APPROVAL OF THE DRUG IS NOT CONCLUSIVE.**[113]

Nearly identical language was used in *Mingo*, substituting the word "Mississippi" for "Louisiana" throughout the instruction.[114]

SUMMARY OF ARGUMENT

At the *Boudreaux* and *Orr* trials, errors were made in precluding material evidence demonstrating Defendants' knowledge and notice of information missing from the U.S. label about the value of tests to assess the anticoagulation status of Xarelto. Additional evidentiary errors were made in *Boudreaux,* when the district court admitted irrelevant and unduly prejudicial evidence from a defense witness about his wife's personal use of Xarelto.

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[113] *Boudreaux* Trial at ROA.17-30845.114341:20-114342:17; *Orr* Trial at ROA.17-30845.116734:19-116735:15.

[114] *Mingo* Trial at ROA.18-30102.19575:14-19576:4.

Additionally, the district court refused to appropriately charge the jury. Consequently, the jury was left without a clear understanding of what certain important federal regulations required, and, more importantly, what a violation of those regulations meant in terms of assessing liability. Each instruction proposed by Plaintiffs as to these issues was both legally supported and necessary to prevent serious impairment of Plaintiffs' ability to present their cases. Yet none of the proposed instructions was included, or otherwise adequately reflected, in the district court's final jury charge.

These errors constitute abuses of discretion, and were far from harmless in effect. Each one substantially prejudiced Plaintiffs and prevented them from having their claims resolved by a jury in possession of all the critical and relevant evidence. Considered individually and/or cumulatively, therefore, errors in rulings and instructions below now support the right of Plaintiffs to have their claims reinstated, remanded, and retried.

Finally, a new Bayer study that was not published until the *Mingo* trial was concluding, which was not disclosed by defense counsel and could not have been discovered with due diligence by counsel for Plaintiff prior to the effective conclusion of the *Mingo* trial, acknowledged the ability and benefits of testing the anticoagulant effect of Xarelto. That evidence is not merely cumulative, and it is not limited to impeachment. It more likely than not would have changed the outcome of

the trial. Failing to grant a new trial following the discovery of evidence so damaging to Defendants' presentation to the jury most assuredly represents an abuse of discretion by the district court, and is further reason to vacate the verdict below and remand the *Mingo* case for a new trial.

ARGUMENT

I. STANDARD OF REVIEW

Abuse of discretion is the standard of review for all alleged errors relating to evidentiary rulings,[115] jury instructions,[116] and denial of the request for a new trial based on newly discovered evidence.[117] Reversal is warranted for an evidentiary error if the error was not harmless, and instead affected a substantial right of the moving party.[118] Reversal is warranted for an omitted jury instruction if the requested instruction was: (1) substantially correct; (2) not otherwise substantially covered; and (3) necessary to prevent serious impairment of the moving party's ability to present his or her case.[119]

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[115] *GE v. Joiner,* 522 U.S. 136, 141 (1997).

[116] *U.S. v. Skilling,* 554 F.3d 529, 547 (5th Cir. 2009).

[117] *Gov't Fin. Servs. One Ltd. Partnership v. Peyton Place,* 62 F.3d 767, 774 (5th Cir. 1995).

[118] *U.S. v. Griffin,* 324 F.3d 330, 348 (5th Cir. 2003).

[119] *Skilling,* 554 F.3d at 548.

II. THE DISTRICT COURT ERRED IN THE *BOUDREAUX* AND *ORR* TRIALS BY PRECLUDING FOREIGN EVIDENCE DEMONSTRATING DEFENDANTS' KNOWLEDGE AND NOTICE OF IMPORTANT SAFETY INFORMATION MISSING FROM THE U.S. LABEL

A. The District Court Erred in the *Boudreaux* Trial by Precluding Evidence of Defendants' Instructions in Foreign Labels

As addressed above, in the *Boudreaux* trial, Plaintiffs were entirely forbidden from admitting any information relating in any way to Xarelto labels in other countries – even statements Defendants made about those labels – simply because those statements happened to be included within foreign labels. That evidence should have been admitted, not to show what a foreign regulatory agency might or might not have required for inclusion in its label, but to rebut and impeach testimony and statements from Defendants and their witnesses that "nobody" outside of the courtroom thinks PT testing works. The jury should have heard the truth, i.e., that "somebody" outside the courtroom setting believes PT testing is of clinical value in Xarelto therapy, and that "somebody" includes Defendants themselves.

As reflected in Defendants' label submissions in Canada, Europe, and New Zealand, and in the actual labels, both Defendants and foreign regulatory authorities clearly acknowledge that PT testing is useful in assessing the anticoagulation status of a Xarelto user in a clinical setting. None of this evidence would have been presented to show that other foreign regulatory agencies thought it necessary to

include this specific language in their labels. It instead would have been presented to rebut the claim that "outside of this courtroom, **nobody thinks this test works.**"[120]

That blatant misrepresentation to the jury likely would not and could not have been made if the jury had heard the evidence that Defendants knew about the use of PT testing, and knew how to instruct prescribers about using PT testing in evaluating the anticoagulant effect of Xarelto for clinical guidance in treating patients. But, regardless, by precluding this evidence, the district court allowed the jury to hear in defense counsel's closing statement that nobody outside of the courtroom thinks PT testing works, without having afforded Plaintiffs the opportunity to expose that statement as demonstrably untrue.

While the district court somewhat corrected its stance in *Orr* by allowing limited testimony about statements Defendants had made to Canadian authorities, this was not enough to erase the prejudice caused by its insistence on keeping out any evidence from the Canadian label itself. By precluding any evidence relating in any way to Bayer's own label in Canada, the district court effectively allowed two of Defendants' witnesses to testify, unchallenged, that it would have been "inappropriate" and "reckless" and "dangerous" to include the language proposed

[120] *Boudreaux* Trial at ROA.17-30845.114295:10 (emphasis added).

by Plaintiffs' expert in their U.S. label, even though Bayer was using the exact same language in its Canadian label.

It is respectfully submitted that the district court erroneously failed to make this critical distinction, with regard to both foreign labels and foreign medical associations, which Plaintiffs sought to bring to the attention of jurors. It was not regulatory standards or guidelines which were at the heart of this evidence, but rather the science in support of same. Science is science, irrespective of natural borders, and jurors surely were entitled to take this scientific evidence into account.

District courts routinely permit the admission into evidence of foreign regulatory materials. For example, the court in *Yaz* denied a motion *in limine* filed by Bayer to preclude foreign regulatory materials, explaining that:

> While the regulatory actions of European Medical regulators are not binding on the FDA . . . the full body of knowledge including the foreign regulatory process that came to bear on the drugs at issue and which were well within the notice and knowledge of Bayer is admissible as part of the fabric of how these drugs came to the United States market and whether all the information which should have been utilized in doing so was utilized. Such evidence is clearly probative and that value outweighs the prejudice to Bayer.[121]

[121] *In re Yasmin & Yaz (Drospirenone) Mktg., Sales Practices & PMF Prods. Liab. Litig.,* No. 3:09-md-2100, 2011 WL 6740391, at *2 (S.D. Ill. Dec. 22, 2011). *See also In re Levaquin Prods. Liab. Litig.,* No. 08-cv-1943, 2010 U.S. Dist. LEXIS 145282, at *12-13 (D. Minn. Nov. 9, 2010) (foreign regulatory materials relevant to notice and motive); *Mahaney v. Novartis Pharms. Corp.,* 835 F. Supp. 2d 299, 318 (W.D. Ky. 2011) (foreign regulatory materials relevant to knowledge and notice); *In*

Most recently, similar evidence was permitted in the *Testosterone* litigation. Specifically, the district court there refused to disregard an analysis by Health Canada, rejecting AbbVie's argument that the analysis was based on "a different label, under a different regulatory regimen, in a different country."[122] The court recognized that "the analysis is not being used to dispute the adequacy of AbbVie's FDA-approved labels. Plaintiffs offer the analysis to show only that the scientific community agreed that more testing was required to determine whether drugs such as AndroGel increased the risk of cardiovascular injury."[123]

The district court abused its discretion in excluding this essential evidence in the *Boudreaux* and *Orr* trials. These errors allowed Defendants to make assertions through counsel and offer testimony through experts that were not simply untrue, but contradicted Defendants' own statements. The exclusion of this evidence affected Plaintiffs' rights in a substantial way, justifying a new trial in each case.

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re Tylenol (Acetaminophen) Mktg., Sales Practices & Prods. Liab. Litig., 181 F. Supp. 3d 278, 307 (E.D. Pa. 2016) (same); *Rheinfrank v. Abbott Labs., Inc.,* No. 13-cv-144, 2015 WL 5258858, at *4 (S.D. Ohio Sept. 10, 2015) (evidence of foreign label relevant to knowledge of risks).

[122] *In re Testosterone Replacement Therapy Prods. Liab. Litig.,* No. 14-cv-1748, 2017 WL 1836435, at *14 (N.D. Ill. May 8, 2017).

[123] *Id.*

B. The District Court Erred in the *Boudreaux* Trial by Precluding a Peer-Reviewed Publication

As addressed above, in the *Boudreaux* trial, Plaintiffs also were forbidden from admitting a peer-reviewed publication discussing that numerous medical associations have recommended PT in their medical guidelines as a reliable screening test in patients taking an anti-Factor Xa inhibitor, including Xarelto. The district court reasoned that the jury might be confused by evidence involving foreign regulatory standards, even though no foreign regulatory standards were addressed. The science behind Xarelto's linear relation of Xarelto to bleeding risk as measured by Neoplastin PT does not vary from country to country; the independent medical associations simply based their global testing recommendations on science.

As a direct result of this abuse of discretion, the jury was left with the misimpression that no medical associations, and no peer-reviewed publications, say that PT testing should be used or think that PT testing works. The jury also was left with the misimpression that the understanding of defense witness Dr. Johnson about the value (or non-value) of PT testing was superior, because her testimony was not challenged. This was defense counsel's intent, as evidenced by inclusion of this argument in her summation. This affected the substantial rights of Plaintiffs, and for this reason, a new trial should be granted in *Boudreaux*.

C. The District Court Erred in the *Orr* Trial by Precluding Evidence of Bayer's Statements in a Draft Response to Health Canada

As addressed above, in the *Orr* trial, Plaintiff also was forbidden from admitting Bayer's draft response to Health Canada addressing the benefits of PT testing and the ability to run anti-Factor Xa assays to assess the anticoagulant effect of Xarelto, initially because the document's recipient said he had not read it, and, ultimately, once he admitted to possibly reading it, because of the danger of causing confusion. This was error.

First, the federal rules do not require a witness to remember reading a document he admittedly kept in the ordinary course of business in order for that document to constitute an admissible business record.[124] If it were otherwise, a witness shown part of his own custodial file could never be questioned about it based on a mere assertion that he did not recall reading it at the time he received it.

Second, for the same reason as stated in the previous two sections, this evidence was relevant in establishing Bayer's knowledge and notice of the benefits of testing for anticoagulant effects that it was disputing at trial.

Third, this evidence was necessary to challenge testimony from a defense witness that was in direct conflict with the business record. This error was an abuse

[124] *See* Fed. R. Evid. 803(6).

of discretion that affected the substantial rights of Plaintiff, and for this reason, a new trial should be granted in *Orr*.

III. THE DISTRICT COURT ERRED BY NOT GRANTING A NEW TRIAL IN *MINGO* BASED ON NEWLY DISCOVERY EVIDENCE

The Fifth Circuit has recognized that "newly discovered evidence" may serve as grounds for granting a new trial if the evidence could not have been discovered earlier with due diligence, is not merely cumulative or impeaching, and probably have changed the outcome of the trial.[125]

The Kreutz article and the evidence contained therein was not released online or available to the public until the second week of trial, on August 14, 2017.[126] Plaintiff's counsel received notice of its existence only four days later, on August 18, 2017, through an alert obtained as a result of their due diligence in regularly monitoring medical literature related to Xarelto and subscribing to services providing alerts when new articles regarding Xarelto are published. These efforts go beyond traditional discovery methods, and even with them, notice was not obtained until the morning of closing statements, *after* the evidence was closed. Because of the timing, Plaintiff's trial counsel could not fully review the article and determine its applicability and significance to the case until after the verdict. Thus, for all

[125] *Diaz v. Methodist Hosp.*, 46 F.3d 492, 495 (5th Cir. 1995) (citations omitted).

[126] Rinder Affidavit at ¶ 2 (ROA.17-30845.97955-97958).

practical purposes, despite counsel's extensive due diligence in staying abreast of relevant medical literature, this new evidence was not discoverable until after trial.

The new evidence at issue is not just material; it was critical to Plaintiff's case and would have probably changed the outcome of the trial. Plaintiff's claims were based on Defendants' failure to instruct doctors that Xarelto's anticoagulant effect could be measured with standard laboratory testing, including Neoplastin PT, or by using anti-Factor Xa assays, and that this measurable anticoagulant effect would be clinically useful in weighing the benefits and risks of Xarelto therapy. The *Kreutz* article shows that Defendants' own scientists currently agree with Plaintiff on both points, and, in fact, currently use Neoplastin PT in a clinical setting to assess the anticoagulant effect in Xarelto users. This new evidence contradicts Xarelto's product label, which specifically informs doctors that "[t]he anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed," and renders testimony from Defendants' experts on issues material to the outcome of the case to be scientifically inaccurate and misleading.

For example, defense expert Dr. Demondes Haynes told the jury that PT is not a useful test for monitoring or treating patients on Xarelto, and that relying on PT test results could be dangerous.[127] Another defense expert, Dr. Vincent Herrin,

[127] *Mingo* Trial at ROA.18-30102.19224:15-19, 19282:24-19283:9.

told the jury that PT testing cannot be used to determine Xarelto's anticoagulant effects, and its use is not helpful could cause harm to patients. He further testified that PT "does not provide a reliable measure whatsoever of the amount of exposure to Xarelto in any given patient or at any given point in time during his/her anticoagulation therapy," such that its results are "meaningless" numbers.[128] Thus, Defendants on the one hand represented to jurors in trials that PT is dangerous, useless, and meaningless in clinical settings, while they were simultaneously taking the opposite position in medical literature.

Defendants no doubt will argue to this Court that the new evidence from the Kreutz article is merely cumulative. However, the article represents current, up-to-date scientific data, and the analysis of same, by Defendants' own scientists, at a time when Defendants were taking trial positions that PT and anti-Factor Xa assays are not clinically helpful. This contradiction goes to the core of Plaintiff's claims, and exposes much of Defendants' in-court arguments and expert testimony as scientifically inaccurate and misleading. The inability to present this evidence substantially prejudiced Plaintiff's rights, and entitles Ms. Mingo to a new trial.

[128] *Id.* at ROA.17-30845.19385:15-19386:6. 19406:25-19407:5, 19443:25-19444:4, 19542:8-12.

IV. THE DISTRICT COURT ERRED IN THE *BOUDREAUX* TRIAL BY ADMITTING EVIDENCE ABOUT THE PERSONAL USE OF XARELTO BY A DEFENSE WITNESS'S WIFE

In the *Boudreaux* trial, the district court allowed evidence of the use of Xarelto by the wife of Dr. Peters, an upper-level defense witness who had decision-making authority in relation to Xarelto. This was error. Evidence of a family member's use of the drug at issue does not go to the credibility of the party-employee witness. It instead reflects upon the interface between a non-party family member and that non-party family member's physician. Additionally, even if this evidence would go to credibility – and it should not – Plaintiffs were not in a position to explore or challenge Dr. Peters' testimony about his wife's use of Xarelto.

Unexamined, personal choices to take a prescription drug, despite the risks posed, should not be seen as probative unless the medical circumstances of that personal use are comparable to the circumstances of use at issue in the trial. The anecdotal potential value of relatives of witnesses with different illnesses, and different prescribing physicians faced with different prescribing decisions, is much too attenuated to have any meaningful value to a jury. Because of the lack of any demonstrated link to the factual circumstances of the case on trial, this testimony

was nothing more than evidence of a "sporadic" and "isolated" occurrence that was irrelevant to the trial proceedings.[129]

To the extent there could be some marginal bearing on credibility – and that is unlikely – it was far outweighed by unfair prejudice to Plaintiff, which was compounded by the inability of Plaintiffs' counsel to effectively cross-examine Dr. Peters about the medical circumstances of his wife, much less about the decision-making process of the absent prescribing doctor referred to in his testimony.

The jury likely viewed this evidence as probative of Xarelto's safety, and not just Dr. Peters' credibility. Indeed, defense counsel exploited that notion in her summation:

> Plaintiffs said to you at the beginning that this was a safety test. Again, why did he say that? Because he wanted you to think we were terrible people. We're actually the big pharmaceutical companies I think he called us, and we don't want to do a simple safety test. Think about what that said. **That all of the doctors who work on our companies who told you they were on Xarelto themselves or prescribe it for their mother, that they**

[129] *See Mooney v. Aramco Servs. Co.,* 54 F.3d 1207, 1219-1221 (5th Cir. 1995). *See also Pfeiffer v. C.I.A.,* 60 F.3d 861, 865 (D.C. Cir. 1995) ("Suffice it to say that anecdotal evidence about what other former employees of other government agencies have done is irrelevant to Pfeiffer's case."); *BASF Corp. v. Old World Trading Co., Inc.,* 86-cv-5602, 1992 WL 232078, at *4 (N.D. Ill. Sept. 8, 1992) ("[A]necdotal evidence, unless accompanied by testimony that such evidence was statistically significant, was irrelevant and would consume too much time.").

> **don't care about safety.** They don't care. That's what he wants you to believe.[130]

Through this summation, Defense counsel invited the jury to construe personal use evidence as indicative of Defendants' emphasis on safety. The prejudicial impact was intended, and it was not only significant, but incurable.

When faced with this issue during the *Vioxx* litigation, the district court either precluded the evidence or stated it was generally inadmissible.[131] Similarly, state courts in other *Vioxx* litigation precluded the evidence, explaining its irrelevance and prejudicial effect:

> Merck is essentially arguing that their employees' actions spoke louder than their words because they would not have consumed the drug, or let their family, if they believed it had the cardiovascular risks the plaintiff claims it had. The individual decision made by a person in consultation with their doctor to take a drug is a personal decision which can be made for many reasons. People are willing to take different risks. Some people, depending on their medical

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[130] *Boudreaux* Trial at ROA.17-30845.114291:22 (emphasis added).

[131] *See, e.g., Dedrick v. Merck & Co., Inc.,* No. 05-cv-2524, slip op., at ¶¶ 5, 3(m) (E.D. La. Nov. 22, 2006) (ROA.17-30845.80013-80025) (excluding "any evidence, discussion, or argument that Merck employees, former employees, or family members of Merck employees took Vioxx prior to the drug's withdrawal from the market," but deferring ruling on "[a]ny comment or personal anecdote from any Merck witness or lawyer that they or their family members used Vioxx"); *Barnett v. Merck & Co., Inc.,* No. 06-cv-485, slip op., at ¶¶ 7, 3(m) (E.D. La. Nov. 18, 2011) (ROA.17-30845.80027-20037) (reserving ruling, but saying this evidence "generally will not be admissible since it is of no relevance since it depends on dosage, time taken, age, prior condition of party, risk factors, etc., which may be different [and] result in a trial w/in a trial [and] only confuse jury").

> condition, may have been willing to gamble on the cardiovascular risks even if they knew of the risk. The exploration at trial of each employee's personal decision would be prejudicial, confusing and time consuming. The court finds that evidence that Merck employees or their family members took VIOXX is substantially more prejudicial than probative and must be excluded during trial.[132]

Here, any probative value from using evidence of Xarelto use by Dr. Peters' wife to bolster the credibility of Dr. Peters was, at best, insufficient to outweigh the unfairly prejudicial impact of the jury taking the evidence to mean the drug must be safe. The potential for prejudice was made even greater when defense counsel's summation invited the jury to consider the sincerity of the company's "personal users" as proof that the company takes drug safety seriously. This error was an abuse of discretion that affected the substantial rights of Plaintiffs, and for this reason, a new trial should be granted in *Boudreaux*.

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[132] *Humeston v. Merck & Co., Inc.*, No. ATL-L-2772-03, slip op., at 3 (N.J. Super. Ct. Sept.2, 2005) (ROA.17-30845.80039-80043); *see also Messerschmidt v. Merck & Co., Inc.*, No. ATL-L-5520-05, slip op. (N.J. Super. Ct. Jan. 18, 2007) (ROA.17-30845.80045-80046); *Doherty v. Merck & Co., Inc.*, No. ATL-L-638-05, slip op., at ¶¶ x, bb (N.J. Super. Ct. June 1, 2006) (ROA.17-30845.80048-80052); *Cona v. Merck & Co., Inc.*, No. ATL-L-3553-05, slip op., at ¶¶ x, bb (N.J. Super. Ct. Mar. 28, 2006) (ROA.17-30845.80054-80059).

V. THE DISTRICT COURT ERRED IN REFUSING TO CHARGE ALL THREE JURIES ABOUT FEDERAL REGULATIONS MANDATING INSTRUCTIONS ABOUT HELPFUL LABORATORY TESTS AND THE ABILITY TO ESTABLISH LIABILITY THROUGH A VIOLATION OF THOSE REGULATIONS

Plaintiffs' proposed instructions were intended to work in tandem. The first instruction would have advised the jury that if a laboratory test might help a physician to follow a patient's response to the drug or to identify possible reactions to the drug, federal regulations require the warning section of the label to identify the test, the range of values expected with the test, and the frequency with which the test should be performed.[133] The second instruction would have advised the jury that if a regulation is violated – such as the regulation to advise of helpful tests – the violation can be considered as evidence of a failure to warn.

The district court's alternate instruction about federal regulation requirements were too general to provide necessary guidance to the jury about a relevant regulatory mandate. All the jury was told in terms of tests was that if Defendants failed to apprise of "appropriate testing to address risks," FDA approval of the drug would not conclusively establish their compliance with the law. The court's instruction provided no guidance with regard to what constituted "appropriate testing to address risks." The jury needed to hear as part of the court's instructions the

[133] *See* 21 C.F.R. § 201.57(c)(6)(iii).

language proposed by Plaintiffs, which effectively defines that phrase. Additionally, the court's instructions were not clear with regard to what import the jury could attach to any failure to comply with federal regulations. They were not told that they could affirmatively use such evidence to conclude that Defendants' instructions were inadequate.

The requested instructions were not challenged as inadequate or confusing in any way, and there was no good reason to refuse to include them. It would have taken less than a minute to provide the instructions, and the only possible effect would have been to clear up potential confusion. The district court instead chose to provide an alternate instruction that did not, in any way, cover the substance of the instructions proposed by Plaintiffs. This was an abuse of discretion, which resulted in the jury lacking any clear understanding of the standards required for a warning to be deemed inadequate under the law. Unfair prejudice is unavoidable in a situation such as this, when a party is required to meet an unclear burden of proof. For this reason, a new trial should be granted in each case.[134]

[134] *See Skilling,* 554 F.3d at 548.

CONCLUSION

For the foregoing reasons, this Court should reverse the judgments of the district court, reinstate Plaintiffs' claims, and remand these cases for further proceedings.

Date: April 23, 2018

Respectfully submitted,

/s/ Frederick S. Longer
Frederick S. Longer
Levin Sedran & Berman
510 Walnut Street, Suite 500
Philadelphia, PA 19106
Telephone: (215) 592-1500
flonger@lfsblaw.com

Attorney of record for Appellants

CERTIFICATE OF SERVICE

Pursuant to Federal Rule of Appellate Procedure 25(d), I certify that on this date, a copy of the foregoing was filed using the electronic filing system for the United States Court of Appeals for the Fifth Circuit.

/s/ Frederick S. Longer
Frederick S. Longer

Attorney of record for Appellants

DATED: April 23, 2018

CERTIFICATE OF COMPLIANCE

This document complies with the type-volume limit of Federal Rule of Appellate Procedure 32(a)(7)(B) because, excluding the parts of the document exempted by Federal Rule of Appellate Procedure 32(f) and Fifth Circuit Rule 32.2, this brief contains 12,744 words.

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/s/ Frederick S. Longer
Frederick S. Longer

Attorney of record for Appellants

DATED: April 23, 2018