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Appendix A

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 18-1010

IN RE: AVANDIA MARKETING, SALES AND PRODUCTS LIABILITY LITIGATION

UFCW Local 1776 and participating Employers Health and Welfare Fund; J.B. Hunt Transport Services, Inc.,

Appellants.

Argued: Mar. 6, 2019
Filed: Dec. 17, 2019

Before: SMITH, *Chief Judge*, AMBRO and RESTREPO, *Circuit Judges*.

OPINION

RESTREPO, *Circuit Judge*.

Plaintiffs, two health benefit plans ("Plans"), appeal the District Court's grant of summary judgment in favor of Defendant, GlaxoSmithKline LLC ("GSK"), the manufacturer of the prescription drug Avandia. The Plans brought suit against GSK under various state consumer-protection laws and the Racketeer Influenced and Corrupt Organizations Act,

18 U.S.C. ch. 96 ("RICO"), based on, among other things, GSK's marketing of Avandia. The District Court granted summary judgment in favor of GSK on the Plans' claims, finding, in relevant part, that (i) the Plans' state-law consumer-protection claims were preempted by the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. ch. 9 ("FDCA"); (ii) the Plans had failed to identify a sufficient "enterprise" for purposes of RICO; and (iii) the Plans' arguments related to GSK's alleged attempts to market Avandia as providing cardiovascular "benefits" were "belated." The Plans assert that the District Court erred in granting summary judgment, and we agree.

Applying the guidance recently provided by the Supreme Court in *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019), we hold that the Plans' state-law consumer-protection claims are not preempted by the FDCA. With respect to their RICO claims, the Plans should have been given the opportunity to seek discovery prior to the District Court's granting summary judgment on such claims. Further, from the inception of this litigation, the Plans' claims have centered on GSK's marketing of Avandia as providing superior cardiovascular outcomes—in other words, cardiovascular *benefits*—as compared to other forms of treatment, and therefore, the District Court's refusal to consider the Plans' "benefits" arguments was in error because those arguments were timely raised.

Therefore, for the reasons that follow, we will reverse in part and vacate in part the order of the District Court granting summary judgment in favor of

GSK, and we will remand to the District Court for further proceedings consistent with this opinion.

I.

In May 1999, the Food and Drug Administration ("FDA") approved Avandia (Rosiglitazone), a drug developed by GSK, for the treatment of type-2 diabetes. Prior to the development of Avandia and similar drugs, physicians primarily treated type-2 diabetes by prescribing metformin and/or sulfonylureas. GSK, however, marketed Avandia at a much higher price point than metformin and sulfonylureas: a one-month supply of Avandia cost approximately $220, approximately $140 of which typically was covered by patients' health benefit plans, whereas a one-month supply of metformin or sulfonylureas cost approximately $50, about $45 of which typically was covered by patients' health benefit plans.

Despite this cost differential, health benefit plans—including the Plans—placed Avandia on their formularies as a "covered" drug. The Plans, for example, determined that it was advantageous to cover the cost of Avandia because GSK allegedly marketed Avandia as being capable of both controlling a patient's blood sugar levels *and* reducing cardiovascular risk, the latter of which is particularly pertinent to type-2 diabetes patients, 65% of whom suffer fatal cardiovascular-related illnesses or complications. Metformin and sulfonylureas—the drugs that constituted the "standard of care" for type-2 diabetes prior to Avandia's development—did not decrease cardiovascular risk, and therefore, according to the Plans, GSK presented Avandia as a cost-

effective alternative to those drugs. As a result, health benefit plans covered a large portion of the expenses related to patients' prescriptions for Avandia, resulting in approximately $2.2 billion in U.S. sales in 2006 alone.

In 2006, however, concerns arose that Avandia may in fact *increase* certain cardiac risks. In August of that year, GSK submitted a Prior Approval Supplement to the FDA, in which GSK sought approval to add information to Avandia's label regarding the results of a recent meta-analysis of various clinical trials. The meta-analysis, "ICT-42," demonstrated that use of Avandia was associated with a statistically significant increase in myocardial ischemic events—events during which the heart does not receive adequate oxygen because blood flow to it is reduced. In May 2007, GSK submitted an update to its Prior Approval Supplement, offering a new formulation of its proposed warning with respect to myocardial ischemic events that would, among other things, make the warning more prominent and clear.

Three days after GSK submitted the update to its Prior Approval Supplement, the *New England Journal of Medicine* published a study authored by Dr. Steve Nissen regarding Avandia ("Nissen Study"), in which Dr. Nissen concluded that Avandia "was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance." J. App. 1064. Following the release of the Nissen Study, a representative of GSK held a telephone conversation with an official at the FDA regarding progress on the FDA's review of the

Prior Approval Supplement. According to GSK's representative, who wrote a memo memorializing the details of the conversation, the FDA official advised that another official within the FDA was "calling for withdrawal of [the] approval" of Avandia, and thus, it was difficult for FDA officials to agree on labeling language for Avandia. Sealed App. 655-56. GSK's representative then proposed implementing the labelling changes with respect to myocardial ischemic events through the Changes Being Effected ("CBE") process, which permits a drug manufacturer to implement a change to its label *prior* to approval of such label by the FDA. The FDA official "strongly advised against proceeding" through the CBE process, stating that doing so "may give legitimacy to Dr. Nissen's data" and "will make people think that GSK must have other information." *Id.* at 656. The FDA official concluded the conversation by reminding the GSK representative that he "knew the regulations," which state that the drug manufacturer is ultimately responsible for making the decision to pursue a labelling change through the CBE process. *Id.*

On June 8, 2007, the FDA sent a letter ("Letter") to GSK regarding the Prior Approval Supplement. In the Letter, the FDA stated that it had "reviewed the data provided [by GSK in its Prior Approval Supplement] and f[ou]nd [that] the information presented [was] inadequate" and that, therefore, the Prior Approval Supplement was "not approvable." *Id.* at 660. The FDA stated that it had "concluded that the pooled data require[d] further analysis to adequately convey the potential risk for increased cardiac ischemia associated" with use of Avandia. In particular, the FDA stated that it had "identified

certain subgroups of patients . . . that may be particularly vulnerable to experiencing an ischemic event" while using Avandia. *Id.* The FDA then directed GSK to provide additional information "to address the deficiency" in the Prior Approval Supplement, including "[d]ata from studies included in a meta-analysis performed by Dr. Steven Nissen published in the *New England Journal of Medicine* that were not included in [GSK's] pooled analysis," as well as data from various other clinical trials. *Id.* at 661.

The FDA expressed its view that the "potential risk of increased cardiac ischemia [was] a significant finding that may impact a large proportion of patients with type[-]2 diabetes," and as a result, the FDA scheduled a joint meeting of two FDA advisory committees ("Joint Meeting") "to discuss the findings from th[e Prior Approval Supplement] submission, additional data recently requested, and accruing information from ongoing clinical trials" of Avandia. *Id.* The FDA stated that the "outcome of th[e Joint M]eeting w[ould] be particularly germane to any labeling or other regulatory action needed for [Avandia] and should be factored into any resubmission to address the above deficiencies." *Id.*

Later in 2007, the FDA required GSK to implement various changes to Avandia's label. Subsequent to issuing the Letter, the FDA directed GSK to add a black-box warning to Avandia's label with respect to the risk of congestive heart failure that (i) advised physicians and patients that Avandia "cause[s] or exacerbate[s] congestive heart failure in some patients," (ii) instructed physicians to "observe

patients [taking Avandia] carefully for signs and symptoms of heart failure," and (iii) warned patients with certain heart conditions not to take Avandia. J. App. 708. Following the Joint Meeting, the FDA additionally directed GSK to add a black-box warning to Avandia's label with respect to the risk of myocardial ischemic events, advising physicians and patients that a "meta-analysis of 42 clinical studies . . . , most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction" and that "[t]hree other studies . . . , comparing Avandia to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk." *Id.* at 743. The FDA also required GSK to include a longer explanation of the data with respect to the risk of myocardial ischemic events elsewhere on Avandia's label.

Approximately three years later, in 2011, the FDA again directed GSK to revise the warning on Avandia's label, including the black-box warning, with respect to the risk of myocardial ischemic events. By that time, GSK had completed fifty-two (52) clinical trials. The FDA's required warning advised physicians and patients that "[a] meta-analysis of 52 clinical trials . . . , most of which compared Avandia to placebo, showed Avandia to be associated with a statistically significant increased risk of myocardial infraction" and that "[b]ecause of the potential increased risk of myocardial infarction, Avandia [was] available only through a restricted distribution program." *Id.* at 786. In a memorandum accompanying its direction to implement the labelling changes, the FDA noted that the "evidence pointing to

a cardiovascular ischemic risk with [Avandia] is not robust or consistent," but that "[n]evertheless, there are multiple signals of concern, from varied sources of data, without reliable evidence that refutes them." *Id.* at 1397.

In November 2013, however, following the readjudication of a particular clinical trial ("RECORD Trial"), the FDA concluded that while "[o]ne cannot entirely discount the results of the meta-analysis" that associated Avandia with a statistically significant increased risk of myocardial ischemic events, "the totality of the available evidence does not support a marked signal of cardiovascular harm." *Id.* at 1656. The FDA determined that, following the readjudication of the RECORD Trial, Avandia "does not appear to be associated with an increased risk of major adverse cardiovascular events or death, although a small amount of residual uncertainty remains." *Id.* at 1657. The FDA directed GSK to revise Avandia's label "to reflect the current level of knowledge regarding [its] cardiovascular risk." *Id.*

In 2014, GSK revised Avandia's label pursuant to the FDA's direction. GSK removed information regarding the restricted-distribution program from the label and information regarding the risk of myocardial ischemic events *from the black-box warning only*. The revised label, however, continued to warn physicians and patients elsewhere on the label that "[i]n a meta-analysis of 52 double-blind, randomized, controlled clinical trials . . . , a statistically significant increased risk of myocardial infarction with Avandia versus pooled comparators was observed"—this information simply was no longer

included in the black-box warning, but this warning nonetheless appeared elsewhere on the label. *Id.* at 829. Avandia's label continued to include a black-box warning that (i) advised physicians and patients that Avandia "cause[s] or exacerbate[s] congestive heart failure in some patients," (ii) instructed physicians to "observe patients [taking Avandia] carefully for signs and symptoms of heart failure," and (iii) warned patients with certain heart conditions not to take Avandia. *Id.* at 825. These warnings remain on Avandia's label to this day.

II.

The Plans brought suit alleging that GSK falsely marketed Avandia and concealed data with respect to its potential cardiovascular risks and side effects, thereby violating RICO and various state consumer-protection laws. The Plans assert that they would not have placed Avandia on their formularies if GSK had disclosed the cardiovascular risks that are in fact associated with Avandia. In other words, the Plans would not have covered the cost of Avandia, which was considerably more expensive than alternatives, if they had known that Avandia not only did not reduce cardiovascular risk in type-2 diabetes patients but also *increased* cardiovascular risk as compared to those alternatives.

The Plans first filed suit in May 2010, and their cases subsequently were consolidated in a multi-district litigation case, which also included consumer and personal-injury suits filed by other plaintiffs. In November 2010, GSK filed a motion to dismiss the Plans' complaints, arguing that the Plans lacked standing to bring claims under RICO. In October 2013,

the District Court denied GSK's motion, and, in October 2015, we affirmed the decision of the District Court on an interlocutory appeal. *See In re Avandia Mktg., Sales Practices & Prod. Liab. Litig. (Avandia I)*, 804 F.3d 633, 646 (3d Cir. 2015).

In May 2016, GSK filed a motion for summary judgment. It argued that it was entitled to summary judgment because, among other things, the Plans' state-law consumer-protection claims were preempted by the FDCA and the Plans had failed to identify a distinct "enterprise" for purposes of RICO. The Plans opposed the motion.

In December 2017, the District Court granted summary judgment in favor of GSK. First, the District Court refused to consider the Plans' arguments that GSK falsely marketed Avandia as providing cardiovascular *benefits* in comparison to alternatives because such arguments were "belated." Unsealed App. 4. The District Court noted that the Plans "seemed to [have] shift[ed] their allegations to focus on Avandia's benefits, rather than the risks," and stated that it only would "address GSK's motion for summary judgment as to [the Plans'] state law claims on cardiovascular *risk*." *Id.* at 3-4. It stated that it would not "entertain" any of the Plans' "benefits" arguments "at th[at] juncture" due to their "belated" nature. *Id.* at 4.

Second, the District Court found that the Plans' state-law consumer-protection claims were preempted by the FDCA under the doctrine of "impossibility" preemption. It found that three separate facts established "clear evidence" that the FDA would not have approved a change to Avandia's label with

respect to cardiovascular risks: (a) "the FDA rejected GSK's [Prior Approval Supplement]," (b) "the FDA advised against using the CBE process to unilaterally change the label," and (c) "the FDA ultimately concluded that there was no increased cardiovascular risk with Avandia use in relation to comparators." *Id.* at 24. With respect to the Prior Approval Supplement, the District Court found that the "rejection of GSK's proposed label on the basis of inconclusive data, considered with other evidence, constitutes clear evidence that the FDA would not have approved the label change . . . , particularly where . . . the FDA wanted to conduct further review of the data." *Id.* at 24-25. Regarding the FDA's advising against using the CBE process, the District Court found that an FDA representative's statements—that she "strongly advised" against using the CBE process and that initializing that process would be "looked on with suspicion" and would "pull the rug out" from the FDA's then-current plans for reviewing Avandia's label—"shows that the FDA advised against using [the] CBE [process] to make the proposed label change prior to November 2007." *Id.* at 25. Finally, the District Court placed an emphasis on the FDA's "remov[al of] the black[-]box warning and restricted[-]access information from Avandia's label," as well as the FDA's "current conclusion that a link between Avandia use and increased cardiovascular risk does not exist." *Id.* at 26. In summary, the District Court found that the "FDA would not have approved of a warning for increased cardiovascular risk in Avandia versus competitors earlier than 2007 . . . and would not approve one now." *Id.*

Third, the District Court concluded that the Plans failed to identify an "enterprise" that satisfies the "distinctiveness" requirement of RICO. Specifically, it determined that "GSK was conducting its own business in selling Avandia, and thus . . . GSK is both the person and the enterprise." *Id.* at 16. Because "RICO liability 'depends on showing that the defendants conducted or participated in the conduct of the *enterprise's* affairs, not just their *own* affairs,'" the District Court found that the Plans had not adequately alleged that an "enterprise" existed because they merely alleged that the "enterprise" in this case consisted of "GSK and its agents." *Id.* (emphasis in original) (quoting *Reeves v. Ernst & Young*, 507 U.S. 170, 185 (1993)).

The Plans timely appealed. They also appealed two orders of the District Court that maintained the vast majority of the summary-judgement record under seal. We considered that appeal in *In re Avandia Mktg., Sales Practices and Prods. Liab. Litig. (Avandia II)*, 924 F.3d 662, 680 (3d Cir. 2019), in which we vacated the District Court's sealing orders.

III.

The District Court had jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1332(d), and we have jurisdiction under 28 U.S.C. § 1291. We exercise plenary review over a district court's grant of summary judgment. *Reedy v. Evanson*, 615 F.3d 197, 210 (3d Cir. 2010). When a district court grants summary judgment without considering a declaration filed by the nonmoving party under Federal Rule of Civil Procedure 56(d), however, we review for abuse of discretion the district court's decision to disregard the

Rule 56(d) declaration. *Shelton v. Bledsoe*, 775 F.3d 554, 568 (3d Cir. 2015).

A.

With the benefit of the Supreme Court's recent guidance in *Merck*, which was decided following oral argument in this case and well after the District Court's issuance of its memorandum opinion,[1] we hold that the Plans' state-law consumer-protection claims are not preempted by the FCDA, and we therefore will reverse the District Court's order granting summary judgment in favor of GSK on such claims.

In *Wyeth v. Levine*, 555 U.S. 555, 570-71 (2009), the Supreme Court recognized that "it has remained a central premise of federal drug regulation that the manufacturer [of a pharmaceutical] bears responsibility for the content of its label at all times" and that the manufacturer "is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." Thus, when it "bec[o]me[s] apparent" that a drug poses a certain risk to the health and safety of persons taking it, the manufacturer of the drug "ha[s] a duty to provide a warning that adequately describe[s] that risk." *Id.* at 571. The manufacturer may warn persons of that risk by altering the drug's label through the CBE process, which "permit[s] it to provide such a warning before receiving the FDA's approval." *Id.*

[1] We subsequently ordered the parties to submit supplemental letter briefs discussing *Merck*'s effect, if any, on the disposition of this case.

Under the FDCA, however, the FDA "retains authority to reject labeling changes made pursuant to the CBE regulation in its review of the manufacturer's supplemental application, just as it retains such authority in reviewing all supplemental applications." *Id.* Therein lies the conflict that may give rise to impossibility preemption: even though a drug manufacturer has the responsibility under state consumer-protection laws to accurately label a drug and may change the label pursuant to the CBE process prior to receiving approval from the FDA, it may reject a label change at any time if it considers the drug to be "mislabeled" under the FDCA. Thus, a situation may occur in which a drug company seeks to change its label to add a warning that it believes is required by state consumer-protection laws, but the FDA considers the drug "mislabeled" under the FDCA in light of the new warning that was added to the label. In that situation, it would be impossible to comply with both state and federal law. In resolving this conflict, the Supreme Court struck a balance in *Wyeth*, holding that the FDCA does not preempt state-law consumer-protection claims regarding the labeling of a drug "absent clear evidence that the FDA would not have approved a change to [the drug]'s label." *Id.*

After we indicated in *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, 852 F.3d 268, 284 (3d Cir. 2017), *vacated*, *Merck*, 139 S. Ct. 1668, that it would be helpful for the Supreme Court to "clarif[y] or buil[d] out the doctrine" espoused in *Wyeth*, the Supreme Court provided such interpretive guidance in *Merck*. "[C]lear evidence," as used in *Wyeth*'s core holding, means "evidence that shows the court that the drug manufacturer fully informed the FDA of the

justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning." 139 S. Ct. at 1672. Thus, to "show[] that federal law prohibited [a] drug manufacturer from adding a warning that would satisfy state law," the drug manufacturer must demonstrate that (1) "it fully informed the FDA of the justifications for the warning required by state law" and (2) "the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Id.* at 1678.

GSK has failed to satisfy either prong of *Merck*'s two-prong test, and it therefore is not "entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). First, GSK has not shown that "it fully informed the FDA of the justifications for the warning required by state law." *Merck*, 139 S. Ct. at 1678. In the Letter, the FDA itself stated that it had "reviewed the data provided [by GSK] and f[ou]nd [that] the information presented is *inadequate*." Sealed App. 660 (emphasis added). Further, the FDA indicated that GSK needed to submit various data and information "in order to address the *deficiency* of this application." *Id.* at 661. Thus, GSK cannot demonstrate that the FDA was "fully informed . . . of the justifications for the warning," *Merck*, 139 S. Ct. at 1678, because the FDA itself stated that it was "inadequate[ly]" informed of the justifications for the warning, Sealed App. 660.

GSK argues that it "fully informed" the FDA because GSK (1) provided all "material" information to the FDA and (2) did not have access to the

information that the FDA requested until *after* the latter issued the Letter, but these arguments are unavailing. GSK concedes that the FDA requested additional data and information in the Letter, yet GSK argues that none of the data and information that the FDA *actually requested* in the Letter was "material" to its proposed warning on cardiac risk, and that therefore, the FDA was "fully informed" for purposes of *Merck*. This argument turns the regulatory regime on its head. The FDA, not GSK, is the entity with power to approve or refuse a change to a drug's label, and in making such a decision, it has the statutory authority to conclude that the data and tests submitted by a manufacturer were not "adequate" or that there is "insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling." 21 C.F.R. §§ 314.125(b)(2), (4). GSK is not the arbiter of which data and information is or is not "material" to the FDA's decision to approve or reject a change to a drug's label—the FDA, and only the FDA, can determine what information is "material" to *its own* decision to approve or reject a labelling change.

Additionally, by arguing that it did not have access to the FDA's requested data and information until after the FDA's issuance of the Letter, GSK undermines its own argument that the FDA was "fully informed." *Merck* noted that "a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." 139 S. Ct. at 1679. Thus we read *Merck* as holding that, in order to prove impossibility preemption, the drug

manufacturer must show that the "FDA would not approve changing the drug's label" and that the FDA was "fully informed . . . of the justifications for the [proposed] warning" *at the time that the FDA rejected the proposed warning*. *Id.* at 1678. In other words, the upshot of *Merck* is that a drug manufacturer must show that the FDA made a fully informed decision to reject a change to a drug's label in order to establish the "demanding defense" of impossibility preemption. *Id.* at 1678. If the question of whether the FDA was "fully informed" was not tethered in time to the question of whether the FDA indeed rejected the proposed warning, the "fully informed" prong of the test espoused in *Merck* would be rendered superfluous.

Thus, if GSK wishes to rely on the Letter as proof that the FDA rejected its proposed label change, it must also demonstrate that the FDA possessed all the information it deemed necessary to decide whether to approve or reject the proposed warning *at the time it issued the Letter*. By arguing that it did not have the FDA's requested data and information until *after* the FDA issued its letter, however, GSK is, in effect, conceding that the FDA was not "fully informed" at the time of the Letter's issuance. For that reason, among the others outlined above, GSK cannot satisfy the first prong of the test espoused in *Merck*.

Second, GSK cannot show that the "FDA . . . informed [it] that the FDA would not approve changing the drug's label to include [the relevant] warning." *Id.* at 1678. GSK directs the Court's attention to the Letter as proof that the FDA rejected the proposed warning. The Letter indeed stated that GSK's Prior Approval Supplement for a

label change was "not approvable," but the FDA indicated that this was so because the "information presented [by GSK wa]s inadequate." Sealed App. 660. The FDA then required GSK to "amend the supplemental application," stating that "[a]ny amendment should respond to all the *deficiencies* listed" in the Letter. *Id.* at 661 (emphasis added). Thus, it is clear from the very text of the Letter that the FDA did not consider GSK's Prior Approval Supplement "not approvable" because it was unconvinced of the need for a strong warning on myocardial ischemic events; rather, the FDA considered the Prior Approval Supplement "not approvable" because it contained various "deficiencies" that the FDA required GSK to ameliorate prior to the FDA's making a final determination. At most, the Letter indicates that it is *possible* that the FDA could have rejected the label change *after* receiving the various data and information it requested from GSK, but as the Supreme Court has reiterated, the "possibility of impossibility [is] not enough." *Merck*, 139 S. Ct. at 1678 (alteration in original) (quoting *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 625 n.8 (2011)). We nevertheless need not speculate regarding the *possibility* that the FDA would have rejected the proposed warning upon the receipt of the requested data and information because it indeed *ordered* GSK to include various warnings regarding cardiac risks on Avandia's label shorty after issuing the Letter, which alone undermines GSK's position that the Letter represents a rejection of its proposed warning.

Finally, we are not persuaded by any of GSK's arguments that the Plans' claims are preempted

because GSK allegedly was unable to avail itself of the CBE process for various reasons. GSK primarily argues that it could not use the CBE process to introduce a warning on ischemic risks prior to mid-2006, when it submitted its Prior Approval Supplement. GSK reasons that ICT-42 served as the basis for its belief that an ischemic-risk warning should be included on the label, and because that study was completed in mid-2006, it did not have the "newly acquired information" necessary to make a labeling change prior to that time. This argument, however, is undermined by GSK's own admissions. For example, GSK itself described the results of "ICT-37," a meta-analysis completed a year earlier in August 2005, as "generally similar" to ICT-42, and GSK stated that "[a]ny numerical differences [between the meta-analyses] were not clinically significant." Sealed App. 861. Thus, at the very least, it appears that GSK could have used the CBE process to add an ischemic-risk warning as early as August 2005 because, by GSK's own admission, ICT-37 and ICT-42 indicated similar results and had clinically insignificant differences.[2] Further, GSK cannot rely on its informal phone conversations with an FDA official to claim that it could not pursue a label change through the CBE process, nor can GSK rely on the stock language at the end of the Letter, which advised GSK that Avandia "may be considered to be misbranded under the [FDCA] if it is marketed with the[proposed] changes before approval of this

[2] We take no position with respect to whether GSK could have used the CBE process, or otherwise sought to change Avandia's label, to add an ischemic-risk warning prior to August 2005.

supplemental application." *Id.* at 661. An informal phone conversation with an FDA official is not an "agency action taken pursuant to the FDA's congressionally delegated authority," *Merck*, 139 S. Ct. at 1679, and the stock language at the end of the Letter is a simple statement of the law: if a manufacturer makes a label change pursuant to the CBE process (i.e., without seeking the prior approval of the FDA), the manufacturer *always* runs the risk that the FDA will later reject the label change and consider the drug as "mislabeled," *see* 21 C.F.R. § 314.70(c)(7). Finally, GSK's argument that it could not implement a black-box warning through the CBE process is a red herring—the Plans are not arguing that GSK should have added the black box *itself* through the CBE process, but rather that GSK should have added the *content* of the black-box warning *anywhere* on the label.

GSK thus has failed to demonstrate that the Plans' state-law consumer-protection claims are preempted by the FDCA, and GSK therefore is not entitled to summary judgment on those grounds. Therefore, we will reverse the order of the District Court granting summary judgment in favor of GSK on the Plans' state-law consumer-protection claims.

B.

The District Court erred in granting summary judgment on the Plans' RICO claims without giving the Plans the benefit of discovery on those claims.

"[A] Court 'is obligated to give a party opposing summary judgment an adequate opportunity to obtain discovery.'" *Doe v. Abington Friends Sch.*, 480 F.3d 252, 257 (3d Cir. 2007) (quoting *Dowling v. City of*

Philadelphia, 855 F.2d 136, 139 (3d Cir. 1988)). "If discovery is incomplete, a district court is rarely justified in granting summary judgment, unless the discovery request pertains to facts that are not material to the moving party's entitlement to judgment as a matter of law." *Shelton*, 775 F.3d at 568.

Rule 56(d) provides that "[i]f a nonmovant shows by affidavit or declaration that, for specified reasons, it cannot present facts essential to justify its opposition, the court may: (1) defer considering the motion or deny it; (2) allow time to obtain affidavits or declarations or to take discovery; or (3) issue any other appropriate order." Fed. R. Civ. P. 56(d). "[D]istrict courts usually grant properly filed requests for discovery under Rule 56(d) 'as a matter of course' . . . ." *Shelton*, 775 F.3d at 568 (quoting *Murphy v. Millennium Radio Grp. LLC*, 650 F.3d 295, 309-10 (3d Cir. 2011)). "This is particularly true when there are discovery requests outstanding or where relevant facts are under control of the party moving for summary judgment." *Id.* A district court abuses its discretion when it grants summary judgment in favor of the moving party "without even considering" a Rule 56(d) declaration filed by the nonmoving party. *See id.*

The Plans never received discovery related to their RICO claims, including with respect to whether an "enterprise" existed for purposes of RICO, and thus when GSK moved for summary judgment on the Plans' RICO claims, the Plans submitted a detailed Rule 56(d) declaration regarding the lack of discovery on the issues related to RICO. *See* J. App. 2195-2198. They subsequently filed a supplemental Rule 56(d)

declaration, further elaborating on their need for discovery on RICO-related issues. *See id.* at 2272-76.

The District Court granted summary judgment in favor of GSK on the Plans' RICO claims without considering their Rule 56(d) declaration and their supplemental Rule 56(d) declaration. This was an abuse of discretion, especially as the District Court granted summary judgment on the ground that the Plans could not prove the existence of an "enterprise," information related to which is "under control of the party moving for summary judgment"—in this case, GSK.[3] *Shelton*, 775 F.3d at 568. We therefore vacate the District Court's order granting summary judgment in favor of GSK on the Plans' RICO claims, and we remand to the District Court to give proper consideration to the Plans' Rule 56(d) declarations.

IV.

Finally, we note that, on remand, the District Court must consider the Plans' arguments that GSK marketed Avandia as providing cardiovascular *benefits*. These arguments and claims are not "belated"; the Plans have pursued this line of argument since the outset of this litigation. In the Plans' complaint itself, the Plans alleged that they "rel[ied] upon[GSK]'s promises of superior treatment *and better cardiovascular outcomes* compared with the older diabetes drugs" in determining that it was worth the increased cost to cover Avandia. J. App. 1273. They

[3] We refuse to construe the District Court's grant of summary judgment in favor of GSK on the Plans' RICO claims as a dismissal on the pleadings pursuant to Rule 12(c), particularly because the Plans' RICO claims previously survived a Rule 12(b)(6) motion to dismiss. *See Avandia I*, 804 F.3d at 646.

alleged that "better cardiovascular outcomes" were a crucial part of GSK's alleged fraudulent marketing: "[t]he notion that Avandia would actually lower diabetics' cardiovascular risk was critical to Avandia's marketing" because GSK "needed justification for the steep price difference between Avandia and the older established diabetes drugs." *Id.* at 1291. While a portion of the Plans' claims center on the assertion that GSK should have disclosed on its label the true nature of the increased cardiovascular *risk* that was presented by Avandia as compared to cheaper alternatives, the increased risk is only relevant to the

Plans' claims insofar as the Plans make the following argument: GSK failed to warn of Avandia's true cardiovascular *risk*, and thus, GSK was continuing—by omission—to promote Avandia as capable of *lowering* patients' cardiovascular risk, and GSK thereby continued to induce the Plans to cover the cost of Avandia based on this perceived "benefit" of lowering cardiovascular risk. *Id.* at 1316. In short, the Plans have never argued that GSK promoted Avandia as capable of actually *improving* patients' cardiovascular health, but rather as capable of *lowering cardiovascular risk* when compared to cheaper alternatives, which indeed is a "benefit."

Because the Plans have raised, throughout these proceedings, arguments that GSK marketed Avandia as providing cardiovascular *benefits*, it was error for the District Court to refuse to consider those arguments. *See, e.g.*, *Hillman v. Resolution Tr. Corp.*, 66 F.3d 141, 144 (7th Cir. 1995). Therefore, on remand, the District Court needs to give proper consideration to these arguments.

V.

For the reasons stated above, we will reverse the order of the District Court granting summary judgment in favor of GSK on the Plans' state-law consumer-protection claims, vacate the order of the District Court granting summary judgment in favor of GSK on the Plans' RICO claims, and remand to it for proceedings consistent with this opinion. On remand, the District Court shall give proper consideration to the Plans' Rule 56(d) declarations, as well as their arguments that GSK marketed Avandia as providing cardiovascular benefits.

Appendix B

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 18-1010

IN RE: AVANDIA MARKETING, SALES AND PRODUCTS LIABILITY LITIGATION

UFCW Local 1776 and participating Employers Health and Welfare Fund; J.B. Hunt Transport Services, Inc.,

Appellants.

Filed: Jan. 28, 2020

Present: SMITH, *Chief Judge*, McKEE, AMBRO, CHAGARES, JORDAN, SHWARTZ, KRAUSE, RESTREPO, BIBAS, PORTER, MATEY, and PHIPPS, *Circuit Judges*.

ORDER

The petition for rehearing filed by Appellee in the above-entitled case having been submitted to the judges who participated in the decision of this Court and to all the other available circuit judges of the circuit in regular active service, and no judge who concurred in the decision having asked for rehearing, and a majority of the judges of the circuit in regular service not having voted for rehearing, the petition for

rehearing by the panel and the Court en banc, is denied.

BY THE COURT,

s/ L. Felipe Restrepo
Circuit Judge

Date: January 28, 2020

Appendix C

UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF PENNSYLVANIA

MDL No. 1871
No. 07-md-1871

IN RE: AVANDIA MARKETING, SALES AND PRODUCTS LIABILITY LITIGATION

This Document Applies To:
All Third-Party Payor Actions

Filed: Dec. 7, 2017

MEMORANDUM OPINION

Rufe, J.

Plaintiffs filed suits against GlaxoSmithKline LC ("GSK") alleging violations of the Racketeer Influenced and Corrupt Organizations Act ("RICO") and various state consumer protection laws in connection with its marketing of Avandia.[1] All actions

[1] There were originally four third-party payor ("TPP") actions to be considered here. These cases were brought by: (1) Allied Services Division Welfare Fund ("Allied") (Civil Action No. 09-730); (2) United Benefit Fund ("UBF") (Civil Action No. 10-5419); (3) UFCW Local 1776 and Participating Employers Health and Welfare Fund ("UFCW") (Civil Action No. 10-2475); and (4) J.B. Hunt Transport Services, Inc. ("J.B. Hunt") (Civil Action No. 11-

were filed into the Avandia Marketing, Sales Practices and Products Liability Multi-District Litigation ("MDL"). As similar factual and legal claims are raised in the actions, GSK has filed a single motion for summary judgment.[2] For reasons set forth below, GSK's motion for summary judgment will be granted.

I. Background

A. Plaintiffs Include Avandia on Their Formularies

GSK produces, markets, and distributes oral medications to treat Type II diabetes mellitus under the brand names Avandia, Avandamet, and Avandaryl (collectively "Avandia").[3] Plaintiffs are

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4013). However, the claims asserted by Allied and UBF have been voluntarily dismissed with prejudice. (Doc. No. 5033, 5041.) Therefore, the Court will consider GSK's motion with respect to the actions brought by UCFW and J.B. Hunt.

[2] GSK's motion for summary judgment raises some of the same issues as its motion for summary judgment in a similar case titled *County of Santa Clara v. SmithKline Beecham Corporation*, Civil Action No. 10-1637. Though not companion cases, the two actions present similar issues and are included in the MDL, and will be dealt with accordingly. In culling through the records in each case, it is clear that the records are not identical. However, GSK points to the same evidence in the two actions to argue that summary judgment is appropriate. Therefore, much of the discussion in this Opinion will mirror that of the Opinion also issued today in *County of Santa Clara.*

[3] As the Court has written at length on this matter, the background section is similar to the background section of a previous opinion for this case. *See In re Avandia Mktg., Sales Practices & Prod. Liab. Litig.*, No. 09-CV-730, 2013 WL 5761202, at *1-2 (E.D. Pa. Oct. 23, 2013). However, facts dispositive to resolving this motion have been added for clarity, and are viewed

employee welfare benefit plans as defined by the Employee Retirement Income Security Act ("ERISA"). Plaintiffs provide medical coverage, including prescription drug coverage, to their members and their members' dependents. Along with other similarly-situated TPPs, Plaintiffs have paid for Avandia since the Food and Drug Administration ("FDA") approved it for sale in 1999.

The FDA approves a drug when its manufacturer can establish, through well-designed, placebo-controlled clinical trials, that the drug is safe to use and effective as a treatment for all conditions listed on its proposed label. The FDA also can direct additional research or conduct limited independent research on drug quality, safety, and effectiveness. Once the FDA approves the drug, its manufacturer can market the drug to doctors, pharmacy benefit managers, health insurance companies, and state and federal agencies.

TPPs generally have Pharmacy Benefit Managers ("PBMs") prepare a formulary, which is a list of drugs approved for coverage when prescribed to the TPPs' beneficiaries. In preparing the formulary, the PBM examines research regarding a drug's safety and efficacy, and also assesses cost-effectiveness. If one drug has some advantage over competing drugs, it can be given a priority status on the formulary, which means that a patient will pay a lower co-payment when his or her doctor prescribes that drug. Because PBMs rely on existing research on safety and efficacy, when a company acts to conceal material information

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in the light most favorable to the TPPs, as the non-moving parties.

about a drug's safety, the PBM will not have the information it needs to make an informed decision.

The Plaintiff TPPs in this case opted to include Avandia on their formularies, sometimes at a higher preference level than competing drugs, and covered Avandia prescriptions at the favorable formulary rate. Plaintiffs relied in part on GSK's representations that Avandia was a safe medication for Type II diabetes that controlled blood sugar levels better than other available medications, such as metformin and sulfonylurea.

Plaintiffs alleged that, from 1999 to 2007, GSK engaged in deceptive marketing practices by failing to disclose information of a potential link between Avandia use and increased cardiovascular risk when compared to other available medications. Plaintiffs further allege that, had they been given this information prior to 2007, they would not have included Avandia on their formularies and would not have paid a higher premium for Avandia prescriptions over other diabetes drugs.

B. GSK's Motion For Summary Judgment And Subsequent Briefing

GSK moved for summary judgment on all of Plaintiffs' claims. GSK argues Plaintiffs have failed to put forth evidence supporting a viable RICO claim, and that federal preemption principles and state safe harbor doctrines bar Plaintiffs' state law claims. Plaintiffs filed a response in opposition, and GSK filed a reply.

Plaintiffs then filed a sur-reply, which seemed to shift their allegations to focus on Avandia's benefits, rather than risks. In the sur-reply, Plaintiffs state

that their claims "do not depend on proving that Avandia posed an increased cardiovascular risk compared to metformin and sulfonylureas." Plaintiffs then elaborate:

> If the TPPs were claiming that GSK should have proposed labeling saying that Avandia was more dangerous than the two cheaper alternatives, that conclusion might be relevant. But the TPPs make no such claims. The TPPs instead take issue with GSK's demonstrably false representations—to the public, to physicians and to PBMs and TPPs—that Avandia had cardioprotective *benefits* above and beyond those of metformin and sulfonylureas.[4]

Although the sur-reply seems to concede Plaintiffs' claims are not based on Avandia's increased cardiovascular risk, Plaintiffs appear to return to the original allegation at oral argument and in later submitted supplemental authority.

GSK contends that the "benefits" claims are untimely, and even if they were not untimely, the claims are not supported by evidence showing that Plaintiffs relied on any representations of purported benefits to make their formulary decisions.

Due to these shifting arguments, the Court will address GSK's motion for summary judgment as to Plaintiff's state law claims on cardiovascular risk; however, it will not rule on any separate, belated arguments on cardiovascular benefits, if any exist, because such issues have not been fully formed and

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[4] Pls.' Sur-Reply at 5-6 (footnote omitted).

were not fully briefed. Moreover, Plaintiffs have failed to identify the specific representations of cardiovascular benefits at issue, at times conceding that "[w]hether one calls [the claim] a benefit or one calls [it] a risk, it's just opposite sides of the same coin."[5] The crux of Plaintiffs' claims is that GSK concealed information about Avandia's cardiovascular risk by stating that the product was safe and effective for patients, and that but for this concealment, Plaintiffs would not have included Avandia on their formularies. Plaintiffs' belated attempt to differentiate the claims to survive summary judgment, therefore, will not be entertained at this juncture.

C. Regulatory Framework of FDA Drug Labeling

The Federal Food, Drug, and Cosmetic Act ("FDCA") regulates the marketing and sale of prescription drugs in the United States.[6] Under the FDCA, a manufacturer must obtain approval from the FDA before marketing a new drug.[7] In a new drug application ("NDA"), the manufacturer must submit a proposed package insert, or drug label, which sets out the drug's medical uses ("indications") and health risks.[8] "To obtain FDA approval, drug companies

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[5] Oral Argument Tr. at 54.

[6] 21 U.S.C. § 301, *et seq*.

[7] *See* 21 U.S.C. § 355(a) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug.").

[8] *See* 21 C.F.R. § 201.57(a) (listing the information that must be included in a prescription drug label).

generally must submit evidence from clinical trials and other testing that evaluate the drug's risks and benefits and demonstrate that it is safe and effective for all of the indications 'prescribed, recommended, or suggested' on the drug's label."[9] "The FDA's approval of a new drug application is conditioned on its approval of the exact text of the drug label."[10]

After a new drug application is approved, the FDA retains the authority to accept or reject amendments to the drug label. Throughout the course of the drug's sales, the manufacturer is charged "with ensuring that its warnings remain adequate."[11] This reflects the underlying premise of the FDA's drug labeling scheme, which assures that "manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times."[12]

Once FDA approval is obtained, a manufacturer can revise a drug label in two ways. First, a manufacturer can apply for "major changes" to a drug label by filing a "Prior Approval Supplement" ("PAS").[13] Major changes include, for example, revised warnings in the highlights or boxed warning section of the drug label.[14] Any alterations requested using a

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[9] *In re Schering Plough Corp. Intron/Temodar Consumer Class Action*, 678 F.3d 235, 239 (3d Cir. 2012) (quoting 21 U.S.C. § 355(d)).

[10] *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, 852 F.3d 268, 272-73 (3d Cir. 2017) (citing 21 C.F.R. §314.105(b),(c)).

[11] *Wyeth v. Levine*, 555 U.S. 555, 571 (2009).

[12] *Id.* at 579.

[13] 21 C.F.R. § 314.70(b).

[14] 21 C.F.R. § 201.57(a)(5); 21 C.F.R. §§ 314.70(b)(2)(v)(C).

PAS require the FDA's approval before these changes can be implemented.[15]

Second, under the "Changes Being Effected" ("CBE") regulation, a manufacturer may unilaterally change a drug label to reflect "newly acquired information," which will be subject to later FDA approval.[16] Using the CBE process, a manufacturer is not required to wait for FDA approval and instead may "add or strengthen a contraindication, warning, precaution, or adverse reaction" upon learning of such newly acquired information.[17] The FDA reviews CBE submissions and may reject proposed changes that do not meet regulatory standards.[18]

It is important to note "that the FDA does not simply approve warnings out of an abundance of caution whenever the manufacturer posits a theoretical association between drug use and an adverse event."[19] Instead, the FDA cautions against "[e]xaggeration of risk, or inclusion of speculative or hypothetical risks, [which] could discourage appropriate use of a beneficial drug . . . or decrease the usefulness and accessibility of important information by diluting or obfuscating it."[20] It explains that "theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to

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[15] 21 C.F.R. § 314.70(b).

[16] 21 C.F.R. § 314.70(c)(6)(iii).

[17] 21 C.F.R. § 314.70(c)(6)(iii)(A).

[18] 21 C.F.R. § 314.70(c)(4)-(6).

[19] *Fosamax*, 852 F.3d at 274.

[20] 73 Fed. Reg. 2848-01, at 2851 (Jan. 16, 2008).

lose its significance."[21] "Accordingly, the FDA will reject a PAS application or CBE amendment if there is insufficient evidence of a causal link between drug use and the adverse event."[22]

D. Avandia's Labeling History

1. GSK's Initial Labeling of Avandia Does Not Contain Warnings of Cardiovascular Risk, Yet Some Studies Suggest an Increased Cardiovascular Risk for Its Users

In November 1998, GSK submitted to the FDA an NDA for Avandia. As part of the NDA, GSK provided cardiovascular safety information from its clinical trials. An FDA Medical Reviewer who was tasked with reviewing the NDA expressed concern with the data provided because it was difficult to discern the number of unique patients experiencing cardiovascular events among patients who took Avandia compared to those who did not use the drug.[23] Nonetheless, on May 25, 1999, the FDA accepted the NDA and approved Avandia for sale.[24]

Following FDA approval, GSK continued to test Avandia's safety, with varied results. For example, GSK monitored patients' use of Avandia and insulin as compared to those taking insulin plus a placebo. In 2000, it submitted this data to the FDA and suggested an additional warning of an increased cardiovascular

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[21] *Id.*

[22] *Fosamax*, 852 F.3d at 274.

[23] Pls.' Fact Proffer at ¶¶ 45-46.

[24] *Id.* at ¶ 53.

risk for patients taking Avandia plus insulin compared to those taking insulin and a placebo.[25] In 2001, the FDA approved this label change.[26]

In addition, GSK studied Avandia users who had pre-existing heart failure. Referred to as Study 211, this data suggested that patients with pre-existing heart failure suffered an increased risk of heart attacks when taking Avandia, compared to those who did not use the drug.[27] Although the FDA initially informed GSK that it did not want the results of Study 211 added via CBE, it later approved of GSK's proposed label change on these results in a PAS.[28]

GSK also conducted a large, long-term, prospective, randomized, and controlled clinical trial designed to evaluate Avandia's cardiovascular outcomes, which it named the RECORD trial.[29] This trial compared patients taking Avandia plus metformin or a sulfonylurea to those taking only metformin plus sulfonylurea.[30] The primary endpoints measured in the RECORD trial were cardiovascular deaths and hospitalizations. Unlike the prior trials mentioned, the interim data from the RECORD trial collected did not confirm an increased cardiovascular risk.[31]

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[25] Def.'s Statement of Undisputed Facts at ¶ 29.

[26] *Id.*

[27] *Id.* at ¶ 32, Def.'s Mot. for Summ. J., Exs. M, N.

[28] *Id.*

[29] Def.'s Statement of Undisputed Facts at ¶ 40.

[30] *Id.*

[31] *Id.*

In 2005, as part of GSK's monitoring of Avandia's safety, it completed a meta-analysis of Avandia's cardiovascular risk using data collected from its prior trials. Based on GSK's analysis of pooled cardiovascular data from 37 clinical trials (the "ICT-37"), it found no "statistically significant association between Avandia and increased risk of ischemic cardiovascular events."[32] The following year, GSK expanded its meta-analysis to include 42 clinical trials (the "ICT-42").[33] Unlike the ICT-37, the ICT-42 demonstrated a statistically significant association between Avandia and ischemic events, suggesting a 31% increase in the risk of such events.[34] On May 9, 2006, GSK submitted the ICT-42 data to the FDA.[35] On August 4, 2006, GSK submitted a PAS to add information about Avandia's cardiovascular risk relative to comparable diabetes medications, such as metformin and sulfonylurea, to the adverse reactions section of the Avandia label.[36]

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[32] *Id.* at ¶ 31.

[33] *Id.* at ¶ 33.

[34] *Id.*

[35] *Id.*

[36] *Id.* at ¶ 34. The proposed label included the following statement:

> In a retrospective analysis of data from pooled controlled clinical studies, which included patients on combination therapy with insulin as well as patients with NYHA Class 1 and 2 heart failure (see WARNINGS, Cardiac Failure and Other Cardiovascular Effects), the overall incidence of myocardial ischemic adverse events was higher for regimens containing AVANDIA 1.99% versus comparators, 1.51% (Hazard ratio 1.31; 95% confidence

2. GSK Changes Avandia's Label to Include a Warning of Cardiovascular Risk

In 2007, the FDA and GSK engaged in substantial discussions that ultimately led the FDA to approve changes to Avandia's label reflecting an increased risk of adverse cardiovascular events, such as heart attacks.

On April 20, 2007, in response to GSK's August 4, 2006 PAS, FDA officials informed GSK that, rather than placing the ICT-42 data in the adverse reactions section of the drug's label, it may require a black box warning to describe the risk of adverse cardiovascular events. The FDA also informed GSK that it intended to convene an advisory committee meeting to discuss with outside experts the potential for cardiovascular risk.[37]

On May 18, 2007, GSK amended the proposed labeling to include the ICT-42 information in the warnings section of the label.[38] Three days later, Dr.

> interval 1.01, 1.70). However, in a large observational study where patients were well-matched at baseline, the incidence of the composite endpoint of myocardial infarction and/or coronary revascularization was 1.75 events per 100 person years for regimens containing AVANDIA and 1.76 events per 100 person years for other anti-diabetic agents (Hazard ratio 0.93; 95% confidence interval 0.80, 1.10). The nature and relationship, if any, of AVANDIA to events related to myocardial ischemia is not clear.

Def.'s Mot. for Summ. J., Ex. P at 25.

[37] Def.'s Statement of Undisputed Facts at ¶ 34.

[38] *Id.* at ¶ 35.

Steven Nissen, an independent researcher, published an article on his own meta-analysis of past Avandia trials in the *New England Journal of Medicine*.[39] Nissen's analysis concluded that, when compared to a placebo, Avandia was "associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance."[40]

During this timeframe, GSK considered making a label change via the CBE process.[41] On May 24, 2007, however, Dr. Mary Parks of the FDA stated that she "strongly advise[d]" against proceeding in this way.[42] She also stated that a CBE would be "looked on with suspicion" in light of the FDA's position that the meta-analysis results required further review.[43]

On June 4, 2007, the FDA rejected the PAS.[44] Its rejection letter stated:[45]

> Dear Dr. Kreider:
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> Please refer to your supplemental new drug application dated August 4, 2006, received

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[39] Pls.' Fact Proffer at ¶ 137.

[40] Pls. Resp. to Mot. for Summ. J., Ex. 35, Steve E. Nissen & Kathy Wolski, *Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes*, 356 (24) N. ENG. J. MED. 2457 (2007).

[41] Def.'s Statement of Undisputed Facts at ¶ 38.

[42] *Id.* (citing Def.'s Mot. for Summ. J., Ex. V).

[43] *Id.* (citing Def.'s Mot. for Summ. J., Ex. W).

[44] *Id.* at ¶ 37 (citing Def.'s Mot. for Summ. J., Ex. U).

[45] Because the parties dispute the reasons that the FDA provided for rejecting the PAS, the rejection letter is provided in full.

August 4, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandia® (rosiglitazone maleate) Tablets, 2 mg, 4 mg, and 8 mg.

We acknowledge receipt of your submissions dated September 8, November 2, and December 7, 2006, and March 29, April 23, and May 18 (labeling), 21, 22, and 31, 2007.

This supplemental application provides for the inclusion of information from a retrospective analysis of pooled data from 42 controlled clinical trials that showed an increased risk of myocardial ischemic events associated with rosiglitazone treatment relative to comparator groups. This supplement also included the results of a balanced cohort observational study that demonstrated similar rates of myocardial infarction and coronary revascularization between rosiglitazone and other anti-diabetic regimens.

We have reviewed the data provided in your supplement and find that information presented is inadequate, and the supplemental application is **not approvable** under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

From our current review of this application, we have concluded that the pooled data require further analysis to adequately convey the potential risk for increased cardiac ischemia associated with rosiglitazone

therapy. In particular, we have identified certain subgroups of patients (e.g., patients using nitrates, ACE-inhibitors, insulin, or metformin) that may be particularly vulnerable to experiencing an ischemic event while on rosiglitazone treatment. Further analyses of these subgroups will need to be extended to other studies not included in this submission.

We recognize that data from these additional studies may be very informative and may possibly address the risk in the subgroups identified from our review of the pooled analysis.

Consequently, in order to address the deficiency of this application you must provide the Agency with the following:

1. Data from studies included in a meta-analysis performed by Dr. Steven Nissen published in the *New England Journal of Medicine* that were not included in your pooled analysis.

2. Information on withdrawals/ discontinuations of patients in ADOPT.

3. Information on use of nitrates and ACE-inhibitors at baseline in ADOPT and DREAM and the relationship to cardiovascular ischemic events.

4. Primary datasets of the recently completed DREAM trial.

5. Information from on-going RECORD and BARI-2D trials as deemed

> appropriate by the respective Data Safety Monitoring Committees and the Steering Committees[.]

The Agency views this potential risk of increased cardiac ischemia to be a significant finding that may impact a large proportion of patients with type 2 diabetes mellitus. Accordingly, a joint meeting of the Endocrine Metabolic and Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee has been scheduled for July 30, 2007, to discuss the findings from this submission, additional data recently requested, and accruing information from ongoing clinical trials of rosiglitazone. The outcome of this meeting will be particularly germane to any labeling or other regulatory action needed for rosiglitazone, and should be factored into any resubmission to address the above deficiencies.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

> This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.
>
> If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager . . . .
>
> Sincerely,
>
> Mary H. Parks, M.D.[46]

On July 30, 2007, the FDA convened an advisory committee to evaluate the data on Avandia's cardiovascular safety and to recommend potential changes to its labeling.[47] After its analysis, the FDA decided that amending the label was necessary. On November 14, 2007, the FDA directed GSK to add information to the Avandia label in a boxed warning that stated, in part:

> A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their

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[46] Def.'s Mot. for Summ. J., Ex. U.

[47] Def.'s Statement of Undisputed Facts at ¶ 40.

> entirety, the available data on the risk of myocardial ischemia are inconclusive.[48]

After this warning was added to Avandia's label, sales of the drug declined.

3. The FDA Makes Further Revisions to Avandia's Label

In 2010 and 2013, the FDA held two advisory committee meetings on Avandia.[49] These committees reviewed all of the data on the drug's cardiovascular safety.

Following the July 2010 advisory committee meeting, the FDA directed GSK to commission an independent re-adjudication of the RECORD trial.[50] The FDA also imposed additional warnings, such as a revised label stating that Avandia would be available on a restricted basis because of a "potential increased risk of myocardial infarction."[51] The FDA issued a memorandum explaining that although "the evidence pointing to a cardiovascular . . . risk with Avandia was not robust or consistent," it was requiring these safeguards until more evidence of Avandia's safety became available.[52] Between 2010 and 2013, the RECORD trial was re-adjudicated.

In 2013, after the TPP lawsuits were filed, the FDA advisory committee examined the re-adjudicated results of the RECORD trial, which confirmed the

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[48] *Id.* at ¶ 41 (citing Def.'s Mot. for Summ. J., Ex. Z).

[49] *Id.* at ¶ 43.

[50] Def.'s Statement of Undisputed Facts at ¶ 44.

[51] *Id.* (citing Def.'s Mot. for Summ. J., Ex. EE).

[52] *Id.*

initial RECORD results and concluded that Avandia was not associated with an increased risk of cardiovascular adverse events when compared to metformin or sulfonylurea.[53] Therefore, the FDA directed GSK to remove the cardiovascular risk and restricted access information from the boxed warning section of the label. In a decisional memorandum dated November 19, 2013, the FDA wrote that "the data continue to support no statistically significant difference between rosiglitazone [Avandia] and metformin/sulfonylurea for the risk of death or major adverse cardiovascular outcomes, other than the known class effect of heart failure."[54] Rather, "the RECORD trial, and its re-adjudication, provide considerable reassurance regarding the cardiovascular safety of rosiglitazone."[55] On May 7, 2014, the FDA approved an updated label that removed the boxed warning for cardiovascular risk.[56] By this time, however, Avandia sales had dwindled and the drug was no longer widely prescribed.

II. Standard of Review

Upon motion of a party, summary judgment is appropriate if "the materials in the record" show "that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law."[57] Summary judgment may be granted only if the moving party persuades the district court that "there

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[53] *Id.* at ¶ 46.

[54] Def.'s Mot. for Summ. J., Ex. B at 20.

[55] *Id.* at 21.

[56] Def.'s Statement of Undisputed Facts at ¶ 49.

[57] Fed. R. Civ. P. 56(a), (c)(1)(A).

exists no genuine issue of material fact that would permit a reasonable jury to find for the nonmoving party."[58] A fact is "material" if it could affect the outcome of the suit, given the applicable substantive law.[59] A dispute about a material fact is "genuine" if the evidence presented "is such that a reasonable jury could return a verdict for the nonmoving party."[60]

In evaluating a summary judgment motion, a court "must view the facts in the light most favorable to the non-moving party," and make every reasonable inference in that party's favor.[61] Further, a court may not weigh the evidence or make credibility determinations.[62] Nevertheless, the party opposing summary judgment must support each essential element of the opposition with concrete evidence in the record.[63] "If the evidence is merely colorable, or is not significantly probative, summary judgment may be granted."[64] This requirement upholds the "underlying purpose of summary judgment [which] is to avoid a pointless trial in cases where it is unnecessary and would only cause delay and expense."[65] Therefore, if,

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[58] *Miller v. Ind. Hosp.*, 843 F.2d 139, 143 (3d Cir. 1988).

[59] *See Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986).

[60] *Id.*

[61] *Hugh v. Butler Cnty. Family YMCA*, 418 F.3d 265, 267 (3d Cir. 2005).

[62] *Boyle v. Cnty. of Allegheny*, 139 F.3d 386, 393 (3d Cir. 1998).

[63] *Celotex Corp. v. Catrett*, 477 U.S. 317, 322-23 (1986).

[64] *Anderson*, 477 U.S. at 249-50 (citations omitted).

[65] *Walden v. Saint Gobain Corp.*, 323 F. Supp. 2d 637, 641 (E.D. Pa. 2004) (citing *Goodman v. Mead Johnson & Co.*, 534 F.2d 566, 573 (3d Cir. 1976)).

after making all reasonable inferences in favor of the non-moving party, the court determines that there is no genuine dispute as to any material fact, summary judgment is appropriate.[66]

III. Discussion

GSK moves for summary judgment on numerous grounds. The Court considers each argument separately.

A. Plaintiffs' RICO Claims

GSK moves for summary judgment on Plaintiffs' claims brought under the Racketeer Influenced and Corrupt Organizations Act ("RICO").[67] Section 1962(c) of RICO makes it "unlawful for any person employed by or associated with any enterprise . . . to conduct or participate, directly or indirectly, in the conduct of such enterprise's affairs through a pattern of racketeering activity."[68] To establish civil liability, a plaintiff "must allege and prove the existence of two distinct entities: (1) a 'person'; and (2) an 'enterprise' that is not simply the same 'person' referred to by a different name."[69] "[A] claim simply against one corporation as both 'person' and 'enterprise' is not sufficient."[70]

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[66] *Celotex*, 477 U.S. at 322; *Wisniewski v. Johns-Manville Corp.*, 812 F.2d 81, 83 (3d Cir. 1987).

[67] 18 U.S.C. § 1961, *et seq.*

[68] 18 U.S.C. § 1962(c).

[69] *Cedric Kushner Promotions v. King*, 533 U.S. 158, 161 (2001).

[70] *Jaguar Cars v. Royal Oaks Motor Car Co.*, 46 F.3d 258, 268 (3d Cir. 1995).

GSK argues that Plaintiffs failed to identify a RICO enterprise because Plaintiffs named GSK as both the person and the enterprise engaged in racketeering activity.[71] Plaintiffs contend that GSK is the person and the enterprise is "[t]he Avandia Promotion Enterprise . . . an association-in-fact made up of GSK, external consultants (including Sir Colin Dollery and Dr. Stephen Haffner), [copromoter] Bristol-Myers Squibb, and other consultants, marketing firms, and distribution agents GSK employed."[72] In other words, Plaintiffs allege that the enterprise in this case is GSK and its agents—individuals and entities that were hired by GSK to research or market Avandia.[73] RICO liability "depends on showing that the defendants conducted or participated in the conduct of the *enterprise's* affairs, not just their *own* affairs."[74] GSK was conducting its own business in selling Avandia, and thus, Plaintiffs allege that GSK is both the person and the enterprise,

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[71] Def.'s Mot. for Summ. J. at 29-30.

[72] Pls.' Resp. to Mot. for Summ. J. at 25-26.

[73] *See Albert Einstein Med. Ctr. v. Physicians Clinical Servs.*, No. 90-3387, 1991 WL 280274, at *3 (E.D. Pa. Dec. 20, 1991) ("The distinction requirement is not satisfied by merely naming a corporation and its employees, affiliates, and agents as an association-in-fact, since a corporation acts through its employees, subsidiaries and agents, and would thereby by merely associating with itself.") (internal quotation marks and citations omitted).

[74] *Reeves v. Ernst & Young*, 507 U.S. 170, 185 (1993) (quoted in *Cedric Kushner Promotions*, 533 U.S. at 163 (internal quotation marks omitted).

which is insufficient to support viable RICO claims.[75] For this reason, summary judgment will be granted in favor of GSK as to Plaintiffs' RICO claims.

B. Plaintiffs' Consumer Protection Law Claims

GSK argues that Plaintiffs' state law claims should be barred by state safe harbor doctrines and federal preemption principles.

1. Safe Harbor Doctrines

GSK asserts that safe harbor doctrines bar Plaintiffs' state law claims. As plaintiffs are citizens of Pennsylvania and Arkansas, the Court examines whether the safe harbor doctrines of those states bar Plaintiffs' claims.

a. Arkansas

GSK argues Arkansas's safe harbor doctrine bars Plaintiffs' claims brought pursuant to the Arkansas Deceptive Trade Practices Act ("ADTPA").[76] The ADTPA prohibits deceptive trade practices, but contains a safe harbor provision stating that the law does not apply to:

> Actions or transactions specifically permitted under laws administered by the Insurance Commissioner, the Securities Commissioner, . . . or other regulatory body or officer acting

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[75] *See, e.g., Ray v. Spirit Airlines, Inc.*, 836 F.3d 1340, 1356 (11th Cir. 2016) (affirming dismissal of claims where "the corporation is the defendant person, and the corporation, together with its officers, agents, and employees, are said to constitute the enterprise.") (collecting cases).

[76] Ark. Code Ann. §§ 4-88-101, *et seq.*

> under statutory authority of this state or the United States, unless a director of these divisions specifically requests the Attorney General to implement the powers of this chapter; . . .[77]

The Arkansas Supreme Court has held that the ADTPA's safe harbor provision specifically exempts conduct that is permitted under the laws administered by a federal agency.[78] In *DePriest v. AstraZeneca Pharmaceuticals, L.P.*, the Arkansas Supreme Court concluded that the plaintiffs' claims against a drug manufacturer alleging that the manufacturer fraudulently advertised its heartburn drug as "new" and "better" than a common comparator were barred by the ADTPA's safe harbor doctrine.[79] The court explained that, because the manufacturer's advertisements were supported by FDA approved labeling and thus were specifically permitted by federal law, the safe harbor doctrine barred the plaintiffs' ADTPA claims.[80]

Here, Plaintiffs allege that GSK engaged in deceptive trade practices by misrepresenting the safety of Avandia over comparable drugs. In particular, Plaintiffs assert that GSK did not disclose

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[77] Ark. Code Ann. § 4-88-101(3).

[78] *DePriest v. AstraZeneca Pharm., L.P.*, 351 S.W.3d 168, 176 (Ark. 2009).

[79] *Id.* at 170, 178.

[80] *See id.* at 178 (finding that the drug manufacturer's "advertisements constituted actions permitted under the laws administered by the FDA, and therefore, the ADTPA, by its own terms, does not apply to the challenged conduct.") (citation omitted).

cardiovascular risk information compared to similar diabetes medications that would have been relevant in the TPPs' decision to authorize Avandia for their members' use. They also allege that GSK's omissions of relative cardiovascular risk "were not FDA approved" and thus were not permitted by federal law.[81] Here, however, when the FDA initially approved the Avandia label, GSK marketed the drug in compliance with its approval. GSK has not made statements on the label that were not approved by the FDA, and Plaintiffs cannot point to any such representations. Moreover, the current label for Avandia states that there is "no difference in overall mortality or in major adverse cardiovascular events" with Avandia "versus metformin and sulfonylureas."[82] This current label was approved by the FDA after extensive study of a potential link between Avandia and increased cardiovascular risk, and as such was permitted by federal law. Summary judgment will be granted for GSK on Plaintiffs' ADTPA claims.

b. Pennsylvania

GSK contends Plaintiffs' claims under Pennsylvania's Unfair Trade Practices and Consumer Protection Law ("UTPCPL")[83] should be barred. Although the UTPCPL does not contain a safe harbor provision, GSK suggests that the Court should construct a common law safe harbor doctrine as courts

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[81] Pls. Resp. to Mot. for Summ. J. at 37.

[82] Def.'s Reply at 26 (citation omitted); Def's Mot. for Summ. J., Ex. II at 6.

[83] 73 Pa. Const. Stat. Ann. § 201-1, *et seq*.

in other states have done.[84] The Court will not do so, as there is no precedent suggesting that Pennsylvania would adopt such a doctrine.[85] Therefore, the Court turns to GSK's argument that the Pennsylvania state law claims are preempted.

2. Preemption

GSK argues that federal preemption doctrines bar Plaintiffs' state law claims. The Supremacy Clause of the United States Constitution establishes that federal law "shall be the supreme Law of the Land."[86] The Supremacy Clause, therefore, preempts "state laws that interfere with, or are contrary to, federal law."[87]

There are three categories of preemption: (1) express preemption, (2) field preemption, and (3) conflict preemption.[88] Only the last category, conflict preemption, is at issue here, and it comes in two sub-varieties: obstacle preemption, which occurs when a state law "stands as an obstacle to the

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[84] Def.'s Mot. for Summ. J. at 36-37.

[85] *See Commonwealth of Pa. v. Monumental Props., Inc.*, 329 A.2d 812, 815-17 (Pa. 1974) (holding that the UTPCPL was designed to "benefit the public at large" and should be "construed liberally to effect its object of preventing unfair or deceptive practices").

[86] U.S. Const., art. VI, cl. 2.

[87] *Hillsborough Cnty., Florida v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712 (1985) (internal quotation marks and citation omitted).

[88] *See Orson, Inc. v. Miramax Film Corp.*, 189 F.3d 377, 381 (3d Cir. 1999) (citing *Pacific Gas & Elec. Co. v. Energy Resources Conservation and Dev. Comm'n*, 461 U.S. 190, 204 (1983); *Int'l Paper Co. v. Ouellette*, 479 U.S. 481, 491 (1987)).

accomplishment and execution of the full purposes and objectives of Congress,"[89] and impossibility preemption, which applies when "compliance with both federal and state regulations is a physical impossibility."[90] "[T]he purpose of Congress is the ultimate touchstone in every preemption case."[91] Courts apply a presumption against preemption,[92] and whenever possible, attempt to reconcile state law and federal law with one another.[93]

a. Obstacle Preemption

First, GSK asserts that obstacle preemption bars Plaintiffs' claims. As noted, obstacle preemption occurs when a state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress."[94]

In *Wyeth v. Levine*,[95] the United States Supreme Court considered obstacle preemption in the context of pharmaceutical regulation and state tort law. There,

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[89] *Maryland v. Louisiana*, 451 U.S. 725, 747 (1981) (internal quotation marks and citations omitted).

[90] *Id.* (internal quotation marks and citation omitted).

[91] *Deweese v. Nat'l R.R. Passenger Corp. (Amtrak)*, 590 F.3d 239, 246 (3d Cir. 2009) (internal quotation marks and citations omitted).

[92] *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005) (If confronted with two plausible interpretations of a federal law, the court therefore has "a duty to accept the reading that disfavors preemption").

[93] *Deweese*, 590 F.3d at 248.

[94] *Maryland*, 451 U.S. at 747 (internal quotation marks and citations omitted).

[95] 555 U.S. 555 (2009).

a drug manufacturer argued that allowing a state tort lawsuit would interfere with the comprehensive federal labeling requirements of the FDCA. The Supreme Court dismissed this contention, writing that "[i]f Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's 70-year history."[96] The Court concluded that Congress's "silence on the issue, coupled with its certain awareness of the prevalence of state tort litigation, is powerful evidence that [it] did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness."[97] The FDCA serves to bolster, not replace, state laws aimed at protecting consumers from harmful pharmaceutical products.[98]

However, the Supreme Court recognized a narrow preemption exception in *Buckman Co. v. Plaintiffs' Legal Committee*.[99] There, the plaintiffs claimed that fraudulent misrepresentations made by defendants to the FDA caused them injury when the medical device in question did not work properly. But for the misrepresentation, the plaintiffs argued, the device would not have been approved by the FDA.[100] The Court explained that state law fraud claims that "exist solely by virtue of the FDCA disclosure requirements,"

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[96] *Id.* at 574.

[97] *Id.* at 575.

[98] *Id.* at 579 ("[T]he FDA [has] long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.").

[99] 531 U.S. 341 (2001).

[100] *Id.* at 343.

necessarily "conflict with the FDA's responsibility to police fraud consistently with the Administration's judgment and objectives."[101] In particular, such claims would create an incentive for applicants "to submit a deluge of information that the Administration neither wants nor needs."[102] Thus, the Court held that these fraud-on-the-FDA claims were impliedly preempted.[103]

Here, to the extent that Plaintiffs assert fraud-on-the-FDA theories to support their claims, they are impliedly preempted. Specifically, to the extent Plaintiffs allege GSK withheld information from the FDA and but for those misrepresentations, the FDA directed GSK to warn Plaintiffs about an increased cardiovascular risk compared to metformin and sulfonylureas, those claims are preempted.[104]

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[101] *Id.* at 350.

[102] *Id.*

[103] It explained that "the conflict stems from the fact that the federal statutory scheme amply empowers the FDA to punish and deter fraud against the [FDA], and that this authority is used by the [FDA] to achieve a somewhat delicate balance of statutory objectives." *Id.* at 348. The Court reasoned that allowing such fraud-on-the-FDA claims could skew that balance. *Id.*

[104] *See, e.g., McLaughlin v. Bayer Corp.*, 172 F. Supp. 3d 804, 825 (E.D. Pa. 2016) (concluding that the plaintiffs' fraudulent concealment claim against the drug manufacturer was impliedly preempted under *Buckman* because it was grounded "exclusively on duties to disclose and exists solely by virtue of FDCA requirements.") (internal quotation marks and citation omitted); *see also In re Tylenol (Acetaminophen) Marketing*, No. 2:13-md-02436, 2015 WL 7076012, at *8 (E.D. Pa. 2015) ("Most of the plaintiff's allegations of fraud and fraudulent concealment center on the information disclosed to consumers and physicians primarily. However, the plaintiff does allege that the defendants

Plaintiffs allege four clinical studies—Studies 011, 020, 079, and 093—were not disclosed to the FDA[105] and that the manner in which the data was provided to the FDA was misleading,[106] but these allegations constitute fraud-on-the-FDA claims and are preempted.[107]

However, to the extent Plaintiffs allege GSK disseminated false or misleading information about Avandia directly to the TPPs, their doctors, or the PBMs, and not solely to the FDA, those claims are not preempted on this basis, as it would not be an obstacle to the FDA's regulation of the pharmaceutical industry, nor would it undermine the FDA's decision-making.

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concealed information from the FDA itself. To the extent that these allegations could be read as a fraud-on-the-FDA claim, they would be preempted.") (internal citations omitted).

[105] Pls.' Resp. to Mot. for Summ. J. at 5-6; Pls.' Fact Proffer at ¶ 44.

[106] Pls.' Resp. to Mot. for Summ. J. at 6.

[107] Furthermore, these allegations are not supported by the evidentiary record. FDA review of Avandia's NDA shows that GSK provided data from Studies 011, 020, and 093 to the FDA, and that the studies were analyzed before the drug's approval. Def.'s Mot. for Summ. J., Ex. D at 1, 4, 12, 21, 36-37. In addition, the data from Study 079 was disclosed to the FDA as part of the RECORD trial and re-adjudication, and was analyzed by the FDA in making its determination that Avandia did not pose an increased cardiovascular risk compared to alternatives. Def.'s Mot. for Summ. J., Ex. DD at 29-32. Moreover, the FDA is staffed with qualified medical reviewers who are tasked with studying data provided to determine a proposed drug's safety. Here, the relevant data was provided to the FDA, and the FDA studied it extensively. These unsupported allegations, therefore, do not create a genuine dispute of material fact.

b. Impossibility Preemption

Second, GSK argues that impossibility preemption bars Plaintiffs' state law claims. As noted, impossibility preemption applies, and a state law must give way, when "it is impossible for a private party to comply with both state and federal requirements."[108] "The proper question for 'impossibility' analysis is whether the private party could *independently* do under federal law what state law requires of it."[109]

In *Wyeth*, the Supreme Court addressed to what extend state law failure-to-warn claims are preempted by the FDCA and federal drug labeling regulation.[110] The Court held that these state law claims against manufacturers generally are not preempted by FDA approval of a drug's warning label. However, such claims are preempted when there is "clear evidence" that the FDA would not have approved the warning label changes that the plaintiff asserts is necessary.[111]

Defining the term "clear evidence" has evaded courts.[112] Recently, the United States Court of Appeals for the Third Circuit in *In re Fosamax* explained that the *Wyeth* Court "intended the term 'clear evidence' to denote a standard of proof" a drug

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[108] *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 618 (2011) (internal quotation marks and citations omitted).

[109] *Id.* (citation omitted).

[110] 555 U.S. at 559-65.

[111] *Id.* at 571.

[112] *See, e.g.*, *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d 1108, 1119 (S.D. Cal. 2015) (noting that the "clear evidence standard remains undefined").

manufacturer must bear to establish an impossibility preemption defense.[113]

A single inquiry is used to determine whether the manufacturer met this standard: that is, "would the FDA have approved the label change that Plaintiffs argue was required?"[114] This question is ordinarily one of fact that "must be answered by a jury" or other factfinder at trial.[115] However, summary judgment is appropriate where any reasonable factfinder would necessarily find it "highly probable that the FDA would not have approved a change to the drug's label."[116]

After *Fosamax*, GSK must establish by clear evidence that the FDA would not have approved the warning about the link between Avandia use and increased cardiovascular risk compared to other diabetes medications prior to 2007.

GSK points to the following evidence: (1) the FDA rejected GSK's PAS, (2) the FDA advised against using the CBE process to unilaterally change the label, and (3) after conducting further research on the potential link between increased cardiovascular risk and Avandia use as compared to other diabetes medications, the FDA ultimately concluded that there was no increased cardiovascular risk with Avandia use in relation to comparators.

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[113] 852 F.3d at 285 ("The manufacturer must prove that the FDA would have rejected a warning not simply by a preponderance of the evidence . . . but by 'clear evidence.'").

[114] *Id.* at 286.

[115] *Id.*

[116] *Id.*

First, GSK notes that in August 2006 it submitted a PAS to the FDA, which proposed a change to Avandia's label to include increased cardiovascular risk versus comparators.[117] On June 4, 2007, however, the FDA rejected the PAS. Plaintiffs contend that the PAS was rejected because it contained "deficiencies."[118] However, it is clear from the FDA's rejection letter that any deficiencies with the PAS stem from the FDA's desire to have "further analysis [conducted] to adequately convey the potential risk for increased cardiac ischemia associated with rosiglitazone therapy."[119] The rejection letter also stated that the FDA sought to hold meetings with advisory committees to discuss the findings from the PAS submission and data from on-going studies.[120] This rejection of GSK's proposed label on the basis of

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[117] Def.'s Statement of Undisputed Facts at ¶ 37.

[118] Pls.' Resp. to Mot. for Summ. J. at 17.

[119] Def.'s Mot. for Summ. J., Ex. U. In *Fosamax*, the Third Circuit determined that the rejection of the drug manufacturer's PAS did not constitute clear evidence that the FDA would not have approved of the changes the plaintiffs claimed were necessary. 852 F.2d at 286. In making this finding, the Court of Appeals focused on the misleading "stress fracture" language the manufacturer included in the PAS to describe the risk of femoral fractures in patients using the osteoporosis drug. *Id.* Unlike the facts in *Fosamax*, in this case the FDA rejected GSK's PAS because the data was inconclusive and it sought to conduct further review before making a label change.

[120] *See* Def.'s Mot. for Summ. J., Ex. U ("[A] joint meeting of the Endocrine Metabolic and Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee has been scheduled for July 30, 2007, to discuss findings from this submission, additional data recently requested, and accruing information from ongoing clinical trials of rosiglitazone.").

inconclusive data, considered with other evidence, constitutes clear evidence that the FDA would not have approved of the label change Plaintiffs claim was necessary,[121] particularly where, as here, the FDA wanted to conduct further review of the data before directing GSK to make the label change it had proposed.

Second, GSK identifies evidence that the FDA advised against using the CBE process to unilaterally amend Avandia's label. On May 24, 2007, Dr. Parks "strongly advise[d]" against proceeding by CBE.[122] She also stated that a CBE would be "looked on with suspicion" in view of the FDA's position that the data required further review.[123] According to Parks, a CBE would "pull the rug out" from the FDA's plan to consult with an advisory committee about cardiovascular risk before taking further labeling steps.[124] Although Plaintiffs note that Parks also stated that "ultimately, it is the sponsor's decision to pursue a . . . CBE,"[125] the evidence shows that the FDA advised against using a

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[121] *See Rheinfrank v. Abbott Labs., Inc.*, 680 F. App'x 369, 385-86 (6th Cir. 2017) (finding clear evidence that the FDA would not have approved of the label change on developmental delay that the plaintiff claimed was necessary in light of the FDA's rejection of a PAS application to add a developmental delay warning to the drug's label, and later rejecting an informal request for advice made by the manufacturer on the same proposal, explaining that "the data do not provide sufficient evidence to support labeling changes at this time").

[122] Def.'s Statement of Undisputed Facts at ¶ 38 (citing Def.'s Mot. for Summ. J., Ex. V).

[123] *Id.* (citing Def.'s Mot. for Summ. J., Ex. W).

[124] *Id.*

[125] Pls.' Resp. to Mot. for Summ. J. at 16 (citation omitted).

CBE to make the proposed label change prior to November 2007.

Third, GSK argues the FDA's ultimate conclusion that Avandia use is not linked to increased cardiovascular risk when compared to other diabetes drugs constitutes clear evidence that it would not have approved of changes to the label prior to 2007. This case presents a unique situation, as far as this Court is aware, where the FDA required a black box warning on increased cardiovascular risk in 2007, and later, after conducting extensive research, concluded that the black box warning should be removed because the data did not support such an association. After adding the black box warning in November 2007, the FDA undertook a substantial review of Avandia's association with increased cardiovascular risk compared to other diabetes medications, and ultimately concluded that such an association does not exist.

Therefore, it removed the black box warning and restricted access information from Avandia's label. In 2013, the FDA concluded that "the data continue to support no statistically significant difference between rosiglitazone [Avandia] and metformin/sulfonylurea for the risk of death of major adverse cardiovascular outcomes, other than the known class effect of heart failure."[126] Rather, "the RECORD trial, and its re-adjudication, provide considerable reassurance regarding the cardiovascular safety of rosiglitazone."[127] The Court is not aware of any similar

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[126] Def.'s Statement of Undisputed Facts at ¶ 47.

[127] Def.'s Mot. for Summ. J., Ex. B at 21.

cases, and the parties cite to none, and thus the Court cannot ignore the FDA's current conclusion that a link between Avandia use and increased cardiovascular risk does not exist.

Although *Fosamax* clarifies the high burden a drug manufacturer must meet to successfully assert an impossibility preemption defense, the evidentiary record in this case would require any reasonable jury to conclude that GSK has met its burden. The FDA's current position, considered with its earlier rejection of GSK's PAS, and its advising against using a CBE, constitute clear evidence that the FDA would not have approved of a warning for increased cardiovascular risk in Avandia versus comparators earlier than 2007, and would not approve one now, although Plaintiffs claim it should have been required at all times. Therefore, impossibility preemption is warranted, and GSK's motion for summary judgment on Plaintiffs' state law claims will be granted.

IV. Conclusion

For the reasons set forth above, GSK's motion for summary judgment will be granted.

An Order follows.

Appendix D

UNITED STATES DEPARTMENT OF HEALTH & HUMAN SERVICES FOOD AND DRUG ADMINISTRATION

NDA 21-071/S-022

SB PHARMCO PUERTO RICO, INC. (D/B/A GLAXOSMITHKLINE)

ATTENTION: MARGARET M. KREIDER, PH.D.

DIRECTOR, THERAPEUTIC AREA, REGULATORY AFFAIRS

Date: June 4, 2007

LETTER

Dear Dr. Kreider,

Please refer to your supplemental new drug application dated August 4, 2006, received August 4, 2006, submitted under section section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandia® (rosiglitazone maleate) Tablets, 2 mg, 4 mg, and 8 mg.

We acknowledge receipt of your submissions dated September 8, November 2, and December 7, 2006, and March 29, April 23, and May 18 (labeling), 21, 22, and 31, 2007.

This supplemental application provides for the inclusion of information from a retrospective analysis of pooled data from 42 controlled clinical trials that

showed an increased risk of myocardial ischemic events associated with rosiglitazone treatment relative to other comparator groups. This supplement also included the results of a balanced cohort observational study that demonstrated similar rates of myocardial infarction and coronary revascularization between rosiglitazone and other anti-diabetic regimens.

We have reviewed the data provided in your supplement and find the information presented is inadequate, and the supplemental application is **not approvable** under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

From our current review of this application, we have concluded that the pooled data require further analysis to adequately convey the potential risk for increased cardiac ischemia associated with rosiglitazone therapy. In particular, we have identified certain subgroups of patients (e.g., patients using nitrates, ACE-inhibitors, insulin, or metformin) that may be particularly vulnerable to experiencing an ischemic event while on rosiglitazone treatment. Further analyses of these subgroups will need to be extended to other studies not included in this submission.

We recognize that data from these additional studies may be very informative and may possibly address the risk in the subgroups identified from our review of the pooled analysis.

Consequently, in order to address the deficiency of this application you must provide the Agency with the following:

1. Data from studies included in a meta-analysis performed by Dr. Steven Nissen published in the *New England Journal of Medicine* that were not included in your pooled analysis.
2. Information on withdrawals/discontinuations of patients in ADOPT.
3. Information on use of nitrates and ACE-inhibitors at baseline in ADOPT and DREAM and the relationship to cardiovascular ischemic events.
4. Primary datasets of the recently completed DREAM trial.
5. Information from on-going RECORD and BARI-2D trials as deemed appropriate by the respective Data Safety Monitoring Committees and the Steering Committees

The Agency views this potential risk of increased cardiac ischemia to be a significant finding that may impact a large proportion of patients with type 2 diabetes mellitus. Accordingly, a joint meeting of the Endocrine Metabolic and Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee has been scheduled for July 30, 2007, to discuss the findings from this submission, additional data recently requested, and accruing information from ongoing clinical trials of rosiglitazone. The outcome of this meeting will be particularly germane to any labeling or other regulatory action needed for rosiglitazone, and should be factored into any resubmission to address the above deficiencies.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

Mary H. Parks, M.D.

Director

Division of Metabolism & Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research