UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

CUMBERLAND PHARMACEUTICALS, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	**No. No. 12 C 3846**
	)	
MYLAN INSTITUTIONAL LLC, and MYLAN INC.,	)	**Judge Rebecca R. Pallmeyer**
	)	
	)	
Defendants.	)	

AMENDED MEMORANDUM OPINION AND ORDER

Plaintiff Cumberland Pharmaceuticals, Inc. ("Cumberland") develops, manufactures and sells pharmaceutical products, including Acetadote, an intravenous treatment for suspected acetaminophen overdoses. In 2012, Cumberland filed this action, charging Defendants Mylan Institutional, LLC and Mylan, Inc. (collectively, "Mylan") with infringing two patents related to Acetadote: United States patents No. 8,148,356 (the "'356 patent") and No. 8,399,445 (the "'445 patent"). Cumberland alleges that Mylan infringed these patents by attempting to obtain FDA approval for a generic formulation of Acetadote in violation of 35 U.S.C. § 271(e)(2). Cumberland has since withdrawn its claims related to the '356 patent, but maintains its infringement charge for the '445 patent. (*See* Signed Stip. & Order of Part. Dismissal [282].) Mylan has admitted infringement of claims 1–14 of the '445 patent (*see* Joint Stip. of Infringement [248]), but contends the patent is invalid on several bases, including derivation, anticipation, and obviousness. Each of these defenses rests, in substantial part, on Mylan's theory that it was an employee of the Food and Drug Administration ("FDA"), rather than a Cumberland employee, who conceived of the patent's subject matter.

The parties filed cross-motions for summary judgment [212] [216] on the issue of the '445 patent's validity, both of which the court denied in an oral ruling on September 12, 2014. (*See* March 23, 2015 Minute Entry [300].) The court then held a bench trial on September 29,

2014 through October 3, 2014, and on October 20 and 21, 2014. Having reviewed the evidence presented at that hearing and the parties' briefs, the court concludes that Mylan has failed to establish the '445 patent's invalidity by clear and convincing evidence. Mylan is therefore liable to Cumberland for infringement of the '445 patent.

BACKGROUND

I. Acetylcysteine: General Overview

Acetaminophen overdose sends as many as 78,000 Americans to the emergency room each year. Jeff Gerth & T. Christian Miller, *Use Only as Directed*, ProPublica, Sept. 20, 2013, http://www.propublica.org/article/tylenol-mcneil-fda-use-only-as-directed (last visited Sept. 28, 2105). Overdoses are common, in part, because acetaminophen (best known under the brand name Tylenol) is found in varying doses in hundreds of common cold remedies and combination pain relievers that patients consume, often together, without monitoring the total amounts of acetaminophen they are ingesting. Acetaminophen poisoning can cause acute liver failure, severe brain damage, and even death. *Id.*

Acetylcysteine is a well-recognized antidote to acetaminophen overdose. For several decades prior to the issuance of the patents-in-suit, acetylcysteine was marketed worldwide generically as well as under several trade names as an inhalable product and as both an injectable and oral agent to treat acetaminophen overdose.[1] ('445 patent, col. 1:26-38.) As the '445 patent explains, however, "[a]cetylcysteine is not a stable molecule and is oxidized and degraded when in solution and exposed to air." ('445 patent, col.1:39–40.) To resolve this stability issue, all acetylcysteine products prior to the issuance of the '356 and '445 patents products contained edetate disodium ("EDTA"). (*See* Jt. Stip. of Undisp. Facts [256-1], ¶ 52; Mylan Resp. to Cumberland's FF [295], ¶ 37.)

[1] Cumberland sold one of these products under the name Acetadote. (Jt. Stip. of Undisp. Facts ¶¶ 54, 56.)

EDTA is a chelating agent, that is, an "organic agent[] that bond[s] with and thereby sequester[s] free metal ions[2] from solution." ('445 patent, col.1:45–48.) EDTA has potential side effects, however. (*See, e.g.*, '445 patent at col. 2:16–22, 34–37) (EDTA known to have cause allergic reactions, or "a significant drop in serum calcium levels . . . which may result in fatality, hypokalemia, hypomagnesemia, hypotension, and EDTA has also been shown to produce reproductive developmental toxicity in test animals.").) An EDTA-free formulation was, thus, a potentially valuable discovery. Cumberland successfully sought patents for acetylcysteine compositions free of chelating agents, specifically the '356 patent and the '445 patent. The '356 patent, which issued on April 3, 2012, "relates to novel acetylcysteine compositions in solution, comprising acetylcysteine and which are substantially free of metal chelating agents, such as EDTA." ('356 patent, Abstract.) The '445 patent issued on March 19, 2013 and claims the methods of administering the compositions covered by the '356 patent.

II. The '445 Patent

A. General Background

Claim 1 of the '445 patent is illustrative of the nature of the invention:

> 1. A method of treating acetaminophen overdose, comprising: using a stable aqueous pharmaceutical composition comprising 200 mg/ml acetylcysteine or pharmaceutically acceptable salts thereof, wherein the composition is free of chelating agents, wherein said composition is in a suitable form for intravenous injection, wherein the pH of the composition is from 6 to 7.5, and wherein said composition is sealed in an airtight container comprising a fill volume of said composition and a headspace volume occupied by a pharmaceutically inert gas; diluting the composition in an aqueous solution; and administering the diluted composition to a patient in need thereof.

('445 patent at col. 9:15–30.) Following a claim construction hearing in August 2013, this court construed three disputed terms in the '445 patent as follows:

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[2] Metal ions are "ubiquitous in pharmaceutical formulations" (Cross Exam. of Dr. Byrn at Tr. Trans. 1300:16–22.), and catalyze the oxidation (and thus cause potential destabilization) of acetylcysteine. (Direct Exam. of Sivilotti at Tr. Trans. 341:19–342:8). Trace amounts of metal are inherent in the formulation itself, and they can also seep into the formulation from processing equipment and glass vials. (*See* Cumberland Resp. to Mylan FF [297], ¶ 351.)

- **Free From A Chelating Agent** and **Free Of A Chelating Agent**: "Lacking one or more chelating agents."

- **Acetylcysteine**: "[T]he nonproprietary name for the N-acetyl derivative of the naturally occurring amino acid, L-cysteine (also known as N–acetyl–L–cysteine and NAC) and impurities associated therewith."

- **Stable Aqueous Pharmaceutical Composition**: "[A] composition that exhibits minimal change over time relative to when it is manufactured."

Cumberland Pharm., Inc. v. Mylan Institutional LLC, No. 12-cv-3846, 2014 WL 787812 (N.D. Ill. Feb. 26, 2014).

B. Leo Pavliv and the '445 Patent

Leo Pavliv, a senior vice president of operations at Cumberland, is the sole named inventor on the '445 patent. (*See* '445 patent; Jt. Stip. of Undisp. Facts ¶ 64.) Pavliv admits that he did not invent anything related to the original, EDTA-containing Acetadote product. (Cross Exam. of Pavliv at 1105:16–25.) Instead, his invention consists of modifying the original Acetadote formulation such that it is "free of chelating agents," as the '445 patent teaches. ('445 patent at col. 9:19–20.) Mylan disagrees that Pavliv invented anything, and also that to the extent the '445 patent is valid, the real inventor is the FDA through one or more of its employees, not Pavliv. The parties cite to the same record evidence as establishing their position, which the court will review below in some detail.

1. EDTA-Containing Acetadote Application

In the process of reviewing Cumberland's New Drug Application ("NDA") for the original, EDTA-containing Acetadote product, on December 10, 2002, the FDA sent Cumberland a letter requesting information concerning the drug's chemistry, manufacturing, and controls (CMC), as well as clinical data. (*See* Mylan Resp. to Cumb. FOF ¶ 110.) One of those information requests is the focus of the current litigation; it read as follows: "Provide scientific and regulatory justification for the inclusion of Edetate as a component in the drug product. In addition, provide a description of the pharmacological properties for Edetate in this product." (Dec. 10, 2002 FDA

Letter, DTX-1045 at CMBLD-AC00010029.) In his deposition, Pavliv explained his understanding of the scope of the FDA's request:

> Q. And how did you come up with the idea to take out EDTA?
>
> A. The FDA in some of the correspondence asked us to substantiate the use of EDTA. And part of the thought process in how to substantiate its use is, one, to determine the safety through publications. The other is to see if there is a need for it; and if there is not a need for it, to potentially remove it.
>
> Q. So FDA asked Cumberland to substantiate the use of EDTA, and that caused the thought process of determining whether or not EDTA was necessary in the prior art Acetadote product?
>
> A. The FDA, in one of the questions, had asked us to substantiate it, yes. And, yes, that was -- our thought process -- or my thought process at the time was to -- as an option was to look at that as one of the options to look at removing or reducing the amount of EDTA.

(Dep. of Leo Pavliv, Tr. Trans. at 422:15–423:4.) Pavliv is correct that this letter asked Cumberland only to "substantiate" the use of EDTA in Acetadote—the agency did not direct Cumberland to conduct studies on the subject. Significantly, the letter did elsewhere require Cumberland to perform a study on a different component of the formulation. (*See* Dec. 10, 2002 FDA Letter, DTX-1045 at CMBLD-AC00010030 ("Provide compatibility studies between the drug product solution and the dextrose solution including test data that are generated at different points. . . .").)

On December 16, 2002, Pavliv participated in a conference call between the FDA and Cumberland regarding the FDA's information requests. (*See* Direct Exam. of Pavliv at 967:11–968:1; Mem. of Telephone Conf., DTX-1046 at CMBLD-AC00015507.) During this call, according to the FDA's records, the agency reiterated its request about information related to the use of EDTA in Acetadote, and "explained that data should be provided to support any justification for the inclusion of Edetate, since a non-trivial amount is included in the formulation." (DTX-1046 at CMBLD-AC00015508.) Pavliv, again, understood the request to mean that the FDA wanted Cumberland to "justify" the use of EDTA in Acetadote by "provid[ing]

data that's in the literature, other sources, you know, justification of why it's in there," not that the FDA wanted Cumberland to conduct a study to see whether EDTA was a necessary ingredient. (Direct Exam. of Pavliv at 970:4–10, 20–21.)

On behalf of Cumberland, on December 20, 2002, Pavliv responded to the FDA's questions (*see* Dec. 20, 2002 Cumberland Letter to FDA, PTX-316),[3] explaining EDTA's pharmacological properties and also suggesting that removal of EDTA from the formulation might have negative repercussions. (*Id.* at CMBLD-AC00036282.) Specifically, Pavliv pointed out that "lowering or removing edetate would raise questions of how the safety and efficacy of the product would be effected [sic]." (*Id.*) Soon after making this statement to the FDA, Pavliv testified, he first conceived of the idea of studying an acetylcysteine formulation that did not contain EDTA. (Direct Exam. of Pavliv at 975:15–19 ("Q. When did you first have the idea of conducting a study of the stability of a formulation with no or lower EDTA? A. It was in December, at this time. Q. At the time you were writing this letter? A. Shortly thereafter.").) He did not raise the issue of studying EDTA's inclusion in the formulation in this response, or in a follow-up letter immediately after he thought of the idea, he explained, because the goal of the response to the FDA was "to obtain approval of the product" (*id.* at 23), and he believed the written justification was sufficient. (*Id.* at 975:23–974:1.)

On March 5, 2003, Cumberland sent a letter to the FDA requesting a teleconference "to obtain FDA input on the [CMC requests from the FDA's December 10, 2002 letter]." (March 5, 2003 Cumberland Letter to FDA, DTX-1012 at CMBLD-AC00014555.) The letter identified certain topics Cumberland sought to discuss with the FDA. One such topic was a request for the FDA's views on Cumberland's use of EDTA in its formulation: "Cumberland believes the use

[3] Amy Rock, Head of Regulatory Affairs at Cumberland, is the individual who signed correspondence from Cumberland to the FDA regarding the NDA. (*See, e.g.*, Dec. 20 Cumberland Letter, PTX-316 at CMBLD-AC00036287.) The court nevertheless credits Pavliv's and Ms. Rock's testimony that Pavliv was primarily responsible for drafting Cumberland's responses to the FDA's CMC requests, including the response to the FDA's request for Cumberland to justify its use of EDTA in Acetadote. (*See* Direct Exam. of Pavliv, 963:1–4; Dep. of Amy Rock at 401:3–4, 402:10–403:1.)

of edetate as a component in the drug product is justified both from a scientific as well as a regulatory point of view. Does FDA agree?" (*Id.* at CMBLD-AC00014558.) The conference call took place sometime later in March 2003, according to Pavliv, though neither party cites to an FDA document reflecting that the call took place. (*See* Direct Exam. of Pavliv at 977:16–20; Cumberland Resp. to Mylan FF ¶ 203.) It was during that call, Pavliv states, that he first "proposed that [he] would be able to do a study to evaluate the impact of EDTA in the solution in the formulation." (*Id.* at 978:10–12.) The FDA, Pavliv testified, approved of his proposal: "[I]t seemed like they thought it was a good idea. They also said to put it in writing, but confirmed positively that that was a good idea." (*Id.* at 978:14–16.)

The plan was eventually memorialized in a July 21, 2003 letter signed by Amy Rock from Cumberland to the FDA. The letter stated:

> As requested by FDA, upon product approval, Cumberland Pharmaceuticals intends to initiate studies to determine the impact on product stability of both decreasing and completely removing edetate disodium from the formulation. Cumberland will submit results of these studies to FDA upon completion of the study.

(July 21, 2003 Cumberland Letter to FDA, PTX-317 at CMBLD-AC00031570.) Pavliv testified that he drafted this language, and maintains that conducting a study to determine the need for EDTA in Acedadote was his idea. (Direct Exam. of Pavliv at 978:24–979:1; *id.* at 980:1–3.) Asked at trial why the reference to that study begins with the words, "As requested by FDA," Pavliv explained that the letter was written this way because the FDA "requested [Cumberland] to put it in writing." (Direct Exam. of Pavliv at 980:3.) Whatever may be inferred from the phrasing, Pavliv insists that the FDA never instructed Pavliv "to conduct any specific set of experiments" regarding eliminating or using lesser concentrations of EDTA, or that the FDA even suggested testing the issue. (*Id.* at 7–10; *see id.* at 940:19–23.)

At least some other documentary evidence is consistent with that account. The FDA issued its official FDA Chemistry Review of the original, EDTA-containing Acetadote product on January 9, 2004. (*See generally* Chemistry Review of Original Acetadote Product, hereinafter

"Chemistry Review," DTX-1047.) The review includes a section entitled "Chemistry Assessment Section," in which the FDA responds to submissions Cumberland had made regarding the "scientific and regulatory justifications and pharmacological properties for Edetate as a component in the drug product." That response states:

> The applicant [Cumberland] provided reasonable justification for including the small amount of edetate sodium in the formulation of drug product. The main points of the arguments focus on:
>
> - Safety of this compound because it had been used in approved drug products
> - Its function as an anti-oxidant reagent
> - The low amount used in acetylcysteine drug product formulation (0.05%) compared to the higher quantities used in other drugs
> - *The applicant proposed commitment regarding initiating a study to determine the impact on stability when edetate disodium is deceased [sic] or removed of from [sic] acetylcysteine formulation.*
>
> . . . *The applicant committed also to perform a study, after NDA approval, to determine if decreasing or removing the amount of edetate disodium in the formulation will have any impact on the stability profile of the drug product.*
>
> [Cumberland's] response is satisfactory.

(Chemistry Review at CMBLD-AC00031463 (emphasis added).) Pavliv testified that he was the person at Cumberland who proposed initiating the study referred to in the FDA Review. (*See* Direct Exam. of Pavliv at 983:3–4.)

2. Approval of EDTA-Containing Acetadote and Post-Marketing Commitments

On January 21, 2004, in a teleconference between the FDA and Cumberland, Pavliv learned that Cumberland was close to receiving approval for EDTA-containing Acetadote. (January 21, 2004 Cumberland Letter to FDA, PTX-315 at CMBLD-AC00031006; Direct Exam. of Pavliv at 984:25-985:10.) In response to the FDA's comments during that phone call, Pavliv drafted language that memorialized his earlier proposal to commit Cumberland to study "the potential benefit of [EDTA], currently in the formulation, on the stability of the drug product." (January 21, 2004 Cumberland Letter to FDA, PTX-315 at CMBLD-AC00031006.) Notably, the proposal was "part of a post-approval commitment," meaning the FDA would first approve

EDTA-containing Acetadote for public use before any study was conducted. The EDTA study, as explained by Pavliv in the letter, was to "include a comparison of the current concentration of edetate to a lower concentration and/or a formulation containing no edetate," but that "[t]he design of the study will be agreed upon by Cumberland and the FDA prior to initiation." (*Id.*)

Cumberland and the FDA held another teleconference the next day, on January 22, 2004. (*See* January 22, 2004 Cumberland Letter to FDA, PTX-314 at CMBLD-AC00031001.) As a result of these discussions, Pavliv testified, he added language augmenting his proposal language from the previous day, setting out deadlines for when a protocol for the EDTA study would be submitted, when the study would begin, and when Cumberland would report its findings to the FDA. (*See id.*; Direct Exam. of Pavliv at 986:4–23.) The next day, on January 23, 2004, the FDA approved EDTA-containing Acetadote. (*See* Approval Letter, DTX-1011 at CMBLD-AC00015566, CMBLD-AC00015569.) In the Approval Letter, the FDA adopted Pavliv's proposed study language verbatim, but did not specify the manner in which the study was to be conducted—the FDA required only that Cumberland submit its study protocols and final reports to the agency. (*See id.* at CMBLD-AC00015566–15568.)

In some internal Cumberland communications, however, Pavliv referred to the testing has having been requested by FDA. In an e-mail to Rhonda Noll, an employee of Bioniche Pharma (Mylan's predecessor company) dated March 15, 2004, Pavliv reported: "I am putting the finishing touches on the proposed set of EDTA experiments *that FDA requested we perform* for [Cumberland's acetylcysteine formulation]. . . ." (March 15, 2004 Pavliv E-Mail, PTX-180 at MYL-ACE0014082.) In another internal e-mail sent on April 2, 2004 from Pavliv to Amy Rock, Pavliv forwarded a draft protocol of the EDTA testing he was in the process of designing. That draft protocol stated that, "[a]s part of a post approval marketing commitment, the FDA requested Cumberland investigate whether EDTA has a beneficial impact on stability and if so whether the level could be reduced." (April 2, 2004 Pavliv E-Mail, DTX-1008 at CMBLD-AC00029350.)

On April 19, 2004, Cumberland submitted a testing protocol to the FDA that had been designed by Pavliv. (EDTA Study Protocol, DTX-1004; E-Mail Chain, PTX-303; Direct Exam. of Pavliv at 989:20–990:8.) The FDA reviewed and approved the EDTA study protocol without making any changes. (FDA Letter, PTX-190; Direct Exam. of Pavliv at 991:3–5.)

3. EDTA Study and Results

Cumberland contracted with Bioniche Pharma ("Bioniche") to perform the EDTA study. (*See* Purchase Order, PTX-302.) On November 18, 2004, a Bioniche employee sent Pavliv the three-month test results for the EDTA study. The study consisted of evaluating the stability of Acetadote without EDTA and with smaller amounts of EDTA than the drug product that the FDA had already approved.[4] (*See* November 18, 2004 E-Mail Pt. 1, PTX-184.) After analyzing the data, Pavliv responded to the Bioniche employee, remarking: "Excellent. The 3 month data looks great. If this continues we may have a new formulation sometime in the future." (*See* Nov. 18, 2004 E-Mail Pt. 2, PTX-183.) Pavliv testified that he felt the data he received "was very encouraging" because there was no difference in stability among the three formulations of Acetadote. (Direct Exam. of Pavliv at 1002:8–13.) He further testified that he was surprised by the results. He would have expected the acetylcysteine formulations that contained less and no EDTA to have been unstable. (*Id.* at 1003:1–8.) It was only after he viewed these test results, he testified, that he believed that an EDTA-free acetylcysteine formulation was viable. (*Id.* at 9–11.) He shared the results of this test with Amy Rock and A.J. Kazimi, Cumberland's CEO. (*See* DTX-1141 ("I received the 3 month stability results from Bioniche today . . . The good news (I think) is that after 3 months there is no discernible differences between no, low, and regular EDTA containing batches. In all cases the product is quite stable.").) Pavliv received the six-month stability data from Bioniche on February 1, 2005. (*See* PTX-189.) He analyzed this data,

[4] Specifically, the formulations in the study included (1) no EDTA, (2) 0.02% EDTA (40% of the amount included in the Acetadote product), and (3) the current level of EDTA in Acetadote, 0.05% from a commercial batch. (EDTA Study Final Report, DTX-1010 at CMBLD-AC00016979.)

which again showed no stability difference among the three formulations. (Dep. of Pavliv, Tr. Trans. at 437:16–19.) Cumberland filed its initial patent application regarding an EDTA-free acetylcysteine formulation on August 24, 2005. (*See* '445 patent, Related U.S. Application Data.)

Cumberland sent the results of its EDTA study to the FDA in the form of a final report on August 13, 2008. (*See* EDTA Study Final Report, DTX-1010 at CMBLD-AC00016976.) In that report, Cumberland stated: "The FDA expressed a potential safety concern with EDTA in the formulation and as such, requested Cumberland investigate whether EDTA provided a stability benefit or could be reduced or removed from the product." (*Id.*) It is unclear who drafted this report; the cover letter is signed by Amy Rock. (*Id.* at CMBLD-AC00016976.) Pavliv testified that this language simply reflected that, as part of the FDA approving the EDTA-containing Acetadote, Cumberland had agreed to conduct a post-approval study examining the product with less and no concentrations of EDTA. (*See* Cross Exam. of Pavliv at 1113:10–22.) The final report stated that "EDTA does not appear to enhance stability of acetylcysteine in the three Acetadote[] formulations." (*Id.* at CMBLD-AC00016980.)

II. Mylan's Abbreviated New Drug Application

In December 2011, Defendant Mylan filed an Abbreviated New Drug Application ("ANDA"), seeking FDA approval of a generic version of an EDTA-free Acetadote. (Mylan Prop. FF ¶ 10; Cumberland Prop. FF ¶ 241.) Mylan subsequently provided the FDA with a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that its ANDA product does not infringe any claim of the '356 patent, or alternatively that the '356 patent is invalid and unenforceable. (*See* Mylan Mem. in Supp. of Mot. for Sum. Judg. [53], 3–4.) This is called a "Paragraph IV certification." (*Id.*) Cumberland filed this suit for infringement on May 17, 2012, pursuant to the Hatch Waxman Act, 21 U.S.C. § 355(j)(5)(B)(iii), alleging that Mylan's filing of its ANDA with a Paragraph IV certification constitutes an act of infringement of the '356 patent under 35 U.S.C. § 271(e)(2)(A). (Pl. Compl. [1], ¶ 14.)

The next day, on May 18, 2012, Cumberland filed a Citizen Petition with the FDA, requesting that the FDA not approve any ANDA for an "acetylcysteine injection . . . for which Acetadote is the reference listed drug if the generic drug product contains [EDTA]." (Citizen Petition, DTX-1023 at MYL-ACE0002790.) In that petition, Cumberland again used language suggesting the FDA proposed the study:

> FDA requested that Cumberland conduct a study on the stability of Acetadote[] that includes a 'comparison of the current concentration of Edetate to a formulation with a lower concentration and no concentration of Edetate.' FDA's request that Cumberland investigate whether EDTA could be reduced or removed from the Acetadote[] formulation was based on the agency's concerns regarding the safety of EDTA.

(*Id.* at MYL-ACE 0002791.) Elsewhere in the Petition, Cumberland stated: "From the outset, FDA wanted Cumberland to investigate reducing or removing EDTA from Acetadote [] because the agency was concerned with the safety of EDTA." (DTX-1023 at MYL-ACE 0002794.) Pavliv testified that "From the outset," in this context, meant from the time that the FDA approved the EDTA-containing Acetadote; this account is consistent with his insistence that he was the person who initially proposed studying the removal of EDTA from the Acetadote formulation. (Cross Exam. of Pavliv at 1124:4–1125:13.) Other language in the Petition, however, appears to suggest that Cumberland viewed the FDA as having proposed that EDTA be removed from the formulation:

> Further, if the agency permits an ANDA applicant to rely on the discontinued formulation, the agency would be taking a position contrary to the position that the agency took with regard to Cumberland's original Acetadote[] formulation. *At FDA's request*, Cumberland investigated the reduction or removal of EDTA. As Cumberland's studies unexpectedly showed, the stability of acetyl cysteine does not require EDTA. Cumberland is also aware that at least one ANDA applicant is seeking approval for an EDTA-free acetylcysteine formulation, further confirming that EDTA is not required. To approve a formulation containing an unnecessary and potentially unsafe ingredient *negates the premise of FDA's request that Cumberland investigate reformulating Acetadote*[]. FDA should not approve as a substitutable drug product a less safe formulation that contains an unnecessary ingredient.

(DTX-1023 at MYL-ACE0002796–0002797 (second emphasis added).) The FDA denied Cumberland's Citizen Petition. *See generally Cumberland Pharms., Inc. v. FDA*, 981 F. Supp. 2d 38 (D.D.C. 2013).

Cumberland later dismissed its claims concerning the '356 patent in order to "streamline the issues and conserve resources at trial." (*See* Mem. in Supp. of Mot. to Diss. Claims Related to '356 patent [261]; Sept. 28, 2014 Stip. of Part. Dismissal [277].) As stated previously, Mylan has agreed that, should the court find the '445 patent valid, it is liable to Cumberland for infringement. (*See* Jt. Stip. of Infring. [248].)

DISCUSSION

As the party challenging the validity of the '445 patent, Mylan bears the burden of demonstrating that the patent is invalid by clear and convincing evidence. *See Microsoft Corp. v. i4i Ltd. Partnership*, 131 S. Ct. 2238, 2242 (2011). The clear and convincing burden, as opposed to a general preponderance standard, reflects the "deference that is due to a qualified government agency presumed to have done its job," in this case, the Patent and Trademark Office. *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012).

Mylan attacks the '445 patent's validity on three distinct grounds. The court addresses each one in turn.

I. Derivation

Mylan's first invalidity argument is derivation—that is, that the patented formulation was not Cumberland's or Pavliv's invention, but in fact was derived from another, specifically, an employee or employees of the FDA. "A person shall be entitled to a patent unless he did not himself invent the subject matter sought to be patented." 35 U.S.C. § 102(f).[5] To establish the defense of derivation, a party challenging a patent's validity must establish two elements: (1)

[5] The America Invents Act of 2011 ("AIA") removed this language; however, the '445 patent has a filing date of August 24, 2005, and is subject to the patent laws in place prior to the AIA's enactment. *See Solvay S.A. v. Honeywell Intern. Inc.*, 742 F.3d 998, 1000 n.1 (Fed Cir. 2014) (AIA only applies to applications and patents with an effective filing date of March 16, 2013, or later) (citing AIA § 3(n)(1), 125 Stat. at 293)).

prior conception of the invention by another, and (2) communication of the conception to the patentee. *See Price v. Symsek*, 988 F.2d 1187, 1190 (Fed. Cir. 1993). The issue of prior conception is a question of law, but the ultimate question of whether a patentee derived an invention from another source is one of fact. *Id.*

Conception is "the completion of the mental part of the invention," *Burroughs Wellcome Co. v. Barr Labs.*, Inc., 40 F.3d 1223, 1227–28 (Fed. Cir. 1994), and occurs "only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation." *Id.* at 1228. The Federal Circuit describes the test for conception as follows:

> [W]hether the inventor had an idea that was definite and permanent enough that one skilled in the art could understand the invention; the inventor must prove his conception by corroborating evidence, preferably by showing a contemporaneous disclosure. An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue.

Burroughs Wellcome Co, 40 F.3d at 1228. "It is well established that when a party seeks to prove conception via the oral testimony of a putative inventor, the party must proffer evidence corroborating that testimony." *Shu–Hui Chen v. Bouchard*, 347 F.3d 1299, 1309 (Fed. Cir. 2003). The dispute with respect to the defense of derivation is whether it was Pavliv, or staff employees at the FDA, who conceived of the invention contained in the '445 patent—namely, an EDTA-free intravenous acetylcysteine product.

Although the parties have generated a voluminous record, there is a surprising paucity of direct evidence concerning what should be a fairly straightforward issue. Mylan strenuously argues that the evidence clearly and convincingly establishes that the FDA conceived of an EDTA-free Acetadote formulation. As the court sees the evidence, however, it is much more equivocal.

On December 10, 2002, the FDA made its initial response to Cumberland's NDA for EDTA-containing Acetadote. In that correspondence, the FDA asked Cumberland to "[p]rovide

scientific and regulatory justification for the inclusion of Edetate as a component in the drug product. In addition, provide a description of the pharmacological properties for Edetate in this product." (Dec. 10, 2002 FDA Letter, DTX-1045 at CMBLD-AC00010029.) Pavliv admits that prior to this request, neither he nor any other Cumberland employee had the idea of removing EDTA from the product. (*See* Dep. of Pavliv, Tr. Trans. at 450:4–19.) Pavliv also admits that it was this request by the FDA that prompted him to consider whether Acetadote required EDTA at all. (*See id.* at 421:23–423:4.)

The December 10, 2002 letter does not satisfy the standard for conception, however. Conception must encompass *all limitations* of the claimed invention, and "is complete only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation." *Singh v. Brake*, 317 F.3d 1334, 1340 (Fed. Cir. 2003) (quoting *Burroughs Wellcome Co.*, 40 F.3d at 1228)). Nothing about the FDA's letter suggests any such clear definition. For example, the letter does not direct Cumberland to "consider removing EDTA and hold every other variable of the Acetadote formulation constant," nor does it otherwise present a concept that could readily be reduced to practice. The letter does not even direct Cumberland to remove or minimize EDTA; instead, it simply asks Cumberland to justify the use of EDTA in the product. This communication thus falls short of conception. *Cf. Burroughs Wellcome Co.*, 40 F.3d at 1228 (conception is only completed "when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, *without extensive research or experimentation*") (citation omitted.)

Further, the communications between Cumberland and the FDA that followed, from late 2002 and continuing through the FDA's approval of EDTA-containing Acetadote in January 2004, do not demonstrate that the FDA conceived of anything. Through Pavliv, Cumberland responded to the FDA on December 20, 2002, citing several justifications for the use of EDTA in Acetadote. (*See* Dec. 20 Cumberland Letter to FDA, PTX-316; Direct Exam. of Pavliv at 974–

975.) At the same time that Pavliv advocated for the use of EDTA in Cumberland's Acetadote NDA, however, he also first considered conducting a study of the stability of the drug formulation without EDTA. (*Id.* at 975:15–17.) In March 2003, the FDA and Cumberland held a conference call to discuss issues related to the Acetadote NDA. (*See* March 5, 2003 Cumberland Letter to FDA, DTX-1012 at CMBLD-AC00014555.) During that call, Pavliv testified, he proposed a study "to evaluate the impact of EDTA in the solution in the formulation." (*Id.* at 978:5–12.) Then in a July 2003 letter, Cumberland reported that "upon product approval," it intended to "initiate studies to determine the impact on product stability of both decreasing and completely removing edetate disodium from the formulation." (July 21, 2003 Cumberland Letter to FDA, PTX-317 at CMBLD-AC00031570.)

As noted above, the sentence referring to the plan for initiating such a study begins with the words, "As requested by FDA." (*Id.*) Pavliv now suggests that this is a reference to the FDA's request that he put his plans in writing—not a confirmation that the FDA itself requested that the testing be performed. (Direct Exam. of Pavliv at 980:3.) Mylan urges suspicion of this explanation. Indeed, the Court of Appeals has held that an inventor's self-serving oral statement is insufficient to establish conception and an earlier priority date. *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 968 (Fed. Cir. 2014) (reversing district court's finding of a conception date preceding prior art references where "[t]he only corroboration of the claimed invention is the oral testimony of an inventor, which we must treat with skepticism") (quoting *Chen v. Bouchard*, 347 F.3d 1299, 1309 (Fed. Cir. 2003)). In this case, however, there is some corroboration of Pavliv's account, in the form of Cumberland's other communications with the FDA, as reflected in the FDA's records. Those records appear to confirm that the proposal to study the necessity for EDTA came from Cumberland: The official FDA Chemistry Review, dated January 9, 2004, includes a section entitled "Chemistry Assessment Section," and notes there that "[the applicant [Cumberland] proposed . . . a study to determine the impact on stability when edetate disodium [is decreased or eliminated] . . ." (Chemistry Review.) The FDA

offered no instructions about how, when, or in what order any experiments or tests should be performed, and it appears undisputed that Pavliv designed the study protocol. (*See* March 15, 2004 Pavliv E-Mail, PTX-180 at MYL-ACE0014082; EDTA Study Protocol, DTX-1004.) In short, the record evidence does not clearly and convincingly support the notion that Pavliv derived his idea from the FDA, so the court will not find the '445 patent invalid on this basis.

In concluding that the Pavliv's invention was not derived from a conception from the FDA, the court recognizes that the evidence does not establish a precise date of conception by Pavliv. Cumberland argues that conception of the idea for an EDTA-free Acetadote formulation merged with the invention's actual reduction to practice (that is, after Pavliv analyzed the three month stability data), because the result was unexpected. There is support for this position in the case law. In *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1224 (Fed. Cir. 1994), Burroughs Wellcome, a drug manufacturer, sued other drug manufacturers for infringement of several of Burroughs Wellcome's patents covering various treatments of the HIV virus. *Id.* at 1227. As in this case, defendant conceded that its ANDA for a generic version of those treatments would infringe the patents, but argued that those patents were invalid because scientists from the National Institute of Health ("NIH") were improperly excluded as co-inventors from Burroughs Wellcome's patents. *Id.* at 1227. The crux of the dispute focused on when Burroughs Wellcome's scientists conceived of the invention. While the generic manufacturers argued that conception could not have occurred before the NIH sent Burroughs Wellcome the results of tests done on the treatments, the Federal Circuit agreed with the trial court that conception occurred by Burrough Wellcome's before its scientists knew what the test results showed. *Id.* at 1231.

Relevant here, the court emphasized that conception does not occur merely when an inventor has "just a general goal or research plan he hopes to pursue," but also emphasized that an "inventor need not know that his invention will work for conception to be complete." *Id.* at 1228. Under the so-called doctrine of simultaneous conception and reduction to practice,

though, the *Burroughs Wellcome* court acknowledged, conception in certain instances does not occur until the idea can be proven to work. *See id.* Mylan insists that this doctrine does not apply here, but the court need not decide the issue. In *Burroughs Wellcome* itself, the court noted that it could not establish a precise date of conception, but that it had occurred prior to the NIH conducting the tests, which confirmed that the invention of Burroughs Wellcome's scientists would work. *Id.* at 1231.

In contrast, in the present case, Mylan has failed to show that the FDA had a "definite and permanent" idea, even assuming that the FDA had a general research goal or research plan to explore removing EDTA from Acetadote that it communicated to Pavliv. *See Hitzeman v. Rutter*, 243 F.3d 1345, 1357 (Fed. Cir. 2001) ("When a research plan requires extensive research before the inventor can have a reasonable expectation that the limitations of the count will actually be met, complete conception has not occurred."). Pavliv himself drafted the testing protocol, and represents that he arrived at conception only after analyzing the testing results that confirmed the formulation's stability without EDTA. (*See* Nov. 18, 2004 E-Mail Pt. 2, PTX-183; Cumberland Prop. FF ¶ 295.) For the purposes of this case, in the final analysis, the salient point is that even if Cumberland cannot establish an exact date of conception by Pavliv, Mylan has failed to persuade the court that anyone other than Pavliv *ever* conceived of a "definite and permanent idea" of an EDTA-free Acetadote formulation. In other words, the precise date of *Pavliv's* conception is not necessary; what matters is that he alone conceived it. Because the court is unable to conclude that Mylan has satisfied its burden to prove conception by another clearly and convincingly, *see* 35 U.S.C. § 102(f), its derivation argument necessarily fails.

III. Anticipation

Mylan's second invalidity defense is that of anticipation. A patent claim is invalid by anticipation if "the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the

United States[.]" 35 U.S.C. § 102(b). Anticipation requires a person in ordinary skill of the art to recognize the presence of "each and every claim limitation in a single prior art reference, either explicitly or inherently." *In re Omeprazole patent Litig.*, 483 F.3d 1364, 1371 (Fed. Cir. 2007). To anticipate, the reference must also "enable one of ordinary skill in the art to make the invention without undue experimentation." *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (quotations omitted). Further, "a prior art reference must place the inventive compound or composition in the possession of the public." *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006). As long as the reference discloses all of the claim limitations and enables the 'subject matter that falls within the scope of the claims at issue,' the reference anticipates—no 'actual creation or reduction to practice' is required." *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 653 F.3d 1296, 1309 (Fed. Cir. 2011) (quoting *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1380–81 (Fed.Cir.2003)). Anticipation is a question of fact. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (2005).

Determining whether a prior art reference anticipates a claim is a two-step process. The first step requires the court to construe the disputed claim terms of the patent-in-suit, and the second step involves comparing the construed claim terms to the prior art. *Helifix Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339, 1346 (Fed.Cir.2000).

Mylan argues that this test is met here. Mylan points to the Approval Letter sent by the FDA to Cumberland, a three-page letter on FDA letterhead that refers to the original Acetadote product, as well as to the approved Package Insert for the product. (*See* Approval Letter, DTX-1011 at CMBLD-AC00015566.) Those documents anticipate the asserted claims of the '445 patent, Mylan contends, because the Package Insert for EDTA-containing Acetadote discloses every claim limitation for the '445 patent except for "free of chelating agents." (*See* Approval Letter, DTX-1011, Draft Package Insert DTX-1089; Mylan Br. at 20–21.) And that claim limitation, according to Mylan, appears in the Approval Letter itself; specifically, it is reflected in the post-marketing commitment that requires Cumberland to

> Commit to evaluate the potential benefit of Edetate disodium on the stability of the drug product. The study shall include a comparison of the current concentration of Edetate to a formulation with a lower concentration and no concentration of Edetate. Generate stability data from the new proposed formulations including compatibility stability with infusion bags.

(Approval Letter at 2.)

The court is not persuaded that the Approval letter, standing alone, or considered along with the Draft Package Insert for the original Acetadote product, anticipates the '445 patent. First, the Approval Letter that was made available to the public (*see* Approval Letter, DTX-1011), is a three page letter from the FDA to Cumberland that approves Cumberland's original Acetadote product.[6] It was posted on the FDA website without the product's accompanying package insert. (*See* Cumberland Prop. FF ¶ 280–81.) And the documents are not otherwise part of a single communication: Mylan's own expert, Dr. Kent, treated the Approval Letter and the Package Insert as two separate documents. (*See* Cross Exam. of Dr. Kent at 622:5–7; Redirect at 780:6–11.) True, one document may incorporate another by reference and still be considered a single prior art reference for the purposes of proving anticipation. *See, e.g.*, *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1346 (Fed. Cir. 2009). But the host document must contain language that "clearly identif[ies] the subject matter" and where to find it, *id.,* and, importantly, "a mere reference to another application, or patent, or publication is not an incorporation of anything therein." *Id.* (quoting *In re De Seversky*, 474 F.2d 671, 674 (C.C.P.A. 1973)).

The approval letter in this case does not "clearly identify" the location of all claim limitations of the '445 patent—it merely references Cumberland's NDA (DTX-1011 at CMBLD-AC00015566), which contains thousands of pages. (*See* Cross Exam. of Kent at 635:12–14.)

[6] Defendant's trial exhibit 1160 (DTX-1160), which contains the Approval Letter and the Draft Package Insert, was produced by Cumberland from its own files and is not a publicly available document, which it must be in order to anticipate the '445 patent. *Cf. OddzOn Products, Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1402 (Fed. Cir. 1997) ("It has been a basic principle of patent law, subject to minor exceptions, that prior art is . . . 'technology already available to the public.'") (quoting *Kimberly–Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1453 (Fed. Cir.1984)).

The Approval Letter does not, for instance, identify where in the NDA one can determine that the drug product's formulation consists of a "unitary composition" "having a concentration of NAC from 200 mg/ml to 250 mg/ml"; the drug product's ph concentration; whether it is sealed in an airtight container; or whether it has a "headspace volume occupied by a pharmaceutically inert gas." (*See* '415 patent at col. 9:15–30.) The "enclosed labeling" that the Approval Letter refers to is the draft package insert language; that language also does not explain where to locate the claim limitations. In short, because the Approval Letter does not cite the Package Insert or any other document containing the claim limitations "in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein," *Cook Biotech Inc. v. Acell, Inc.*, 460 F.3d 1365, 1376 (Fed. Cir. 2006), the documents cannot be considered as a single prior art reference, and Mylan's anticipation argument necessarily fails on this score alone.

Second, even assuming for argument's sake that the Approval Letter and original Package Insert can be combined into a single prior art reference, the prior art does not anticipate the '445 patent. Most importantly, the reference to Cumberland's commitment to study the removal of EDTA from Acetadote nowhere specifies that the *exact* same drug formulation without EDTA must be used. Indeed, the language itself simply proposes comparison of "the current concentration of Edetate to *a formulation* with a lower concentration and no concentration of Edetate." (DTX-1011 at 2.) "A formulation" could contain, for instance, a chelating agent other than EDTA. (*See* Cross Exam. of Sivilotti at 189:3–22.) This composition would be free of EDTA and satisfy the study requirement, but would not be "free of chelating agents," which the parties agree means "lacking any chelating agents," and which every claim of the '445 patent requires. *Cumberland Pharms., Inc.*, 2014 WL 787812 at *4; ('445 patent.) Mindful that the standard for proving anticipation under 35 U.S.C. § 102 requires that a person of ordinary skill not be required to perform "undue experimentation" to extract the invention from the prior art reference, *see In re Gleave*, 560 F.3d at 1334, this court concludes

that, even considering the Approval Letter and Package Insert as a single prior art reference, it still fails to anticipate the '445 patent. *See In re Omeprazole patent Litig.*, 483 F.3d at 1371 (every claim limitation must be disclosed in a single prior art reference); *cf. Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) ("An invitation to investigate is not an inherent disclosure.").

IV. Obviousness

Mylan's final proposed invalidity defense is a claim of obviousness. Section 103(a) precludes a patent's issuance when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). "Obviousness is a question of law based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the prior art and the claimed invention; and (4) the extent of any objective indicia of non-obviousness." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1308 (Fed. Cir. 2010). Relevant secondary considerations include skepticism, commercial success, and unexpected results. *KSR Int'l Co.*, 550 U.S. at 406. Because issued patents received a presumption of validity, as with the other invalidity challenges presented in this case, Mylan must establish obviousness of the '445 patent by clear and convincing evidence. *Allergan, Inc.*, 726 F.3d at 1291. Mylan presents several reasons for the court to invalidate the '445 patent on obviousness grounds. As before, the court concludes that the issue is arguable but that Mylan has failed to marshal clear and convincing evidence necessary to invalidate the patent on this basis.

First, the scope and content of the prior art presented to the court do not convincingly demonstrate that there was motivation for a person of ordinary skill in the art to remove EDTA from an acetylcysteine formulation. True, the undesirable characteristics of chelating agents are well-recognized in the prior art. The language of '445 patent notes that

> chelating agents such as EDTA can cause undesirable effects when administered to humans or animals. Some of these undesirable effects include a significant drop in serum calcium levels, which may result in fatality, hypokalemia, hypomagnesemia, hypotension, and EDTA has also been shown to produce reproductive developmental toxicity in test animals. EDTA has also been associated with dose-related bronchoconstriction when used as a preservative in nebulizer solutions. Based on the adverse effects of EDTA, particular care should be taken when administering EDTA to patients with renal impairment, liver toxicity, tuberculosis, and impaired cardiac function.

('445 patent at col. 2:16–28 (citation omitted).) The language of the patent also notes that some people have allergic reactions to chelating agents. (*Id.* at 34–37.) But Mylan's own pleadings undercut its argument that a person of ordinary skill in the art would be motivated to attempt to develop an EDTA-free acetylcysteine formulation. Specifically, in its proposed findings of fact submitted to the court, Mylan asserts that "[t]here was little incentive or reason to change the acetylcysteine formulation, especially since EDTA-containing acetylcysteine formulations were both safe and efficacious." (*See* Cumberland Resp. to Mylan FOF ¶ 321.) Mylan's own expert agreed: Dr. Sivilotti testified that he had no preference, "from a medical point of view, between administering EDTA-containing and EDTA-free acetylcysteine for acetaminophen overdose[.]" (*See* Direct Exam. of Sivilotti at 179:20–180:5.).) Nor is the court convinced that the Approval Letter and Chemistry Review provided the requisite amount of motivation to a person of ordinary skill in the art to attempt to create an EDTA-free acetylcysteine formulation.

Next, Mylan argues that a person of ordinary skill in the art would be motivated to remove EDTA because it was "mere surplusage," but this argument suffers from considerable hindsight bias. *See KSR*, 550 U.S. at 421 (fact-finders must be cautious of "the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning") (citation omitted). Until Pavliv conducted his studies, it was generally understood in the relevant scientific community that EDTA or some other chelating agent was necessary to maintain stability of the formulation. The Waterman study, for instance, which the parties agree is prior art for the purposes of this case (*see* Waterman, K.C., et al., *Stabilization of Pharmaceuticals to Oxidative Degradation*, Pharm. Devel. & Tech., 7(1): 1-32 (2002), PTX-085, hereinafter

"Waterman"), noted that "[t]race metals are almost ubiquitous in dosage forms, and since they are often catalysts rather than consumed, they can affect rates even at low levels. . . . Mitigating metal contamination involves the following possibilities: 1. Adding of chelating agents to the formulation." (Waterman at 20.) Also, U.S. patent No. 5,700,653, which claimed a liquid stable thiol activator (acetylcysteine is a thiol activator), noted that such formulations have "notorious instability in solution" ('653 patent, PTX-147 at col. 3:12–13), and that chelating agents such as EDTA can be used to improve the stability of the solution. (*Id.* at col. 3:1–9.) Mylan's expert Dr. Kent corroborated this state of scientific knowledge. (*See* Direct Exam of Dr. Kent at 524:4–7 ("Sulfhydryls are well-known -- or thiol groups are well-known to oxidize.").)

Mylan also cites Prescott, a study that looked at a treatment for acetaminophen overdose that is similar to Acetadote. (L.F. Prescott et al., *Intravenous N-acetylcysteine: The Treatment of Choice for Paracetamol Poisoning*, 3 Brit. Med. J. 1097 (1979).) But Prescott nowhere suggests using EDTA-free acetylcysteine formulations (*see* Direct Exam. of Byrn 1229:13–1230:2). Nor is it reasonably inferred from the study, so combining that reference with Waterman does not move the needle toward invalidity—Waterman teaches using chelating agents in tandem with other methods to prevent oxidization, so it would not prompt a person of ordinary skill in the art to remove EDTA all together. (*See* Direct Exam. of Byrn at 1230:3–11; Cumberland Prop. FF ¶ 102–104.)

On balance, the court's review of the evidence supports the conclusion that persons of ordinary skill in the art would have assumed that EDTA, or some other chelating agent, was necessary to maintain stability in an acetylcysteine formulation. For this reason, Mylan's other arguments about motivation for removing EDTA, such as the FDA's Quality by Design[7] initiative, must fail too. (*See* Cumberland Resp. to Mylan FOF ¶ 339.) In short, Mylan's arguments that a

[7] FDA's Quality by Design movement looked at the necessity of the components in a drug product. (*See* Cumberland Resp. to Mylan FF ¶ 339; Cross Exam. of Byrn at 1329:10–15.)

person of ordinary skill in the art would view EDTA as mere surplusage are rejected as against the weight of the evidence.

Mylan makes one other argument in favor of obviousness: that the Approval Letter or Chemistry Review combined with the Original Acetadote Product label would motivate a person of ordinary skill in the art to develop an EDTA-free acetylcysteine formulation. This argument ultimately fails, too, as it ignores the law's requirements that a person of ordinary skill would predict that such modifications to an already efficacious product would have yielded successful results. *See Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361–62 (Fed. Cir. 2011). Indeed, in the pharmaceutical field, "'potential solutions are less likely to be genuinely predictable' as compared with other arts such as [mechanical devices]." *Eisai Co. v. Dr. Reddy's Labs.*, 533 F.3d 1355, 1359 (Fed. Cir. 2008). In this case, all acetylcysteine formulations, including the original Acetadote product, contained EDTA to help stabilize the product. (*See* '445 patent at 2:9–13.) No prior references, with the possible exception of Guilford (discussed below), taught or even suggested that an acetylcysteine formulation would be safe without a chelating agent of some kind. (Cross Exam. of Kent at 673:22–674:1–4.) And a drug composition lacking stability is "not even a product," meaning no physician would administer it. (*See* Cross Exam. of Kent at 610:10–19.) Indeed, Kent conceded that a "full-blown study" would be needed to understand whether EDTA was necessary to stabilize an acetylcysteine formulation. (*See* Cross Exam. of Kent at 680:3–681:17.) Given that all prior acetylcysteine formulations contained EDTA, and given that the prior art taught that EDTA or another chelating agent was necessary to stabilize the formulation, the court rejects the argument that the Approval Letter or Chemistry Review, which contained the EDTA study commitments, would reasonably lead to a stable acetylcysteine formulation.

And the court rejects the argument that Guilford combined with the Original Acetadote Product renders the claim obvious. Guilford is a patent for the use of an acetylcysteine formulation to treat bioterror exposures to chemicals such as anthrax, smallpox, or radiation.

(*See* U.S. patent No. 289,934, DTX-1101.) Guilford provides no stability data (*See* Cross Exam. of Dr. Kent at 732:19–21; Cross Exam. of Dr. Byrn at 135314–25 (agreeing that Guilford is not evidence that a chelating agent is unnecessary in his acetylcysteine formulation).) Second, Acetadote contains 20 percent acetylcysteine in its formulation, while Guilford's product contains only 8 percent. (*See* Direct Exam. of Byrne at 1217:13–1218:6.) This is important because the higher the concentration, the more rapidly the formulation would be expected to destabilize (and thus, presumably require a chelating agent). (*Id.*) In addition, Guilford does not use pH control in creating his formulation. This is in contrast to the '445 patent and other similar formulations, which require pH to control stability. (*See* Direct Exam. of Byrn at 1228:1–25.) Guilford thus holds too little predictive power, in combination with Acetadote and other similar formulations, to render the '445 patent's exclusion of EDTA obvious.

Lastly, the court finds the objective evidence of nonobviousness equivocal, but this is no help to Mylan, since it has failed to establish a *prima facie* case of obviousness in the first instance. "[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR*, 550 U.S. at 416. First, as discussed earlier, there is some evidence that prior art taught away from the '445 patent. A person of ordinary skill in the art would not be motivated to produce an EDTA-free acetylcysteine formulation, given the accepted wisdom that a chelating agent of some kind was necessary to stabilize the product. Second, there is some evidence that an EDTA-free acetylcysteine product was an unexpected result, another objective indicia of non-obviousness. *See Graham*, 383 U.S. at 17–18. In any event, Mylan has failed to muster clear and convincing evidence in the first instance to demonstrate the obviousness of the '445 patent. Because Mylan has failed to satisfy that burden, its challenge necessarily fails.

CONCLUSION

Mylan has failed to establish by clear and convincing evidence that the '445 patent is invalid on any ground. Accordingly, as Mylan has previously stipulated to infringement absent a

finding of invalidity, the court enters partial summary judgment in Cumberland's favor, finding that Mylan is liable to Cumberland for infringement of the '445 patent. The parties' trial-related motions [251, 252, 253, 254, 255] are stricken as moot.

ENTER:

Dated: October 2, 2015

REBECCA R. PALLMEYER
United States District Judge