UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

IN RE: XARELTO (RIVAROXABAN) PRODUCTS LIABILITY LITIGATION	*	MDL 2592
	*	SECTION L
THIS DOCUMENT RELATES TO ALL CASES	*	JUDGE ELDON E. FALLON
	*	MAG. JUDGE NORTH

* *

PLAINTIFFS' STEERING COMMITTEE'S REPLY TO DEFENDANTS' RESPONSE TO MOTION TO COMPEL DISCOVERY

With the permission of the Court, the PSC respectfully submits this reply to the response of Defendants Janssen Pharmaceuticals, Inc., Janssen Research & Development, LLC, Janssen Ortho, LLC, and Johnson & Johnson (collectively "Defendants") to the PSC's motion to compel documents in response to Plaintiffs' Third Request for Production of Documents.

I. INTRODUCTION

Defendants' opposition in response to the PSC's motion to compel the production of documents reveals a strategy that stands to impede the discovery process in this litigation and, even more importantly, block Plaintiffs' rightful access to documents and information relevant to their claims and to imminent public health and safety concerns. Having purposefully marketed Xarelto as a drug that is superior in safety and efficacy to alternative anticoagulants, and in particular, warfarin, Defendants cannot be allowed to withhold information in their custody, possession and control that directly contradicts the very premise on which the approval, launch, and labeling of Xarelto was based.

Defendants claim protection over documents relating to two re-analyses of data from the Phase III Clinical Trial, ROCKET AF. As the Court is aware, the ROCKET AF trial was the pivotal Phase III Clinical Trial upon which Defendants relied to obtain approval of the prevention of ischemic stroke in patients with nonvalvular atrial fibrillation indication. This indication is, by far, the primary indication for which Xarelto is prescribed.

The re-analyses were required to assess the impact of a defective device used in the course of the ROCKET AF trial for critical monitoring of anticoagulation in the double blind study comparing patients treated with warfarin and rivaroxaban. Two categories of documents are at issue. The first category includes data, analysis, and documents (including internal emails and their attachments, memoranda, reports, drafts and other documents generated and kept in the ordinary course of business) related to the re-analysis conducted by the Duke Clinical Research Institute ("DCRI") on behalf of Defendants. The second category includes data, analysis, and documents (including internal emails and their attachments, memoranda, reports, drafts and other documents generated and kept in the ordinary course of business) developed and written by Defendants themselves, but which Defendants purport are protected because they were submitted to, or relate to submissions to, the European Medicines Agency ("EMA") in regards to the EMA's investigation into the defective device and the ROCKET AF trial. Although Defendants' internal re-analysis has been completed and submitted to regulators, and the DCRI re-analysis has been submitted for peer-review and publication, Defendants have yet to make public the results and implications for the safe use of Xarelto. Nor have Defendants produced the completed data, re-analyses and related

documents to Plaintiffs despite the fact that the information is responsive to Plaintiffs' requests for production and should be produced. Defendants' arguments against production ignore the fact that the Protective Order governing document production in this litigation (PTO No. 16) would wholly protect the information from the premature public disclosure that Defendants claim to fear.

The INRatio® PT/NR Monitor system used in the ROCKET AF trial conducted by Defendants was recalled in December of 2014 due to evidence that the system was registering INR ("International Normalized Ratio") results that were "clinically significantly lower" than results from screening with the use of laboratory methods. *See* Exhibit A (Dec. 5, 2014 Letter from Alere to Healthcare Professionals). This is significant to the facts of the present litigation as such a defect would lead to the over anti-coagulation of patients in the warfarin arm of ROCKET AF. Such an over-anti-coagulation would lead to more bleeding events in the patients given warfarin. This is important as Xarelto was approved by the FDA under a non-inferiority, "no worse than," standard when compared to warfarin. The increased number of bleeds due to the over-anti-coagulation of patients in the warfarin arm inappropriately increased the number of bleeds that would be allowed in the Xarelto arm while still maintaining non-inferiority. In other words, many of the bleeds in the warfarin arm were caused by inappropriate dosing and had such inappropriate dosing not occurred, it would have been shown that Xarelto was inferior to warfarin when comparing the risk of a bleeding event. The end result of this information is that the results of the pivotal Phase III trial that Defendants' relied upon for approval are invalid and call into question the approval of this drug.

Incredibly, Defendants waited until September of 2015, after a reporter from the British Medical Journal inquired about the subject, to act on the recall's impact on the ROCKET AF trial. *See* Exhibit B (filed under seal) (Sept. 14, 2015 INRatio Power Point, page 10). In response to Janssen's inquiries, Alere, the recalled device's manufacturer, confirmed that the defective devices were in fact used in the clinical trial. *Id.* (Sept. 14, 2015 INRatio Power Point, page 13).

The Defendants also waited approximately 10 months to notify global regulators, including the EMA, which immediately undertook an investigation and sought information from Defendants on their analysis of the impact. Defendant Bayer was fully aware that the EMA considered this to be a significant issue pertaining to the safety of Xarelto as Bayer was advised that "[redacted]." Exhibit C (filed under seal) (Oct. 1, 2015 letter from EMA to Dr. Sabine Frenzen, Bayer Pharma).[1] The EMA posed a series of specific "[redacted]" to be addressed by Bayer "[redacted]," including concerns over the delay in notification to EMA, requesting "[redacted]."[2] *Id.* Internal email correspondence demonstrates that Defendants sought to unduly narrow the focus of the analyses and clarifications sought by EMA by assessing the impact only on a small subgroup of patients identified in the

[1] EMA's October 1, 2015 correspondence appears to be in response to correspondence from Bayer dated September 23 and 29, 2015, but Plaintiffs have been unable to locate those letters in Defendants' production. In a meet and confer yesterday about these very documents, Defense counsel confirmed that they withheld them for the reasons set forth in their response to the instant motion.

[2] Plaintiffs have also been unable to locate the October 15, 2015 response to EMA in Defendants' productions.

Alere recall notice rather than engaging in a more broad and thorough assessment of all patients in the clinical trial. *See* Exhibit D (filed under seal) (Nov. 11, 2015 email exchange between Janssen and Bayer personnel on response to EMA request in which they endorse a response strategy that evades points that "[redacted]").

Email correspondence between Defendants also reveals that Defendants internally identified the applicable international standard for evaluating the performance of the device. *See* Exhibit E (filed under seal) (Nov. 12, 2015 email correspondence, quoting ISO 17593 guidance establishing "[redacted]").[3] Internal documents further reveal that the device used in the ROCKET AF trial failed to meet the international standard. *See* Exhibit F (filed under seal) (Table of Discrepancies Between Lab Based INR and Device Based INR – XARELTO_JANSSEN_15522180). An astonishingly high percentage of the INRatio data were shown to be out of range. To date Plaintiffs have been unable to determine whether this information has been shared with global regulators. Whether this is a defect in production to Plaintiffs or lack of transparency with regulators is uncertain at this point.

Defendants' response in opposition attempts to paint a picture of cooperation and candor in dealing with this most serious issue. Yet, the documents produced thus far, as

[3] The "[redacted]" were also referenced in earlier email correspondence and circulated to Defendants' ROCKET AF task force members, but Defendants have inexplicably withheld the attachments to that email correspondence as "Not Responsive." Exhibit G (filed under seal) (Oct. 2, 2015 email (XARELTO_JANSSEN_15319552-15319553). Again, if the PSC is unable to resolve the missing and withheld documents by meeting and conferring with Defendants, it will file another motion to compel.

exemplified by those described above, demonstrate the fallacy of Defendants' position. Indeed waiting approximately 10 month to identify the recall is hardly "promptly" informing regulators "of the recall and their own efforts to reassess the ROCKET AF data." Def. Brf. at 4. As EMA observed, they were not informed of the problem until about 10 months after the recall. Now, with responses to EMA having been submitted and Defendants' re-analyses having been completed,[4] Defendants throw up meritless excuses for failing to produce the documents that would tell the full story. Without full disclosure of Defendants' internal analyses and related information and that of its agent DCRI, Plaintiffs cannot adequately prepare for upcoming depositions and expert disclosures. As shown, the "peer-review and foreign regulatory processes" focusing on this critical issue do not shield Defendants from their obligation to produce documents and information responsive to discovery requests in this litigation.

II. LEGAL ARGUMENT

A. Discovery Obligations Attendant to a Party Can Not Be Avoided by the Assertion of the Peer Review Process Privilege Enjoyed by a Third-Party

Defendants seek to avoid compliance with the ordinary application of the Federal Rules of Civil Procedure addressing discovery directed to parties by cloaking themselves in the mantle of protections afforded to third-party academic institutions from intrusive subpoenas. Plainly, their analogy is inapt. Here, the Defendants have conducted their

[4] Internal email correspondence again confirms that Defendants have completed their re-analyses, but are withholding the results from Plaintiffs even though those results and related documents are clearly responsive to and within the scope of Plaintiffs' discovery requests and would be protected from public disclosure by the Protective Order. *See, e.g.,* Exhibit H (filed under seal) (December 5, 2015 email exchange regarding data and the ROCKET AF task force's "[redacted]" (XARELTO_JANSSEN_15320147-15320151)). The data, analysis, and "[redacted]" attachments to the December, 5, 2015 email have not been produced on privilege grounds.

own re-analysis of the ROCKET AF study and they possess a separate re-analysis conducted by their research contractor, DCRI. None of the cases they cite address the factual circumstances presented by this case, where the party-defendants are the targets of document requests regarding data and findings of an as-yet unpublished analysis that are in their possession, control and custody. In this situation, deference is owed to the law's basic presumption that the public is entitled to every person's evidence.[5]

DCRI is a research organization that is attempting to have its secondary analysis of the ROCKET AF trial published. However, that attempt to publish its analysis in a peer-reviewed publication is an endeavor undertaken by DCRI, *not* the Defendants. Under these circumstances, there is no threat of a "chilling-effect" on DCRI since the information is being sought from Bayer or Janssen, and the information that would be produced to Plaintiffs is subject to a protective order. Finally, there is no "chilling-effect" on scientific endeavors since the Defendants concede that DCRI has already made known the conclusion of its "findings from the analysis," Def. Brf. at 4 (quoting Def. Exh. 2).

Dow Chemical Co. v Allen, 672 F.2d 1262 (7th Cir. 1982), the principal authority on which the Defendants' base their argument, is factually distinguishable from the circumstances attending this litigation. In that enforcement proceeding, at Dow's request the administrative law judge issued a broad subpoena upon University of Wisconsin researchers who had been studying the toxic effects of Dow's herbicide. The scientists successfully moved for a protective order, which motion was supported by uncontested affidavits testifying about the deleterious effects "public access" would have on their

[5] *See, e.g., Blackmer v. United States*, 284 U.S. 421, 438 (1932).

research. *Id.* at 1273 (public access would make their studies unacceptable for publication, it could negatively affect their careers if not published, and risk "total destruction" of their research). Dow appealed. Based, in part, on the researchers' uncontroverted affidavits, the Seventh Circuit found that the subpoenas were overbroad. *Id.* at 1276 (the subpoenas "would compel the researchers to turn over every scrap of paper and every mechanical or electronic recording made ...."). The court was especially concerned that the subpoena's obligation to continually update Dow with "additional useful data" improperly threatened "substantial intrusion into the enterprise of university research" which could chill the "exercise of academic freedom." *Id.* The Court noted the fact that the researchers being non-parties to the proceedings weighed in favor of non-disclosure. *Id*. at 1277. Finally, the court recognized that an effective protective order might have eliminated the burden of the subpoenas but for the fact that inadvertent disclosures of raw data had already occurred. *Id.*[6]

None of concerns animating the decision in *Dow Chemical* exist here. The defendants have not provided any evidence (i.e., an affidavit) supporting their argument that release of the re-analysis of the ROCKET AF study would chill anyone's academic freedom. There is no risk of intruding on the defendants' academic freedom since they are not academic institutions, and DCRI is simply their contractor (who is not even the

[6] In a separate concurrence in *Dow Chemical*, one circuit court judge noted that no protection should be afforded to claims based upon academic freedom. *Id.* at 1278 (Pell, J., concurring). Judge Pell was especially concerned that a request for mere data, as opposed to the conclusions drawn from the analysis of that data, should not chill any academic's motivation. He noted: "A researcher's reputation perhaps deserves to be subject to some questioning if he or she cannot accurately observe and record specific factual matters." *Id.* Applying this reasoning here, plaintiffs, at a minimum, are entitled to the underlying data that animates any re-analysis performed by the Defendants or DCRI.

subject of the motion to compel). The defendants are obviously not third-parties, and this Court's PTO No. 16 (protective order) exists to protect any confidential information from being disclosed prior to publication.[7]

Indeed, better reasoned opinions caution against blanket protection against production of completed but unpublished medical research. For example, in *Burka v. United States Dept. of Health and Human Services,* 87 F.3d 508, 521 (D.C. Cir. 1996), after conducting a survey of the law in the context of an appeal from a Freedom of Information Act ("FOIA") request that was denied under the "confidential research information" Exemption 5 of FOIA, the court refused to find "a well-settled practice of protecting research data in the realm of civil discovery on the grounds that disclosure would harm a researcher's publication prospects."

Likewise, in *In re Methyl Tertiary Butyl Ether ("MTBE") Products Liab. Litig.,* 269 F.R.D. 360 (S.D. N.Y. 2010), the MDL court required production of raw data from one of the defendants' research contractor who was four months away from publishing a study regarding MTBE. The court noted that the defendant had already been ordered to produce "any documents" from its research contractor containing relevant search terms.

[7] In this regard, Defendants' reliance on *Deitchman v. E.R. Sqibb & Sons, Inc*., 740 F.2d 556, 564-66 (7th Cir. 1984), is also misplaced. In that case, the court vacated the district court's order quashing the defendants' subpoena on a third-party academic, and remanded the matter with instructions to permit *some* discovery subject to an appropriate protective order. The other cases relied upon by the Defendants are equally inapposite as they address discovery directed to third-parties where the need for the data by the party issuing the discovery could not be established, and they were unable to show that a protective order could reduce any prejudicial impact imposed by the production. *See Plough Inc. v. National Academy of Sciences*, 530 A.2d 1152, 1160 (D.C. App. Ct. 1987) ("In a case in which a higher level of need were shown, disclosure under such an order might be appropriate.") and *Application of R.J. Reynolds Tobacco Co.*, 518 N.Y.S.2d 729, 732, 733 (N.Y. Sup. Ct. 1987) (Court found subpoenaed witnesses were "complete strangers to underlying litigation" and that their "academic freedom is not absolute and must be balanced against competing interests.").

Id. at 363. At issue was whether the defendant and the contractor should produce the remaining study documents. Taking into account the procedural posture of the litigation, the court observed that the plaintiff "will benefit from having documents relating to this study sooner rather than later." *Id.* at 364. The court noted that because the study was commissioned by the defendant that was heavily involved as a litigant regarding the product that "special circumstances" were presented by the discovery requests. *Id.* Thus, the court held that "by virtue of its connection to [the defendant, the research contractor] is not entitled to the same level of protection ordinarily accorded to non-party research institutions." *Id*. at 365. It therefore ordered the research contractor to immediately produce the raw data from its study, and the final report when completed. *Id*. Unlike the present case, the defendant disclaimed possession of the requested documents, and therefore the district court denied the motion to compel *viz*. the defendant with this caveat: "[defendant] remains under a continuing obligation to produce any documents relating to the study that come into its possession in the future." *Id.* at 366. In the instant case, the fact that the Defendants possess the DRCI study, they are obliged to produce the documents they hold today under the reasoning of the *MTBE* court.[8]

[8] In contrast to the reasoning of *MTBE*, the Defendants also rely on Judge Herndon's opinion in *Pradaxa. See In re Pradaxa Products Liab. Litig.*, MDL No. 2385, CMO 58 (S.D. Ill. Feb 21, 2014). The facts in that case immediately distinguish it from the facts presented here. In *Pradaxa,* the court noted that the plaintiffs were demanding "a virtual place at the table" by seeking the study's results in "real time (on a rolling basis as they termed it)." *Id.* at 4. Obviously, that is not the case here, since the findings of the re-analyses have already been submitted, *i.e.,* , the DCRI submission has been submitted for publication and the Defendants' reanalysis has been presented to regulators. Def. Brf. at 4 & Def. Ex. 2.

Whereas the defendants are currently in possession of the documents related to the re-analyses of the ROCKET AF study, regardless of the peer-review analysis, by law they are under a duty to produce them immediately.

B. Regulatory Proceedings Can Not Insulate Defendants From Discovery Obligations Imposed by the Federal Rules of Civil Procedure

Defendants attempt to withhold documents they have internally generated that are of utmost relevance to this litigation on the grounds that disclosure would unduly influence or have a "chilling effect" on the EMA's investigation into the impact of the defective INR monitoring device on the results of the ROCKET AF clinical trial. Defendants' argument sidesteps the concern raised by Plaintiffs and their right to discovery.

The documents and information sought are not those being generated by EMA, and hence, they do not fall under EMA Policy No. 0043 governing Access to Documents. Defendants quote this policy in response (Def. Brf. At 11) claiming that Defendants' data and documents fall within the confidentiality provisions that preclude EMA from disclosing to the public information that would "undermine the decision-making process." In context, however, it is clear that this protection extends to the agency's internal documents and analysis, including "disclosure preparatory documents, i.e. working documents, internal notes, and documents containing opinions for internal use [footnote omitted] or related to preliminary consultations *within the Agency*" and not to the internal documents within Defendants' custody, possession, and control being sought through the PSC's motion. Exhibit I (EMA Policy 0043, Nov. 30, 2010) at 4 (emphasis added). EMA's policy even recognizes there are times when disclosure prior to

finalization of documents and reports is necessary where it would serve "an overriding public interest." *Id.*

It is no wonder that Defendants seek cover under the EMA policy. The defective device stands to jeopardize the approval of Xarelto and Defendants' ability to continue reaping substantial profits from sales of the drug. Not surprisingly, Defendants seek to delay production the re-analyses data and related information given the significance of this issue to Plaintiffs' claims in this litigation. Without full production, Plaintiffs cannot adequately explore the issue in the upcoming scheduled depositions or prepare for upcoming expert disclosures. Without the relief sought, the depositions will have to be continued or taken again. Defendants' dismissive attempt to address this point with its claim that "[n]ew documents are created each day in this litigation where the medicine remains on the market" (Def. Brf. at 6, n.9) ignores the fact that the documents sought are not "new." Many have been in existence since well before Defendants' custodial sweeps, and even more importantly, Defendants' argument ignores their obligation to supplement disclosures made in response to requests for production. See Fed.R.Civ.P. 26(e)(1).

The recall of the INR device used in the ROCKET AF trial now dates back well over a year. Defendants' failures to acknowledge and respond in a timely manner to the critical concerns over the implications of the defective device for the integrity of the ROCKET AF trial and Xarelto's approval should not be condoned, even if it is the subject of ongoing investigations by the EMA. Thus, Defendants' argument that disclosures to regulatory authorities for the purpose of on-going regulatory investigations must also be protected from civil discovery until those proceedings are concluded (Def. Brf. at 9-10, *citing In re LTV Sec. Litig.*, 89 F.R.D. 595, 619 (N.D. Tex. 1981), is

baseless. According to DCRI and the Defendants, both of their submissions have already been submitted to regulators or for publication, are responsive to plaintiffs discovery requests, are not privileged, and as such should be produced immediately. Any additional delay impairs plaintiffs' ability to prepare for upcoming depositions scheduled to begin next month.

III. CONCLUSION

For the reasons set forth above, as well as in the PSC's moving papers, the motion to compel should be granted.

DATE: January 29, 2016

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that on January 29, 2016, the foregoing pleading was filed electronically with the Clerk of Court using the CM/ECF system. Notice of this filing will be sent to Liaison Counsel for Plaintiffs and Defendants by operation of the court's electronic filing system and served on all other plaintiff counsel via MDL Centrality, which will send notice of electronic filing in accordance with the procedures established in MDL 2592 pursuant to Pre- Trial Order No. 17.

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