No. 16-4050

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

The Honorable Dee Benson, United States District Judge
District Court Case No. 2:14-CV-00545

BRIEF OF APPELLANTS

Oral Argument is Requested

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CORPORATE DISCLOSURE STATEMENT

All of the Plaintiffs are individuals, with no corporate parents.

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There are no prior or related appeals.

JURISDICTIONAL STATEMENT

(A) The district court had subject-matter jurisdiction pursuant to 28 U.S.C. § 1332(a). There is complete diversity between the parties. The Plaintiffs were residents of Utah at the time of all relevant events, and they are now residents of Colorado. (Aplt. App. at 012). Defendant Aventis, Inc., is a Pennsylvania corporation with its principal place of business in New Jersey. (*Id.* at 013). The amount in controversy is greater than $75,000. (*Id.* at 013-14).

(B) This Court has jurisdiction pursuant to 28 U.S.C. § 1291. The district court issued a final judgment as to all claims and parties when it granted the motion for summary judgment filed by Defendant Aventis. (Aplt. App. at 732).

(C) Plaintiffs filed their notice of appeal on April 13, 2016. (*Id.* at 009). The district court granted summary judgment on March 16, 2016. (*Id.*). Thus, the appeal was timely under Rule 4(a)(1)(A).

(D) The appeal is from a final order or judgment that disposed of all of the Plaintiffs' claims against the Defendant.

STATEMENT OF ISSUES PRESENTED FOR REVIEW

I. State-law failure-to-warn claims are preempted only where there is "clear evidence" that it was impossible to make the proposed label change because the FDA would have rescinded the change if it was made unilaterally. Can there be "clear evidence" of impossibility when the manufacturer never sought the proposed label change, and when the only evidence supporting preemption is the FDA's rejection of a citizen petition?

II. Is there "clear evidence" that the FDA would have rescinded a label change warning that using Clomid to achieve pregnancy could lead to birth defects, when the FDA proposed a similar warning during the relevant timeframe?

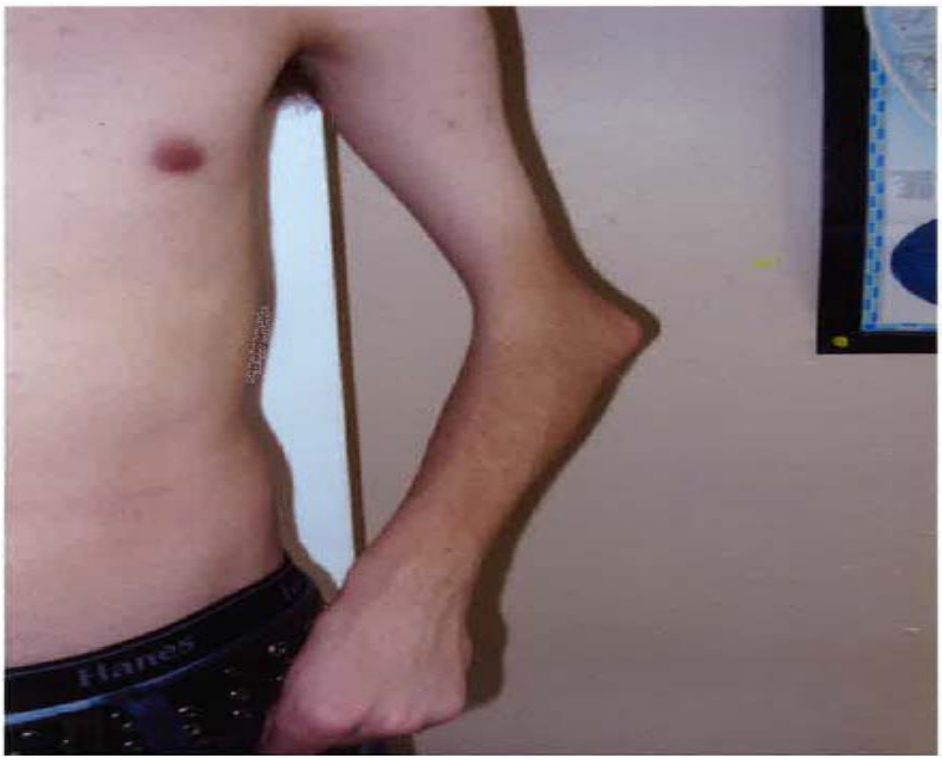
III. Did the district court err by deciding impossibility preemption, which is a question of fact, without allowing any substantial period of time for discovery?

IV. If the district court's failure-to-warn decision is upheld, should this Court nonetheless remand for litigation of Plaintiffs' remaining claims, none of which were addressed in the district court's order granting summary judgment?

STATEMENT OF THE CASE

I. Alexander's birth defects after Mrs. Cerveny used Clomid

The Plaintiffs/Appellants are Alexander Cerveny and his parents, Victoria and Charles Cerveny (collectively, "Plaintiffs" or "the Cervenys"). (Aplt. App. at 462). In September and October 1992, Victoria ingested the drug Clomid, hoping that it would help her to conceive a child. (*Id.* at 462, 602). Clomid, which is manufactured by Defendant/Appellee Aventis, Inc. ("Aventis"), has the chemical name clomiphene citrate. Mrs. Cerveny did become pregnant after taking Clomid in October 1992, and Alexander was born on July 27, 1993. (*Id.*). Alexander was born with substantial birth defects—a left elbow flexion deformity that required multiple surgeries and interventions, and only three digits on his left hand:



(*Id.* at 462, 602, 605).

There is no family, genetic or other history of the type of birth defects form which Alexander suffers. (*Id.* at 463, 603). After giving birth to Alexander, the Cervenys conceived another child without the use of fertility drugs, and that child was born without any birth defects or other genetic defects. (*Id.*). Before taking Clomid, Mrs. Cerveny understood that there was a risk of multiple pregnancies with the drug. However, she had no knowledge that taking Clomid to become pregnant could present a risk to the baby that was conceived. (*Id.*). Had Mrs. Cerveny known in September 1992 that use of Clomid could present a risk to the child that she hoped to conceive, she would not have used Clomid and would have continued to try to conceive a child naturally. (*Id.*).

II. Clomid label changes, and Aventis's communications with the FDA

The FDA approved Clomid in 1967. (Aplt. App. at 453). In August 1975, the FDA requested that Aventis conduct studies to gather data on the occurrence of congenital anomalies associated with the drug. (*Id.* at 458, 523). In 1980, Aventis revised the Clomid label. The new label asserted that "[a]lthough no causative evidence of a deleterious effect of Clomid therapy on the human fetus has been seen, such evidence in regard to rat and rabbit has been presented." (*Id.* at 460, 579). The label asserted the Clomid should not be taken during pregnancy, and it included some statistics about birth defects in pregnancies associated with Clomid

use. (*Id.* at 460-61, 580-81). However, there was no language describing any risk to the fetus associated with those using Clomid to become pregnant. (*See id.* at 579-82).

In a November 1986 letter, the FDA told Aventis to amend its label to include a "Pregnancy Category X" designation. (*Id.* at 461, 584). Pregnancy Category X was used[1] to indicate "positive evidence of a fetal risk based on adverse reaction reports," and that "the risk of use of the drug in a pregnant woman clearly outweighs any benefit." (*Id.* at 458-59), citing 21 C.F.R. 201.80(f)(6)(i)(e) (2006) (Aplt. App. at 544-45). Although the 1980 label clearly indicated evidence of a fetal risk from animal studies, Aventis pushed back against the FDA, arguing that the drug should be placed into "Pregnancy Category B." (*Id.* at 461, 586-87). Pregnancy Category B was appropriate when "animal reproduction studies have failed to demonstrate a risk to the fetus … ." (*Id.* at 461), citing 21 C.F.R. 201.80(f)(6)(i)(b) (2006) (Aplt. App. at 543). On March 5, 1987, the FDA proposed that the following information be added to the Clomid label:

> Pregnancy Category X. See Contraindications and Information for Patients. Contraindications: Clomid is contraindicated in pregnant women. Since there is a reasonable likelihood of the patient becoming pregnant while receiving Clomid, the patient should be apprised of the potential hazard to the fetus.

[1] As of 2015, the FDA no longer uses designations such as "Pregnancy Category X." (Aplt. App. at 459), citing 21 C.F.R. 201.80(f)(6)(i)(e).

(Aplt. App. at 461-62, 596). However, Aventis never added that language to the label. (*Id.* at 462, 525-36 (current label)). In fact, Aventis did not change the label at all until December 1993, after Alexander was born. (*Id.* at 463, 500). That label has not been produced in discovery. (*Id.*).

Aventis changed the label again in 1994, and that label finally added the Pregnancy X category. (*Id.* at 463-64, 599-600).[2] Aventis, however, did not add the proposed language warning those attempting to use Clomid to become pregnant about the potential danger to the fetus. (*See id.*). Aventis revised the label again in 1995, but no changes were relevant to this case. (*Id.* at 465, 607-16). The label was not revised again until 2012, which is the current label. The 2012 label finally included language somewhat similar to what the FDA had proposed in 1987 regarding the risk to the fetus:

> 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 risk to the fetus.

(*Id.* at 465, 528).

[2] The Pregnancy X language may have been added in December 1993. Plaintiffs have no way of knowing since that label has not been produced. But that is not a material distinction for this case.

III. Terry Mix's citizen petition

Terry Mix is an attorney who was at one time involved in litigation regarding Clomid. He won several cases, but had his expert excluded on another. (Aplt. App. at 786). He is not a medical professional. (*Id.*).

In 2007, Mr. Mix filed a citizen petition with the FDA regarding Clomid. (*Id.* at 454). Any citizen may file a petition asking the FDA to take a particular action, including asking the FDA to require a change to a prescription drug label. (*Id.* at 469); 21 C.F.R. 10.25. If the FDA grants the petition, it will take action to force a label change by the manufacturer.[3] (*Id.* at 470). Mr. Mix's petition did not seek any specific label change, but it asked for the following relief from the FDA:

a. Order changes to the labeling and package insert for Clomid (clomiphene citrate) and its generics, setting forth reasonable and effective warnings of teratogenic risks;

b. 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] Before a 2007 change to the regulations, the FDA's principal power was to declare a drug "misbranded," and therefore unable to be sold, if the FDA did not believe that the warnings on a drug were sufficient. *See* 21 U.S.C. 331(a)-(b). With the 2007 change, the FDA gained the power to force a particular label change based on new safety information. *Wyeth*, 555 U.S. at 567.

c. 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.

(Aplt. App. at 248).

The petition itself was only a three-page document. (*Id.* at 248-50). The petition explains that Clomid is often ingested four-to-five days before conception, and yet it can remain in the body for as many as 54 days after ingestion. (*Id.* at 248). Thus, the drug has the opportunity to affect the developing fetus. (*Id.* at 248-49). The petition further described various studies in which spina bifida, neural tube defects, and other birth defects have been shown to occur with statistically significant increased frequency in various trials. (*Id.* at 249). Mr. Mix also attached three chapters of a book that he was in the process of writing, which expanded on his arguments. (*Id.* at 253-350). He supplemented his petition twice in 2008. (*Id.* at 352-73).

The FDA rejected the citizen petition in 2009. (*Id.* at 379-95). The FDA addressed Mr. Mix's arguments point by point and held that the evidence he presented was insufficient for the FDA to require a label change. Thus, the petition was denied. (*Id.*). This rejection indicates that the FDA declined to force Aventis to change its label. (*See id.* at 382). Mr. Mix filed a petition for

reconsideration in September 2009, and the FDA also denied reconsideration in March 2012. (*Id.* at 399-423). However, as noted, the Clomid label was updated that same year. (*Id.* at 500).

IV. Proceedings in the district court

The Cervenys filed this case on July 28, 2014. (Aplt. App. at 003). Though this filing occurred long after Alexander was injured, there is no statute of limitations issue because the statutory period is tolled during minority. Utah Code Ann. § 78B-2-108. Plaintiffs did not advocate for a specific warning in laying out their failure-to-warn claims. (*Id.* at 028-29). However, the basic premise of this claim is that those using Clomid to become pregnant needed to be apprised that doing so presented a risk to the fetus. (*See, e.g.*, *id.* at 016, ¶¶ 22-23). Aventis filed a motion to dismiss most of Plaintiffs' claims, and after a hearing the district court granted the motion in part and denied it in part on July 14, 2015. (Aplt. App. at 006). After disposition of the motion, Plaintiffs retained claims for: failure to warn (both strict liability and negligence), breach of implied warranty, negligent misrepresentation, and fraud. (*Id.* at 224 n.1).

The Court held a scheduling conference on September 9, 2015, and issued a scheduling order on September 30, 2015. (*Id.* at 007-08). Just over a month later, Aventis filed a motion for summary judgment and memorandum in support. (*Id.* at 008). Plaintiffs opposed the motion and alternatively argued that there should be

further discovery before the court ruled on the motion. (*See id*. at 447-48, Table of Contents). After holding a hearing on the motion, the Court granted summary judgment by Memorandum Decision on March 16, 2016. (*Id*. at 009, 706-33). Plaintiffs timely appealed to this Court. (*Id.* at 734-35).

SUMMARY OF THE ARGUMENT

Alexander Cerveny and his family seek the opportunity to present their case to a jury. They allege that Mrs. Cerveny's use of the drug Clomid caused Alexander to be born with substantial birth defects that have left him with a badly damaged left arm and only three digits on his left hand. The district court denied them the chance to present their case when it granted summary judgment on federal preemption grounds.

In the seminal case of *Wyeth v. Levine*, 555 U.S. 555 (2009), the Supreme Court held that a state-law failure-to-warn claim based on prescription drug labels **are not** preempted by the FDA's approval of the label. The Court noted that the manufacturer has the ultimate responsibility for the label, and the power to change the label unilaterally. The Court noted that the FDA had the power to rescind a unilateral label change, but the Court stated that this power does not establish preemption in the absence of "clear evidence" that the FDA would have rejected a proposed label change.

As at least one federal court has held, there likely cannot be preemption in the absence of an actual submission by the manufacturer, seeking a label change, which was then rejected. Nothing else establishes "clear evidence" as to how the FDA would have reacted to such an effort. In this case, there is no evidence that

Aventis or any of its corporate predecessors has ever tried to add a warning about an increased risk of birth defects when Clomid is used to achieve pregnancy.

Such a rule is supported by *Wyeth*, but the Court can decide this case without drawing such a firm line. It appears that no court, before the district court in this case, had found "clear evidence" of preemption based solely on the result of a citizen petition. As several courts have noted, the fact that the FDA did not **force** Aventis to change its label after a single citizen requested such action does not conclusively reveal how the FDA would have responded, had Aventis changed its label unilaterally. FDA inaction in both situation leads to opposite results. This Court, therefore, should hold that a rejected citizen petition, alone, cannot establish impossibility preemption.

In addition, the FDA's communications with Aventis support reversing the district court's decision. The relevant question is whether it was impossible to add a warning to Clomid before 1992 about the risk of birth defects presented by the drug. In 1987, the FDA asked Aventis to add a "Pregnancy X" designation, indicating that the drug should not be used by those who are pregnant, due to the risk to the fetus. The FDA also proposed that the label warn those seeking to become pregnant of the risk to the fetus. Mrs. Cerveny—who later conceived a second healthy child without fertility drugs—testified by affidavit that she would not have used Clomid if she had known of this risk. Thus, it was not impossible to

add a meaningful warning about the risk to the fetus when the prospective mother uses Clomid; the FDA actually proposed it.

Finally, this Court should remand the case even if the Court is not persuaded to reject the preemption argument in its entirety. Impossibility preemption based on *Wyeth* presents a question of fact, yet Plaintiffs were given little time to discover facts relevant to the issue. In addition, the Cervenys had five viable claims after the district court's order on Aventis's motion to dismiss. Preemption should only apply to the two failure-to-warn claims, leaving claims for fraud, negligent misrepresentation, and breach of implied warranty. The district court did not even address these additional claims in granting summary judgment.

For these reasons, Alexander, Victoria, and Charles Cerveny respectfully request that this Court reverse the district court's grant of summary judgment and allow them to present their claims to a jury.

ARGUMENT

I. Introduction

The district court effectively held that one well-meaning citizen's decision to petition the government has prevented all people who have suffered birth defects after their mother's use of Clomid from seeking redress in a court of law. This Court should reverse that decision.

In granting summary judgment and denying the Cervenys the chance to present their claims, the district court relied on implied impossibility preemption. In this context, that doctrine stems from the Supreme Court's opinion in *Wyeth v. Levine*, 555 U.S. 555 (2009). As discussed below, federal courts employ a presumption against preemption, and impossibility preemption is a high standard. *Wyeth* strongly rejected the argument that it was impossible for a drug manufacturer to change an FDA-approved warning label, and it further rejected the argument that state-law tort suits frustrate the purpose of the FDA. Thus, an argument for impossibility preemption based on *Wyeth* should be held to an extremely high standard. Yet, the district court granted summary judgment based on nothing more than one citizen's petition to the FDA.

Given the general tenor of *Wyeth*, it is highly unlikely that the Court intended to create a playbook for manufacturers to insulate themselves against

liability.[4] It was an anti-preemption decision. But defendants, including Aventis here, have seized on one sentence, in which the Court implied that a claim would be preempted if there was "clear evidence" that the FDA would have prevented the manufacturer from adding the warning proposed by the plaintiff.

As noted in *Wyeth*, manufacturers can universally change their labels to add safety warnings, through the Changes Being Effected ("CBE") process. But in this case, the district court held that the FDA's 2009 denial of a citizen petition seeking to add warnings to the Clomid label was "clear evidence" that had Aventis added such a warning before Mrs. Cervenys use in 1992, the FDA would have forced Aventis to remove that language. In doing so, the district court became—to the best of undersigned counsel's knowledge—the first court to hold a claim to be preempted based on only the FDA's denial of a citizen petition.

This Court should reverse that decision. This Court should conclude that "clear evidence" as to how the FDA would have reacted to a manufacturer's label change cannot exist unless the manufacturer tried to change the label; or, at least, that there can be no "clear evidence" with nothing more than a failed petition from one citizen to support preemption.

[4] There is no doubt that Mr. Mix strongly believed in his petition. But if this decision is upheld, there will be an incentive for manufacturers in the future to find someone to craft a citizen petition which, if denied, would insulate the manufacturer from liability.

In addition, the district court erred because the FDA actually proposed a warning in 1987 that would have prevented Mrs. Cerveny from taking the drug in 1992. Aventis never added the proposed warning, though parts of it eventually appeared on the label in 1994 and 2012. Evidence of the 1987 FDA proposal is far stronger as to how the FDA would have reacted to a label change expressing the risk of birth defects when one uses Clomid to achieve pregnancy than is the rejection of a citizen petition 22 years later.

Alternatively, this Court should reverse the decision and remand for further discovery, as the preemption issue presents a question of fact and Plaintiffs have had little time to assess the facts. And, if necessary, the Court should remand for litigation of the Cervenys' claims for fraud, negligent misrepresentation, and breach of implied warranty, none of which were addressed by the district court's summary judgment order.

II. Legal Standards

A. Standard of Review

This Court reviews a grant of summary judgment de novo. *Seifert v. Unified Gov't of Wyandotte County/Kan. City*, 779 F.3d 1141, 1150 (10th Cir. 2015). A district court should not grant summary judgment unless the moving party establishes "that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a); *see also, e.g.*,

Borchardt Rifle Corp. v. Cook, 684 F.3d 1037, 1042 (10th Cir. 2012). "When applying this standard [courts should] view the evidence and draw reasonable inferences therefrom in the light most favorable to the nonmoving party." *Foster v. Alliedsignal, Inc.*, 293 F.3d 1187, 1192 (10th Cir. 2002).

B. Impossibility Preemption

There are three types of federal preemption: express preemption, where a federal statute reveals Congress's intention to preempt state law; implied field preemption, where federal regulations are "so pervasive that Congress must have intended to leave no room for a State to supplement" them; and implied conflict preemption, "which occurs either when compliance with both the federal and state laws is a physical impossibility, or when the state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Mount Olivet Cemetery Ass'n v. Salt Lake City*, 164 F.3d 480, 486 (10th Cir. 1998). Here, Defendants have argued that implied conflict preemption applies—specifically, impossibility preemption. (Aplt. App. at 219).

The Supreme Court has stated that "impossibility preemption is a demanding defense." *Wyeth*, 555 U.S. at 573. One guiding principle of the Supreme Court's preemption jurisprudence is that "'the purpose of Congress is the ultimate touchstone in every pre-emption case.'" *Id.* at 565 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)). Another guiding principle is that the Court starts

"'with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.'" *Id.* (quoting *Lohr*, 518 U.S. at 485).

This rule is often described as the "presumption against preemption." *See, e.g.*, *Cook v. Rockwell Int'l Corp.*, 790 F.3d 1088, 1094 (10th Cir. 2015); *see also Tarrant Reg'l Water Dist. v. Herrmann*, 656 F.3d 1222, 1242 (10th Cir. 2011) *aff'd*, 133 S. Ct. 2120 (2013) ("'We rely on the presumption [against preemption]' out of 'respect for the States as independent sovereigns in our federal system.'" (quoting *Wyeth*, 555 U.S. at 595 n. 3 (Thomas, J., concurring))). The presumption is particularly strong in cases where "Congress has legislated ... in a field which the States have traditionally occupied." *Lohr*, 518 U.S. at 485 (quotations omitted).

III. In *Wyeth v. Levine*, the Supreme Court rejected the argument that FDA regulations preempt state-law claims for failure to warn; thus, the exception should be read narrowly when a defendant relies on *Wyeth* in advocating for federal preemption of state-law claims.[5]

The Supreme Court's opinion in *Wyeth* offers only a narrow exception to the rule that FDA regulations do not preempt state-law tort claims based on the failure to warn about the dangers of prescription drugs. The opinion is rife with analysis—based on federal regulations, case law, and policy considerations—as to why state tort claims complement federal regulations, such that FDA approval of

[5] **Preservation:** Section III primarily contains legal discussion, but to the extent it needed to be preserved, there was a similar discussion at Aplt. App 473-76.

drug labeling provides no barrier to state tort claims. Yet, because of a single sentence in the decision, defendants routinely rely on *Wyeth* in arguing **for** federal preemption. This Court's analysis should begin with *Wyeth*, which largely rejects federal preemption of state-law drug claims.

A. The Supreme Court held in *Wyeth* that state tort suits complement federal drug regulations, and under the CBE process it is possible to comply with both the regulations and state law.

In *Wyeth*, the Supreme Court analyzed the same question at issue here: whether "it is impossible for [a manufacturer] to comply with both the state-law duties underlying [the plaintiff's] claims and its federal labeling duties." *Wyeth*, 555 U.S. at 568.

The Court held that the FDA's labeling regulations do not preempt state tort-law claims. The Court explained that it was possible for Wyeth to change the label on Phenergan, the drug at issue, unilaterally, through the FDA's Changes Being Effected ("CBE") process. *Id.*; *see also* 21 C.F.R. 314.70(c)(6)(iii)(A),(C). The CBE process allows manufacturers to change labeling upon filing an application with the FDA; they do not need to wait for approval. *Wyeth*, 555 U.S. at 568. The Court rejected arguments that a new label would have made Phenergan a "new drug," such that the New Drug Application process would have restarted, or that the drug would have been "misbranded" by having a label that was not FDA-

approved. *Id.* at 570. Rather, the FDA "proscribes labels that fail to include 'adequate warnings.'" *Id.* (citing 21 C.F.R. § 352(f)).

The Court further rejected Wyeth's efforts to place the responsibility for the content of drug labels with the FDA, stating that "through many amendments to the FDCA [Food Drug & Cosmetic Act] and to FDA regulations, it has remained a central premise of federal drug regulation that **the manufacturer bears responsibility for the content of its label at all times**." *Id.* at 570-71 (emphasis added). Therefore, when Wyeth acquired information about the risks associated with a particular use of its drug, it had a duty to change the label. *Id.* at 571. As further explained by Justice Thomas in his concurrence, "FDA regulations require a drug manufacturer—after initial federal approval of a drug's label—to revise the federally approved label 'to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug.'" *Id.* at 592 (Thomas, J., concurring) (quoting 21 CFR § 201.80(e)).

Wyeth also argued that state tort claims are preempted because they "obstruct the purposes and objectives of federal drug labeling regulation." *Id.* at 573. The Court firmly rejected this argument, noting that "Congress enacted the FDCA to bolster consumer protection against harmful products." *Id.* at 574. State tort suits have been ongoing for decades, and yet Congress has never enacted an express preemption provision that applies to prescription drugs, as it has done for

medical devices. *Id.* As Justice O'Connor wrote: "The case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to stand by both concepts and to tolerate whatever tension there [is] between them." *Id.* at 575 (quoting *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166–67 (1989)).

The FDA has traditionally viewed state tort suits as complementary to FDA regulations. Such suits uncover unknown hazards and encourage injured consumers to come forward with information. *Id.* at 578-79. "The FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." *Id.* at 578-79 (footnote omitted). "Thus, the FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation." *Id.* at 579.[6]

B. In *Wyeth*, decades of communication between the FDA and the drug's manufacturer about "IV-push" warnings did not establish that the manufacturer was unable to strengthen the warning label.

Clearly, *Wyeth* should not be viewed as endorsing preemption on anything approaching a broad scale. The district court's preemption ruling derives from a single statement made as the Court was **rejecting** another of Wyeth's arguments.

[6] The FDA had changed its view on preemption as of the 2009 *Wyeth* opinion, but the Court gave no weight to the FDA's revised view on that issue. *Id.* at 577.

Wyeth claimed that, even though it could unilaterally change the label through the CBE process, the FDA could ultimately reject the change. The Court agreed that "the FDA retains authority to reject labeling changes made pursuant to the CBE regulation in its review of the manufacturer's supplemental application … ." *Id.* at 571. "But," the Court continued, "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." *Id.*

Any suggestion that some claims might be preempted was dictum in *Wyeth*. However, federal courts, including this Court, have treated this statement as announcing a rule of law. This Court wrote that "the Supreme Court established a new standard for a federal preemption defense against a failure to warn claim, holding that the pharmaceutical company must demonstrate 'clear evidence' that the Food and Drug Administration would have rejected a label change had the pharmaceutical company unilaterally strengthened its drug's warning label." *Dobbs v. Wyeth Pharm.*, 606 F.3d 1269, 1270 (10th Cir. 2010).

In *Wyeth*, the Court 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. The plaintiff, Ms. Levine, was given the drug Phenergan through an "IV-push" method of delivery. *Id.* at 558-59. She developed gangrene because of this method of administration. *Id.* at 559.

Concerns about "IV-push" administration of Phenergan had long been on the FDA's radar. Representatives from the FDA and Wyeth met in 1975 to discuss changes to the warning label. *Id.* at 613 (Alito, J., dissenting). The next year, the FDA convened an advisory committee to study the issue. *Id.* As a result, the FDA required additional warnings as to the IV-push method, in all capital letters. *Id.* at 613-14 (Alito, J., dissenting). In 1987, the FDA further directed Wyeth to amend its label to strengthen warnings regarding IV-push administration. *Id.* at 614 (Alito, J., dissenting). The FDA cited "voluminous materials" in support of this labeling order, including a study recommending that "IV-push" be counter-indicated. *Id.* at 614-15 (Alito, J., dissenting).

Despite that history, the Court had no trouble finding an absence of "clear evidence" that the FDA would have rejected a stronger warning on Phenergan. *Id.* at 571. Although the Court had some disagreement with the statement of facts as laid out by Judge Alito in dissent, the Court said that even Judge Alito's version of history would not meet the threshold of "clear evidence." *Id.* at 573 n.6.

Thus, everything about *Wyeth*, factually and legally, endorses a skeptical view toward federal preemption. *Wyeth* did crack the door open for a preemption claim in the right case. However, in light of the heightened "clear evidence" standard, in light of the general difficulty of establishing impossibility preemption, and in light of the anti-preemption stance taken by the Court in *Wyeth*, this Court

should begin with the assumption that the *Wyeth* Court intended the "clear evidence" standard to be extremely difficult to meet.

IV. This Court should conclude that where, as here, the only evidence supporting preemption is the FDA's rejection of a citizen petition seeking a change to the drug's label, there is no "clear evidence" that the FDA would have rescinded a label change had the manufacturer changed the label through the CBE process.[7]

A court within this circuit wrote in 2015 that "courts applying the clear evidence standard have almost 'universally found the manufacturer's evidence inadequate to support conflict preemption.'" *Shipley v. Forest Labs., Inc.*, No. 1:06-CV-00048-TC, 2015 WL 4199739, at *10 (D. Utah July 13, 2015) (quoting *Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1270 (W.D. Okla. 2011)). This statement further underscores that the exception of *Wyeth* should be read narrowly.

The context of *Wyeth*, and statements in several other decisions, strongly suggest that the required "clear evidence" should never be found in the absence of an effort by the manufacturer to change the label that the FDA rejected. After all, when 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. But this Court need

[7] **Preservation:** The argument that the Court should not find "clear evidence" when the only evidence is a citizen petition was Section II of Plaintiffs' summary judgment response, at Aplt. App. 479-83. The point that courts should only find clear evidence if a manufacturer attempted to change the label is made at Aplt. App. 479-81.

not make such a sweeping pronouncement to decide this case. Here, the only evidence allegedly supporting preemption is the citizen petition that the FDA rejected. This Court should conclude that rejection of a citizen petition, alone, is insufficient to establish "clear evidence" that the FDA would have rejected a label change by the manufacturer, had the manufacturer used the CBE process to make the change advocated by the plaintiff. Here, the rejection of Mr. Mix's citizen petition—which advocated non-specific warnings regarding the teratogenic risks posed by Clomid—is the only evidence supporting impossibility preemption. This Court, therefore, should reverse the grant of summary judgment.

A. There cannot be "clear evidence" that the FDA would have rescinded a manufacturer's label change in the absence of any evidence that the manufacturer ever sought a label change.

The district court's first error was 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—whether formally or informally.

Two points are particularly important in evaluating whether "clear evidence" could ever exist in the absence of action by the manufacturer. The first is that the manufacturer has the ultimate responsibility for the content of a prescription drug label. The Supreme Court rejected the argument that Wyeth would have violated federal law by using the CBE process to change the label unilaterally, without prior

FDA approval. *Wyeth*, 555 U.S. at 570. The regulation for misbranding focuses on the substance of the label and, among other things, proscribes labels that fail to include "adequate warnings." *Id.* (citing 21 U.S.C. § 352(f)).

Further, Defendant Wyeth's argument was "premised on a more fundamental misunderstanding." *Id.* Wyeth, the Court noted, "suggests that the FDA, rather than the manufacturer, bears primary responsibility for drug labeling." *Id.* "Yet through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." *Id.* at 570-71.

The second critical point is that the "clear evidence" standard arose in response to an argument that, had Wyeth changed the Phenergan label, the FDA could have forced Wyeth to **rescind** the label change. *Id.* at 571. The *Wyeth* court recognized that the FDA retained this authority, but said a claim would not be preempted "absent clear evidence that the FDA would not have approved a change to Phenergan's label." *Id. See also PLIVA, Inc. v. Mensing*, 564 U.S. 604, 624 n.8 (2011) (stating that "the Court noted that Wyeth could have attempted to show, by 'clear evidence,' that the FDA **would have rescinded** any change in the label and thereby demonstrate that it would in fact have been impossible to do under federal law what state law required") (emphasis added).

Thus, in this case, there must be "clear evidence" that if Aventis had changed the label on Clomid before 1992, to warn of possible birth defects in the children of mothers who use Clomid to become pregnant, the FDA would have forced Aventis to remove that language—even though Aventis, not the FDA, "bears responsibility for the content of its label at all times." Without 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 as to how the FDA would have reacted had Aventis used the CBE process to add the proposed warning.

The District of Minnesota seized on this point in concluding that the necessary "clear evidence" likely could not be established without evidence that the manufacturer had sought a label change. *Schedin v. Ortho-McNeil-Janssen Pharm., Inc.*, 808 F. Supp. 2d 1125, 1132-33 (D. Minn. 2011), *aff'd in part, rev'd in part sub nom. on other grounds by In re Levaquin Products Liab. Litig.*, 700 F.3d 1161 (8th Cir. 2012). Based on its analysis of *Wyeth* and *Mensing*, the court concluded that "a brand-name manufacturer must show that the FDA would not have approved a proposed label change that is the basis for a state law failure to warn claim; indeed, the brand name manufacturer likely must proffer evidence of the FDA's **rejection of an actual label change**." *Id.* at 1132 (emphasis added). *See also* Michael M. Gallagher, *Clear Evidence of Impossibility Preemption after*

Wyeth v. Levine, 51 GONZ. L. REV. 439, 474 (2015-16) (advocating for the adoption of the rule expressed in *Schedin*).

The district court in this case asserted that courts have "universally rejected" the argument that *Wyeth's* "clear evidence" standard requires a showing that the manufacturer attempted to add the warning at issue and was rejected by the FDA. (Aplt. App. at 720). Respectfully, there is little support for this claim. The district court cites to four cases, only one of which arguably supports the position. (*See id.* at 721 n.4). The district court cited to *Wyeth*, but as addressed above, the issue arose in rejecting the argument that, had *Wyeth* made the proposed change, the FDA could have rescinded the change. *Wyeth* also categorically dismissed the idea that the "clear evidence" standard had been met in that case, despite evidence of years of communication between the manufacturer and the FDA about the content of the warning label. *Id.* at 571. At best, from Defendants' perspective, *Wyeth* is silent on the issue, but the totality of *Wyeth* supports the Cervenys' argument.

The cited passage from *Reckis v. Johnson & Johnson*, 28 N.E. 445, 459 n.29 (Mass. 2015), only states that it is "not to say" that the "clear evidence" standard requires a showing that the manufacturer proposed a warning that was rejected. *Id.* In other words, the court viewed it as an open question. Notably, the *Reckis* court rejected preemption, upheld a large jury verdict, and wrote that "even assuming for sake of argument that we could predict the FDA would have rejected a citizen

petition proposal to add only this warning, that would not answer whether the FDA would have rejected the warning had it been sought by the defendants themselves." *Id.* at 459. Thus, *Reckis* recognized the important distinction between a warning proposed by a third party through a citizen petition and a warning affirmatively added to the label by the drug's manufacturer.

The district court also relied on the dissent in *Mensing*. (*See* Aplt. App. at 720-21 n.4). Of course, nothing in the dissent could announce a rule of law. Justice Sotomayor was merely hypothesizing about how the rule might work if the Supreme Court applied the same standard to generic manufacturers as it had applied to brand-name manufacturers in *Wyeth*—an argument rejected by the Court. *Mensing*, 564 U.S. at 637 (Sotomayor, J., dissenting). She also applied the wrong standard in suggesting that the FDA might have "considered whether to request enhanced warnings" in light of certain evidence. *Id.* The majority framed the question not as whether the FDA would have "requested" stronger warnings. Instead, the issue is whether the FDA would have rescinded a warning placed by the manufacturer. *Id.* at 624 n.8.

The remaining case did agree with the district court's position. *See In re Incretin-Based Therapies Products Liab. Litig.*, 142 F. Supp. 3d 1108, 1124 (S.D. Cal. 2015). That decision is presently on appeal. Regardless, a single case does not support the proposition that courts have "universally" rejected the argument

that the "clear evidence" standard requires evidence of action by the manufacturer—particularly when another federal district court has accepted the argument.

In addition, the cases cited by the *Incretin* court as having found "clear evidence" to support preemption do not reject the principle that a manufacturer must have sought the proposed warning for there to be "clear evidence" of preemption.[8] Three of the four cases cited involved efforts **by the manufacturer** to strengthen the warning at issue, or a similar warning, which the FDA then rejected. *See id.* at 1117-18 (citing *Dobbs v. Wyeth Pharmaceuticals*, 797 F. Supp. 2d 1266, 1276-77 (W.D. Okla. 2011) ("The court finds the FDA's rejection of the pediatric warning added by Wyeth under the CBE regulations to be highly persuasive evidence."); *Rheinfrank v. Abbott Laboratories, Inc.*, No. 1:13cv114, 2015 WL 4743056 (S.D. Ohio, Aug. 10, 2015); *In re Fosamax Products Liability Litigation*, 951 F. Supp. 2d 695 (D.N.J. 2013). The other cited case was *Reckis*, which ultimately rejected the preemption argument.[9]

[8] Before engaging in its own analysis, the *Incretin* court discussed four cases in which other courts found preemption to some degree. *Incretin*, 142 F. Supp. 3d at 1116-18. The court then discussed several cases in which preemption had been rejected. *Id.* at 1118-19.

[9] *Reckis* found a sliver of preemption based on the FDA's rejection of specific language in a proposed warning. *Reckis*, 28 N.E.3d at 458. But *Reckis* generally found the plaintiffs' claims not to be preempted, stating that a similar warning with different language could have been added to the label. *Id.* at 459-60.

It appears that no circuit court has addressed the question head on. If this Court does so, it should conclude that for impossibility preemption to apply, there must be some showing that the manufacturer attempted to add the warning proposed by the Plaintiff, which was then rejected by the FDA.

B. This Court should conclude that the rejection of a citizen petition, without more, cannot establish "clear evidence" as to whether the FDA would have required a manufacture to rescind a label change made through the CBE process.

While *Wyeth* and other authorities support the rule discussed in Part A, this Court can decide this appeal with a less expansive decision. This Court should hold that the FDA's rejection of a citizen petition, without more, fails to establish clear evidence that the FDA would have rescinded a warning had the manufacturer added a warning through the CBE process.

1. *No court, until this case, has found a claim to be preempted based on only the FDA's rejection of a citizen petition.*

To the best of undersigned counsel's knowledge, the district court's decision was the first to hold any claim to be preempted based solely on the FDA's rejection of a citizen petition.[10] By contrast, many courts have rejected claims of

[10] The district court presented its decision as relying on two factors: the rejection of the citizen petition and the FDA's consistent approval of Clomid labels that did not warn of a risk of birth defects for users who were not yet pregnant. (Aplt. App. at 727-28). However, every case of this type involves a plaintiff contesting a warning that the FDA has approved. The Supreme Court in *Wyeth* clearly rejected the FDA's approval of prior warnings as a basis for preemption. *Wyeth*, 555 U.S. at 558-59 ("The question we must decide is whether the FDA's approvals provide

preemption where a defendant relied, at least in part, on the rejection of a citizen petition. *See, e.g.*, *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. *Cf. Forst v. Smithkline Beecham Corp.*, 639 F. Supp. 2d 948, 954 (E.D. Wis. 2009) (denying preemption argument despite FDA's rejection of a manufacturer's warning because "the agency did not prohibit all enhanced warnings").

These courts relied on a variety of factors, so not all of them drew a bright line as to when a claim might or might not be preempted. But several courts have recognized the important distinction between these scenarios, from the FDA's perspective. If a citizen petition is filed, the FDA must decide whether to **force** a label change upon the presumably unwilling manufacturer. If the manufacturer changes the label through the CBE process, the FDA must decide whether to **accept** a change already made by the manufacturer—the party that "bears responsibility for the content of its label at all times." *Wyeth*, 555 U.S. at 570-71. Statements by courts regarding this distinction include:

Wyeth with a complete defense to Levine's tort claims. We conclude that they do not."). Thus, the issue presented here is whether the rejection of a citizen petition, standing alone, is "clear evidence" that adding a warning about the risk of birth defects from using Clomid was impossible.

- Rejections of citizen petitions "constituted determinations that the warnings should not be *mandated*; they were not determinations that manufacturers could not choose to add warnings that they believed were scientifically substantiated." *Dorsett*, 699 F. Supp. 2d at 1157.
- "[E]ven assuming for sake of argument that we could predict the FDA would have rejected a citizen petition proposal to add only this warning, that would not answer whether the FDA would have rejected the warning had it been sought by the defendants themselves." *Reckis*, 28 N.E.3d at 459.
- "That the FDA did not require a label change … in the face of a Citizen's Petition, not supported by the manufacturer[,] does not constitute clear evidence that the FDA would have **rejected** a label change proposed by Ortho–McNeil before Schedin was prescribed Levaquin." *Schedin*, 808 F. Supp. 2d at 1133 (emphasis in original).

These statements are entirely logical. The district court here concluded that the FDA's denial of a citizen petition provides "clear evidence" that the FDA would have rescinded a change to the label. (Aplt. App. at 727). This conclusion ignores that FDA inaction in both cases leads to opposite results—thereby leaving serious doubt about the correlation. This conclusion also ignores the weight that is given to different presenters. In a legal context, this conclusion is akin to holding

that a *pro se* litigant's failure in court necessarily establishes that the judge would have denied the same relief if the other side had **consented** to it.

Therefore, the denial of a citizen petition, without more, can never provide "clear evidence" as to how the FDA would have responded to a label change made by the manufacturer through the CBE process.

2. Dobbs and Incretin, which involved citizen petitions and findings of preemption, are clearly distinguishable from this case.

In those few cases involving a citizen petition where preemption was found, the circumstances were much different. In *Dobbs*, the FDA had rejected three citizen petitions regarding suicide warnings. *Dobbs*, 797 F. Supp. 2d at 1274. But the court relied heavily on other factors. The FDA had also rejected a label submitted by the manufacturer through the CBE process that included a similar warning to the one proposed, only for pediatric patients. *Id.* at 1276-77. Importantly, anti-depressant drugs are in a class for which the FDA requires uniform labeling. Thus, "the FDA would be highly unlikely to permit a brand-specific warning." *Id.* at 1278. Those factors are not present here.

In *Incretin*, there were several factors favoring preemption, in addition to a rejected citizen petition advocating a warning similar to that sought by the plaintiffs. The FDA reviewed its adverse reporting database in 2009, looking for evidence of pancreatic cancer associated with the drugs at issue. The FDA concluded that there was "little inference for risk." *Incretin*, 142 F. Supp. 3d at

1121. After receiving the citizen petition in 2012, the FDA issued an official bulletin stating that it was "investigating reports of possible increased risk of pancreatitis and pre-cancerous findings associated with incretin mimetics." *Id.* In 2013, the FDA participated in a National Institute of Diabetes and Digestive Kidney Diseases and National Cancer Center Institute workshop on Pancreatitis-Diabetes-Pancreatic Cancer. The FDA reiterated that it had found no link between the drugs and pancreatic cancer. *Id.* at 1121-22. The FDA noted that the drug sponsors had completed studies that did not demonstrate a link to adverse events. *Id.* at 1122.

Perhaps most importantly, the FDA in 2014 published a peer-reviewed assessment of pancreatic safety in the New England Journal of Medicine, engaging in a comprehensive review of studies. The FDA concluded that "assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data." *Id.* The FDA formally rejected the citizen petition in 2014 and, months later, the FDA again assessed pancreatic cancer concerns and issued a briefing document. *Id.* at 1122-23. Thus, the FDA comprehensively studied the issue over the course of five years, including doing the research necessary to publish in one of the world's pre-eminent medical

journals. The FDA relied on far more than a citizen petition in reaching its conclusion.[11]

3. The FDA is far more likely to allow a label change to stand than to force a change upon a manufacturer.

In addition to the lack of case law supporting the district court's decision granting summary judgment, this Court should consider evidence showing that the FDA is infinitely more likely to grant a manufacturer's application to change a label than a citizen petition asking the FDA to require a label change.

Such evidence is important because the dispositive question is factual: Had Aventis added a warning before 1992, highlighting the risk of birth defects when taking Clomid to achieve pregnancy, would the FDA have forced the removal of that warning? Evidence of the FDA's usual practice is highly probative as to what the FDA would have done in that circumstance. Yet, the district court barely addressed this evidence, dismissing it as merely "anecdotal." (Aplt. App. 718).

Plaintiffs retained David B. Ross, M.D., Ph.D., M.B.I., as an expert witness. Dr. Ross served from 1996 through 2006 as a medical officer with the FDA. (*Id.* 467, 504). Dr. Ross began as a medical reviewer and then took on leadership roles within the FDA. (*Id.* at 467, 504-05). He was involved in several high-profile new drug applications and worked on medical counter-measures to biological weapons.

[11] As noted, *Incretin* is on appeal. Plaintiffs disagree with the court's conclusion, but *Incretin* is highly distinguishable even if it is viewed as correctly decided.

(*Id.*). Dr. Ross oversaw the review of **hundreds** of CBE supplements submitted by manufacturers to change a drug's label, and he only recalls **one** that was denied by the FDA in his 10 years there. (*Id*. at 471, 510). Conversely, he does not recall overseeing the granting of a single citizen petition. (*Id.*). Only 19% of citizen petitions are granted, and that statistic covers all petitions. Dr. Ross opines that the percentage is likely much smaller for citizen petitions that seek a change to the label for an FDA-approved drug. (*Id*. at 470, 509).

The manufacturer has an affirmative responsibility to demonstrate the safety of its drug. *Wyeth*, 555 U.S. at 570-71. Granting a citizen petition requires approaching the manufacturer and forcing a label change; due to likely pushback, such an effort would require substantial resources and effort by the FDA. (Aplt. App. at 470, 509). The preferred method of approval is through the CBE process, whereby the manufacturer unilaterally changes the label and the FDA reviews the change, or by a Prior Approval Supplement, through which the manufacturer seeks approval before changing the label. (*Id*.). Such methods allow for dialogue between the sponsor of the change and the FDA, which rarely occurs with citizen petitions. (*Id*. at 471, 510).

The importance of this distinction is evidenced by what happened with the Clomid label in 2012. During this same time frame as when the FDA rejected Mr. Mix's motion for reconsideration, Aventis submitted an application to change the

label, and in fact the label was updated. (*Id*. at 465, 500). The label change highlighted several fetal abnormalities reported with human births, as well as those found in animal studies. The new (current) label also states that "[i]f 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." (*Id*. at 528).

It is true, as the district court noted, 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. (*Id*. at 720). However, 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. This is why several courts have held that the FDA's rejection of a citizen petition "does not constitute clear evidence that the FDA would have **rejected** a label change" proposed by the manufacturer. *Schedin*, 808 F. Supp. 2d at 1133 (emphasis in original). This Court should reach the same conclusion.

Because the only evidence supporting preemption in this case is the denial of Mr. Mix's citizen petition, this Court should conclude that there is no "clear evidence" as to how the FDA would have responded had Aventis added a warning, before 1992, regarding the risk of birth defects when using Clomid to conceive.

V. There could be no clear evidence that it was impossible to add a warning about birth defects because the FDA proposed such a warning in 1987, and that exact warning would have prevented Mrs. Cerveny from taking the drug.[12]

A. The FDA proposed that Aventis place Clomid into Pregnancy Category X and add a warning to women using Clomid to become pregnant about the possible harm to the fetus.

Even if this Court believes that there could be preemption based entirely on the rejection of a citizen petition, this Court should conclude that there is no preemption in this case. In 1987, the FDA proposed that Aventis place Clomid into Category X, as a drug presenting a danger to the fetus.

Specifically, the FDA proposed to Aventis that it add the following language to the label:

> PREGNANCY CATEGORY X. See Contraindications and Information for Patients
>
> CONTRAINDICATIONS: 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 apprised of the potential hazard to the fetus.

(Aplt. App. at 461, 595). Aventis rejected the FDA's suggestion, and for years the label did not change. During that period of years, Mrs. Cerveny used Clomid and became pregnant with Alexander, who was born on July 27, 1993, with a left elbow flexion deformity and only three digits on his left hand. (*Id*. at 462, 602).

[12] **Preservation:** This argument regarding the impact of the FDA's 1987 proposed label change appears at Aplt. App. 485-90.

In 1994, Aventis finally updated its label to indicate that Clomid was a "Pregnancy Category X" drug. (*Id*. at 465). A Category X label indicates that "the use of the drug in a pregnant woman clearly outweighs any possible benefit." (*Id*. at 458), citing 21 C.F.R. § 201.80(f)(6)(i)(e). In addition, the Pregnancy Contraindication was strengthened to read: "CLOMID should not be administered during pregnancy. CLOMID may cause fetal harm in animals … . Although no causative evidence of 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." (*Id*. at 463, 597). That 1994 warning was not ideal, but the change shows that updating the label was possible. In fact, 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*. at 460, 463-67, 500). Conversely, Defendant has produced no evidence that it ever submitted a proposed label change to the FDA that was rejected.

Several courts have denied claims of preemption by citing differences in what was rejected by the FDA and what was proposed by the plaintiff. *See Mason*, 596 F.3d at 395 (failure to act on different proposed warnings does not establish that the FDA would have rejected a suicide warning for young adults); *Hunt*, 6 F. Supp. 3d at 700-01 (listing several adverse events that are caused by Children's

Motion that were not addressed by the FDA in response to a citizen petition); *Dorsett*, 699 F. Supp. 2d at 1158 n.14 (FDA's rejection of proposed suicide language in 2007 was not clear evidence that the FDA would have rejected "a broader suicidality warning that pertained to young adults in 2004"). *See also Cross v. Forest Labs.*, No. 1:05-CV-00170-MPM-SA, 2015 WL 1534458, at *3 (N.D. Miss. Apr. 6, 2015) (FDA's rejection of label warning of suicide risk did not preempt plaintiff's claim that drug's label should have cautioned physicians and patients about the need for close observation and about certain symptoms that indicated a suicide risk).

Here, the argument to reject preemption is even stronger. Plaintiffs assert that, at least, Aventis should have added a warning that was **expressly proposed** by the FDA, five years before Mrs. Cerveny ingested the drug. But Aventis failed to add the proposed warning.

B. The proposed warning is not "irrelevant," as the district court held. The Pregnancy X label would have prevented Mrs. Cerveny from using the drug, and it indicates that the FDA would have accepted a warning about risks when using Clomid to become pregnant.

The district court rejected this argument because the 1987 proposed warning did not express a risk of using Clomid to conceive. (Aplt. App. at 730). The court deemed the proposed warning to be "irrelevant" because there is no allegation in this case that Mrs. Cerveny took Clomid while she was pregnant. (*Id*. at 731).

The district court erred in holding the proposed warning to be irrelevant. The proposed warning states that Clomid is contraindicated for pregnant women, and that women who are attempting to become pregnant need to be warned of the "potential harm to the fetus." (*Id.* at 465, 528). The sole indication for Clomid is to induce ovulation in women desiring pregnancy. (*Id.* at 527). Mrs. Cerveny—like, presumably, everyone who takes fertility drugs—was using Clomid in an effort to become pregnant. (*Id*. at 602). Thus, the warning was intended for her. Further, Mrs. Cerveny testified by affidavit that she would not have taken the drug had the warning language that the FDA proposed in 1987 been on the label in 1992. (*Id*. at 603).

The district court cited no authority for its conclusion that there can be impossibility preemption even where a proposed warning was clearly possible, and where there is evidence that the proposed warning would have changed the outcome. If anything, the issue raised by the district court is one of proximate causation, not an issue of impossibility preemption. Proximate causation was not raised as a basis for summary judgment. (*Id*. at 214-37). Also, the complaint was not limited to any precise warning about the risk of using Clomid to become pregnant. The Cervenys pleaded that Aventis "neglected to provide Victoria Cerveny with warnings that could have been expected to catch the attention of a reasonably prudent person under similar circumstances," and neglected to provide

warnings about "the scope, severity and likelihood of serious injury resulting from use of its product." (*Id*. at 028). Aventis failed to provide such a warning when it was clearly possible—in fact, it was proposed by the FDA. As a result, Alexander Cerveny was born with a deformed arm and hand.

But even if this Court subscribes to the theory that the 1987 proposed warning, as written, is "irrelevant," the proposed warning is strong evidence that the FDA would have allowed a warning about the risk of using Clomid to become pregnant, had Aventis used the CBE process to change its label.

Clomid generally leads to ovulation within four of five days from use. (*Id*. at 248). Following use, Clomid remains in a woman's system for a considerable period of time after ingestion, thereby giving the drug an opportunity to affect the developing fetus. (*See id.* at 257-61; *see also id.* at 259 (half-life chart)). The complaint identified two studies that expressed early concern about the lengthy half-life of Clomid and the potential damage that it could cause as it remained in a woman's body after conception. (*Id*. at 017). The Clomid label also acknowledges that "some active drug may remain in the body during early pregnancy in women who conceive in the menstrual cycle during Clomid therapy." (*Id*. at 462, 526).

So, the FDA knew that there was a risk to the fetus if the drug was taken after conception, and the FDA knew that the drug remains in the body long after conception. 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—particularly when the FDA was advocating that women attempting to become pregnant be warned of the "potential harm to the fetus." (*Id.* at 465, 528). What **is** a stretch is concluding that there is "clear evidence" that the FDA would have insisted that Aventis remove such a warning, had Aventis added one through the CBE process before 1992.

To put it another way, the district court's ruling requires at least two, large inferential leaps. The first is that the FDA would have required Aventis to **remove** a warning about the risk of birth defects when Clomid is used to attain pregnancy, based on the FDA's decision not to force Aventis to **add** such a warning after receiving a citizen petition. The second is that the FDA would have reacted the same way before 1992 that it reacted approximately 20 years later, despite a different pool of evidence and different personnel making the decision. Conversely, the Cervenys' argument requires only one, small inferential leap: that the same FDA which proposed warning of a "potential hazard" to the fetus, and which sought a Pregnancy Category X designation, would have allowed Aventis to warn about the risk to the fetus when Clomid is used to become pregnant. Even if the Court views these inferential leaps as equal, summary judgment should be reversed, because in that case there is no "clear evidence" as to what the FDA would have done if Aventis had added the proposed warning.

This Court, therefore, should conclude that Aventis has not established clear evidence of impossibility, and should reverse the district court's grant of summary judgment.

VI. At minimum, this Court should remand the case for further discovery. The question presented is an issue of fact, and Plaintiffs should have the opportunity to develop the factual record before their case is dismissed on summary judgment.[13]

For reasons already expressed, the Court should remand with instructions to deny the summary judgment motion. Alternatively, the Court should allow for more discovery. Plaintiffs should have the opportunity, at minimum, to explore communications between the FDA and Aventis, as such communications would shed light on which label changes were "possible" at various times; and to have their experts develop their opinions as to the ways in the which the 1992 Clomid label was inadequate.

Defendants filed the summary judgment motion on preemption very early in the case. The Court issued its ruling on a motion to dismiss on July 14, 2015. (Aplt. App. at 006). At a hearing on September 9, 2015, Defendants indicated their desire to file an early summary judgment motion as to preemption. (*Id*. at 175). The Court issued a scheduling order on September 30, 2015, setting trial for April

[13] **Preservation:** Plaintiffs alternatively asked for further discovery at Aplt. App. 494-95.

2017, with a motion deadline in November 2016. (*Id.* at 008). Only 40 days later, Aventis moved for summary judgment. (*Id.*).

A motion asserting preemption based on "clear evidence" presents a question of fact. *See Incretin*, 142 F. Supp. 3d at 1115 (stating that "application of the standard is necessarily fact-specific"); *see also Mensing*, 131 S. Ct. at 2589 (Sotomayor, J., dissenting) (stating that such a motion presents "questions of fact to be established through discovery"). In *Incretin*, a case heavily relied upon by the district court, the court allowed more than a year for discovery on preemption issues. *Incretin*, 142 F. Supp. 3d at 1113.

As part of Plaintiffs' summary judgment response, attorney Chris Schnieders executed an affidavit pursuant to Rule 56(d). In the affidavit, Mr. Schnieders stated that more discovery was needed on several points, including but not limited to the following:

- Correspondence between Aventis and the FDA regarding labeling;
- Aventis internal documents on various issues;
- The complete New Drug Application for Clomid;
- Testimony from Aventis employees about Clomid and birth defects;
- Expert discovery to develop their opinions about what should have been added to the Clomid label. (Aplt. Appx at 618-19).

Communications between Aventis and the FDA might shed light on the FDA's mindset in rejecting the citizen petition. Expert reports would better frame the issue so that any warnings that the Plaintiffs argue should have been added before Mrs. Cerveny's use of Clomid—in addition the Pregnancy X warning proposed by the FDA in 1987—can be evaluated in comparison to the citizen petition.

As discussed above, several courts have denied preemption arguments because the rejected warning did not match the warning that a particular plaintiff argued should have been placed on the drug. In addition, Utah law does not require a particular proposed warning to establish a failure-to-warn claim. Rather, the adequacy of a warning is measured by whether the warning is designed to capture the consumer's attention, whether it gives a fair indication of the risks associated with the product, and whether it is "of an intensity justified by the magnitude of the risk." *House v. Armour of Am., Inc.*, 886 P.2d 542, 547 (Utah Ct. App. 1994) *aff'd* 929 P.2d 340 (Utah 1996).

The district court simply assumed, based on certain information in the pleadings, that Plaintiffs' theories are identical to those of Mr. Mix. But as noted, the failure-to-warn count does not advocate for a particular warning, precaution,

adverse event, or other specific label change.[14] The Cervenys should be able to develop those theories further before the court determines whether their theories are similar to what the FDA rejected—if the Court assigns relevance to the citizen petition at all. Therefore, at minimum the Court should overturn the summary judgment and remand the case for further discovery.

VII. Even if the Court upholds summary judgment as to the failure-to-warn claim, the district court provided no basis for granting summary judgment as to certain other claims.[15]

After the Defendants' motion to dismiss was granted in part and denied in part, the Cervenys had five remaining claims: two for failure to warn—based on strict liability and on negligence; one for fraud; one for negligent misrepresentation; and one for implied warranty. (Aplt. App. at 224 n.1).

Defendants' memorandum in support of summary judgment barely addressed those claims, simply arguing that they should be lumped in with the failure-to-warn claims. (*Id.* at 224 & n.1). But claims for fraud and negligent misrepresentation are based on false, affirmative statements; they are not based on the failure to provide particular information. *See Schwartz v. Celestial Seasonings, Inc.*, 124 F.3d 1246, 1252 (10th Cir. 1997) (explaining that a fraud allegation must

[14] The FDA rejected a request for an additional warning, applying the standard of reasonable evidence of an association. That standard does not apply, however, to other sections of the label, such as precautions and adverse events.

[15] **Preservation:** Plaintiffs argued that dismissing the failure-to-warn claims should not lead to full summary judgment at Aplt. App. 493-94.

set out specifics regarding the "false representations" alleged); *Christenson v. Commonwealth Land Title Ins. Co.*, 666 P.2d 302, 305 (Utah 1983) (listing elements of negligent misrepresentation, including "carelessly or negligently" making a false representation).

Clearly, FDA regulations did not make it impossible for Aventis to **refrain** from making false statements in the label, whether it was done intentionally (fraud) or negligently (negligent misrepresentation). Plaintiffs also retain a claim for breach of implied warranty (Count IV). The implied warranty of merchantability requires that goods be "merchantable." One requirement for merchantability is that the goods "conform to the promises or affirmation of fact made on the container or label if any." Utah Code Ann. § 70A-2-316(2)(f). As such, an implied warranty claim may be based on false, affirmative representations. This claim, therefore, should be excluded from the preemption analysis for the same reason as the fraud and negligent misrepresentation claims should be excluded. In addition, the product is not merchantable if it is not "fit for the ordinary purposes for which such goods are used." Utah Code Ann. § 70A-2-316(2)(c). Because Plaintiffs have alleged that Clomid causes birth defects, there is a question of fact as to whether it is fit for its ordinary purpose, which is aiding conception.

The district court did not even address this argument made by the Cervenys. The district court simply granted summary judgment in full, based on the

preemption analysis as to the failure-to-warn claims. Therefore, the Court should at least reverse the district court's decision as to claims for fraud, negligent misrepresentation, and breach of implied warranty.

CONCLUSION

The Cervenys respectfully request that this Court reverse the district court's grant of summary judgment and hold that none of their claims are preempted. Alternatively, the Cervenys request that this Court remand the case for further discovery before any preemption issues are decided.

Finally, if the Court upholds the grant of summary judgment as to the failure-to-warn claims, the Cervenys request that the Court reverse the summary judgment as to the claims for fraud, negligent misrepresentation, and breach of implied warranty, none of which are subject to preemption.

Respectfully Submitted,

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STATEMENT AS TO ORAL ARGUMENT

Per Rule 28.2(C)(4), Plaintiffs-Appellants request that this Court hear oral argument in this case. The case presents complex and important issues of fact and law. Federal preemption is an issue that is pervasive in litigation over prescription drugs. The dialogue at argument likely would assist the Court in relating the case law on impossibility preemption to the facts of this case.

/s/ Adam S. Davis
Attorney for Plaintiffs/Appellants

CERTIFICATE OF SERVICE

I hereby certify that I filed the foregoing brief on July 11, 2016, using the Court's CM/ECF electronic filing system, thereby sending notice of the filing to all counsel of record for this appeal.

/s/ Adam S. Davis
Attorney for Plaintiffs/Appellants

CERTIFICATE OF COMPLIANCE WITH RULE 32(a)(7)

I hereby certify that the foregoing brief has 11,639 words, excluding those items that are referenced in Rule 32(a)(7)(B)(iii). Thus, the brief complies with the type volume limitation listed in Rule 32(a)(7)(B)(i).

/s/ Adam S. Davis
Attorney for Plaintiffs/Appellants

CERTIFICATE OF DIGITAL SUBMISSION

I hereby certify that with respect to the foregoing:

(1) All required privacy redactions have been made per 10th Cir. R. 25.5;

(2) If required to file additional hard copies, that the ECF submission is an exact copy of those documents;

(3) The digital submissions have been scanned for viruses with the most recent version of a commercial virus scanning program, Kaspersky Endpoint Security 10 for Windows, Version 10.2.434 (Network Agent), Version 10.2.4.674 (Anti-Virus), last update 7/10/2016, and according to the program are free of viruses.

/s/ Adam S. Davis
Attorney for Plaintiffs/Appellants

No. 16-4050

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,
Hon. Dee Benson, District Judge,
District Court Case No. 2:14-CV-00545

ADDENDUM OF APPELLANT VICTORIA CERVENY, at al.

INDEX TO APPELLANT'S APPENDIX

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF UTAH, CENTRAL DIVISION

VICTORIA CERVENY, CHARLES CERVENY, and ALEXANDER CERVENY, Plaintiffs, v. AVENTIS, INC., Defendant.	**MEMORANDUM DECISION AND ORDER** Case No. 2:14-CV-00545 District Judge Dee Benson

Before the Court is Defendant Aventis, Inc.'s ("Aventis") Motion for Summary Judgment on Federal Preemption Grounds. (Dkt. No. 38.) The Court held a hearing on Aventis's motion on February 24, 2016. At the hearing, Plaintiffs Victoria Cerveny, Charles Cerveny, and Alexander Cerveny were represented by Christopher L. Schnieders and Eric D. Barton. Aventis was represented by Eric A. Swan and Gary T. Wright. At the conclusion of the hearing, the Court took the motion under advisement. After consideration of the memoranda submitted by the parties, the relevant law, and the oral argument presented by counsel, the Court renders the following Memorandum Decision and Order.

BACKGROUND

The Court finds the undisputed facts as follows. On February 1, 1967, the Food and Drug Administration ("FDA") approved Clomid (or "clomiphene citrate") for the treatment of infertility. (Dkt. No. 39, p. vii.) Aventis is the current manufacturer of Clomid and the successor in interest to the former manufacturers of Clomid. (Dkt. No. 8, ¶ 5.) Relevant to Aventis's motion is how Clomid's labeling addresses Clomid's risks to pregnant women, how Clomid's

labeling addresses the risks, if any, to a fetus if Clomid is taken prior to pregnancy, and how Plaintiffs allege Clomid's labeling is inadequate.

A. Clomid's Risks When Administered During Pregnancy

Clomid is a selective-estrogen-receptor modulator used to induce ovulation in women who are unable to ovulate. (Dkt. No. 38, Ex. G.) Clomid's manufacturers have consistently warned that while Clomid is effective in inducing ovulation, Clomid should not be taken while pregnant. In 1967, Clomid's label stated:

> 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.*

(Dkt. No. 39, Ex. 10, p. 2 (emphasis in original).) In 1980 and 1991, Clomid's label was revised but the 1980 and 1991 labels continued to maintain the same pregnancy warning as the 1967 label. (*See* Dkt. No. 39, Ex. 7, p.2; Dkt. No. 38, Ex. A, p. 1.)

In March 1987, the FDA suggested that Clomid carry a Category X labeling. Prior to 2015, the FDA required a Category X label if "studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk . . . 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). The Category X labeling suggested by the FDA in 1987 stated: "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." (Dkt. No. 39, Ex. 11, p. 1.)

Clomid's label did not contain a Category X labeling until 1994. In 1994, the Clomid Category X label stated:

> 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 (see Fetal/Neonatal Anomalies and Mortality, ADVERSE REACTIONS).
>
> To avoid inadvertent CLOMID administration during early pregnancy, appropriate tests should be utilized during each treatment cycle to determine whether ovulation occurs. The patient should be evaluated carefully to exclude pregnancy, ovarian enlargement, or ovarian cyst formation between each treatment cycle. The next course of CLOMID therapy should be delayed until these conditions have been excluded.

(Dkt. No. 39, Ex. 12, p. 1.) Similarly, Clomid's current label, approved on October 22, 2012, contains a Category X labeling which states:

> 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.

(Dkt. No. 39, Ex. 4, p. 4.)

Consistent with Clomid's risk to pregnant women, Clomid is administered during carefully timed intervals with specific instructions to avoid a patient accidently ingesting Clomid while pregnant. Clomid is administered in five-day intervals to induce ovulation. (Dkt. No. 38, Ex. G, p. 2.) If used as directed, Clomid will typically induce ovulation within five to ten days. (Dkt. No. 39, Ex. 4, p. 9.) A patient taking Clomid is warned to time coitus to coincide with ovulation to ensure that Clomid is not ingested while pregnant. (*See, e.g.*, Dkt. No. 39, Ex. 4, p. 9; Dkt. No. 39, Ex. 7, p. 5.) Additionally, Clomid's label instructs that a patient should be

observed closely during Clomid treatment to exclude pregnancy between treatment cycles. (*See, e.g.*, Dkt. No. 39, Ex. 4, p. 4, 10; Dkt. No. 39, Ex. 12, p. 1.)

B. Clomid Use Prior to Pregnancy and Clomid's Association with Birth Defects

As explained above, since 1967, Clomid's labeling has consistently warned about the risk to a fetus if Clomid is ingested during pregnancy. However, in the nearly five decades Clomid has been used to induce ovulation, the FDA has never required that the Clomid label warn that if ingested prior to pregnancy, Clomid can cause birth defects.

In 1994, Clomid's label was revised to include a Contraindications subsection entitled "Fetal/Neonatal Anomalies and Mortality." (Dkt. No. 39, Ex. 12, p. 1.)[1] The 1994 Fetal/Neonatal Anomalies and Mortality subsection listed the incidents of birth defects reported from Clomid use. (*Id.*) However, the 1994 label 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 1995 label contained the same conclusion. (Dkt. No. 39, Ex. 15, p. 4.)

On November 29, 2007, Terence Mix ("Mix") submitted a citizen petition to the FDA requesting that the FDA: (1) order changes to the labeling and package insert for Clomid and its generics to include warnings of Clomid's ability to cause birth defects if ingested prior to conception; (2) order a risk evaluation and mitigation strategies for Clomid to determine if the benefits of Clomid outweighed its risks; and (3) order post-market studies or clinical trials for Clomid to determine if the use of dietary supplements of cholesterol can mitigate or eliminate the increased risk of birth defects from using Clomid. (*See* Dkt. No. 38, Ex. B, p. 1.)

[1] The parties dispute whether the Fetal/Neonatal Anomalies and Mortality subsection was added in 1993 or 1994. (Dkt. No. 40, p. vii–viii, ¶ 30.) However, for purposes of Aventis's motion it is irrelevant whether the label was revised in 1993 or 1994.

Mix argued that the scientific research available suggested that Clomid "has a long half-life and is still biologically active well into the second month of pregnancy when most organs are being formed . . . [Clomid] thus has the *opportunity* to malform the human embryo in every woman who conceives during a [Clomid] treatment cycle." (*Id.* (emphasis in original).) Mix contended that Clomid "acts on the enzyme delta(24)-dehydrocholesterol reductase, resulting in the impaired biosynthesis of cholesterol and an elevation of its precursor, desmosterol." (*Id.* at 1–2.) Therefore, Mix argued, "during the first two months of pregnancy, every woman who conceives during a treatment cycle with [Clomid] . . . has a cholesterol-inhibiting drug present in the maternal and embryonic circulation when most organs are being formed." (*Id.* at 2.) Mix supplemented his petition to the FDA five times to include scientific literature that he claimed supported his theories. (Dkt. No. 38, Exs. C, D, E, F.)

On September 8, 2009, the FDA denied Mix's petition. (Dkt. No. 38, Ex. G.) To evaluate Mix's petition, the FDA reviewed and tested the scientific merit of the research submitted by Mix. (*Id.* at 3.) Additionally, the FDA "independently surveyed the literature regarding clomiphene citrate." (*Id.*) In rejecting Mix's petition, the FDA found:

> 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. Therefore, the scientific literature does not justify ordering changes to the labeling that warn of such risk beyond those presently included in labeling.

(*Id.*) The FDA noted that Mix "failed to establish that short courses of clomiphene citrate, as used for ovulation induction, cause severe inhibition of cholesterol synthesis in women . . ." (*Id.* at 6.) Furthermore, the FDA concluded that "based on the scientific evidence reviewed, there is insufficient data to demonstrate reasonable evidence of an association between clomiphene

exposure in the periconceptional [preconception] period and the risk of teratogenicity [the capability of causing congenital abnormalities]." (*Id.* at 10.)

In response to Mix's claim that Clomid can be shown to be biologically active well into the second month of pregnancy, the FDA concluded that any half-life resulting from Clomid is the result of one of Clomid's two racemic isomers, en-clomiphene and zu-clomiphene. (*Id.* at 6.) The FDA found that "[e]n-clomiphene disappears rapidly from the circulation, whereas zu-clomiphene is cleared slowly and may accumulate across consecutive cycles of treatment." (*Id.*) However, the FDA concluded that the "[c]urrently available clinical data" suggested that "the level of zu-clomiphene present at the time of organogenesis is insufficient to cause significant inhibition of cholesterol synthesis even after multiple cycles of treatment." (*Id.* at 6–7.)

The FDA made several findings in response to Mix's theory that ingestion of Clomid prior to conception is associated with birth defects. With respect to Mix's assertion that Clomid is associated with neural tube defects, the FDA stated: "[w]e have reviewed the references submitted, along with our own independent review of the literature, and we find that, overall, the scientifically reliable published literature does not support an association between the use of clomiphene citrate and an increased risk of [neural tube defects]." (*Id.* at 10.) With respect to cardiovascular defects, digestive tract defects, genitourinary defects, musculoskeletal defects, Down Syndrome, and orofacial defects, the FDA found, "the evidence is insufficient to establish that the use of clomiphene citrate is associated with these congenital abnormalities." (*See id.* at 12.) Furthermore, the FDA concluded "the evidence is insufficient to establish that the use of clomiphene citrate is associated with any other congenital abnormalities." (*See id.* at 12–13.)

On September 29, 2009, Mix filed an eighteen-page Petition for Reconsideration asking the FDA to reconsider changing the labeling of Clomid to include warnings suggesting an

association with preconception use of Clomid and birth defects. (Dkt. No. 38, Ex. H.) During 2010, Mix supplemented his Petition for Reconsideration with more scientific data to support his theories. (Dkt. No. 38, Exs. L, M.)

On March 8, 2012, the FDA denied Mix's Petition for Reconsideration. The FDA responded to Mix's Petition for Reconsideration, stating: "Contrary to the statements you make in the Reconsideration Petition, we find that our Original Petition Response was properly founded upon relevant and reliable scientific evidence, including available epidemiology studies regarding clomiphene citrate." (Dkt. No. 38, Ex. I, p. 3.) The FDA further stated: "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 is due to the drug and not to the disease process being treated by clomiphene citrate." (*Id.*)

Clomid's current label, approved on October 22, 2012, does not contain warnings suggesting an association between Clomid use prior to pregnancy and birth defects. (Dkt. No. 39, Ex. 4.) The "Precautions" section of the 2012 Clomid label states: "Inform the patient that the available data suggest no increase in the rates of spontaneous abortion (miscarriage) or congenital anomalies with maternal CLOMID use compared to rates in the general population." (*Id.* at 6.) Additionally, under the "Precautions" subsection entitled "Pregnancy", the 2012 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." (*Id.* at 7.)

C. Plaintiffs' Failure-to-Warn Theory

In September 1992, Plaintiff Victoria Cerveny ("Mrs. Cerveny") was prescribed Clomid. (Dkt. No. 2, ¶ 21.) Mrs. Cerveny took "Clomid as prescribed and as directed in the package insert until approximately late October 1992." (Dkt. No 8, ¶ 11.) In November 1992, "following her second round of Clomid, [Mrs. Cerveny] discovered she was pregnant" and subsequently delivered her son Alexander Cerveny ("Alexander"). (*Id.* at ¶¶ 12, 14.) Alexander was born without his first and fifth digits on his left hand. (*Id.* at ¶ 15.) Alexander was also born with "a congenital dislocation of the left radial head" on his left elbow. (*Id.* at ¶¶ 16, 18.)

The Plaintiffs contend that Alexander's birth defects are the result of Clomid remaining present in Mrs. Cerveney's body during conception and organogenesis. (*Id.* at ¶ 13.) Specifically, Plaintiffs allege that "Clomid impairs the biosynthesis of cholesterol," which in turn causes birth defects. (*Id.* at ¶¶ 22, 45.) Plaintiffs contend Clomid use prior to pregnancy can cause several birth defects, including:

> ventricular septal defects, atrial septal defects, hypoplastic left or right heart syndrome, aortic and ventricular outflow tract obstruction defects, craniosynostosis, omphalocele, gastroschisis, persistent pulmonary hypertension of the newborn (PPHN), Tetralogy of Fallot, pulmonary atresia, limb deformations, limb reductions, spina bifida, cleft palate, and patent ductus arteriosus.

(*Id.* at ¶ 22.) Plaintiffs' Amended Complaint cites numerous scientific studies in support of their theory. (*Id.* at ¶¶ 25–54.) Every piece of scientific literature cited in the Plaintiffs' Amended Complaint was presented to the FDA in Mix's citizen petitions. (Dkt. No. 38, Ex. F (comparing the scientific literature submitted by Mix and the scientific literature cited in the Plaintiffs' Amended Complaint); Dkt. No. 39, p. ix.)

Plaintiffs allege that Aventis falsely represented that there was "no causative evidence of a deleterious effect of Clomid therapy on the human fetus . . . ." (Dkt. No. 8, ¶ 57.) Plaintiffs

argue that Aventis had a duty to warn Mrs. Cerveny's prescribing physician that Clomid can cause birth defects if taken prior to pregnancy. (*Id.* at ¶ 22.) Plaintiffs contend 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. (*Id.* at ¶ 21.)

STANDARDS OF REVIEW

Pursuant to Rule 56(a) of the Federal Rules of Civil Procedure, "[t]he court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." "A fact is 'material' if, under the governing law, it could have an effect on the outcome of the lawsuit. A dispute over a material fact is 'genuine' if a rational jury could find in favor of the nonmoving party on the evidence presented." *Tabor v. Hilti, Inc.*, 703 F.3d 1206, 1215 (10th Cir. 2013) (citations omitted). In evaluating a motion for summary judgment, the Court reviews the facts in a light most favorable to the nonmovant and draws all reasonable inferences in the nonmovant's favor. *Jones v. Norton*, 809 F.3d 564, 573 (10th Cir. 2015). "To survive a motion for summary judgment, a nonmoving party 'must set forth specific facts showing that there is a genuine issue for trial as to those dispositive matters for which he [or she] carries the burden of proof.'" *Christy v. Travelers Indem. Co. of Am.*, 810 F.3d 1220, 1233 (10th Cir. 2016) (citations omitted).

Whether federal law preempts a plaintiff's state tort law claims presents a pure question of law appropriate for resolution by summary judgment. *See Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1267 (W.D. Okla. 2011); *In re Incretin-Based Therapies Prods. Liab. Litig.*, No. 12-md-2452, 2015 WL 6912689, at *3 (S.D. Cal. Nov. 9, 2015).

DISCUSSION

The Supremacy Clause of the United States Constitution 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. The Supremacy Clause "invalidates state laws that 'interfere with, or are contrary to,' federal law." *Hillsborough Cnty. Florida v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712 (1985) (citations omitted). To determine whether federal preemption exists, the Court is "guided by two cornerstones" of preemption jurisprudence. *Wyeth v. Levine*, 555 U.S. 555, 565 (2009). "First, 'the purpose of Congress is the ultimate touchstone in every preemption case.'" *Id.* (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)). Second, when preemption involves a field in which the States have traditionally occupied, the "historic police powers of the States [are] not to be superseded by . . . Federal Act unless that [is] the clear and manifest purpose of Congress." *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947).

"There are three forms of preemption . . . express preemption, conflict preemption, and field preemption." *Devon Energy Prod. Co., L.P. v. Mosaic Potash Carlsbad, Inc.*, 693 F.3d 1195, 1203, n.4 (10th Cir. 2012) (citing cases). Express preemption exists where Congress utilizes "explicit statutory language" to supersede state law. *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990). Field preemption "'occurs when the federal scheme of regulation is so pervasive that Congress must have intended to leave no room for a State to supplement it.'" *US Airways, Inc. v. O'Donnell*, 627 F.3d 1318, 1324 (10th Cir. 2010) (citations omitted). Conflict preemption arises "where it is impossible for a private party to comply with both state and federal requirements . . . or where state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.'" *English*, 496 U.S. at 79 (1990) (citations omitted).

Aventis's motion relies on conflict preemption. Specifically, Aventis contends that the FDA would not have permitted Aventis to include the warnings suggested by the Plaintiffs. Therefore, Aventis argues, Plaintiffs' state tort law claims are conflict preempted because it is impossible for Aventis to comply with both state and federal law. To evaluate Aventis' Motion, the Court must first examine the regulatory burden imposed on Aventis by the FDA. Next, the Court will consider whether Aventis has established a preemption defense by satisfying the "clear evidence" standard announced in *Wyeth v. Levine*, 555 U.S. 555 (2009).

A. Federal Regulation of Drug Labeling

Under the Federal Food, Drug, and Cosmetics Act, Congress has delegated authority to the FDA to regulate pharmaceutical manufacturers and their products. 21 U.S.C. § 301. Before taking a drug to market, drug manufacturers are required to obtain FDA approval for both a proposed drug and the exact labeling text accompanying the drug. *See* 21 U.S.C. § 355; 21 C.F.R. § 314.105(b). The FDA requires a drug label to include several different types of information, including indications and usage, contraindications, warnings, precautions, and adverse reactions. *See* 21 C.F.R. § 201.80. The FDA will approve a drug application if the FDA determines "that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling." 21 C.F.R. § 314.105(c).

A "central premise of federal drug regulation [is] that the manufacturer bears responsibility for the content of its label at all times." *Levine*, 555 U.S. at 570. A drug manufacturer is not only responsible for ensuring the label is adequate when approved by the FDA, but the manufacturer also has an ongoing responsibility to ensure that the drug's label remains adequate as long as the drug remains on the market. *See* 21 C.F.R. 314.80(b) (ordering manufacturers to engage in post-market drug research and drug surveillance and to report

findings to the FDA); 21 C.F.R. § 201.80(e) (mandating that a drug manufacturer revise a drug label "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug"). Additionally, the FDA is responsible for monitoring the safety of approved drugs. 21 U.S.C. § 355(e). The FDA must withdraw its approval of a drug if it determines, based on "clinical or other experience, tests, or other scientific data," that a "drug is unsafe for use under the conditions of use upon the basis of which the application was approved." *Id*. Furthermore, the FDA is required to revoke approval if "on the basis of new information" the FDA concludes that the drug's labeling "is false or misleading in any particular." *Id.*

Generally, a drug manufacturer cannot change the labeling of a drug without seeking prior approval from the FDA. *See* 21 C.F.R. § 314.70(b). However, the FDA's "changes being effected" ("CBE") regulation allows a drug manufacturer to strengthen certain aspects of a label "to reflect newly acquired information" prior to seeking FDA approval. 21 C.F.R. § 314.70 (c)(6)(iii).[2] Specifically, after a manufacturer files a supplemental application to change a drug label, a manufacturer can "add or strengthen a contraindication, warning, precaution, or adverse reaction" or "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product" before the FDA approves the supplemental application. *Id.* at § 314.70(c)(6)(iii)(A), (C). The FDA has defined "newly acquired information" to not only include newly acquired data but also to encompass "new analyses of previously submitted data." Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics,

[2] The FDA initially proposed the CBE preapproval process in 1982. *See* New Drug and Antibiotic Regulations, 47 Fed. Reg. 46622, 46623 (Oct. 19, 1982) (to be codified 21 C.F.R. pts. 310, 312, 314, 430, 431, and 733) ("These supplements would describe changes placed into effect to correct concerns about newly discovered risks from the use of the drug.").

and Medical Devises, 73 Fed. Reg. 49603, 49604 (Aug. 22, 2008) (to be codified at 21 C.F.R. pts. 314, 601, and 814).

In addition to CBE submissions, the FDA has process whereby interested parties may submit citizen petitions arguing for alterations of a drug's labeling. *See* 21 C.F.R. 10.30. Whether a request for a warning labeling change comes from a manufacturer through a CBE submission or from a citizen through a citizen petition, the FDA's standard of review is the same. *In re Incretin-Based Therapies Prods. Liab. Litig.*, 2015 WL 6912689, at *12, 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.").[3] FDA regulations require that "[t]he labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.80(e).

B. Application of the "Clear Evidence" Standard

In the context of pharmaceutical drug regulation, the Supreme Court in *Wyeth v. Levine*, 555 U.S. 555, 568 (2009) announced a context specific standard for determining whether state tort failure-to-warn claims are preempted by the FDA's pervasive regulation of drug labeling. In *Levine*, the plaintiff was administered the drug Phenergan through the IV push method. *Id.* at 559. The IV push method caused the drug to enter the plaintiff's artery resulting in gangrene and the eventual amputation of the plaintiff's right arm. *Id.* The plaintiff brought a state tort failure-to-warn claim arguing that Phenergan's labeling inadequately warned that Phenergan is

[3] Plaintiffs argue that "[a] citizen petition submitted under 21 CFR 10.30 and submission of a labeling supplement by a pharmaceutical sponsor under 21 CFR 314.70 are fundamentally different." (Dkt. No. 38, p. 5.) However, besides merely pointing to anecdotal conjecture, the Plaintiffs do not cite any statute, regulation, or FDA guidance to support their speculation that an FDA citizen petition is reviewed with any less rigor than a manufacturer's CBE submission.

dangerous when administered by the IV push method. *Id.* at 560. Phenergan's manufacturer, Wyeth, argued that the plaintiff's claims were preempted because it was impossible to comply with state law and the FDA's labeling requirements. *Id.* at 563. Specifically, Wyeth contended that the FDA's regulations did not permit Wyeth to change Phenergan's labeling until there was "newly acquired information" that allowed Wyeth to utilize the FDA's CBE regulation to strengthen Phenergan's label. *Id.* at 568–69.

The *Levine* Court held that the FDA's initial approval of a drug label does not preempt all subsequent failure-to warn claims. *Id.* at 588. To evaluate Wyeth's preemption defense, the Court looked beyond the FDA's initial approval of Phenergan's label and considered four factors, including: (1) whether Wyeth tried to strengthen Phenergan's label; (2) whether the FDA prohibited Wyeth from strengthening Phenergan's label; (3) whether the FDA or Wyeth focused on the risks associated with Phenergan IV push administration; and (4) whether Wyeth had provided the FDA with its evaluation of the risks associated with Phenergan IV push administration. *Id.* at 572–73; *see In re Incretin-Based Therapies Products Liab. Litig.*, 2015 WL 6912689, at *4 (breaking down the factors analyzed by the Supreme Court in *Levine*).

The Court concluded that Wyeth had not attempted to give a warning specific to Phenergan's risks when administered through the IV push method. *Levine*, 555 U.S. at 572. Additionally, the Court concluded that the record demonstrated that the FDA and Wyeth had given Phenergan's IV push method risks only "'passing attention.'" *Id.* (citations omitted). Furthermore, Wyeth had not provided the FDA with an evaluation of the risks associated with IV push method of administration of Phenergan. *Id.* Rejecting Wyeth's preemption defense, the Supreme Court held, "[t]he CBE regulation permitted Wyeth to unilaterally strengthen its warning, and the mere fact that the FDA approved Phenergan's label does not establish that it

would have prohibited such a change." *Id.* at 573. The Court further held that "absent clear evidence that the FDA would not have approved a change to Phenergan's label" the Court would "not conclude that it was impossible for Wyeth to comply with both federal and state requirements." *Id.* at 571.

"*Levine* does not define 'clear evidence,' nor does it suggest the level of proof required to constitute such evidence." *Dobbs*, 797 F. Supp. 2d at 1270. However, courts applying *Levine* agree that "the clear evidence standard is a fact based inquiry that depends on the express type of warning at issue and the particular facts of each case." *Koho v. Forest Labs., Inc.*, 17 F.Supp.3d 1109, 1118 (W.D. Wash. 2014); *Dobbs*, 797 F. Supp. 2d at 1270 ("[A]pplication of the clear evidence standard is necessarily fact specific."). In support of preemption, Aventis contends that there are two sources of evidence that suggest the FDA would not have approved a stronger warning label on Clomid prior to 1992. First, Aventis contends the FDA's rejection of Mix's citizen petitions of 2009 and 2012 are clear evidence the FDA would not have approved a warning on Clomid's label suggesting an association between Clomid use prior to pregnancy and birth defects. (Dkt. No. 38, p. 12.) Second, Aventis argues, the FDA's history of approving Clomid labeling that includes statements contrary to the Plaintiffs' theories is further evidence that the FDA does not associate Clomid use prior to pregnancy with birth defects. (Dkt. No. 40, p. 9 (stating, "every official action by FDA over the last 20 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").) Each of Aventis's arguments will be discussed in turn.

i. The FDA's Denial of a Citizen Petition as "Clear Evidence"

Courts have universally rejected the notion that *Levine* requires a showing that the manufacturer attempted to apply the warning suggested by the plaintiff but that the labeling

change was ultimately rejected by the FDA.[4] While Courts have found the actual rejection of a CBE submission to be "highly persuasive evidence" of preemption, a rejection of a CBE submission is not the only way a manufacturer can satisfy the *Levine* "clear evidence" standard. *Dobbs*, 797 F. Supp. 2d at 1276–77. Indeed, several courts have concluded that "citizen petition responses . . . [are] indicative of whether the FDA would reject a proposed labeling change." *In re Incretin-Based Therapies Prods. Liab. Litig.*, 2015 WL 6912689, at *13 (citing *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 395 (7th Cir. 2010); *Koho v. Forest Labs., Inc.*, 17 F. Supp. 3d 1109, 1117 (W.D. Wash. 2014); *Dorsett v. Andoz*, 699 F. Supp. 2d 1142, 1157 (C.D. Cal. 2010)). The Supreme Court and the Tenth Circuit have yet to address the evidentiary strength of a citizen petition denial in the context of *Levine*. However, several courts provide the Court guideposts on which to evaluate the FDA's denial of a citizen petition.

Many courts have held that denial of a citizen petition is insufficient evidence of preemption where the citizen petition predates the injury. *See, e.g.*, *Dorsett v. Andoz*, 699 F. Supp. 2d 1142, 1157 (C.D. Cal. 2010) ("The FDA's rejections of citizen petitions in the 1990s do not constitute clear evidence that warnings of such an association in July 2004 would have been false and misleading, and hence not permitted."); *Koho*, 17 F. Supp. 3d at 1117; *Dobbs*, 797 F. Supp. 2d at 1277 ("This court agrees with [the manufacturer] that the FDA rejection of the

[4] *See, e.g.*, *Levine*, 555 U.S. at 572–73 (noting that the FDA, in addition to the manufacturer, had not evaluated the risks of administering Phenergan through the IV push method); *In re Incretin-Based Therapies Prods. Liab. Litig.*, 2015 WL 6912689, at *13 ("In reaching its conclusion that clear evidence exists, the Court rejects Plaintiffs' position that Defendants cannot establish preemption absent express rejection of a proposed labeling change."); *Reckis v. Johnson & Johnson*, 28 N.E.3d 445, 459, n.29 (Mass. 2015) *cert. denied*, 136 S. Ct. 896 (2016) ("The court in [*Levine*] 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 [*Levine*] standard of clear evidence can be satisfied only by the FDA's rejection of a manufacturer's request for an additional warning." (citations omitted)); *see also PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2588–89 (2011) (Sotomayor, J. dissenting) (noting in the context of "clear evidence" that "[a] generic manufacturer might . . . show 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").

citizen petitions [in 1997] is not, without more, sufficient because [the patient's] suicide . . . occurred several years after 1997, and additional studies were conducted in the interim."). Indeed, in theory, scientific information improves over time and therefore a citizen petition rejected years prior to the injury is not clear evidence that the FDA would not approve a later warning on a drug label.[5]

For example, in *Koho v. Forest Labs., Inc.*, 17 F. Supp. 3d 1109, 1111 (W.D. Wash 2014), the plaintiff brought a failure-to-warn-claim against a drug manufacturer after her husband committed suicide in 2002. The plaintiff's husband had been prescribed the anti-depressant Celexa, which the plaintiff contended was associated with suicidality. *Id.* at 1116–17. Celexa is a part of a class of drugs known as Selective Serotonin Reuptake Inhibitors or SSRIs. *Id.* at 1111. In an attempt to show that the FDA would have rejected a stronger suicide warning, Clexa's manufacturer provided the court three citizen petitions for the SSRI Prozac that were reviewed and rejected by the FDA in 1990, 1991, and 1997. *Id.* at 1112. The citizen petitions alleged that there is a causal connection between SSRI use and suicide. *Id.* The FDA rejected each of the Prozac petitions because the FDA concluded that there was "insufficient causal evidence to support an association between SSRIs and suicidality." *Id.* The court found that the latest rejection of a citizen petition in 1997, five years prior to the alleged injury, did not constitute "clear evidence" that the FDA would have rejected a warning in 2002. *Id.* at 1117.

[5] Plaintiffs' counsel misrepresented the law on this issue. Plaintiffs' counsel stated: "Several other federal courts have similarly rejected the argument that a tort claim was preempted because a citizen petition—or a series of citizen petitions—had been rejected by the FDA." (Dkt. No. 39, p. 7 (citing cases).) Plaintiffs' counsel failed 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" that the FDA would reject a proposed label change. *See Koho*, 17 F. Supp. 3d at 1117; *Hunt v. McNeil Consumer Healthcare*, 6 F. Supp. 3d 694, 701 (E.D. La. 2014) ("[T]he FDA's response in 2006 to the Citizen Petition is not clear evidence the agency would have rejected in 2010 the stronger warnings Plaintiff proposes."); *Dorsett*, 699 F. Supp. 2d at 1157; *Dobbs*, 797 F. Supp. 2d at 1277.

The court held, "[i]n light of the evolving nature of the data regarding the effects of prescription drugs, the temporal gap between the latest rejection of a citizen petition in 1997 and [the patient's death] in 2002 is significant." *Id.*

Similarly, courts have found citizen petitions to be unpersuasive where the citizen petition fails to address the theory proffered by the plaintiff. *See, e.g.*, *Hunt v. McNeil Consumer Healthcare*, 6 F. Supp. 3d 694, 701 (E.D. La. 2014); *Newman v. McNeil Consumer Healthcare*, No. 10-CV-01541, 2012 WL 39793, at *6 (N.D. Ill. Jan. 9, 2012) (noting "in its response to the Citizen Petition, the FDA did not reject the warning Plaintiffs claim is required"). For example, in *Hunt v. McNeil Consumer Healthcare*, 6 F. Supp. 3d 694, 701 (E.D. La. 2014), the court concluded that the FDA's 2005 denial of a citizen petition was not clear evidence that the FDA would not have approved a stronger warning on a Children's Motrin label prior to the plaintiff's injury. The plaintiff brought a failure-to-warn claim after suffering personal injury as the result of ingesting Children's Motrin. *Id.* at 696. The active ingredient in Children's Motrin is ibuprofen. *Id.* at 697.

In 2005, a group of citizens petitioned the FDA to add warnings to ibuprofen labels that would include the risk of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis ("SJS/TEN") associated with ibuprofen use. *Id.* at 699–7001. The FDA agreed to require manufacturers to list the symptoms of SJS/TEN, but rejected listing SJS/TEN by name on the label. *Id.* The FDA concluded that "'most consumers are unfamiliar with these terms" and a "'description of symptoms is more appropriate.'" *Id.* (citations omitted). The court found that the plaintiff's failure-to-warn claims went beyond a mere lack of SJS/TEN warnings on the Children's Motrin label. The plaintiff suggested that the Children's Motrin label should have warned that use of Children's Motrin may result in:

> 'massive skin loss or sloughing of skin; blindness or eye injuries; burns over large portions of the body; massive scarring; damage to bodily organs; extensive external or internal injuries; severe and permanent disability; transient and/or permanent mucosal injuries, including injuries to the genitalia; recurrent and/or irreversible damage to hair and nails; and potential long-term dental injures or deformities.'

Id. at 701 (citations omitted). In the context of *Levine*, the court concluded that the 2005 citizen petition denial was unpersuasive because "the FDA did not clearly reject *any* of . . . [the plaintiff's] warnings." *Id.* (emphasis in original).

Conversely, where a citizen petition post-dates the alleged injury and addresses the failure-to-warn claim proffered by a plaintiff, a citizen petition denial can be evidence to support a manufacturer's preemption defense. *See, e.g.*, *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir. 2010) ("The '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 so [in the citizen petition] to which the agency was responding."); *In re Incretin-Based Therapies Prods. Liab. Litig.*, 2015 WL 6912689, at *13.

For example, in *In re Incretin-Based Therapies Products Liability Litigation*, No. 13-md-2452, 2015 WL 6912689, at *1 (S.D. Cal. Nov. 9, 2015) the plaintiffs brought failure-to-warn claims alleging that drugs commonly used to treat type 2 diabetes, Januvia, Janumet, Byetta, and Victoza, create or cause an increased risk of pancreatic cancer. To determine the plaintiffs' failure-to-warn claims were conflict preempted, the court relied on several types of evidence, including "the FDA's rejection of a citizen petition requesting the withdrawal of Victoza." *Id.* at *9. In April 2012, the FDA received a citizen petition demanding that the FDA remove Victoza from the market. *Id.* at *9–10. The citizen petition alleged that scientific data available suggested an increased risk of pancreatic cancer associated with Victoza use. *Id.*

The FDA rejected the citizen petition, finding: "'In our review of 49 unique cases recovered from [FDA Adverse Reporting System] we found no new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza that would support any changes to the current approved labeling.'" *Id.* at *10 (citations omitted). The FDA also concluded that "'[a]ny causal association between exposure to Victoza and pancreatic cancer is indeterminate at this time.'" *Id.* The court concluded that "responding to citizen petitions is within the FDA's regulatory authority" and served as evidence that the FDA would have rejected stronger warnings on Victoza's label. *See id.* at *13.

In this case, the FDA heard and rejected the Plaintiffs' theory embodied in Mix's citizen petitions, which post-dates Mrs. Cerveny's Clomid use by over fifteen years. Plaintiffs' failure-to-warn theory is twofold. First, Plaintiffs contend Clomid has a long half-life and is still biologically active in a woman's body during conception and organogenesis. (Dkt. No. 8, ¶ 13.) Second, Plaintiffs argue that Clomid impairs the biosynthesis of cholesterol by inhibiting the function of certain enzymes. (*Id.* at ¶¶ 22, 45.) Plaintiffs believe that Clomid's alleged ability to inhibit cholesterol causes several birth defects when administered prior to pregnancy. (*Id.* at ¶ 22.)

Mix's 2007 Citizen Petition and Mix's 2009 Petition for Reconsideration argued the Plaintiffs' theories to the FDA. (Dkt. No. 38, Ex. F (comparing the scientific literature submitted by Mix and the scientific literature cited in the Plaintiffs' Amended Complaint).) Mix argued that Clomid has a long half-life and is "still biologically active well into the second month of pregnancy when most organs are being formed." (*See* Dkt. No. 38, Ex. B, p. 1.) Mix contended that Clomid "acts on the enzyme delta(24)-dehydrocholesterol reductase, resulting in the impaired biosynthesis of cholesterol and an elevation of its precursor desmosterol." (*Id.*) Mix

proffered that Clomid's interference with cholesterol synthesis can cause severe birth defects. To support this theory, Mix provided the FDA with the same scientific research that the Plaintiffs cite in the Amended Complaint as support for their theories. (Dkt. No. 38, Ex. F.)

On September 8, 2009, the FDA rejected Mix's theories and, by proxy, rejected the Plaintiffs' theories. (Dkt. No. 38, Ex. F.) In evaluating Mix's 2007 petition, the FDA not only reviewed the scientific research submitted by Mix, the FDA also "independently surveyed the literature regarding clomiphene citrate [or Clomid]." (*Id.* at 3.) The FDA concluded:

> 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. Therefore, the scientific literature does not justify ordering changes to the labeling that warn of such risk beyond those presently included in labeling.

(*Id.*) The FDA noted that Mix "failed to establish that short courses of clomiphene citrate, as used for ovulation induction, cause severe inhibition of cholesterol synthesis in women . . ." (*Id.* at 6.) Furthermore, the FDA concluded that "based on the scientific evidence reviewed, there is insufficient data to demonstrate reasonable evidence of an association between clomiphene exposure in the periconceptional [preconception] period and the risk of teratogenicity [the capability of causing congenital abnormalities]." (*Id.* at 10.)

Specifically, the FDA concluded that the scientific research showed that any half-life resulting from Clomid "is insufficient to cause significant inhibition of cholesterol synthesis even after multiple cycles of treatment." (*Id.* at 6–7.) Furthermore, the FDA concluded that there was no reliable scientific data that proved an association between Clomid and an increased risk of neural tube defects, cardiovascular defects, digestive tract defects, genitourinary defects, musculoskeletal defects, Down Syndrome, and orofacial defects. (*Id.* at 10–13.) The FDA

further found that "the evidence is insufficient to establish that the use of [Clomid] is associated with *any* other congenital abnormalities." (*Id.* at 12–13 (emphasis added).)

In 2009, Mix filed a Petition for Reconsideration, supplementing his petition with more scientific data to support his theories. (Dkt. No. 39, Exs. H, L, M.) On March 9, 2012, the FDA once again concluded that Mix's petitions "fail[ed] to provide reasonable evidence to demonstrate that the association between clomiphene citrate exposure and neural tube defects o*r other congenital abnormalities* is due to the drug and not to the disease process being treated by clomiphene citrate." (Dkt. No. 39, Ex. H, p. 3 (emphasis added).)

Mix's request to alter Clomid's label is the exact theory and substance on which the Plaintiffs' case relies. Importantly, the FDA's rejection of the Plaintiffs' theories occurred many years after Mrs. Cerveny took Clomid to induce ovulation. If the FDA concluded in 2009 and 2012 that (1) Clomid is not a significant inhibitor of cholesterol and (2) if used as directed, Clomid does not pose a risk of causing birth defects, the Court cannot say the FDA would have approved a contrary warning prior to 1992. Indeed, the FDA's regulations only require a warning if there is "reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R. § 201.80(e). The FDA's denial of the Plaintiffs' theories embodied in Mix's citizen petitions is clear evidence that the FDA would not have permitted Aventis to strengthen Clomid's label prior to 1992.

ii. The FDA's Inaction as "Clear Evidence"

The FDA's denials of Mix's citizen petitions, standing alone, is clear evidence that the FDA would not have permitted Aventis to strengthen Clomid's label to include warnings of the risks of birth defects if taken prior to pregnancy. However, the Court also finds it dispositive

that the FDA, in addition to rejecting Mix's citizen petitions, has consistently approved Clomid labeling that includes affirmative rejections of the Plaintiffs' theories.

In *In re Incretin-Based Therapies Products Liability Litigation*, in addition to finding the FDA's rejection of a Victoza citizen petition to be evidence of preemption, the court also found persuasive the FDA's "subsequent approval of other incretin-based therapies without any reference to pancreatic cancer in the product labeling." 2015 WL 6912689, at *9. The court concluded that "[t]he FDA's subsequent inaction regarding [incretin-based] drug labeling supports the conclusion that the FDA does not consider available scientific evidence of a causal association sufficient to warrant inclusion in the labeling." *Id.* at *11. Specifically, the court found, "[t]he FDA has . . . not required any of the Defendants to add a pancreatic cancer warning, or required the inclusion of a warning in newly approved incretin-based therapies." *Id.* In support of preemption, the court held "[w]hile FDA inaction is insufficient on its own to establish preemption, it is highly persuasive given the FDA's comprehensive review of pancreatic safety and ability to mandate a labeling change if it concluded the regulatory standards were satisfied." *Id.*

Just like *In re Incretin-Based Therapies Products Liability Litigation*, the FDA's inaction with respect to Clomid's labeling is highly persuasive evidence that the FDA would not have approved strengthening Clomid's label prior to 1992. Since 1967, Clomid's label has consistently warned about the risk to a fetus if Clomid is ingested during pregnancy. However, in the nearly five decades Clomid has been used to induce ovulation, the FDA has never required Clomid to carry warnings suggesting birth defects associated with Clomid use prior to pregnancy. Furthermore, since 1994, the FDA has approved Clomid labeling that acknowledges

that Clomid exposure prior to pregnancy does not cause birth defects at a rate greater than that observed in the general population.

In 1994, Clomid's label was revised to include a new contraindications subsection entitled "Fetal/Neonatal Anomalies and Mortality." (Dkt. No. 39, Ex. 12, p. 1.) The 1994 Fetal/Neonatal Anomalies and Mortality subsection listed the incidents of birth defects reported from Clomid use. (*Id.*) However, the 1994 label 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 1995 label contained the same conclusion. (Dkt. No. 39, Ex. 15, p. 4.)

After the FDA reviewed and rejected Mix's citizen petitions in 2009 and 2012, Clomid's current label was revised. Clomid's current label does not contain warnings suggesting Clomid use prior to pregnancy causes birth defects. (*See* Dkt. No. 39, Ex. 4.) Under the "Precautions" section, the label states: "Inform the patient that the available data suggest no increase in the rates of spontaneous abortion (miscarriage) or congenital anomalies with maternal CLOMID use compared to rates in the general population." (*Id.* at 6.) 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." (*Id.* at 7.)

In other words, Clomid's current label states that there is no statistically significant evidence to suggest that Clomid carries a risk of causing birth defects above the risk of birth defects found in the general population. The FDA's inaction alone cannot support a preemption defense. The Court finds, however, that the FDA's inaction, coupled with the FDA's

comprehensive review of any association between Clomid ingestion prior to pregnancy and birth defects, to be highly persuasive evidence that the FDA would not permit Aventis to strengthen Clomid's labeling as the Plaintiffs suggest.

The Plaintiffs rely heavily on the FDA's history of requiring that Clomid carry a Category X warning. Clomid's history of carrying a Category X warning is irrelevant to Plaintiffs' case and is certainly not dispositive as to whether the FDA would have permitted Aventis to strengthen Clomid's warning to include warnings suggesting exposure to Clomid prior to pregnancy causes birth defects. Prior to 2015, the FDA utilized a five category system to indicate the potential of a drug to cause birth defects if used during pregnancy. A Category X label was required if "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 that will eliminate the FDA's pregnancy category system. *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 1987, the FDA suggested that the Clomid label be revised to include the following language: "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." (Dkt. No. 39, Ex. 11, p. 1 (emphasis

added).) Clomid's label did not contain a Category X labeling until 1994. However, previous iterations of the Clomid label contained a similar warning as the pregnancy warning suggested by the FDA in 1987. (*See* Dkt. No. 39, Ex. 7, p.2; Dkt. No. 38, Ex. A. p.1.) Clomid's current label, approved in October 2012, states:

> 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.

(Dkt. No. 39, Ex. 4, p. 4 (emphasis added).) The Plaintiffs contend that the FDA's suggestion in 1987 and the post 1992 Clomid Category X warnings are clear evidence that the FDA would have permitted Aventis to strengthen its warning prior to 1992. Therefore, Plaintiffs' argue, Aventis's preemption defense fails.

The Plaintiffs' arguments are inapposite. The FDA's history of requiring Clomid to carry a Category X labeling is irrelevant to the Plaintiffs' case. The Plaintiffs claim that Clomid carries a risk of causing birth defects if the drug is ingested *prior* to pregnancy. Indeed, the Plaintiffs are not alleging that Mrs. Cerveny took Clomid while she was pregnant. (*See* Dkt. No 8, ¶¶ 11, 12, 14.) It 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 plaintiff's case. If anything, Clomid's Category X labeling indicates that the FDA has always maintained the position that a patient using Clomid to induce ovulation should not continue to take Clomid while pregnant. Clomid's Category X labeling is not an indication that the FDA would have permitted Aventis to warn about the risks of causing birth defects if Clomid is taken prior to pregnancy.

CONCLUSION

Aventis's Motion for Summary Judgment on Federal Preemption Grounds is GRANTED.

Dated: March 16, 2016.

BY THE COURT:

Dee Benson
United States District Judge

Code of Federal Regulations
Title 21. Food and Drugs
Chapter I. Food and Drug Administration, Department of Health and Human Services (Refs & Annos)
Subchapter D. Drugs for Human Use
Part 314. Applications for FDA Approval to Market a New Drug (Refs & Annos)
Subpart B. Applications

21 C.F.R. § 314.70

§ 314.70 Supplements and other changes to an approved application.

Effective: September 22, 2008
Currentness

(a) Changes to an approved application.

(1)(i) Except as provided in paragraph (a)(1)(ii) of this section, the applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the application under paragraph (d) of this section.

(ii) The submission and grant of a written request for an exception or alternative under § 201.26 of this chapter satisfies the applicable requirements in paragraphs (a) through (c) of this section. However, any grant of a request for an exception or alternative under § 201.26 of this chapter must be reported as part of the annual report to the application under paragraph (d) of this section.

(2) The holder of an approved application under section 505 of the act must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with § 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the cover letter.

(b) Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

(i) Except those described in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved application;

(ii) Changes requiring completion of studies in accordance with part 320 of this chapter to demonstrate the equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug;

(iii) Changes that may affect drug substance or drug product sterility assurance, such as changes in drug substance, drug product, or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation;

(iv) Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter; and

(C) Any change to the information required by § 201.57(a) of this chapter, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

(1) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(2) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

(vi) Changes in a drug product container closure system that controls the drug product delivered to a patient or changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of a packaging component that may affect the impurity profile of the drug product.

(vii) Changes solely affecting a natural product, a recombinant DNA–derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody for the following:

(A) Changes in the virus or adventitious agent removal or inactivation method(s);

(B) Changes in the source material or cell line; and

(C) Establishment of a new master cell bank or seed.

(viii) Changes to a drug product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application.

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

(vi) For a natural product, a recombinant DNA–derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section; and

(vii) For sterilization process and test methodologies related to sterilization process validation, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section.

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: "Prior Approval Supplement–Expedited Review Requested."

(c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the drug product, except those described in paragraphs (b) and (d) of this section; and

(ii) Changes solely affecting a natural protein, a recombinant DNA–derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves different equipment; and

(B) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

(i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another;

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

(d) Changes to be described in an annual report (minor changes).

(1) Changes in the drug substance, drug product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product must be documented by the applicant in the next annual report in accordance with § 314.81(b)(2).

(2) These changes include, but are not limited to:

(i) Any change made to comply with a change to an official compendium, except a change described in paragraph (c)(2)(iii) of this section, that is consistent with FDA statutory and regulatory requirements.

(ii) The deletion or reduction of an ingredient intended to affect only the color of the drug product;

(iii) Replacement of equipment with that of the same design and operating principles except those equipment changes described in paragraph (c) of this section;

(iv) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form drug product, without a change from one container closure system to another;

(v) A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(vi) An extension of an expiration dating period based upon full shelf life data on production batches obtained from a protocol approved in the application;

(vii) The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, or deletion of an alternative analytical procedure;

(viii) The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint;

(ix) A change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength or dosage form; and

(x) An editorial or similar minor change in labeling, including a change to the information allowed by paragraphs (b)(2)(v)(C)(1) and (2) of this section.

(3) For changes under this category, the applicant is required to submit in the annual report:

(i) A statement by the holder of the approved application that the effects of the change have been assessed;

(ii) A full description of the manufacturing and controls changes, including the manufacturing site(s) or area(s) involved;

(iii) The date each change was implemented;

(iv) Data from studies and tests performed to assess the effects of the change; and,

(v) For a natural product, recombinant DNA–derived protein/polypeptide, complex or conjugate of a drug substance with a monoclonal antibody, sterilization process or test methodology related to sterilization process validation, a cross-reference to relevant validation protocols and/or standard operating procedures.

(e) Protocols. An applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. Any such protocols, if not included in the approved application, or changes to an approved protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of a drug product produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(f) Patent information. The applicant must comply with the patent information requirements under section 505(c)(2) of the act.

(g) Claimed exclusivity. If an applicant claims exclusivity under § 314.108 upon approval of a supplement for change to its previously approved drug product, the applicant must include with its supplement the information required under § 314.50(j).

Credits

[50 FR 14212, April 11, 1985; 50 FR 21238 May 23, 1985; 57 FR 17983, April 28, 1992; 58 FR 47352, Sept. 8, 1993; 58 FR 47959, Sept. 13, 1993; 59 FR 50364, Oct. 3, 1994; 62 FR 39900, July 24, 1997; 63 FR 66399, Dec. 1, 1998; 65 FR 56479, Sept. 19, 2000; 67 FR 9586, March 4, 2002; 69 FR 18764, April 8, 2004; 71 FR 3997, Jan. 24, 2006; 72 FR 73600, Dec. 28, 2007; 73 FR 49609, Aug. 22, 2008; 77 FR 5699, Feb. 6, 2012]

SOURCE: 73 FR 39607; 39 FR 11718, March 29, 1974; 50 FR 7493, Feb. 22, 1985; 50 FR 21238, May 23, 1985; 54 FR 39636, Sept. 27, 1989; 55 FR 37322, Sept. 11, 1990; 58 FR 47351, Sept. 8, 1993; 59 FR 13200, March 21, 1994; 62 FR

51516, Oct. 1, 1997; 63 FR 26698, May 13, 1998; 63 FR 59712, Nov. 5, 1998; 64 FR 401, Jan. 5, 1999; 65 FR 64617, Oct. 30, 2000; 72 FR 58999, Oct. 18, 2007; July 10, 2008; 79 FR 33088, June 10, 2014; 80 FR 38938, July 8, 2015, unless otherwise noted.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 356a, 356b, 356c, 356e, 371, 374, 379e, 379k–1.

Notes of Decisions (69)

Current through July 7, 2016; 81 FR 44482.

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