UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

IN RE: ZOFRAN (ONDANSETRON) PRODUCTS LIABILITY LITIGATION	**MDL No. 1:15-md-2657-FDS**
THIS DOCUMENT RELATES TO: ALL CASES	

PLAINTIFFS' MOTION TO COMPEL ADVERSE EVENT DATA AND SOURCE DOCUMENTS FROM GSK'S DRUG SAFETY DATABASE

I. INTRODUCTION

GSK routinely urges this Court to take up a "Science Day" and the expert discovery process as soon as possible. It is becoming all too clear why GSK has been forcing the issue: GSK wants to sequence the science so that Plaintiffs will be deprived of key evidence that GSK is sitting on relative to notice of Zofran-related adverse events reported to the company. GSK collected the information, made causality assessments of the internal information and collected follow-up documentation. GSK will produce none of that to Plaintiffs. GSK's justifications for its plain refusal to produce the relevant evidence are all form over substance: HIPAA privacy claims, technology burden claims and that some of the information is buried within the previously produced IND/NDA production. The prejudice to Plaintiffs should be obvious, but GSK seems to think that forcing the Plaintiffs to rush to confront science without production of its own evidence of Zofran's dangers is a fair fight. This gamesmanship and delay tactic should be rejected and GSK should be compelled to reveal the notice evidence it is trying to obscure.

GSK keeps, in its ordinary course of business, a drug safety database, called [redacted] or "Argus." Argus is used to track Zofran-related adverse

events and enables GSK to report those that it deems reportable to the U.S. Food and Drug Administration ("FDA"). Argus houses all known Zofran adverse events in a centralized location so that they are readily accessible, searchable and sortable. In this litigation alleging that GSK was on notice of, and negligently responded to, Zofran's adverse events concerning birth defects, Plaintiffs asked GSK to produce reasonably usable birth defect-related adverse event data from Argus. GSK refused.

GSK's knowledge of adverse events related to Zofran and what GSK did or did not do with that information goes to the heart of Plaintiffs' claims. The database is the primary source, and the most comprehensive and useable source of adverse event data in GSK's possession. It contains information from every known Zofran-related adverse event, worldwide, occurring at any time since clinical trials began, including adverse events GSK chose not to report to regulatory authorities. Recent depositions of GSK employees who work with the database have raised serious issues about whether GSK was accurately maintaining its adverse event database and accurately reporting adverse events to the FDA and the public, including doctors whom GSK induced to believe that Zofran was safe for use in pregnancy.

Plaintiffs requested a data extraction of the Zofran-related adverse events from the database. This data is highly relevant to the question of when GSK was or should have been aware that Zofran posed more severe birth defect risks than represented by GSK. It is also necessary to oppose GSK's defense of federal preemption because the adverse events constitute post-product launch safety information that required GSK to correct its misrepresentations about Zofran's alleged safety for use in pregnancy.

GSK's employees have and will continue to use the database to prepare its defense in this litigation, and they have testified that database information is readily accessible. A level playing

field is possible only if Plaintiffs are provided with a useable form of data from the database, giving Plaintiffs an equal ability to analyze adverse event safety information. Absent this ability, Plaintiffs are at a significant and unfair disadvantage.

Drug safety databases like GSK's database are routinely disclosed in pharmaceutical litigation. Plaintiffs have tried to resolve this dispute, engaging in meet-and-confer discussions, written correspondence, and formal discovery addressing this topic. GSK refuses to produce the requested data, instead contending that its production of incomplete and fragmented adverse event information in .tiff format fulfills its discovery obligation—ignoring that such information is different, in content, organization and usability, from the safety information Plaintiffs seek from this database. Accordingly, Plaintiffs bring this motion to compel production.

II. STATEMENT OF FACTS

A. ARGUS CONTAINS UNIQUE, RELEVANT INFORMATION IN A USEABLE FORM.

As is typical among drug manufacturers, GSK's Argus database is a "signal management tool" that contains data from all known adverse event reports submitted to GSK in association with its drugs. The database contains information on adverse events occurring during clinical trials and post-marketing surveillance efforts, as well as spontaneously reported adverse events.[1] The database also contains information on adverse events not submitted to the FDA.

Unlike information contained in various documents GSK has produced in .tiff format, information in Argus is organized in numerous data fields, enabling users to easily search, filter and organize the data in, for example, a Microsoft Excel spreadsheet. Individual printouts from the database do not replicate the search and sorting functions available from an export of the data,

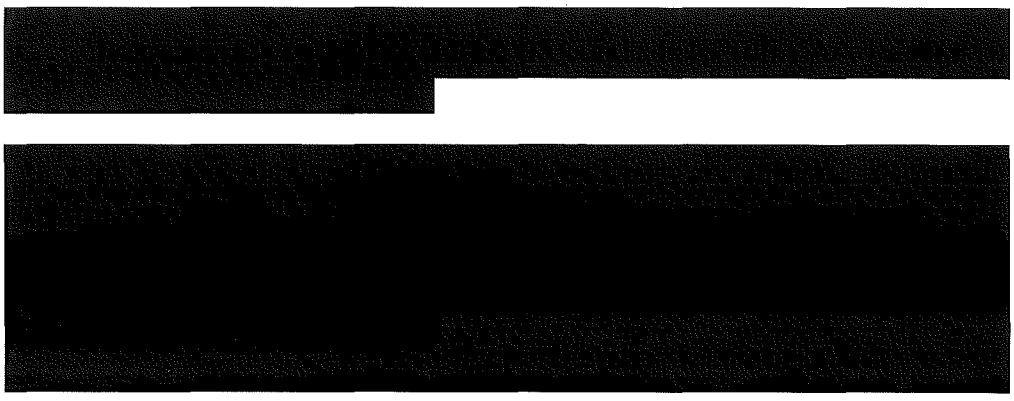
[1] [redacted]

and GSK has produced such data in a way that makes it virtually impossible for Plaintiffs to compile all of the adverse event data in one place and compare the data received by GSK to the data reported to the FDA. By contrast, an export of all relevant adverse events from Argus can be completed in clicks of a button.

For the present litigation, the database contains unique information that facilitates "signal detection"— that is, analysis of birth defect reports to determine if and when GSK should have known that Zofran, which was heavily marketed and used off label in pregnancy, presented risks of birth defects. Signal detection requires significant analyses possible only with an export of data, rather than .tiff images of secondary sources. For example, an assessment of the notice to GSK will involve consideration of a patient's Zofran use, the route of administration, the indications for use, concomitant drug use, the specific birth defect(s) reported, the period of pre-natal exposure to Zofran, term of the pregnancy, pregnancy complications, and other relevant factors and patient history, all of which have assigned fields in the database to capture the information. Evaluation of these various factors will be exponentially facilitated by the production of searchable database information that organizes the adverse event information in a centralized location.

B. INFORMATION FROM THE ARGUS DATABASE IS READILY ACCESSIBLE TO GSK.

GSK's safety scientist for Zofran, who relies on the database regularly, agreed that the adverse event data from Argus is readily available:



[redacted]

See Ex. 2, LaCroix Dep. at pp. 123, 151-52. [redacted] *E.g., id.* at p. 159. GSK has produced examples of data extracts from Argus performed by its employees, but only for limited time periods. It can easily generate a similar extract that includes all relevant adverse event information related to pregnancy outcomes where the mother ingested Zofran. [redacted]

C. GSK USED THE ARGUS DATABASES TO CONDUCT ITS OWN EVALUATIONS OF ADVERSE EVENT DATA AND WILL CONTINUE TO DO SO IN DEFENDING THE LITIGATION.

GSK has on several occasions since being sued for Zofran-induced birth defects used the Argus databases to search for, evaluate and summarize the adverse event data related to the use of Zofran during pregnancy. [redacted]

[2] According to a similar GSK report in October 2015, GSK had by then identified a total of 1,257 reports in the Argus database that it labeled "pregnancy and neonatal topics" involving Zofran reported as a suspect drug. *See* Ex. 4, ZFN00011889.

[redacted]

[redacted]		

[redacted]

D. PLAINTIFFS HAVE REQUESTED THE ADVERSE EVENT DATA FROM ARGUS, AND MET AND CONFERRED WITH GSK COUNSEL, BUT GSK CONTINUES TO REFUSE DISCLOSURE.

Plaintiffs requested Zofran adverse event reports, source documents, documentation of GSK's efforts to investigate the AERs and reports and analyses of the AERs from Argus. *See, e.g.*, Pls.' First RPD, Section IV, Pharmacovigilance, Request Nos. 1, 5, 8, 9, 10-13, and 16. GSK responded that "information concerning adverse event reports" for Zofran is contained in the IND/NDA files and that it would continue to search for and produce adverse event reports and MedWatch forms, but only those listing minor plaintiffs' mothers' use of Zofran.

On February 1, 2018, Plaintiffs' counsel wrote GSK counsel describing the need for adverse event information from Argus. *See* Ex. 6. Plaintiffs have not asked for a data extraction for all Zofran adverse events of any kind, only those relating to pregnancy outcomes, which [redacted]. On February 16, 2018, GSK counsel responded, stating that GSK would not produce the requested information and instead would insist that Plaintiffs rely on the IND/NDA files for Zofran. *See* Ex. 6. These files comprise roughly 538,000 pages of .tiff files mostly related to Zofran's on-label uses as an anti-nausea drug for cancer patients. As to adverse events arising from the off-label use of Zofran to treat morning sickness in pregnancy, the adverse event information in the files is incomplete, disorganized, scattered among irrelevant information, and different in content and form from the data housed in Argus. Counsel on both sides participated in a teleconference on February 20, 2018, but reached an impasse concerning production of the requested information.

III. ARGUMENT

A. PLAINTIFFS ARE ENTITLED TO PRODUCTION OF THE UNIQUELY ESSENTIAL DATABASE INFORMATION AS SEARCHABLE, FIELD-BASED DATA.

Given that the database contains unique information regarding Zofran-related pregnancy adverse events, and is critically important to analysis of the GSK's notice, the information is unquestionably relevant to Plaintiffs' claims.[3]

The database is also relevant to GSK's anticipated preemption defense. GSK has moved to dismiss Plaintiff's claims arguing, that there is "clear evidence" that the FDA would not have approved an update to the Zofran product label if GSK tried to update it. (GSK Motion, DE # 95 and 96) (relying on *Wyeth v. Levine*, 555 U.S. 555, 571 (2009)). This Court rejected GSK's motion because Plaintiffs "are entitled to an opportunity to develop the record as to how the FDA would have responded to a proposal had GSK submitted one," that is, a proposal by GSK to update its Zofran warnings about the risk of birth defects. Order (DE # 39, at p. 6).

The adverse event data is necessary discovery for Plaintiffs to oppose GSK's forthcoming summary judgment motion on preemption because it constitutes newly acquired safety information known to defendant that GSK should have reported to the FDA and should have prompted GSK to strengthen its representations to doctors and patients about the safety risks of Zofran use in pregnancy. *See Wyeth*, 555 U.S. at 569 (stating that if a drug manufacturer "submits adverse event information to FDA, and then later conducts a new analysis of data showing risks of a different type or of greater severity or frequency than did reports previously submitted to FDA, the sponsor

[3] *In re Tylenol (Acetaminophen) Mktg., Sales Practices & Prod. Liab. Litig.*, 181 F. Supp. 3d 278, 285–86 (E.D. Pa. 2016)) ("The purpose of recording AERs is to serve as a warning system or signaling system for drug manufacturers. Drug manufacturers are expected to report AERs to the FDA, which compiles them into a database. . . . Drug manufacturers are expected to take certain steps to ensure their products are safe for consumers. These steps are known as 'pharmacovigilance.' Reporting AERs to regulatory authorities is at the heart of pharmacovigilance. Whether the defendants undertook the appropriate steps to carry out their duty of pharmacovigilance is important to the plaintiff's failure-to-warn and design defect claims. With all this in mind, AERs would be admissible to show notice.").

meets the requirement for 'newly acquired information,'" triggering the company's ability to update its product warnings without prior FDA approval). Indeed, in *Wyeth*, the plaintiff depended on the manufacturer's adverse event information to oppose the preemption defense. *Id.* at 569-70.

GSK, appreciating the direct relevance of its adverse event information, acknowledged the relevance of the adverse event information when it served a request for admission on Plaintiffs about the topic. GSK RFA No. 5 ("Admit Plaintiffs have no evidence GSK has withheld from the FDA any spontaneous reports of birth defects associated with Zofran®, including, but not limited to, heart defects, orofacial defects, renal/urogenital defects, digestive tract defects, musculoskeletal defects, or lymphatic system defects.").[4] How can GSK reasonably suggest that it has not withheld adverse events from the FDA when it refuses discovery from the database where all of the adverse events reside?

B. PLAINTIFFS ALSO NEED ACCESS TO THE INFORMATION IN THE DATABASE TO INVESTIGATE RECENT EVIDENCE REVEALING THAT GSK INACCURATELY MAINTAINED THE ADVERSE EVENT DATABASE AS IT RELATES TO PREGNANCY OUTCOMES.

[redacted] Recent depositions [redacted] have, however, raised issues concerning GSK's identification, analyses and reporting of the AERs in the documents produced by GSK to date. A reasonable inference from GSK's inconsistent classification of the pregnancy-related adverse events is that GSK organizing the same adverse events into different buckets so

[4] Plaintiffs' response to this request still holds true today: "RESPONSE: Plaintiffs object to the timing of this request as premature. To date, Plaintiffs have not received all spontaneous reports of birth defects from GSK. As manufacturer of Zofran, GSK is best situated to receive and maintain all safety data regarding the safety of its product. GSK did not begin producing documents in response to Plaintiffs' requests until December 20, 2016, and the vast majority of GSK's voluntary INDA/NDA production concerned Zofran use for Cancer treatment and Post-Operative Nausea, the drug's only approved indications, and not Zofran use for treating morning sickness. GSK is expected to make full and complete production of adverse events in discovery, including spontaneous reports of birth defects. Plaintiffs reserve the right to supplement their response as Defendants produce discovery relevant to this Request."

that no buckets so that no bucket had so many that the FDA or the public would detect a safety signal. For example, [redacted]

Given that recent depositions reveal that GSK organized and reported birth defects inconsistently and in a manner prone to inaccuracy, Plaintiffs need discovery from the database to determine the correctness and completeness of GSK's identification, evaluation and reporting of all relevant adverse events that GSK received since the international birthdate of the drug. [redacted] Resolving these issues raised by the depositions must begin with a searchable, usable information extraction from

the safety database. *See* Ex. 9, *In re Neurontin*, Order, No. 1:04-cv-06704-JSR, (S.D. N.Y. Feb. 22, 2005) ("Plaintiffs reasonably need access to multiple databases in order to ascertain whether defendants were accurately maintaining their adverse event database, as well as to determine whether defendants marketed the drug for uses not approved by federal regulators.").

C. ADVERSE EVENT DATABASES ARE ROUTINELY DISCLOSED IN PHARMACEUTICAL LITIGATION.

Due to their importance and utility, adverse event databases like the Argus database are routinely disclosed in pharmaceutical litigation. *See Kilpatrick v. Breg*, 2009 WL 64358, at *4-5 (S.D. Fla. Jan. 9, 2009) (noting that adverse event databases are "typically a fundamental document in similar [pharmaceutical] cases"); *In re Seroquel Prods. Liab. Litig.*, 244 F.R.D. 650, 660-61 (M.D. Fla. 2007) (sanctioning party that failed to produce usable or reasonably accessible electronic documents and noting that although parties can have reasonable disputes about the scope of discovery, "such disputes should not entail endless wrangling about simply identifying what records exist and determining their format"); *Madden v. Wyeth*, 2006 WL 568015, at *1-2 (N.D. Tex. Mar. 7, 2006) (compelling production of searchable adverse event database); *Jannx Med. Sys,, Inc. v. The Methodist Hosp., Inc.*, 2010 WL 478275 (N.D. Ind. Nov. 17, 2010).

In *Jannx*, the movants argued that production of .pdf format documents in response to a demand to produce a searchable database was improper because "the information contained in the[] documents is normally maintained in a fully searchable and manipulable electronic format, and that providing them only in .pdf form destroys [the opposing party's] ability to effectively search or analyze the information." *Jannx*, 2010 WL 478275 at *3. The withholding party argued that the .pdf production was sufficient because the requesting party did not specify the form in which the documents were to be produced. *Id.* at *4. The court sided with the movants, and ordered a searchable database produced, citing the Advisory Committee Notes to Rule 34, which requires

parties to produce information in a way that is searchable especially where, as here, the party "ordinarily maintains the information it is producing in a way that makes it searchable by electronic means." *Id.* The court sided with the movants, and ordered a searchable database produced:

> [T]he option to produce in a reasonably usable form does not mean that a responding party is free to convert electronically stored information from the form in which it is ordinarily maintained to a different form that makes it more difficult or burdensome for the requesting party to use the information efficiently in the litigation... It appears that this is exactly what Plaintiff has done in this case. Therefore, the Court grants [the] Motion to Compel... Plaintiff [must] produce responsive information in an electronic database format that allows the information to be reasonably usable, i.e., fully searchable and manipulable, with the connections between data fields intact.

Id. at *12 (citations omitted). The same reasoning applies here. GSK has a critical file that is ordinarily maintained as a useable, searchable electronic document. Production of derivative documents drawn from select searches conducted using the database is insufficient. Courts in these cases properly recognized that it is only fair for both sides to have access to the same robust, searchable dataset provided by the database.

D. GSK Is Not Unduly Burdened by Having to Produce Adverse Event Information from the Database.

During the recent meet and confer, GSK did not dispute the relevance of the adverse event information, and the only basis GSK counsel stated for not producing the requested information was claimed burden based on having to review and redact information before it is produced. GSK's anticipated claim of burden fails for several reasons. First, [redacted] None of this information, not even the narrative description of the adverse events, contains personal identifying information that needs to be redacted. [redacted]

[redacted] Therefore, the adverse event information can be exported from Argus for Plaintiffs without any need for redaction. As GSK already maintains the database in the ordinary course of business, it can export the data easily.

Second, the volume of the requested data is limited, and none of it is privileged. Therefore, the burden of producing would be limited, even if some of it contained personal identifying information that needed to be redacted. *See, e.g., In re Incretin-Based Therapies Prod. Liab. Litig.*, 2017 WL 6030735, at *2 (9th Cir. Dec. 6, 2017) (concluding that the trial court abused its discretion in denying plaintiffs' motion to compel production of information from a drug company's adverse event database, notwithstanding the "relatively modest task of redacting identifying information of patients and reporters").

Third, GSK, Plaintiffs and the Court already anticipated the discovery of the adverse event information and gave GSK the ability to redact patient identifying information in adverse event information. This provision was included at GSK's request. GSK's contention that the redacting is too burdensome is inconsistent with the fact that GSK fought for the right to do it. *See* MDL Order No. 13 (DE # 242), at p. 14 Para. 12(d).[5] In short, there is no unfair burden to GSK in having to produce the AER information. *See United States ex rel. Liotine v. CDW Gov't Inc.*, 2011 WL 1576555, at *3 (S.D. Ill. Apr. 26, 2011) (granting order to compel production even though defendant had already produced hardcopy spreadsheets, ruling that "to the extent the information sought . . . is available in an electronically-stored format, such as a database, [defendant] is ORDERED to produce such information in the same format or in a similarly manipulable format").

[5] "(d) Permissible Redactions. In order to protect against unauthorized disclosure of Confidential Information, a ***defendant may redact portions of a document***, but only to the extent reasonably necessary to prevent disclosure of the following categories of Confidential Information: (i) names and information that would identify clinical trial subjects or ***patients referred to in adverse reaction reports, product experience reports, and consumer complaints***, except for patient identifiers (e.g., randomly assigned numeric or alphanumeric identifiers) that do not reveal the patient's identity, date of birth, address or other personal identifying information . . . ."

Fourth, the adverse event data contained in the database cannot be obtained from an alternative source. To the contrary, creating a document or documents as comprehensive and useful as the database information would be vastly more expensive and burdensome than simply producing an extract of the database. Given that a data extraction would be simple for GSK to produce, any burden of the production is substantially outweighed by the benefit. Searchable, field-based data is critically important to analyses of the safety signal posed by Zofran – a fundamental issue in the litigation. Faced with the importance of such uniquely essential information, compelling production of the database would be proper even if it entailed substantial burden. The fact that an extract from database can easily be reproduced weighs heavily in favor of production. *See CDW Gov't Inc.*, 2011 WL 1576555, at *3.

Thus, production of the data extraction would not be duplicative because GSK has never produced the database. While it is true that limited adverse event information appears sporadically among the voluminous IND/NDA files, the safety database is the primary and the only comprehensive and usable source of the adverse event data. The safety database allows the adverse event information to be exported to a sortable Excel spreadsheet with clicks of a button. The IND/NDA files are more than 538,000 pages of .tiff files with adverse event information fragmented among other irrelevant information. It cannot be relied upon to compile a comprehensive list of relevant adverse events.

The IND/NDA also files contain only those adverse events that GSK reported to the FDA. By contrast, the safety database contains all adverse events known to GSK, regardless of whether GSK reported them to the FDA. When GSK performed its safety evaluations of Zofran after it was sued in this litigation, it relied on the Argus database, not the IND/NDA files. Therefore, the

requested extraction is not duplicative of the IND/NDA files. Plaintiffs need to have the ability, as GSK has, to compile and evaluate all of this important adverse event data.

IV. CONCLUSION

Plaintiffs respectfully request this Court enter an order directing GSK to fully and completely produce the requested information from the Argus database.

Dated: February 23, 2018

Respectfully submitted,

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CERTIFICATE OF SERVICE

I, Robert K. Jenner, hereby certify that on this 23rd day of February, 2018, I electronically filed the foregoing Motion to Compel, using the CM/ECF system and thereby delivered by electronic means to all registered participants as identified on the Notice of Electronic Filing.

/s/ *Robert K. Jenner*
Robert K. Jenner