Trials@uspto.gov
571-272-7822

Paper No. 37
Date: December 22, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MOMENTA PHARMACEUTICALS, INC.,
Petitioner,

v.

BRISTOL-MYERS SQUIBB COMPANY,
Patent Owner.

Case IPR2015-01537
Patent 8,476,239

Before JACQUELINE WRIGHT BONILLA, GRACE KARAFFA OBERMANN, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318 and 37 C.F.R. § 42.73

We instituted a trial under 35 U.S.C. § 314 to review a challenge brought by Momenta Pharmaceuticals, Inc. ("Petitioner") against all of the claims, claims 1–15, of U.S. Patent No. 8,476,239 (Ex. 1001, "the '239 patent") in the Petition (Paper 1 ("Pet.")). *See* Paper 7 ("DI"). *See also* Decision Denying Patent Owner's

Request for Rehearing, Paper 21. Bristol-Myers Squibb Company ("Patent Owner") filed a Response under 37 C.F.R. § 42.120 (Paper 14 ("PO Resp.")) and Petitioner filed a Reply (Paper 32 ("Pet. Reply")). Patent Owner does not seek to amend the challenged claims under 37 C.F.R. § 42.121.

Neither party filed a motion to exclude evidence, but, as authorized (Paper 28), Patent Owner filed a Listing of New Arguments and Evidence in Petitioner's Reply (Paper 30). Patent Owner also submitted objections to evidence (Paper 27).

An oral argument was held on September 23, 2016. Transcript, Paper 36.

We conclude that the preponderance of the evidence does not support Petitioner's argument that the challenged claims would have been obvious.

A. The '239 patent (Ex. 1001)

The '239 patent issued July 2, 2013, claiming priority to an international application filed December 19, 2006, and a provisional application filed December 20, 2005. Ex. 1001, coversheet. According to Petitioner, none of the rejections entered during prosecution of the application that became the '239 patent were based on the references cited by Petitioner in this challenge. *See* Pet. 15–19.

The claims of the '239 patent are directed to stable liquid formulations of the therapeutic molecule CTLA4Ig. CTLA4Ig is a protein molecule that is used to treat immune system diseases and disorders such as rheumatoid arthritis and adverse transplant reactions. Ex. 1001, 3:45–49. According to the '239 patent, there are advantages to delivering CTLA4Ig subcutaneously, including home administration and improved compliance. *Id.* at 1:24–34.

Claims 1 and 7 are the only independent claims of the '239 patent. Claim 1 recites:[1]

[1] Bracketed numbers and indentations added.

A stable formulation suitable for subcutaneous administration comprising
[1] at least 100mg/ml CTLA4Ig molecule,
[2] a sugar selected from the group consisting of sucrose, lactose, maltose, mannitol and trehalose and mixtures thereof and
[3] a pharmaceutically acceptable aqueous carrier,
wherein the formulation has a
[4] pH range of from 6 to 8 and
[5] a viscosity of from 9 to 20 cps, and
[6] the weight ratio of sugar:protein is 1.1:1 or higher.

Ex. 1001, 55:16–23. Claim 7 recites:[2]

7. A stable formulation comprising
[1] the CTLA4Ig molecule having the amino acid sequence shown in SEQ ID NO:2 starting at methionine at position 27 or alanine at position 26 and ending at lysine at position 383 or glycine at position 382 in an amount of about 125 mg/ml,
[2] sucrose in an amount of about 170 mg/ml,
[3] at least one buffering agent,
[4] sterile water for injection and
[5] optionally a surfactant.

Ex. 1001, 55:35–56:17.

B. Asserted Ground of Unpatentability

Petitioner challenges the patentability of claims 1–15 of the '239 patent as being obvious over the combination of the teachings of Cohen[3] (Ex. 1003), Carpenter[4] (Ex. 1004), and Shire[5] (Ex. 1005).

[2] Bracketed numbers and indentations added.
[3] US Patent Application Publication 2003/0083246 A1, published May 1, 2003.
[4] RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS (John F. Carpenter and Mark C. Manning. eds., 2002).
[5] Shire et al., "Challenges in the Development of High Protein Concentration Formulations," 93 JOURNAL OF PHARMACEUTICAL SCIENCES 1390 (2004).

Analysis

Subject matter is unpatentable "if 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." 35 U.S.C. § 103.[6] A patent challenger carries the burden of showing that a person of ordinary skill in the art would have had reason to make modifications to the prior art and would have had a reasonable expectation of success in doing so. *See PharmaStem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

In this proceeding, the Petitioner has the burden of proof to establish that the subject matter of the challenged claims would have been obvious to a person of ordinary skill in the art at the time of the invention, including that there would have been a reasonable expectation of success in modifying the claimed CTLA4Ig formulations from those in the prior art, by a preponderance of the evidence. *See* 35 U.S.C. § 316(e); 37 C.F.R. § 42.20(c).

1.

After reviewing Petitioner's arguments and citations to the record, we accept the following as findings of fact supported by a preponderance of the evidence. Cohen teaches that CTLA4Ig was a known protein with known therapeutic effects in known amounts. Ex. 1003 ¶¶ 237–284, Pet. 27. Cohen also teaches that CTLA4Ig requires chronic administration every two to twelve weeks. Ex. 1003 ¶ 28; Pet. 28. Shire teaches that subcutaneous injection allows for home administration and, thus, improved compliance. Ex. 1005, 1391–92; Pet. 28.

[6] Because the application that matured into the '239 patent was filed before the effective date of the Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284 (2011), we apply the pre-AIA version of 35 U.S.C. §§ 103.

Carpenter teaches that even though it was known that proteins could be unstable in the relatively high concentrations required for subcutaneous formulations (*see* Ex. 1005, 1391[7]), a limited set of possible excipients could be used to develop a stable liquid protein formulation. Ex. 1004, 182, 186–88, 195; Pet. 33. Carpenter teaches that

> [i]f a solution dosage form [of a protein] is indicated, then there will be a finite set of possible excipients, restricting choices to those that are found in approved products and have been shown to be effective in protein formulations. For solution formulations, a list of possible excipients is given in Table 2.

Ex. 1004, 186, Table 2; *see* Pet. 34.

Carpenter teaches that sucrose was known to be a "first-line choice" stabilizer for liquid protein formulations. Ex. 1004, 187–188; Pet. 35. Carpenter teaches using high concentrations of sugars to stabilize proteins, approximately greater than 0.2 M. Ex. 1004, 187; Pet. 36. Petitioner's witness, Dr. Staples,[8] testifies that 0.2 M is approximately equal to 70 mg/ml. Ex. 1006 ¶ 47; Pet. 36. This range overlaps with the range recited in Patent Owner's claim 1 ("weight ratio of sugar:protein is 1.1:1 or higher), as well as the range recited in claim 7 ("sucrose in an amount of about 170 mg/ml") and claims 14 ("weight ratio of sucrose:protein is 1.3:1 to 1.5:1") and 15 ("weight ratio of sucrose:protein is 1.4:1"). Pet. 36.

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[7] Page numbers of exhibits refer to the page of the underlying document, not the numbering as presented in the exhibit, unless otherwise stated.

[8] Dr. Staples testifies that he has a Ph.D. in biological sciences and has worked in the field of protein formulation and dosage form development, including the liquid formulation of protein drugs, in several different companies since 1988. Ex. 1006 ¶¶ 2–14. We consider Dr. Staples qualified to offer opinions on drug formulation and the formulation of proteins as liquids. Patent Owner argues that Dr. Staples is not qualified to testify about the pharmacokinetics of drugs. *See* PO Resp. 3, 27. Because we do not reach issues regarding that topic in this decision, we do not need to consider Dr. Staples's qualifications on that issue.

Carpenter and Shire teach that isotonicity[9] may be necessary for subcutaneous formulations. Ex. 1004, 65; Ex. 1005, 1396; Pet. 37. Shire also teaches that a formulation above 20 cps would be too concentrated to be administered through a syringe. Pet. 40, citing Ex. 1005, 1397.

2.

Petitioner argues that there would have been a reasonable expectation that a balance between the amount of sugar necessary and tonicity and viscosity concerns could be achieved with a trial-and-error approach to successfully develop a stable liquid formulation of CTLA4Ig. Pet. 38–40. In opposition, Patent Owner argues that achieving a stable liquid formulation of a protein at the time of the invention was an unpredictable and highly protein-specific challenge. PO Resp. 13–26. The question of whether there would have been a reasonable expectation of success is a question of fact. *See Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014). We review the evidence presented by both parties to determine whether one of skill in the art would have had a reasonable expectation of success.

Petitioner cites to Dr. Staples's testimony that routine trial-and-error optimization could be used to obtain the claimed formulations. Pet. 36–37. Specifically, Dr. Staples testifies that "the precise amount of sugar claimed, though impossible to precisely predict for any particular protein, reflects nothing more than the routine, trial-and-error optimization of a single variable (the amount of sugar) based on two known, competing considerations (the protein's stability against the solution's viscosity and tonicity)." Ex. 1006 ¶ 45; *see also id.* ¶ 33

[9] We understand "tonicity" to be a measure of the relative concentration of particles dissolved in solution, which determines the direction and extent of diffusion across a membrane. A cell in a hypertonic solution may shrink as the water flows out. The parties do not dispute the meaning of the term "tonicity" and their use is consistent with this understanding. (*See* Ex. 1001, 6:10-11.)

(stating that there were general principles that would have set the lowest and highest reasonable values of sucrose that would have been expected to work.). Dr. Staples testifies further that "[t]his trial-and-error determination could have been done quickly and efficiently within an acceptable timeline in which a protein formulator would have expected to successfully develop a stable liquid protein formulation." *Id.* ¶ 46; Pet. 36–37.

Dr. Staples does not provide any further explanation of how this approach would actually be done, but Petitioner cites to the actual approach used in the '239 patent to arrive at the claimed ranges of sugar and argues that there would have been a reasonable expectation of success in making the claimed formulations. Pet. 39–40. Specifically, Petitioner argues that Example V describes "formulation development studies" that were conducted to evaluate the effect of sucrose on CTLA4Ig, wherein three ratios of sucrose to protein were tested and the ratio with the optimum stability for a subcutaneous formulation was chosen. *Id.* (citing Ex. 1001, 30:65–31:36). Petitioner notes that the '239 patent acknowledges that this ratio would cause some increased tonicity, but that in the background section, the inventors reported that isotonicity was not necessarily required. *Id.* at 40 (citing Ex. 1001, 2:29–31).

We also note that the Wang reference cited by Patent Owner (Ex. 2011) suggests a trial-and-error approach to protein formulation. *See* Ex. 2011 ("Very often, proteins have to be evaluated individually and stabilized on a trial-and-error basis."). Thus, we credit Dr. Staples's testimony regarding the use of trial-and-error optimization because it appears that this was a known approach for formulating proteins. We do not agree that because the approach was known, it was necessarily expected to be successful.

Petitioner cites to the statement in Carpenter that the authors were "quite confident" the generalized high throughput formulation procedure they describe "can be coupled successfully with high throughput screening strategies of protein drugs and facilitate drug development within the inherent time and resource constraints of the pharmaceutical industry." Ex. 1004, 195. We note that, although in isolation Carpenter's proclamation of being "quite confident" appears to demonstrate a reasonable expectation of success, when considered in context it refers to a general trend in the industry, not to the ability to formulate specific proteins. The full statement does not indicate that there was confidence that any particular drug could be successfully formulated as a liquid. Thus, this evidence is not persuasive.

To oppose the evidence provided by Petitioner, Patent Owner cites to statements in the literature regarding the success of generalized strategies for protein formulation. *See* PO Resp. 2. For example, Carpenter warns of the difficulties in the actual formulation of specific proteins. PO Resp. 16. Specifically, Carpenter cautions that "[t]he exquisite sensitivity of protein structure, function, and stability to the primary sequence does not readily lend itself to a generic approach for protein formulation." Ex. 1004, 185. Carpenter explains that, although stable liquid formulation is desirable, "for most proteins maintaining physical and chemical stabilities in aqueous solution for an extended period of time is extremely difficult." Ex. 1004, 184. Carpenter states that "[i]t can be assumed that most proteins will *not* exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed." Ex. 1004, 188 (emphasis added).

Given the statements in Carpenter that cast doubt on whether the guidance it provides will result in a successful formulation, we are not persuaded that even

highly skilled artisans would have expected success, as Petitioner argues. *See* Pet. 39.

Patent Owner also cites to statements in Wang (Ex. 2011), which was published in 1999, that "the structural differences among different proteins are so significant that generalization of universal stabilization strategies has not been successful." Ex. 2011, 130; *see* PO Resp. 2. Patent Owner cites further to statements in the prosecution of a patent application filed by Dr. Staples regarding the unpredictability of liquid formulation of proteins. PO Resp. 55. In that application, Cleland[10] was provided as evidence "that the skilled worker would have understood at the earliest effective filing date of the application that the conditions necessary for stabilizing one protein would not necessarily be effective, or even reasonably predictive, in stabilizing another protein." Ex. 2022, 14.

We are not persuaded by the statements in Wang or those in Cleland. As Petitioner argues, much of this evidence was published long before Carpenter and Shire were published. Pet. Reply 9–10. For example, the cited statement in the prosecution of Dr. Staples's patent application concerned the state of the art in 1996 and cited to evidence, Cleland, published in 1993, while Wang (Ex. 2011) was published in 1999. *Id.* In contrast to these older statements, we consider the statements in Carpenter to carry more weight. Carpenter is the prior art cited by Petitioner as guidance for formulating proteins. Therefore, statements in Carpenter that this guidance may not lead to a successful result are the most significant.

We are also not persuaded by Patent Owner's arguments based on the testimony of its witness, Dr. Klibanov[11]. Dr. Klibanov testifies that in contrast to

[10] Cleland et al., 1993, Critical Reviews in Therapeutic Drug Carrier Systems, 10(4): 307-377.

[11] Dr. Klibanov testifies that he is a Professor of Chemistry and Bioengineering at the Massachusetts Institute of Technology and has been teaching and conducting

the "high throughput formulation" strategy of Carpenter, those of skill in the art would have known it was critical to begin by analyzing the specific protein of interest, including specific degradation pathways. PO Resp. 17–18 (citing Ex. 2015 ¶¶ 33–36). According to Patent Owner, such "preformulation study" is consistent with the studies provided in Examples V, VII, VIII, and IX of the '239 patent. PO Resp. 10. Patent Owner argues that Dr. Staples agreed on cross-examination that such studies must be done before a protein could be formulated in a liquid solution. PO Resp. 10–11 (citing Ex. 2012, 62:19–63:1, 63:14–20, 84:1–7).

Whether or not these "preformulation studies" are required, as discussed above, the examples in the '239 patent demonstrate trial-and-error studies that, at first blush, support a determination of the claimed formulation by routine optimization. Although Patent Owner argues that they must be performed before formulating a protein, Patent Owner does not direct us to evidence showing that such studies are outside of the skill of one with ordinary skill in the art and that, once performed, would not be expected to lead to a successful result. Accordingly, we are not persuaded by Patent Owner's arguments regarding preformulation studies.

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research there for over 36 years. Ex. 2015 ¶ 4. Dr. Klibanov testifies that his experience includes publishing hundreds of scientific papers, presenting hundreds of lectures, and being named as an inventor on many issued U.S. patents. *Id.* ¶ 9. Dr. Klibanov testifies that many of these publications, patents, and lectures have dealt with protein chemistry, stability, stabilization, formulation, delivery, and biological evaluation. *Id.* Dr. Klibanov testifies further that he has earned numerous awards and honors, including election to the U.S. National Academy of Sciences and U.S. National Academy of Engineering. *Id.* ¶ 7. We consider Dr. Klibanov qualified to offer opinions on drug formulation and the formulation of proteins as liquids.

Patent Owner argues further, relying on Dr. Klibanov's testimony, that it would have been a "lengthy and arduous" process taking many months or years to formulate a protein as a stable liquid. PO Resp. 11–12 (citing Ex. 2015 ¶ 46). Petitioner points to contradictory evidence from Carpenter, wherein "[t]ypical time scales for preformulations can range from one to three months depending on what assay systems have been established by the research groups and whether they can be utilized as stability-indicating." Ex. 1004, 186; Pet. Reply 8. Furthermore, as Petitioner notes, on cross-examination Dr. Klibanov testified that in actual practice, drug formulation would take advantage of short-cuts and assumptions to get to a result. Pet. Reply 2, 7. Dr. Klibanov testified:

> I mean, it is extremely rare, and I actually have never even seen it, and I have seen a lot of things, it is very rare that in doing protein formulation work, you dot all the Is and cross all the Ts. I mean, that's what you would like to have in an ideal world. Sadly that's not the world that we live in. So you will have to cut some corners because you would like to deliver a drug to a patient who would benefit from this drug, and that's why they had to make some educated guesses and some scientific judgments. And that's what they did here. So that is what -- that is very typical of the formulation development process. That's what people typically do.

Ex. 1019, 146:19–147:10. Accordingly, we are not persuaded by Dr. Klibanov's testimony that the time and effort required to formulate a protein as claimed are indicative of a lack of reasonable expectation of success.

Petitioner replies to Patent Owner's arguments about the need for preformulation studies by arguing that it was already known that CTLA4Ig was relatively stable before the filing of the '239 patent. Pet. Reply 8–9. Specifically, Petitioner points to Paborji (Ex. 1016).[12] Paborji is entitled "Stabilization of

[12] Patent Owner listed arguments based on Paborji as new arguments and evidence provided by Petitioner in its Reply Brief. Paper 30, 1. Because Petitioner

CTLA4Ig, a Genetic Fusion Protein" and reports on the solution stability and degradation pathways of the protein. Paborji states: "Aqueous solutions of CTLA4Ig in phosphate buffer at pH 8 are relatively stable at 2-8° C, but the stability is not sufficient for long-term storage." Ex. 1016, 2. Paborji continues by stating that lyophilization of CTLA4Ig with the sugars maltose, lactose and also with L-arginine provided excellent stabilization. *Id.* According to Petitioner "a formulator would still have reasonably expected to develop a liquid formulation of CTLA4Ig, because it was known to be 'relatively stable.'" Reply 9. Petitioner also notes that Paborji was published in 1994, before Carpenter in 2002. Petitioner argues that formulators at the time of Paborji did not have the benefit of Carpenter or Shire, which were published later, for guidance on preparing liquid formulations of proteins. *Id*.

Petitioner does not direct us to testimony explaining how one of skill in the art would have understood Paborji. Thus, Petitioner fails to direct us to evidence indicating that the report in Paborji of a "relatively stable" formulation would have suggested to an ordinarily skilled artisan that there would have been a reasonable expectation of success in achieving the "stable formulation" recited in the challenged claims.

Petitioner also refers to a partial statement in Hovgaard[13] that the formulation of stable protein solutions may offer significant challenges, but that "these challenges can overcome through sound, rational formulation approaches

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presented Paborji in response to Patent Owner's arguments that without preformulation studies there would have been no reasonable expectation of success, we do not consider it or Petitioner's arguments based on it to be in violation of 37 C.F.R. § 42.23(b). *See* Reply 7–9.

[13] Frokjaer and Hovgaard, eds., Pharmaceutical Formulation Development of Peptides and Proteins, Taylor & Francis: London (2000).

with manufacturing processes and packaging systems designed to maintain stability and other quality features of the formulation." Reply 8 (citing Ex. 1015, 171). This generalized statement does not provide any information about the specific doubts expressed in Carpenter or any information about CTLA4Ig. Furthermore, Petitioner's statement that other proteins had been successfully formulated as stable liquids (*see* Reply 8) does not negate Carpenter's statement that most cannot be.

3.

After considering the evidence to which we have been directed by the parties, we determine, on balance, that Petitioner has not established sufficiently that an ordinary artisan would have had a reasonable expectation of success in formulating CTLA4Ig as a stable liquid formulation as recited in the challenged claims. Specifically, in the challenge to Patent Owner's claims, Petitioner relies on Carpenter to show that an ordinarily skilled artisan would have known how to prepare a stable liquid formulation of CTLA4Ig for subcutaneous administration. Pet. 33–40. The statements in Carpenter are the most significant evidence of whether there would have been an expectation of success in achieving the claimed formulation. But Carpenter expressly states that "[i]t [could] be assumed that most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed." Ex. 1004, 188; PO Resp. 16. Carpenter also states that although a stable liquid formulation is desirable, "for most proteins maintaining physical and chemical stabilities in aqueous solution for an extended period of time is extremely difficult." Ex. 1004, 184. These statements indicate that there would not have been a reasonable expectation of success in achieving the claimed formulations. Dr. Staples's testimony about routine trial-and-error optimization does not overcome these statements.

Petitioner's citation to Paborji (Ex. 1016) does not persuade us otherwise. Even though Paborji states that CTLA4Ig in phosphate buffer is "relatively stable," without testimony to explain how this would be interpreted by a skilled artisan, the strong doubt about success expressed in Carpenter is not overcome.

Petitioner argues that the claimed formulations are "nothing more than the efforts of a skilled formulator choosing from a limited set of known formulations to subcutaneous liquid formulations." Pet. 23; *see also* Pet. Reply 2 ("The '239 patent follows the same formulation approach outlined in the Carpenter Handbook, and endorsed by Drs. Staples and Klibanov. The inventors went to the formulator's toolbox and tried the first line of excipients and formulation parameters. And they worked."). We agree that Carpenter and Shire provide general guidance for formulating proteins as stable liquids and that Patent Owner followed certain aspects of those general teachings when creating its stable liquid formulation comprising CLTA4Ig, a protein taught in Cohen. The evidence to which Petitioner cites, however, does not persuade us that an ordinarily skilled artisan would have reasonably expected to be successful in achieving the claimed formulations.

As stated by the Supreme Court:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the *anticipated success*, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007) (emphasis added); *compare Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) ("Reached by means of routine procedures, and producing *only predictable results*,

the recited dosages therefore do not distinguish the claims of the ’430 patent from the amiloride/hydrochlorothiazide combination that the district court properly found was disclosed in the ’813 patent.” (emphasis added)). For the reasons discussed above, Petitioner fails to sufficiently establish that an ordinary artisan would have reasonably expected success in making the claimed stable liquid formulations of the CTLA4Ig protein by following the teachings of the prior art cited in the Petition.

C. Conclusion

We have considered the evidence to which we have been directed by the parties regarding obviousness. We have not been directed to evidence of unexpected results or other secondary considerations. The preponderance of the evidence does not show sufficiently that there was a reasonable expectation of success in formulating CTLA4Ig as a stable liquid. Thus, we conclude that Petitioner has not shown that the challenged claims would have been obvious.

D. Order

Accordingly, it is ORDERED that claims 1–15 of the ’239 patent have NOT been shown to be unpatentable as obvious over Cohen, Shire, and Carpenter.

Any party seeking judicial review of this Final Written Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

For Petitioner:

Dorothy P. Whelan
Anita L. Meiklejohn
Michael J. Kane
whelan@fr.com
IPR14131-0120IP1@fr.com

For Patent Owner:

Andrea G. Reister
Enrique D. Longton
Christopher Sipes
areister@cov.com
elongton@cov.com
csipes@cov.com