No. 16-4050

IN THE UNITED STATES COURT OF APPEALS
FOR THE TENTH CIRCUIT

ALEXANDER CERVENY, VICTORIA CERVENY,
AND CHARLES CERVENY

Plaintiffs/Appellants

v.

AVENTIS, INC.,

Defendant/Appellee

Appeal from the United States District Court for the District of Utah
Case No. 2:14-CV-00545
The Honorable Dee Benson, United States District Judge

Brief of Appellee Aventis, Inc.

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CORPORATE DISCLOSURE STATEMENT

In accordance with Rule 26.1 of Federal Rules of Appellate Procedure, Appellee Aventis, Inc., hereby declares as follows:

Aventis Inc. is a subsidiary or other affiliate of a publicly held corporation that owns 10% or more of its stock.

Aventis, Inc. is owned, 100% by sanofi-aventis Amerique du Nord.

Sanofi, a publicly traded French entity, indirectly owns Aventis Inc.

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There are no prior or related appeals.

GLOSSARY

FDA……....United States Food And Drug Administration

CBE……..…FDA's "Changes Being Effected" Regulation

STATEMENT OF THE ISSUES

1. Did the District Court correctly find that there was "clear evidence" that FDA would have rejected a warning that Clomid causes birth defects when used as indicated prior to pregnancy and, therefore, that the Cervenys' claims were preempted by federal law, based upon (1) FDA's unequivocal rejection of a citizen petition seeking to add a warning of this exact risk, (2) FDA's independent survey of the literature done concurrently with its consideration of the citizen petition, (3) FDA's conclusion that "the data is insufficient to demonstrate reasonable evidence of an association between [Clomid] and congenital abnormalities," (4) FDA's rejection of a petition for reconsideration of the citizen petition, and (5) FDA's continued approval, over a period of 45 years, of statements in Clomid's labeling that the evidence is insufficient to demonstrate a reasonable association between Clomid and birth defects?

2. Did the District Court err in declining to adopt bright-line rules that (1) there can never be "clear evidence" that FDA would have rejected a plaintiff's proposed warning if the manufacturer has not attempted to amend its labeling, and (2) that FDA's rejection of a citizen petition can never be clear evidence that FDA would have rejected the warning proposed by the plaintiff?

3. Did the District Court correctly hold that Clomid's Pregnancy Category X designation, which warns of the risks of taking Clomid during pregnancy, was

irrelevant to the Cervenys' claims, where it is undisputed that Mrs. Cerveny did not take Clomid while pregnant?

4. Did the District Court abuse its discretion by granting Aventis' motion for summary judgment without allowing additional time for discovery when the Cervenys filed a 52-page opposition asking the District Court to deny the motion and when the Cervenys' "precautionary" Rule 56(f) affidavit did not describe discovery needed to present facts opposing summary judgment, but rather described discovery needed to develop facts "essential to the prosecution" of the case?

5. Did the District Court correctly grant judgment in Aventis' favor on all of the Cervenys' remaining claims based on its holding that the Cervenys' failure-to-warn claim was preempted when the Cervenys' other claims relied on the same allegations as their failure-to-warn claim?

STATEMENT OF THE CASE

Clomid (clomiphene citrate) is an FDA-approved fertility medication indicated for use in women seeking to become pregnant. It was approved by FDA on February 1, 1967, and is one of the oldest and most successful fertility treatments available. Appx. 014 ¶ 10. Clomid works by inducing ovulation in women who are unable to ovulate. *See* 1991 Clomid Label, Appx. 239-44.

While Clomid's labeling has long carried warnings against *administration during pregnancy*, FDA has never required Clomid to carry direct warnings of fetal harm allegedly associated with Clomid's use *prior to pregnancy*. This distinction is critical to the issues in this case.

I. Clomid Labeling Regarding Use During Pregnancy Versus Use Prior to Pregnancy.

Since its initial approval, Clomid has been approved for use in women seeking to become pregnant. Since that same time it has been **contraindicated**[1] for use by women who were already pregnant because it provides them no benefit. Appx. 528. Its 1967 label explained that precautions should be taken to avoid administration during pregnancy:

> **CONTRAINDICATIONS**
>
> *Pregnancy*

[1] Contraindications are defined by FDA regulations as "those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit." 21 C.F.R. § 201.80 (d).

> Although no causative evidence of a deleterious effect of Clomid therapy on the human fetus has been seen, such evidence in regard to the rat and rabbit has been presented (see Animal Pharmacology and Toxicology). *To avoid inadvertent Clomid administration during early pregnancy, the basal body temperature should be recorded throughout all treatment cycles, and the patient should be carefully observed to determine whether ovulation occurs*.

Appx. 590 (emphasis in original). Clomid's label was revised in both 1980 and 1991; the revised labels contained this same pregnancy contraindication. *See* Appx. 579; Appx. 239.

In 1987, FDA suggested designating Clomid as Pregnancy Category X[2] and adding the following statement to its label: "Clomid may cause fetal harm when *administered to pregnant women*. Since there is a reasonable likelihood of a patient becoming pregnant while receiving Clomid, the patient should be apprised of potential hazard to the fetus." Appx. 596 (emphasis added). This label was not implemented.

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[2] Pregnancy Category X labels were intended for medications where "studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the *use of the drug in a pregnant woman* clearly outweighs any possible benefit." Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37434, 37464 (June 26, 1979) (to be codified 21 C.F.R. pts. 201, 202) (emphasis added). On June 30, 2015, the FDA finalized a rule to eliminate the pregnancy category system because "the pregnancy categories were confusing and did not accurately and consistently communicate difference in degrees of fetal risk." *See* Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products— Content and Format, 79 Fed. Reg. 72064, 72065 (Dec. 4, 2014) (to be codified 21 C.F.R. pt. 201).

In 1992, when Victoria Cerveny ingested Clomid the pregnancy contraindication stated:

> **CONTRAINDICATIONS**
>
> *Pregnancy*
>
> Although no causative evidence of a deleterious effect of Clomid therapy on the human fetus has been seen, such evidence in regard to the rat and rabbit has been presented (see Animal Pharmacology and Toxicology). Therefore, Clomid should not be administered during pregnancy.

Appx. 239. The labeling told prescribing physicians that Clomid should not be administered to women *who were presently pregnant*. In 1994, two years after Alexander Cerveny was born, FDA designated Clomid as Pregnancy Category X. The Pregnancy Category X statement referred readers to the contraindication.

> **PRECAUTIONS**
>
> * * *
>
> **Pregnancy**
>
> Pregnancy Category X. (See CONTRAINDICATIONS.)

Appx. 444. The contraindication statement in the 1994 label was similar to prior versions of the pregnancy contradiction and made clear that "no causative evidence of a deleterious effect of Clomid therapy on the human fetus has been established":

> **CONTRAINDICATIONS**
>
> * * *
>
> **Pregnancy**

> CLOMID should not be administered during pregnancy. CLOMID may cause fetal harm in animals (see Animal Fetotoxicity). Although no causative evidence of a deleterious effect of Clomid therapy on the human fetus has been established, there have been reports of birth anomalies which, during clinical studies, occurred at an incidence with the range reported for the general population.
>
> * * *

Appx. 443. The Pregnancy Category X designation added no new information to the label since it simply indicates that "studies in animals or humans have demonstrated fetal abnormalities…and the risk of the *use of the drug in a pregnant woman* clearly outweighs any possible benefit," and the label already contraindicated the medication in women who were pregnant and mentioned evidence of fetal abnormalities in animal studies. In addition, the labeling was revised to include a subsection addressing "Fetal/Neonatal Anomalies and Mortality." This section concluded: "[t]he overall incidence of reported birth anomalies from pregnancies associated with maternal CLOMID ingestion during clinical studies was within the range of that reported for the general population." *Id.*

Clomid's current FDA-approved label is more direct. It explains that Clomid is contraindicated for pregnant women because it does not offer any benefit to them and reiterates that the available data does not suggest that Clomid increases the risk of birth defects when used as indicated:

> CLOMID use in pregnant women is contraindicated, as *CLOMID does not offer benefit in this population.* Available human data do not suggest an increased risk for congenital anomalies above the background population risk when used as indicated. However, animal reproductive toxicology studies showed increased embryo-fetal loss and structural malformations in offspring. If this drug is used *during pregnancy*, or if the patient becomes pregnant *while taking this drug*, the patient should be apprised of the potential risks to the fetus.

Appx. 528. In the "Precautions" section, it states: "Inform the patient that the available data suggest no increase in the rates of … congenital anomalies with maternal CLOMID use compared to rates in the general population." Appx. 530. Additionally, under the "Precautions" subsection entitled "Pregnancy" the label states: "The available human data from epidemiologic studies do not show any apparent cause and effect relationship between clomiphene citrate periconceptional [or preconception] exposure and an increased risk of overall birth defects, or any specific anomaly." Appx. 531.

II. The 2007 Citizen Petition and 2009 Petition for Reconsideration.

On October 1, 2007, a letter was sent to FDA requesting FDA change the Clomid labeling based on alleged "new safety information." Appx. 429. FDA responded to the letter in November 2007, stating that it "raises potentially serious safety issues that are of interest to FDA, and we appreciate your bringing them to our attention." *Id*. FDA requested the author submit his letter as a citizen petition, to allow others to comment and participate in the decision-making process and

establish "an administrative record on which the Agency may base any future decision." *Id*. The author of the original letter was Terence J. Mix, Esq.

Mr. Mix is no ordinary citizen. He is a California plaintiffs' attorney who previously brought several lawsuits against the manufacturer of Clomid from the 1970s through the 1990s alleging that Clomid use before pregnancy caused women to deliver children with birth defects. During that litigation, he conducted significant discovery against the company, collecting over 10,000 pages of documents and taking depositions of company employees. Appx. 741. Also significant for this case, Mr. Mix shared the information he gained from his prior discovery with the Cervenys' attorneys. Appx. 425. Finally, Mr. Mix authored at 516-page book, entitled *The Price of Ovulation*, in which he argues extensively that Clomid causes birth defects when used prior to pregnancy. Appx. 250; Appx. 252-350.

On November 26, 2007, Mr. Mix filed a citizen petition urging FDA to change the Clomid label to state that Clomid increases the risk of fetal harm when taken before pregnancy. The petition specifically requested that FDA: (1) "order post-market changes in the product labeling, including the package insert, setting forth reasonable and effective warnings of the teratogenic risks of said drug;" (2) "order risk evaluation and mitigation strategies (REMS) for Clomid and its generics to determine if the benefits of the drug products outweigh the risks;" and

(3) "order postmarket studies and/or clinical trials regarding Clomid and its generics to determine whether the concurrent use of dietary supplements of cholesterol and/or a high cholesterol diet can mitigate or eliminate the increased risk of defects from using clomiphene citrate." Appx. 248.[3] He argued that Clomid "has a long half-life and is still biologically active well into the second month of pregnancy when most [fetal] organs are being formed." Appx. 248. He asserted that Clomid can cause congenital abnormalities including cardiovascular defects, digestive tract defects, genitourinary defects, musculoskeletal defects, and orofacial defects. Appx. 249. Mr. Mix also alleged that Clomid is a cholesterol inhibitor and that numerous scientific studies have shown that impaired cholesterol production can cause neural tube defects and "other congenital abnormalities." *Id.* As part of his submission, he included three chapters of his book, which set forth "all of the supporting evidence establishing that Clomid (clomiphene citrate) and its generics as human teratogens." Appx. 250; Appx. 252-350. At the request of FDA, Mr. Mix Supplemented his Petition five times—on February 13, 2008; February 19, 2008; February 21, 2008; February 22, 2008; and April 2, 2008—attaching voluminous medical literature and multiple additional chapters and

[3] The citizen petition documents are publically available at http://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&D=FDA-2007-P-0234 (last visited Sept. 12, 2016).

excerpts from *The Price of Ovulation*, which cite to even more medical literature. Appx. 252-374.

On September 8, 2009, in a 15-page, single-spaced letter, FDA formally denied the petition. Appx. 381-95. FDA stated that it had "reviewed the references submitted with the petition" and "evaluated the scientific merit of each reference that was submitted." Appx. 383. As part of its review, FDA also "independently surveyed the literature regarding clomiphene citrate." *Id*. FDA found the evidence did not support the conclusion that Clomid is teratogenic when used to induce pregnancy:

> For the reasons described below, we find that the currently available, relevant, and reliable scientific evidence does not establish that clomiphene citrate is a clinically significant cholesterol inhibitor that carries teratogenic risks when used at the recommended dosage of 50 to 100mg for the treatment of ovulatory dysfunction in women.

Appx. 383. FDA explained that "the Petition fails to provide reasonable evidence to demonstrate an association between clomiphene citrate exposure and neural tube defects or other congenital abnormalities." Appx. 387; *see also* Appx. 389 ("the data is *insufficient to demonstrate reasonable evidence of an* ***association*** between clomiphene citrate and congenital abnormalities.") (emphasis added); Appx. 394 ("[W]e find that the available scientific evidence is insufficient to establish reasonable evidence of an association between the use of clomiphene citrate during a treatment cycle and teratogenic risks."); Appx. 394 ("Because there is no

reasonable evidence of teratogenic risks, there is no new safety information upon which FDA could require a REMS [Risk Evaluation and Mitigation Strategies]…"). FDA concluded that "the scientific literature does not justify ordering changes to the labeling that warn of such risks beyond those presently included in labeling." Appx. 383. The FDA further stated that there was insufficient evidence to support requiring either (1) a REMS for Clomid or clomiphene citrate drug products to determine if the benefits of the drug products outweigh the risks" or (2) "postmarket studies and/or clinical trials to determine whether the concurrent use of dietary supplements of cholesterol and/or a high cholesterol diet can mitigate or eliminate the increased risk of birth defects associated with using clomiphene citrate." *Id*.

Not satisfied with FDA's response, Mr. Mix filed a thirteen-page petition for reconsideration on September 29, 2009. Appx. 399-411. He argued that "to allow the language of the product labeling to remain without change … is to perpetuate and sanction a fraud on the American public." Appx. 399. He also criticized the labeling in effect at the time, Appx. 400-01, and argued that animal studies and epidemiologic evidence supported his position. Appx. 401-05; Appx. 307-10. Mr. Mix then supplemented his petition for reconsideration on September 7, 2010, and again on December 6, 2010. Appx. 431-35; Appx. 436-40.

On March 8, 2012, FDA denied the petition for reconsideration. Appx. 418-23. Although FDA stated it need not consider the new evidence raised in the petition for reconsideration, Appx. 420, Nevertheless, FDA scientists, "on [their] own initiative, [] reviewed the article," and concluded that it was not sufficient to cause for FDA "to change our Original Petition Response." *Id*. Based on this review, FDA explained that it continues to "believe that the Original Petition and Reconsideration Petition fail to provide reasonable evidence to demonstrate that the association between clomiphene citrate exposure and neural tube defects or other congenital abnormalities [birth defects] is due to the drug …." *Id*. FDA explained that it's "Original Petition Response was properly founded upon relevant and reliable scientific evidence …." Appx. 422.

The Cervenys filed this action in the District of Utah on July 28, 2014. The Cervenys allege that in September of 1992, Victoria Cerveny was prescribed and took her first round of Clomid with the intent that it help her conceive. Appx. 014 at ¶ 11. Victoria Cerveny took a second round of Clomid in approximately October 1992 and subsequently conceived Alexander Cerveny. *Id*. at ¶ 11. Alexander Cerveny was born on July 27, 1993. Appx. 012 at ¶ 3. Alexander Cerveny was born without the thumb and pinky finger on his left hand. Appx. 015 at ¶ 15. An MRI taken on October 13, 1993 revealed that Alexander's elbow possessed a congenital dislocation of the left radial head. Appx. 015 at ¶ 18.

The Cervenys allege that the Clomid warnings in place in 1992—when Victoria Cerveny allegedly ingested Clomid and became pregnant—failed to adequately warn her prescribing physician that Clomid can cause birth defects *if taken prior to pregnancy*. *See, e.g.,* Appx. 016 ¶ 22, Appx. 022 ¶ 55. Plaintiffs allege that Aventis "knew or should have known that ingesting [Clomid] prior to pregnancy increases the risk of serious birth defects." Appx. 016 at ¶ A. The Cervenys also claim that, Aventis falsely represented that "no causative evidence of a deleterious effect of Clomid therapy on the human fetus has been seen." Appx. 022 at ¶ 57.

Like Mr. Mix, the Cervenys contend that Clomid "can cause serious birth defects when ingested to achieve pregnancy" because it inhibits cholesterol synthesis. Appx. 016 ¶ 22, Appx. 020-22 ¶¶ 45 ("Clomid impairs the biosynthesis of cholesterol by inhibiting the function of enzymes…"), 48, 50, 51, 52, 53, 54. Like Mr. Mix, the Cervenys claim that Clomid "has a long half-life and is still biologically active well into the second month of pregnancy when most [fetal] organs are being formed." Appx. 017 at ¶ 26. The Cervenys base these allegations on various scientific studies and numerous documents Appx.17-22 at ¶¶ 25–54. Each article and study cited in the Cervenys' Complaint was included in Mr. Mix's citizen petition. Appx. 376-77.

The Cervenys' Complaint asserted substantive claims for Design Defect, Manufacturing Defect, Failure to Warn, Breach of Implied Warranty, Breach of Express Warranty, Negligence, Punitive Damages, Fraud, Negligent Misrepresentation, Negligence Per Se, and Unjust Enrichment. Appx. 025-41. On July 14, 2015, the District Court issued an Order granting in part and denying in part Aventis' Motion to Dismiss and dismissing the Cervenys' claims for Design Defect, Manufacturing Defect, Breach of Express Warranty, Negligence, Negligence Per Se, and Unjust Enrichment, and dismissing in part the Cervenys' claim for Failure to Warn to the extent that claim was based on a failure to warn Mrs. Cerveny directly. Appx. 099-103. The Cervenys do not challenge these dismissals. Following the Order on the Motion to Dismiss, the Cervenys were left with claims for Failure to Warn (based on the duty to warn Mrs. Cerveny's prescribing physician), Breach of Implied Warranty, Fraud, and Negligent Misrepresentation.

On September 9, 2015, the District Court conducted a scheduling conference to discuss the timing and sequencing of discovery and dispositive motions. Appx. 175-208. At the conference, the parties argued about whether the Court should entertain an early summary judgment motion addressing federal preemption. The Court then opened discovery and set a briefing schedule for the preemption motion. Appx. 205. The Court specifically cautioned Cervenys' counsel to: "front-

load any discovery they need with respect to preemption to get that done in time to be able to respond by December 9th." Appx. 205. Following the Scheduling Conference, the Cervenys served discovery and Aventis responded. The Cervenys did not file any motions to compel, nor did they ever move the Court to push the briefing schedule to allow for more discovery.

On November 9, 2015, in line with the schedule set by the Court, Aventis filed a motion for summary judgment arguing that all the Cervenys' remaining claims were preempted by federal law. On December 9, the Cervenys filed a 52-page opposition setting forth 52 alleged "Additional Material Facts," including 25 pages of argument, and attaching 16 exhibits. Appx. 446-671. One of exhibits was a Rule 56(f) affidavit that the Cervenys attached "as a precaution." Appx. 618-19. On March 16, 2016, the Court granted Aventis' Motion for Summary Judgment, concluding that the Cervenys' remaining claims were preempted. Appx. 706-32. On March 29, 2016, the Court issued final judgment, dismissing the Cervenys' claims with prejudice. Appx. 733. On April 13, 2016, the Cervenys filed a notice of appeal. Appx. 734-35.

SUMMARY OF THE ARGUMENT

The District Court's grant of judgment to Aventis on all of the Cervenys' remaining claims was correct and should be affirmed. Under federal law, warnings-based tort claims against manufacturers of name-brand prescription medications are preempted if there is "clear evidence" that FDA would have rejected the warnings a plaintiff alleges should have accompanied the product. Here, Plaintiffs' claims are premised on the allegation that Aventis failed to adequately warn prescribing physicians that Clomid increases the risk of birth defects if taken before pregnancy.

The evidence that FDA would have rejected such warnings could not be clearer. Here, in response to a citizen petition, FDA considered the scientific evidence upon which the Cervenys' claims are based, conducted its own independent review of the scientific literature, and twice unequivocally determined that the evidence did not meet the regulatory standard for adding a warning. The first such rejection came in 2009 after Mr. Mix submitted a detailed citizen petition asking FDA to require revisions to Clomid's labeling. The second came in 2012, when Mr. Mix sought reconsideration of his petition.

FDA carefully considered Mr. Mix's petition, reviewed each authority cited, and conducted its own independent review of the medical literature. After its review, FDA concluded that the "currently available, relevant, and reliable

scientific evidence does not establish that clomiphene citrate is a clinically significant cholesterol inhibitor that carries teratogenic risks when used at the recommended dosage of 50 to 100mg for the treatment of ovulatory dysfunction in women." Appx. 383. Based on this conclusion, FDA not only stated that it would not require changes to Clomid's labeling but also stated that it would not require any post-market trials or clinical studies to further explore the issue. Appx. 383. Its conclusion with respect to Mr. Mix's petition for reconsideration three years later remained the same: that there was not "reasonable evidence to demonstrate that the association between clomiphene citrate exposure and neural tube defects or other congenital abnormalities [birth defects] is due to the drug." Appx. 419.

While FDA's rejection of the citizen petition is sufficient to support the District Court's finding, it is not the only evidence supporting preemption. Clomid has an extensive regulatory history. It has been on the market since 1967 and is one of the most prescribed fertility medications. Its risks and benefits are well understood. Over the decades there have been a number of revisions to Clomid's labeling, but one thing has remained consistent: Clomid's labeling has always expressly stated that there is no evidence of a causal relationship between Clomid use and birth defects when used prior to pregnancy.

Unable to refute these facts, the Cervenys ask the Court to adopt two bright-line rules: (1) that clear evidence to support preemption can never be found unless

the manufacturer has sought to revise its label to include the warning sought by the plaintiff, and (2) that denial of a citizen petition can never support a finding of clear evidence. The first of these proposed rules is directly contrary to the United States Supreme Court's decision in *Wyeth v. Levine*, 555 U.S. 555 (2009). As other federal courts have recognized: "[t]he Supreme Court stated a manufacturer must demonstrate by clear evidence the FDA *would* have rejected a label change, not whether the FDA *did* reject the labeling change sought by a plaintiff." *In re Incretin-Based Therapies Prod. Liab. Litig.*, 142 F. Supp. 3d 1108, 1124 (S.D. Cal. 2015). The Cervenys' suggestion that a citizen petition can never support a finding of clear evidence is against the weight of authority and ignores the simple fact that standard for including a warning is the same whether the warning is submitted by a manufacturer or requested in a citizen petition. *Id.* at 1125 n. 18 ("[r]egardless of what prompts the FDA's review of an issue … the same regulatory standard applies."). The District Court properly declined to adopt these tests.

The Cervenys then suggest that the District Court erred because FDA proposed designating Clomid as Pregnancy Category X in 1987, before Mrs. Cerveny took Clomid, and ultimately designated Clomid as Pregnancy Category X in 1994, after Mrs. Cerveny took Clomid. But the Cervenys ignore that a Pregnancy Category X designation generally, and the specific Pregnancy Category X statement proposed by FDA in 1987, did not warn of birth defects generally,

rather it specifically warned that taking Clomid *while pregnant* could cause birth defects. It is undisputed that Mrs. Cerveny did not take Clomid while pregnant with Alexander Cerveny. Therefore she completely avoided the risk of harm that the proposed Pregnancy Category X statement warned of. As the District Court explained, the Cervenys' failure-to-warn claim is a claim that Aventis failed to warn that Clomid when used *before* pregnancy to induce ovulation can cause birth defects. The Pregnancy Category X designation, accordingly, has nothing to do with the Cervenys' claim. The District Court did not err in finding that the Pregnancy Category X designation was irrelevant. Furthermore, the Pregnancy Category X label did not substantively change Clomid's labeling as Clomid was already contraindicated for use in pregnant women.

The Cervenys' other arguments to avoid preemption are similarly unpersuasive. The District Court did not abuse its discretion in entering summary judgment without allowing the Cervenys to conduct additional discovery as it had advised the Cervenys that it was going to allow Aventis to submit an early summary judgment motion and cautioned their counsel to promptly serve any preemption-related discovery. Furthermore, the Cervenys' thorough and detailed opposition to Aventis' motion undercuts their claim that they needed more discovery to respond, and their Rule 56(f) affidavit falls well short of what is required under the Federal Rules. The District Court also correctly held that its

preemption holding applied with equal force to each of the Cervenys' remaining claims as those claims were premised on the same allegations as their failure-to-warn claim.

The District Court's judgment was correct and should be affirmed.

ARGUMENT

I. Standard of Review.

A district court's grant of summary judgment is reviewed *de novo*, and federal preemption is a legal question that is reviewed *de novo*. Summary judgment is viewed "not as a disfavored procedural shortcut, but rather as an integral part of the Federal Rules as a whole, which are designed to secure the 'just, speedy, and inexpensive determination of every action.'" *Celotex Corp. v. Catrett*, 477 U.S. 317, 327 (1986) (quoting FED. R. CIV. P. 1).

A district court's decision to deny a request for discovery prior to ruling on a motion for summary judgment is reviewed only for abuse of discretion. *F.D.I.C. v. Arciero*, 741 F.3d 1111, 1116 (10th Cir. 2013); *Valley Forge Ins. Co. v. Health Care Mgmt. Partners, Ltd.*, 616 F.3d 1086, 1096 (10th Cir. 2010).

II. The Undisputed Facts Establish Clear Evidence that The FDA Would Have Rejected Efforts To Revise Clomid's Labeling to Warn Of Birth Defects When Used Before Pregnancy.

Federal Preemption arises out of the Supremacy Clause of the United States Constitution which provides that the "Constitution and Laws of the United States ... shall be the Supreme Law of the Land …." U.S. Const. art. VI, Cl. 2. Preemption exists when state laws "'interfere with or are contrary to' federal law." *Hillsborough Cnty. Fl. V. Automated Med. Labs., Inc.*, 471 U.S. 707, 712 (1985). "There are three forms of preemption … express preemption, conflict preemption, and field preemption. *Devon Energy Prod. Co., V. Mosaic Potash Carlsbad, Inc.*,

693 F.3d 1195, 1203 n.4 (10th Cir. 2012). This case involves conflict preemption, specifically, impossibility preemption, which applies when it would be impossible for a defendant to simultaneously comply with federal law and the duties imposed by state law. *See English v. Gen. Elec. Co*., 496 U.S. 72, 79 (1990).

The Supreme Court recently addressed conflict preemption in two seminal cases: *Wyeth v. Levine*, 555 U.S. 555 (2009) and *Pliva, Inc. v. Mensing*, 564 U.S. 604 (2011). In *Levine*, the Court outlined the elements of conflict preemption in the context of name-brand prescription drug manufacturers. *Levine* rejected the broad argument that all state-law warning-based tort claims are preempted simply because FDA approves a name-brand manufacturer's product and labeling. Instead, the Court held that such warnings claims are preempted only if there is clear evidence that FDA would not have approved the warnings the plaintiff proposes. 555 U.S. at 571 ("But absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements."); *see also Dobbs v. Wyeth*, 797 F. Supp. 2d 1264 (W.D. Okla. June 13, 2011). In so holding, the Court explained that it was not always impossible for a brand-name manufacturer to simultaneously comply with both its state law duties and the labeling requirements under the FDCA, because, under certain narrow circumstances, a brand-name manufacturer may utilize the changes being effected ("CBE") regulations to add or

strengthen a warning without waiting for FDA approval. *Id*.[4] While *Levine* enunciated the clear evidence standard it did not speak to what type of evidence would satisfy it. *See Dobbs*, 797 F.Supp.2d at 1270 ("*Levine* does not define 'clear evidence', nor does it suggest the level of proof required to constitute such evidence.").

Two years later, the Supreme Court revisited the issue of preemption in *Mensing*, this time in the context of generic pharmaceutical manufacturers. While *Mensing* held that federal law preempts failure-to-warn claims against generic manufacturers because they lack the ability to unilaterally change their labeling, the dissenting Justices, two of whom had been in the majority in *Levine*, discussed *Levine's* "clear evidence" standard, thereby, shedding light on the kind of evidence a brand-name manufacturer could offer to demonstrate that the FDA would not have allowed it to revise its labeling. *Mensing*, 564 U.S. at 626–46 (Sotomayor, J., dissenting).[5] The dissenting Justices explained that a manufacturer could

[4] The CBE regulation is set forth in 21 C.F.R. § 314.70(c)(6)(iii)(A)-(C) and provides that a manufacturer of a brand-name prescription drug may change its label to "add or strengthen a contraindication, add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." The regulation allows the manufacturer to implement the label change upon filing its supplemental application without waiting for the FDA to approve the application.

[5] The dissenting Justices argued that the clear evidence standard should govern whether claims against pharmaceutical manufacturers are preempted, irrespective of whether the defendant is a generic or a brand-name manufacturer. 564 U.S. at 636 ("I would apply the same approach in these cases."). Accordingly, the dissent's discussion of the type of evidence that could satisfy the "clear evidence" standard is applicable here.

demonstrate "clear evidence" not only by showing that it had "proposed a label change to the FDA" but also by showing "that the FDA had itself considered whether to request enhanced warnings in light of the evidence on which a plaintiff's claim rests but had decided to leave the warnings as is." *Id*. at 637.

A. The Standard FDA Uses To Determine Whether a Stronger Warning is Appropriate Is Identical Regardless of Whether the Request Comes From a Manufacturer or a Citizen Petition.

Any discussion of whether there is clear evidence demonstrating that FDA would not have allowed a manufacturer to change its labeling should begin with the standards that govern the FDA's action. FDA does not act arbitrarily; rather its labeling decisions are driven by the science and the applicable regulatory standards. FDA "permits labeling statements with respect to safety only if they are supported by scientific evidence and are not false or misleading." Labeling and Prescription Drug Advertising, 44 Fed. Reg. 37,434, 37,441 (June 26, 1979); *see also* Supplemental Applications Proposing Labeling Changes, 78 Fed. Reg. 67,985, 67,987 (Nov. 13, 2013) (proposed rule). For a potential adverse event to be included in the "Warnings and Precautions" section of the labeling there must be "reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R. § 201.80 (e). These regulations govern the initial label and any subsequent revisions. 73 Fed. Reg. 49,603, 49,604–05 (Aug. 22, 2008) (the standards are "uniform standards for drug labeling").

This "reasonable-evidence" standard applies regardless of the entity requesting the label change. *See In re Incretin-Based Therapies*, 142 F. Supp. 3d at 1125 n. 18 ("Regardless of what prompts the FDA's review of an issue, whether as part of initial drug approval, a CBE submission, or the FDA's own review of a safety signal, the same regulatory standard applies."). It applies to changes made by manufacturers using the CBE process. 21 C.F.R. § 314.70(c)(6)(iii)(A) (CBE submissions must "satisf[y] the standard for inclusion in the labeling …."). It also applies to changes the FDA imposes on manufactures. 73 Fed. Reg. 49,603, 49,604–05 (Aug. 22, 2008). Similarly, it applies to changes requested as part of a citizen petition. The Cervenys begrudgingly concede, as they must, "that the standard for adding a new warning is the same, regardless of whether it is added by a manufacturer through the CBE process or is requested by a citizen through a petition." App. Br. at 38. FDA, in fact, applied this standard when it reviewed Mr. Mix's citizen petition and concluded "that the available scientific evidence is insufficient to establish reasonable evidence of an association between the use of clomiphene citrate during a treatment cycle and teratogenic risks." Appx. 394.

B. The Clear Evidence Standard is Undoubtedly Met Here Where the FDA Has Considered the Science Upon Which Plaintiffs Rely And Unequivocally Stated That It Fails to Meet the Standard.

In evaluating whether the "clear evidence" standard is met, courts consider several pieces of evidence including citizen petition denials, whether FDA

independently analyzed the evidence, and whether FDA approved subsequent labels without making the changes proposed by the plaintiffs. *In re Incretin-Based Therapies*, 142 F. Supp. 3d at 1124.

Here there is extensive unequivocal evidence demonstrating that FDA would not have allowed Aventis to revise Clomid's label to include warnings about risks of birth defects from taking Clomid before pregnancy. Perhaps the most compelling, but certainly not the only evidence, is FDA's denials of Mr. Mix's citizen petition and his petition for reconsideration in 2009 and 2012.

In 2007, Mr. Mix filed his citizen petition. In it he requested that FDA: (1) "order post-market changes in the product labeling, including the package insert, setting forth reasonable and effective warnings of the teratogenic risks of said drug;" (2) "order risk evaluation and mitigation strategies (REMS) for Clomid and its generics to determine if the benefits of the drug products outweigh the risks;" and (3) "order postmarket studies and/or clinical trials regarding Clomid and its generics to determine whether the concurrent use of dietary supplements of cholesterol and/or a high cholesterol diet can mitigate or eliminate the increased risk of defects from using clomiphene citrate." Appx. 248. He argued that Clomid inhibits the production of cholesterol and, as a result, increases the risk of birth defects. Appx 249. He also argued that Clomid posed a risk even in women who take it prior to pregnancy because it has a long half-life and is present in a

woman's body long after she stops taking the medication. Appx. 248. Over the next two years, Mr. Mix supplemented his petition five times and sent the FDA 90 scientific journal articles and abstracts that allegedly supported his claim. Appx. 354, 356-57, 359-60, 362-63, 372-73. In addition, he sent FDA three chapters of his then unpublished book. Appx. 252-350. These chapters laid out in extensive detail Mr. Mix's theory for how Clomid causes birth defects and cited to over 100 scientific articles. *Id.*

FDA reviewed the information cited by Mix and "independently surveyed the literature regarding clomiphene citrate." Appx. 383. As a result of this evaluation, FDA issued a fifteen-page, single-spaced response accompanied by twenty-five footnotes. Appx. 381-95. FDA repeatedly stated that the evidence relied on and cited in Mr. Mix's petition and the evidence from its own independent survey did not meet the regulatory standard for revising the Clomid labeling:

- the "available scientific evidence is insufficient to establish reasonable evidence of an association between the use of clomiphene citrate during a treatment cycle and teratogenic risks." Appx. 394.
- "For the reasons described below, we find that the currently available, relevant, and reliable scientific evidence does not establish that clomiphene citrate is a clinically significant cholesterol inhibitor that carries teratogenic risks when used at the recommended dosage of 50 or 100 mg for the treatment of ovulatory dysfunction in women." Appx. 383.

FDA's conclusion that the "available scientific evidence is insufficient to establish reasonable evidence of an association," is a direct statement that the scientific evidence does not support additional warnings. 21 C.F.R. § 201.80 (e).

Shortly after his citizen petition was rejected, Mr. Mix filed a petition for reconsideration. Appx. 399-411. In it he claimed that "to allow the language of the product labeling to remain without change, including its assurance about the safety to the fetus demonstrated in the premarket clinical investigations, is to perpetuate and sanction a fraud on the American public." Appx. 399.

FDA then considered the additional evidence provided with Mr. Mix's petition for reconsideration and again concluded that there was not reasonable evidence of an association, stating: "[b]ased on our review, we continue to believe that the Original Petition and Reconsideration Petition fail to provide reasonable evidence to demonstrate that the association between clomiphene citrate exposure and neural tube defects or other congenital abnormalities [birth defects] is due to the drug." Appx. 422.

The Cervenys' allegations are identical to those raised by Mr. Mix. They contend that Clomid "can cause serious birth defects when ingested to achieve pregnancy" because it inhibits cholesterol synthesis. Appx. 016 ¶ 22, Appx. 020-22 ¶¶ 45 ("Clomid impairs the biosynthesis of cholesterol by inhibiting the function of enzymes…"), 48, 50, 51, 52, 53, 54. They claim that Clomid "has a long half-life

and is still biologically active well into the second month of pregnancy when most [fetal] organs are being formed." Appx. 017 at ¶ 26. Additionally, they cite fourteen articles, all of which were cited by Mr. Mix in his citizen petition. Appx. 376.[6] FDA's denial of Mr. Mix's citizen petition and petition for reconsideration was, therefore, an unequivocal denial of the Cervenys' central theory. The undisputed facts establish that here FDA "itself considered whether to request enhanced warnings in light of the evidence on which a plaintiff's claim rests but had decided to leave the warnings as is." *Mensing,* 131 S.Ct. at 2588-89 (Sotomayor, J. dissenting).

C. The FDA's Continued Approval of Clomid Labeling Stating That There Is No Reasonable Evidence That Clomid Is Associated Birth Defects When Taken Before Pregnancy Is Further Clear Evidence Supporting Preemption.

The Cervenys repeatedly state that the only evidence supporting the District Court's preemption holding is FDA's denial of Mix's citizen petition and petition for reconsideration. App. Br. at 14 ("the district court granted summary judgment based on nothing more than one citizen's petition to the FDA"); 24 ("the only evidence supporting preemption is the FDA's rejection of a citizen petition"); 31. This misrepresents the facts and the District Court's holding. The District Court cited and expressly relied on additional evidence that further supports preemption.

[6] This is not surprising since their Counsel is working with Mr. Mix. Appx. 425, Appx. 741, Appx. 786.

This evidence included the long regulatory history of Clomid. Clomid has been the most prescribed fertility drug in the United States for decades. In the entire time it has been on the market, the FDA has never suggested that Clomid's labeling should carry a warning that, when used before pregnancy to induce ovulation, it increases the risk of birth defects. Additionally, as the Cervenys point out, the Clomid labeling has been updated several times since 1992, when Mrs. Cerveny ingested Clomid, and in every case FDA never required a warning that Clomid increases the risk of birth defects in women who take it before pregnancy. In fact, in every instance the FDA affirmed that there was no causative evidence of increased risk of birth defects. For example, when Clomid's label was revised in 1994 it continued to state:

> CLOMID should not be administered during pregnancy. CLOMID may cause fetal harm in animals (see Animal Fetotoxicity). Although *no causative evidence of a deleterious effect of CLOMID therapy on the human fetus has been established*, there have been reports of birth anomalies which, during clinical studies, occurred at an incidence within the range reported for the general population.

Appx. 443 (emphasis added). Likewise, in 2012, after FDA's rejection of Mr. Mix's citizen petition and petition for reconsideration, FDA again updated some of Clomid's labeling. Yet again, FDA approved labeling that stating that the data does not support the conclusion that Clomid increases the risk for birth defects in women who take it to become pregnant:

> CONTRAINDICATIONS

> * * *
>
> Available human data do not suggest an increased risk for congenital anomalies above the background population risk when used as indicated…

Appx. 528.

> PRECAUTIONS
>
> * * *
>
> Available human data do not suggest an increased risk for congenital anomalies above the background population risk when used as indicated.

Appx. 530. The continued approval of labeling contradicting the central premise of the Cervenys' claims supports the District Court's holding and provides additional clear evidence that FDA would not have approved warnings that suggested Clomid increases the risk or causes birth defects in women who take it to become pregnant.[7] *In re Incretin-Based Therapies*, 142 F. Supp. 3d at 1124 (noting the continued approval of warnings without the language proposed by plaintiffs supported preemption).

[7] The Cervenys attempt to suggest that it was somehow improper for the District Court to rely on this regulatory history because "every case of this type involves a plaintiff contesting a warning that the FDA has approved" App. Br. at 31 n. 10. However, not every case involves the regulatory history present here. The Cervenys then try to take regulatory history completely off the table stating "the Supreme Court in *Wyet*h clearly rejected the FDA's approval of prior warnings as a basis for preemption." *Id.* citing *Levine* at 558-59. But the Court did no such thing. Rather, the Court considered the regulatory history to evaluate whether, in that case, it provided clear evidence. While *Levine* held that FDA approval of a medication, by itself, is not sufficient to attain preemption, it never suggests that regulatory history is irrelevant to the clear evidence inquiry.

While the Cervenys point out that *Levine* "rejected preemption even though there had been communication between the FDA and the manufacturer over a period of decades regarding the primary issue in the case" (App. Br. at 22), they wholly ignore the nature of the communication in *Levine* and how it materially differs from regulatory history here. As the Cervenys' brief highlights, *Levine* involved decades of repeated discussions about, and strengthening of, the warning of the dangers of IV push administration of Phenergan, including multiple label revisions strengthening the warnings at issue. App. Br. at 22-23 (citing *Levine*, 555 U.S. at 613-15 (Alito, J., dissenting)). In contrast, the regulatory history with respect to Clomid is one where FDA continually and consistently approved labels stating that the evidence does not suggest that Clomid is associated with birth defects when used before pregnancy. FDA has never required, or even proposed, warnings stating that Clomid, when used as directed to induce ovulation, poses any risk of fetal harm. Simply put, every official action by FDA over the last 40 years has reaffirmed that FDA does not believe Clomid causes or increases the risk of birth defects in women who take it prior to pregnancy. These actions provide clear evidence that FDA would not have approved a label change indicating that Clomid causes or increases the risk of birth defects in women who take it prior to pregnancy. This Court should affirm.

D. The Timing of the FDA's Denial of the Citizen Petition Strengthens the District Court's Finding Of Clear Evidence.

Also supporting clear evidence is the fact that FDA's review of Mr. Mix's citizen petition took place in 2009, seventeen years after Mrs. Cerveny took Clomid. Thus, when evaluating Mr. Mix's and the Cervenys' theories, FDA had the benefit not only of the evidence available in 1992, but also the evidence that had developed over the next seventeen years. Even with this additional evidence FDA found the scientific record insufficient. Significantly, FDA did not base its finding on the existence of any exonerating evidence that had come to light after Mrs. Cerveny's ingestion of Clomid. *See generally* Appx. 381-95; Appx 418-21. So the only difference in the scientific record, between the time of Mrs. Cerveny's ingestion of Clomid and FDA's denial of the citizen petition was additional "evidence" that accumulated over the years that allegedly supported Plaintiffs' argument.

As the District Court recognized, when FDA rejected Mr. Mix's citizen petition, it "by proxy rejected [the Cervenys'] theories." Appx. at 726. The District Court's conclusion that there is "clear evidence that the FDA would not have permitted Aventis to strengthen Clomid's label prior to 1992" was correct and should be affirmed. Appx. at 727.

III. The Court Should Reject The Cervenys' Proposed Bright-Line Rules As Contrary to *Levine*.

Despite recognizing that *Levine's* clear evidence standard is fact-specific, the Cervenys argue that this Court should adopt one of two bright-line rules. First the Cervenys ask this Court to hold that clear evidence can never exist unless the manufacturer has attempted to change its labeling to include the plaintiffs' proposed warning. In the alternative, the Cervenys ask the Court to hold that, regardless of the facts at issue, the FDA's denial of a citizen petition can never constitute clear evidence.

The Cervenys argue for these bright-line rules because they have nothing to say about the facts. They cannot dispute that FDA carefully considered Mr. Mix's citizen petition, including conducting its own independent survey of the literature. They cannot dispute that FDA found no "reasonable evidence of an association" and concluded that "the scientific literature does not justify ordering changes to the labeling that warn of such risks." And they cannot dispute that FDA further concluded that there was insufficient evidence to even warrant further study. The Cervenys' only hope is to get the Court to adopt broad and unprecedented rules categorically declaring that, regardless of the facts and circumstances, preemption can never exist outside very limited circumstances. However, as discussed below, neither of the Cervenys' proposed rules is supported by either *Levine* or its progeny and this Court should reject them.

A. *Levine* Expressly Contemplates That Preemption Can Exist Even Where the Manufacturer Has Not Sought To Amend Its Label to Add The Warning Sought By The Plaintiff.

The Cervenys' argument that the District Court erred in "concluding that there could be clear evidence that the FDA would have rescinded a manufacturer's label change in the absence of any evidence that the Defendants tried to change the label" is contrary to the express language of *Levine*. *Levine* stated that preemption can be established by "clear evidence that the FDA *would not have approved* a change" to the label. *Levine*, 555 US at 571. (emphasis added). In *Mensing*, the Court reiterated this standard, explaining: "Wyeth could have attempted to show, by 'clear evidence,' that the FDA would have rescinded any change in the label" *Mensing,* 564 U.S. at 624 n. 8. The Supreme Court has never suggested that preemption can only be found if a manufacturer submits a label change to FDA that is either rejected or rescinded. Indeed, as another federal court has explained, any such ruling would be inconsistent with *Levine*: "[t]he Supreme Court stated a manufacturer must demonstrate by clear evidence the FDA *would* have rejected a label change, not whether the FDA *did* reject the labeling change sought by a plaintiff." *In re Incretin-Based Therapies*, 142 F. Supp. 3d at 1124. This concept is further supported by the dissent's discussion in *Mensing.* There, the Justices gave numerous examples how a manufacturer could demonstrate "clear evidence," including by showing that "the FDA had itself considered whether to request

enhanced warnings in light of the evidence on which a plaintiff's claim rests but had decided to leave the warnings as is." 564 U.S at 637 (Sotomayor, J. dissenting).

Not surprisingly, several other courts have explicitly rejected the argument that "clear evidence" can only be found if the manufacturer has requested the label change sought by the plaintiffs and the FDA rejected it. *In re Incretin-Based Therapies*, 142 F. Supp. 3d at 1124 ("The Court rejects Plaintiffs' position that Defendants cannot establish preemption absent express rejection of a proposed labeling change. … though a CBE or PAS submission and rejection would readily meet the clear evidence standard, it is not the only means by which a manufacturer can establish conflict preemption."); *Reckis v. Johnson & Johnson*, 28 N.E.3d 445, 460 n. 29 (Mass. 2015) ("The court in *Wyeth* specifically suggested that 'clear evidence' could be established by the FDA's rejection of a drug maker's attempt to give the warning underlying a claim of failure to warn. That is not to say that the *Wyeth* standard of clear evidence can be satisfied only by the FDA's rejection of a manufacturer's request for an additional warning."); *In re: Byetta Cases*, No. JCCP 4574, at pp. 28–30 (Cal. Sup. Ct. Nov. 13, 2015) (the state court consolidated action for incretin-based therapies also finding preemption) (Appx. 660-91). The single case upon which Plaintiffs rely on for this point, *Schedin v. Ortho-McNeil-Janssen Pharm., Inc.*, 808 F. Supp. 2d 1125, 1132-33 (D. Minn. 2011), is contrary

to the clear weight of authority and the express language of *Levine*; and should be disregarded.

The Cervenys argue that requiring a manufacturer to submit a proposed label is consistent with "the context of" *Levine* because "[w]hen addressing the 'clear evidence' requirement, the *Wyeth* Court was addressing the argument that the FDA could have rejected a label change after the manufacturer had universally implemented such a change." App. Br. at 24. What the Cervenys miss is that *Levine* involved a situation where the manufacturer had not attempted to amend its labeling. 555 US at 569. Had the Court wanted to limit preemption to situations where the manufacturer had actually attempted to revise its labeling, it could have simply announced that standard and dispensed with the preemption argument on that basis. But the Court did not do so; rather it explained that it would find preemption where the manufacturer offers clear evidence that the FDA would not have allowed it to amend its labeling. 555 US at 571. *Levine* is properly read as allowing a manufacturer to establish preemption when it had not actually sought to amend its label.

The Cervenys also argue that "[w]ithout any action by the manufacturer to try to change the label, the evidence as to how the FDA would have reacted to such a change can never be 'clear.' The most any court can do is speculate …." App. Br. at 27. But this ignores the standard that the FDA applies when deciding whether to

permit an enhanced warning. There is no need to speculate. The Court can look at the evidence offered and determine whether it clearly demonstrates that there is no reasonable association between the drug and a potential adverse outcome. Here, where the FDA has reviewed the literature, unequivocally stated that there is no "reasonable evidence of an association," and concluded that "the scientific literature does not justify ordering changes to the labeling," the evidence could not be clearer. The District Court's finding of preemption was based on clear evidence, not speculation.

Given the lack of authority supporting their argument, the Cervenys also cite a law review article written by an attorney who represents plaintiffs in litigation against pharmaceutical manufacturers. App. Br. at 27 (citing Michael M. Gallagher, *Clear Evidence of Impossibility Preemption after Wyeth v. Levine*, 51 GONZ. L. REV. 439, 474 (2015-16)).[8] Mr. Gallagher's article is of little help to the Cervenys however, as Mr. Gallagher actually advocates *replacing* the clear evidence standard with the requirement that a manufacturer actually submit the plaintiffs' proposed label to the FDA. Gallagher, 51 GONZ. L. REV. at 444 ("[T]he Court should adopt the following rule: a claim is preempted when FDA previously rejected the proposed label change sought by the plaintiffs."). Mr. Gallagher concludes his article by suggesting that the Supreme Court "revisit its holding in

[8] The Cervenys neglect to mention Mr. Gallagher's rather obvious bias. *See* 51 GONZ. L. REV. 439 n.a1 (disclosing that Mr. Gallagher served as plaintiffs' counsel in two of the cases discussed in his article).

Levine, discard the 'clear evidence' standard, and conclude that failure to warn claims are preempted only if the FDA rejects the proposed label change before the plaintiff's injury." *Id.* at 480. While it is understandable that the Cervenys would prefer the rule advanced by Mr. Gallagher, it is not the law and the District Court did not err in rejecting it.

B. Denials of Citizens Petitions Can Provide Clear Evidence That FDA Would Have Rejected A Warning.

The Cervenys also ask the Court to adopt a bright-line rule that the denial of a citizen petition, standing alone, can never support a finding of clear evidence. They argue that "no court until this case has found a claim to be preempted based on only the FDA's rejection of a citizen petition." App. Br. at 31. Contrary to the Cervenys' assertions, courts *have* found preemption based solely on the "clear evidence" garnered by FDA's denial of citizen petitions. For example, in *Reckis v. Johnson & Johnson*, the court found plaintiffs' claims partially preempted based solely on FDA's denial of a citizen petition requesting that over-the-counter ibuprofen include a specific reference to the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis. 38 N.E.3d at 458 ("…the FDA's explicit rejection of the 2005 citizen petition's proposed inclusion of a specific mention of SJS or TEN by name on OTC ibuprofen drug labels…provides the necessary 'clear evidence' that the FDA would have rejected the addition of [such] a warning."); *see also Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir. 2010)

(noting "[t]he 'clear evidence' in this case is the agency's refusal to require a reference to SJS/TEN on the label of over-the-counter drugs containing ibuprofen, when it had been asked to do in a submission to which the agency was responding"). Other courts have found the "clear evidence" standard satisfied based largely on FDA's denial of a citizen petition. *See In re Incretin-Based Therapies,* 142 F. Supp. 3d at 1127.

The Cervenys cite to several cases they claim support their argument that the denial of a citizen petition cannot satisfy the "clear evidence" standard. App. Br. at 32 (*citing Mason v. SmithKline Beecham Corp*., 596 F.3d 387, 393-96 (7th Cir. 2010); *Koho v. Forest Labs., Inc*., 17 F. Supp. 3d 1109, 1117 (W.D. Wash. 2014); *Hunt v. McNeil Consumer Healthcare*, 6 F. Supp. 3d 694, 700-01 (E.D. La. 2014); *Schedin*, 808 F. Supp. 2d at 1133; *Dorsett v. Sandoz*, *Inc.*, 699 F. Supp. 2d 1142, 1157 (C.D. Cal. 2010); *Reckis*, 28 N.E.3d at 459). Most of these cases, however, did *not* find that the denial of a citizen petition is *ipso facto* insufficient to meet the "clear evidence" standard. Instead, the majority of them held that the specific citizen petition denials at issue were insufficient because those denials occurred *years before the plaintiff ingested the medication*. *See Mason*, 596 F.3d at 395 ("Even the latest of these [citizen petitions] was made several years before [plaintiff's] suicide. This temporal gap is especially important in the analysis of prescription drugs because it constantly evolves as new data emerges."); *Koho*, 17

F. Supp. 3d at 1117 (noting that the latest of the citizen petition denials in that case occurred five years *before* the plaintiff ingested the medication); *Hunt*, 6 F. Supp. 3d at 701 ("FDA's response in 2006 to the Citizen Petition is not clear evidence the agency would have rejected *in 2010* the stronger warning…")(emphasis in the original); *Dorsett*, 699 F. Supp. 2d at 1157-58 (explaining that "the FDA's position was changing" and "given these developments in the state of scientific knowledge in the SSRI industry leading up to July 2004, it cannot be said that there is clear evidence that in July 2004 the FDA would have prohibited additional suicidality warning language.").

These courts reasoned that new research and scientific information could have been generated between the time the citizen petitions were denied and the time the plaintiffs ingested the medication. As such, FDA could have permitted the change requested by the plaintiffs based on this new information. Indeed, it is surprising that the Cervenys would assert this argument and point the Court to *Koho*, *Hunt*, and *Dorsett* after the District Court specifically called out their counsel for "misrepresent[ing] the law on this issue" and "fail[ing] to mention that several of the cases cited in the Plaintiffs' brief found the denial of a citizen petition to be unpersuasive because the denial predated the injury—not that a denial of a citizen petition can never serve as 'clear evidence' … ." Appx. 722 at n. 5.

Mason illustrates this point, it involved claims that Paxil, a Selective Serotonin Reuptake Inhibitor ("SSRI") anti-depressant medication caused the plaintiff's daughter to commit suicide. The Defendant pointed out that FDA had, on three occasions, rejected citizen petitions to add a suicide warning to Prozac, another SSRI. The Seventh Circuit said that the citizen petition rejections did not provide clear evidence because "the latest of these findings was made several years before [the] suicide." 596 F.3d at 395. Second, while Paxil and Prozac are both SSRIs the Court stressed "they are different drugs made by different manufacturers" and gave "little weight to the administrative history of Prozac …." *Id.* Finally, when denying the third citizen's petition, FDA stated that there needed to be more research "to explore the relationship between antidepressants and suicidality." *Id.*

That is the complete reverse of the situation here. Here, the citizen petition was denied years *after* Mrs. Cerveny ingested Clomid. Therefore, FDA had in front of it at least 17 additional years of evidence to support any alleged association between Clomid and birth defects, and FDA still found the evidence wanting. Unlike in *Mason*, the citizen petition here addressed the drug at issue. Finally, unlike *Mason* the FDA stated that the evidence here did not support ordering either post-market studies or clinical trials.

While *Schedin* arguably stands for the proposition that the denial of citizen petition alone cannot constitute the "clear evidence," 808 F. Supp. 2d at 1133,[9] its analysis is flawed for two reasons: (1) it depends on an erroneous reading of *Levine* as standing for the proposition that preemption can only be found if the manufacturer actually requests a label change which is subsequently denied by FDA; and (2) it ignores that there is no legal basis for distinguishing between FDA's denial of a citizen petition and FDA's denial of an application submitted by the manufacturer—in both cases FDA applies the exact same standard. *See In re Incretin-Based Therapies*, 142 F. Supp. 3d at 1125.

The crux of the Cervenys' argument is that a citizen petition cannot be preemptive because it proves only that FDA would not *mandate* a label change, not that FDA would not *allow* one if the manufacturer asked for it. This argument, that FDA applies a different standard to citizen petitions than it does to submissions by the manufacturer, has no basis in the law. As discussed above, the Cervenys concede that the standard is the same. App. Br. at 38. When FDA applied that standard to Mr. Mix's citizen petition, it concluded "that the available scientific evidence is insufficient to establish reasonable evidence of an association between the use of clomiphene citrate during a treatment cycle and teratogenic risks." Appx. 394.

[9] *Schedin's* discussion of the preemptive effect of citizen petitions was dicta as the letter reflecting the denial of the petition was not properly in the record. 808 F. Supp. 2d at 1133.

The Cervenys attempt to argue around the fact that the standard is the same by claiming that: "the action required by the FDA is very different. Granting a citizen petition requires the FDA to insist that the manufacturer change the label, while allowing a label change that has already been made requires no action at all." App. Br. at 38. But regardless of what the ultimate action is, the regulatory standard controls and dictates when and how FDA should act. The Court should reject the Cervenys' suggestion that FDA would shirk its regulatory responsibilities by either rejecting citizen petitions that established a reasonable association between a drug and an adverse event because it is easier not to "insist that the manufacturer change the label" or allowing CBE changes to add warnings when no such association was established because it is easier to take "no action at all."

An alternative way of framing the Cervenys' argument is that FDA somehow gives more deference to applications submitted by manufacturers than those submitted via a citizen petition. This is essentially what their expert, Dr. Ross, argues. Appx. 508. Again, the Cervenys cite to no statute, regulation, or guidance in support of this position. There can be many explanations for the disparate success of applications filed by manufacturers versus those filed as citizen petitions, not the least of which is that manufacturers understand the standard, are thoroughly familiar with the scientific evidence, are able to identify

when evidence meets the standard, and only propose labeling changes when they believe that there is a reasonable association. As Mr. Mix's petition demonstrates; citizens, particularly those who, like Mr. Mix, have an agenda, do not show such restraint. This disparity in success does not mean that FDA defers to manufacturers.

Contrary to the Cervenys' arguments, FDA does not hesitate to reject labeling changes proposed by the manufacturer when there is not reasonable evidence of a causal association. *See, e.g.*, *Dobbs*, 797 F. Supp. 2d at 1276. FDA requires a reasonable association before permitting a warning because of the danger of over-warning which, "just like underwarning, can similarly have a negative effect on patient safety and public health." 71 Fed. Reg. 3935 (FDA Jan. 24, 2006). FDA has explained that warnings about "speculative or hypothetical risks, could discourage appropriate use of a beneficial drug, biologic, or medical device." 73 Fed. Reg. 2848, 2851 (FDA Jan. 16, 2008); *see also Mason*, 596 F.3d at 392 ("Overwarning can deter potentially beneficial uses of the drug … and can dilute the effectiveness of valid warnings."). Given these concerns, the Court should reject the Cervenys' speculative arguments that the FDA, after definitively stating that the evidence does not establish a reasonable association between Clomid and birth defects, would have ignored the evidence and simply allowed a warning had it been proposed by Aventis.

Furthermore, the Cervenys' suggestion that FDA does not carefully consider citizen petitions is refuted by FDA's handling of Mr. Mix's actual petition. The record established that FDA gave it careful consideration including reviewing the cited references and independently surveying the literature. It was only after this thorough review that FDA concluded that there was no evidence of a reasonable association and denied the petition. Given this factual record, the Court need not concern itself with how FDA generally approaches citizen petitions, what matters is how it approached Mr. Mix's petition here.

As the regulatory standard for evaluating warnings proposed by manufacturers via the CBE process and by citizens via the citizen petition process is identical, the District Court correctly held that the denial of a citizen petition can provide clear evidence that the FDA would have rejected a labeling change proposed by the manufacturer. This Court should affirm.

IV. The District Court Correctly Concluded That The 1994 Inclusion of Pregnancy Category X Warnings Is Irrelevant Because It Is Undisputed that Mrs. Cerveny Did Not Take Clomid While Pregnant.

The Cervenys next argue that the District Court's preemption holding was erroneous and should be reversed because the Clomid label was in fact amended to designate Clomid as a Pregnancy Category X medication. They point out that FDA first proposed designating Clomid as Pregnancy Category X in 1987 (five years before Mrs. Cerveny took Clomid), and that Clomid was ultimately so designated

in 1994 (two years after Mrs. Cerveny took Clomid). App. Br. at 40. The Cervenys' argument ignores, however, that to establish that the Cervenys' claim is preempted, Aventis does not need to establish every single conceivable failure-to-warn claim that could be asserted by a plaintiff who took Clomid is preempted, it merely needs to show that the Cervenys' claim is preempted.[10]

The Cervenys argue that the eventual designation of Clomid as Pregnancy Category X and revisions to the language of the pregnancy contraindication in 1994 shows "that updating the label was possible." App. Br. at 40. They also state that "the 1994 change was one of five labeling revisions for Clomid, three of which occurred from 1993 through 1995, shortly after Mrs. Cerveny ingested Clomid." *Id*. But, labeling revisions are always possible provided that the standard for labeling revisions is met. The question is whether FDA would have permitted the

[10] The Cervenys also ignore that the addition of a Pregnancy Category X statement would not have substantively altered the information that was contained on the 1992 Clomid label. Clomid was contraindicated for use in pregnant women and its label stated that "although no causative evidence of a deleterious effect of Clomid therapy on the human fetus has been seen, such evidence in regard to the rat and rabbit has been presented." A pregnancy category X label is nothing more than a statement that a medication should not be used during pregnancy because the risks of its use during pregnancy outweigh its benefits. 44 Fed. Reg. 37434, 37464 (June 26, 1979) (Pregnancy Category X appropriate where "studies in animals or humans have demonstrated fetal abnormalities … and the *risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit*"). A pregnancy contraindication means the risks of the medication outweighed the benefit in women who are pregnant. Therefore, even if the "Category X" designation had been included in the Clomid label, it would not have conveyed to prescribing physicians any information that was not already present there.

manufacturer to revise the label to include or strengthen a warning addressing the harm to which the plaintiff was exposed.

It is undisputed that Victoria Cerveny did not take Clomid *while pregnant*; rather she ingested Clomid *prior to* pregnancy. Appx. 011 ¶ 1 (Alexander Cerveny suffered birth defects "caused by the ingestion of…Clomid by his mother…prior to her pregnancy."); Appx. 014 ¶ 12 ("following her second round of Clomid, Victoria Cerveny discovered she was pregnant."). The Cervenys' entire Complaint is based on the assertion that Aventis should be liable for failing to warn that Clomid causes or increases the risk of birth defects in women who take it prior to pregnancy. *See*, *e.g.*, Appx. 022 ¶¶ 55, 56. As the District Court explained, the Cervenys' failure-to-warn claim was that "Aventis had a duty to warn Mrs. Cerveny's prescribing physician that Clomid can cause birth defects if taken prior to pregnancy" and that "if Mrs. Cerveny had 'been aware of the hazards associated with the use of Clomid prior to pregnancy, she would not have purchased and/or consumed' Clomid." Appx. 714 (quoting Am. Compl.at ¶¶ 21, 22).

Therefore, the Pregnancy Category X label, like the pregnancy contraindication which was in place in 1992, would not have applied to her. It warned of risks that she was never exposed to. A plaintiff cannot allege as a defect in a label a warning that would not have applied to them. *See Rivera v. Wyeht-Ayerst Labs.,* 283 F.3d 315, 321 (5th Cir. 2002) (rejecting as "absurd" and "too

speculative to establish Article III standing" a claim based on the allegation that "an extra warning, though inapplicable to [the plaintiff], might have scared her and her doctor from Duract"); *see* also Dan B. Dobbs, Paul T. Hayden and Ellen M. Bublick, *The Law of Torts* § 468 (2d ed.) ("[T]he injury suffered [by a plaintiff] must be within the class of injury that the warning requirement was meant to avoid"). If the proposed warning did not apply to the plaintiff, the label cannot be defective for lacking the warning. *See Kapps v. Biosense Webster, Inc.*, 813 F. Supp.2d 1128, 1157 (D. Minn. 2011) ("if a plaintiff's proposed warning would not have changed anyone's behavior, a product cannot be defective for lacking that warning."); *Martin v. Hacker*, 628 N.E. 2d 1308, (N.Y. 1993) ("since it is undisputed that [plaintiff] had no history of mental depression, we are not concerned with the adequacy of the contraindications section of the insert").

The Cervenys point to *Mason*, *Hunt*, and *Dorsett* as examples of courts that "have denied claims of preemption by citing differences in what was rejected by the FDA and what was proposed by the plaintiff." App. Br. at 40-41. But they fail to appreciate the significance of those cases. Just as a defendant cannot establish preemption by highlighting that FDA would not have allowed it to add a warning that does not relate to the plaintiff's claim, a plaintiff cannot avoid preemption by arguing that FDA would have allowed a similarly unrelated label change that warns of a risk to which the plaintiff was not exposed. To hold otherwise leads to

the absurd conclusion that preemption can never exist if the manufacturer theoretically could have "strengthened" some warning about some condition, regardless of its relevance to the pending case. Plaintiffs cite no law in support of this contention. Indeed, as the District Court stated "[i]t would be a nonsensical result if a plaintiff could avoid a preemption defense by arguing that a drug label could have been strengthened in any form, regardless of its relevance to the plaintiffs' case." Appx. at 731.

The Cervenys attempt to argue that the Pregnancy Category X label is not irrelevant to their claim by pointing to the language proposed in 1987: "Clomid is contraindicated in pregnant women. Clomid may cause fetal harm when administered to pregnant women. Since there is a reasonable likelihood of the patient becoming pregnant while receiving Clomid, the patient should be appraised of the potential harm to the fetus." App. Br. at 42. The Cervenys paraphrase the proposed warning suggesting that it states "that women who are attempting to become pregnant need to be warned of the potential harm to the 'fetus.'" App. Br. at 42. They then argue that because Mrs. Cerveny was attempting to become pregnant, "the warning was intended for her." *Id.* The Cervenys ignore however, that the risk the warning intended to prevent was not harm to the fetus generally, but rather specifically the harm to the fetus posed by continuing to take the medication after becoming pregnant. Because Mrs. Cerveny did not take Clomid

while pregnant, she completely avoided the risk that the Pregnancy Category X label warned of. In other words, neither Mrs. Cerveny nor Alexander Cerveny were exposed to the risk that the Pregnancy Category X label would have warned of. And, accordingly, the District Court correctly concluded that it was irrelevant to her claims.

In attempt to evade this obvious result, the Cervenys argue that "the complaint was not limited to any precise warning about the risk of using Clomid to become pregnant." App. Br. at 42. But even this argument concedes the point. Whatever the precise wording might have been, the complaint necessarily was limited to "warning[s] about the risk of using Clomid to become pregnant." As the District Court explained "the plaintiffs claim that Clomid carries a risk of causing birth defects if the drug is ingested *prior* to pregnancy." Appx. 731 (emphasis in original). The Pregnancy Category X designation has nothing to do with risks of using Clomid to become pregnant. It is factually and legally irrelevant to the Cervenys' claim.

The Cervenys then argue that the Pregnancy Category X designation is "strong evidence that the FDA would have allowed a warning about the risk of using Clomid to become pregnant" because "Clomid remains in a woman's system for a considerable period of time after ingestion. App. Br. at 43. This exact argument, however, was presented in Mr. Mix's citizen petition and rejected by

FDA. As FDA explained at the time, any Clomid remaining in a woman's body after conception "is insufficient to cause significant inhibition of cholesterol synthesis even after multiple cycles of treatment." Appx. 387. The bottom line is that the Cervenys' speculative suggestion that "it is not a stretch, then, to conclude that the FDA would have allowed an additional warning about the risk to a fetus conceived using Clomid" (App. Br. 43-44) cannot be squared with what has actually happened. When FDA approved the Pregnancy Category X designation in 1994, it reaffirmed that "no causative evidence of a deleterious effect of CLOMID therapy on the human fetus has been established." Appx. 443. This position has been subsequently affirmed multiple times, including when FDA rejected the Mix citizen petition and petition for reconsideration, and in 2012 when FDA approved Clomid labeling that stated "[a]vailable human data do not suggest an increased risk for congenital anomalies above the background population risk when used as indicated." Appx. 530.

Accordingly, the District Court's conclusion that the addition of the Pregnancy Category X designation to the Clomid labeling is irrelevant to the question of preemption was correct. This Court should affirm.

V. The District Court Did Not Abuse Its Discretion By Not Allowing Additional Discovery Before Granting Summary Judgment.

The Cervenys also argue that even if this Court agrees with the District Court's preemption analysis, this Court should not affirm, but should instead

reverse and remand for more discovery. The Cervenys express the hope that with more discovery they will be able to "shed light on which label changes were possible at various times." App. Br. at 45. The decision whether to allow additional discovery before ruling on a motion for summary judgment is committed to the sound discretion of the District Court. *Valley Forge Ins. Co.*, 616 F.3d at 1096.[11]

There was no abuse of discretion here. On September 9, 2015, the District Court conducted a scheduling conference to discuss the timing and sequencing of discovery and dispositive motions. Appx. 175-208. At the conference, the District Court specifically cautioned the Cervenys to "front-load any discovery [they] need with respect to preemption to get that done in time to be able to respond by December 9th." Appx. 205. Following the Scheduling Conference, the Cervenys served discovery and Aventis responded. The Cervenys did not file any motion to compel nor did they seek to push the briefing deadline to allow for more discovery.

Aventis filed its Preemption Motion on November 9, 2015. On December 9, the Cervenys filed a thorough, 52-page opposition, including: (1) substantive responses to each of the 22 facts contained in Aventis' Statement of Undisputed Material Facts, (2) 52 alleged "Additional Material Facts" and (3) 25 pages of Argument. Appx. 446-97. The Cervenys urged the District Court to deny Aventis'

[11] In making this argument the Cervenys erroneously state that "preemption based on clear evidence presents a question of fact." App. Br. at 46. However, as the Cervenys themselves recognize in their statement of the standard of review: "Whether federal law preempts a plaintiff's state tort law claims presents a pure question of law appropriate for resolution by summary judgment." App. Br. at 9.

Motion. The Cervenys also attempted to submit a Rule 56(f) affidavit "as a precaution." Appx. at 295. However, the Cervenys' "precautionary" Rule 56(f) affidavit falls far short of this Court's requirements.

This Court has explained that Rule 56(f)'s "protections … can be applied only if a party satisfies certain requirements." *Price v. Western Resources, Inc.*, 232 F.3d 779, 783 (10th Cir. 2000). "[A] party seeking to defer a ruling on summary judgment under Rule 56(f) must provide an affidavit 'explain[ing] why facts precluding summary judgment *cannot be presented*.'" *Valley Forge Ins. Co.*, 616 F.3d at 1096 (*quoting Comm. for the First Amendment v. Campbell*, 962 F.2d 1517, 1522 (10th Cir. 1992)) (emphasis added). The affidavit must identify "(1) 'the probable facts not available,' (2) why those facts cannot be presented currently, (3) 'what steps have been taken to obtain these facts,' and (4) 'how additional time will enable [the party] to' obtain those facts and rebut the motion for summary judgment. *Id.*

The Cervenys' precautionary affidavit falls short of the requirements for several reasons. Perhaps most fundamentally, the Cervenys cannot explain "why facts precluding summary judgment cannot be presented" when they actually filed a detailed opposition presenting 52 additional "facts." Furthermore, their affidavit does not request discovery to identify facts that would preclude summary judgment; rather it states that "factual discovery is necessary to present facts

essential to the prosecution of this case." Appx. 618. It then broadly lists discovery the Cervenys would like to take to develop the case generally, including depositions of "the treating physicians and healthcare providers to outline the facts of the case, describe the damages, and for expert foundation" and time "to further develop experts with the discovery material to be obtained." Appx. 617. The affidavit makes no effort to tie this discovery to the federal preemption issues raised by Aventis' motion.

Under these circumstances, the District Court's decision to proceed with Aventis' summary judgment motion was well within its discretion. This Court should affirm.

VI. The District Court Correctly Held that All of The Cervenys' Remaining Claims Were Preempted.

The Cervenys conclude by arguing that even if their failure-to-warn claims are preempted, the District Court should have allowed them to proceed on their fraud, negligent misrepresentation and breach of implied warranty claims. The Cervenys ignore, however, that these claims all involve the same issues as their failure-to-warn claim, and the conclusion that the FDA would not have allowed Aventis to change its label necessarily compels a conclusion that each of these claims is preempted.

The Cervenys seek to obscure this by discussing their claims generally and focusing on the elements of the claims as opposed to the underlying allegations.

The Cervenys argue that "claims for fraud and negligent misrepresentations are based on false, affirmative statements; they are not based on the failure to provide particular information" and that "[t]he implied warranty of merchantability requires that goods be 'merchantable'" and that "an implied warranty claim may be based on false affirmative representations." App. Br. at 48-49. However, the issue is not how the Cervenys could have stated their claims, and what allegations might support them, the issue is how they actually pled them. The Cervenys' Complaint demonstrates that their fraud, negligent-misrepresentation, and breach-of-implied-warranty claims are substantively identical to their failure-to-warn claim. As other courts have recognized, "[r]egardless of the label assigned," to the extent a plaintiff contends that the defendant manufacturer failed to inform them about risks allegedly associated with the product at issue, any such claim "is, 'at bottom, a failure to warn claim.'" *Timberlake v. Synthes Spine, Inc.*, No. V-08-4, 2011 WL 711075, at *7 (S.D. Tex. 2011) (quoting *Talbott v. C.R. Bard, Inc.*, 865 F. Supp. 2d 37, 45 (D. Mass. 1994)).

The Cervenys' negligent-misrepresentation claim is based on the allegation that: "[p]rior to September of 1992, Defendants became aware of the risks of ingesting Clomid prior to pregnancy, however Defendants failed to communicate to Victoria Cerveny and other members of the general public, that the ingestion of this drug while pregnant could have the increased risks of serious birth defects."

Appx. 038 ¶ 129. The Cervenys also allege that "Defendant failed to warn the Plaintiff, and other consumers, of the defective condition of Clomid, as manufactured and/or supplied by Defendants." Appx. 038 ¶ 130. These allegations are identical to their failure-to-warn claim. The District Court correctly concluded that its preemption holding applied with equal force to this claim.

The Cervenys' breach-of-implied-warranty claim is also substantively identical to their failure-to-warn claim. The Cervenys allege that Clomid was not merchantable because "Victoria Cerveny could not have known about the nature of the risks and side effects associated with Clomid until after she used it." Appx. 030 ¶ 90. Where the FDA would not have allowed Aventis to warn of scientifically unsupported risks associated with taking Clomid prior to pregnancy, a state cannot hold that Clomid is not merchantable without such warnings.

The same is true for the Cervenys' fraud claim. It is based on the allegations that Aventis: (1) "had a duty to disclose material information about serious side effects to consumers"; (2) "had a duty to disclose … the potential for the medication to cause severe birth defects when used prior to pregnancy"; and (3) "intentionally failed to disclose this information." Appx. 036 at ¶ 120. These allegations track the failure-to-warn claim. The Cervenys also allege that Aventis "represented to prescribing physicians and patients that no causative evidence of a deleterious effect of Clomid therapy on the human fetus has been presented" and

that "Clomid were [sic] a safe and effective treatment." The FDA's denial of Mr. Mix's citizen petition because there is no reasonable evidence of a causal relationship between Clomid and birth defects, directly undercuts the Cervenys' fraud claim.

The District Court's preemption holding applied to all of the Cervenys' remaining claims. This Court should affirm.

CONCLUSION

In twice rejecting Mr. Mix's citizen petition, FDA unequivocally explained that "the available scientific evidence is insufficient to establish reasonable evidence of an association between the use of clomiphene citrate during a treatment cycle and teratogenic risks." Appx. 394. This statement, that the evidence does not meet the regulatory standard for allowing a warning of a risk, is clear evidence that FDA would not have allowed Aventis to revise Clomid's labeling to warn of such risks. Accordingly, the District Court's holding that the Cervenys' claims were preempted was correct and should be affirmed. For the foregoing reasons, Aventis respectfully requests that this Court affirm the District Court's Judgment.

STATEMENT REGARDING ORAL ARGUMENT

Aventis requests that the Court allow oral argument in this case. Oral argument is appropriate because this case presents important and complex

questions of first impression relating to federal preemption of state law failure-to-warn claims in litigation involving prescription medications. The Court's resolution of the questions raised here will have broad applicability to pharmaceutical litigation both inside and outside the Circuit. Argument will allow the Parties to fully address the issues and any questions the Court may have regarding the underlying facts and law.

Respectfully Submitted,

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CERTIFICATE OF SERVICE

I hereby certify that I filed the foregoing Appellee's Brief with the United States Court of Appeals for the Tenth Circuit with notice to be generated and sent electronically by the Court's ECF system to all designated persons this 12th day of September, 2016.

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because this brief contains 13,672 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii).

This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft Word 2007 in 14-point Times New Roman font. I relied on the word count of that software to obtain the word count above.

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Per the Court's CM/ECF User's Manual, the undersigned certifies as follows:

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