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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MAIA PHARMACEUTICALS, INC.,
Petitioner

v.

BRACCO DIAGNOSTICS INC.,
Patent Owner

Case No. IPR2019-00345
U.S. Patent No. 6,803,046

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,803,046

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EXHIBIT LIST

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1001	U.S. Patent No. 6,803,046 to Metcalfe et al.
1002	Prosecution History excerpts for the ’046 patent
1003	Declaration of Christian Schöneich, Ph.D.
1004	CV of Christian Schöneich, Ph.D.
1005	Physicians’ Desk Reference For Radiology and Nuclear Medicine, 1977/78 (1977) (“PDR”)
1006	PCT Publication No. WO 00/5169 to Sato
1007	PCT Publication No. WO 00/5169 to Sato (English Translation with affidavit) (“Sato”)
1008	Bacarese-Hamilton *et al.*, “Prevention of Cholecystokinin Oxidation During Tissue Extraction,” 448 Neuronal Cholecystokinin 571 (1985) (“Bacarese-Hamilton I”)
1009	Bacarese-Hamilton *et al.*, “Oxidation/Reduction of Methionine Residues in CCK: A Study by Radioimmunoassay and Isocratic Reverse Phase High Pressure Liquid Chromatography,” 6 Peptides 17 (1985) (“Bacarese-Hamilton II”)
1010	U.S. Patent No. 7,329,644 to Saviano et al. (“Saviano”)
1011	Rational Design of Stable Protein Formulations: Theory and Practice, Chapters 5 & 8 (Carpenter and Manning, ed., April 30, 2002).
1012	Liddle, R. A., *On the Measurement of Cholecystokinin*, 44 Clinical Chemistry 5 (1998) (“Liddle 1998”)

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1013	Akers *et al.*, "Peptides and Proteins as Parenteral Solutions," in *Pharmaceutical Formulation Development of Peptides and Proteins* (2000) ("Akers")
1014	DeLuca, *et al.*, "Formulation of Small Volume Parenterals," in *Pharmaceutical Dosage Forms: Parenteral Medications Volume 1* (1992) ("DeLuca")
1015	U.S. Patent No. 3,937,819 to Ondetti et al. ("Ondetti")
1016	Wang *et al*., "Review of Excipients and pHs for Parenteral Products Used in the United States," 34 PDA J. Pharm. Sci and Tech. 452 (1980) ("Wang 1980")
1017	*Nema et al*., "Excipients and Their Use in Injectable Products," 51 PDA J. of Pharma. Sci. and Tech. 166 (1997) ("*Nema*")
1018	U.S. Patent Publication No. 2003/0104996 to Li et al. ("Li")
1019	Wang *et al.*, "Parenteral Formulations of Proteins and Peptides: Stabilities and stabilizers," 42 J. Parenteral Sci. and Tech. S4 (1988) ("Wang 1988")
1020	Wünsch, E., "Peptide Factors as Pharmaceuticals: Criteria for Application," 22 Biopolymers 493 (1983) ("Wünsch")
1021	Yagami, *et al.*, "Stabilization of a tyrosine O-sulfate residue by a cationic functional group: formation of a conjugate acid-base pair," 56 J. Peptide Res. 239 (2000) ("Yagami")
1022	Huttner, W. B., "Determination and Occurrence of Tyrosine O-Sulfate in Proteins," 107 Methods in Enzymology 200 (1984) ("Huttner")
1023	Moroder *et al.*, "Gastrin and Cholecystokinin, An Arduous Task for the Peptide Chemist" in *Natural Product Chemistry* (1986) ("Moroder")

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1024	Yoshioka, *et al*., "Stability of Peptide and Protein Pharmaceuticals" in *Stability of Drugs and Dosage Forms* (2002) ("Yoshioka")
1025	Marseigne, *et al.*, "Full Agonists of CCK_8 Containing a Nonhydrolyzable Sulfated Tyrosine Residue," 32 J. Med. Chem. 445 (1989) ("Marseigne")
1026	Gorman *et al.*, "Proton Affinities of the 20 Common α-Amino Acids," 114 J. Am. Chem. Soc. 3986 (1992)
1027	Liddle, R. A., "Cholecystokinin Cells," 59 Annu. Rev. Physiol. 221 (1997) ("Liddle 1997")
1028	Wang, Y.J., "Parenteral Products of Peptides and Proteins," in *Pharmaceutical Dosage Forms: Parenteral Medications Volume 1* (1992) ("Wang 1992")
1029	Package Insert for "KINEVAC® Sincalide for Injection," November 1994 ("Kinevac 1994 Package Insert")
1030	Essentials of Nuclear Medicine Science (Hladik, et al., eds., 1987) ("ENMS")
1031	Uffelman, W., "Unexpected Shortfalls of Two Nuclear Medicine Pharmaceuticals," 42 J. Nuc. Med. 16N (2001) ("Uffelman")
1032	U.S. Patent No. 5,272,135 to Takruri ("Takruri")
1033	FDA Approval Package for NDA Application Number 017697-S012.
1034	Fendler *et al.*, "Hydrolysis of Nitrophenyl and Dinitrophenyl Sulfate Esters," 33 J. Org. Chem. 10 3852 (1968) ("Fendler")
1035	Handbook of Pharmaceutical Excipients, Third Edition, Arthur H. Kibbe, Ed. (2000) ("Handbook")

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1036	Jensen *et al.*, "Metal-Catalyzed Oxidation of Brain-Derived Neurotrophic Factor (BDNF): Analytical Challenges for the Identification of Modified Sites," 17 Pharm. Research 190 (2000) ("Jensen I")
1037	Jensen *et al.*, "Metal-Catalyzed Oxidation of Brain-Derived Neurotrophic Factor (BDNF): Selectivity and Conformational Consequences of Histidine Modification," 46 Cellular and Molecular Biology 685 (2000) ("Jensen II")
1038	Swadesh, *et al.*, "Sodium Sulfite as an Antioxidant in the Acid Hydrolysis of Bovine Pancreatic Ribonuclease A," 141 Analytical Biochemistry 397 (1984) ("Swadesh")
1039	Mattern *et al.*, "Formulation of Proteins in Vacuum-Dried Glasses. II. Process and Storage Stability in Sugar-Free Amino Acid Systems," 4 Pharm. Development and Tech. 199 (1999) ("Mattern")
1040	Wang *et al.*, "Lyophilization and Development of Solid Protein Particles," 203 Int. J. of Pharm. 1 (2000) ("Wang 2000")
1041	Bush *et al.*, "A critical evaluation of clinical trials in reactions to sulfites," 78 J. Allergy Clin. Immunol. 191 (1986) ("Bush")
1042	Liddle, *et al.*, "Cholecystokinin Bioactivity in Human Plasma," 75 J. Clin. Invest. 1144 (1985) ("Liddle III")
1043	Konturek, *et al.*, "Effect of Cholecystokinin Receptor Antagonist on Pancreatic Responses to Exogenous Gastrin and Cholecystokinin and to Meal Stimuli," 94 Gastroenterology 1014 (1988) ("Konturek")
1044	Banga, A.K., "Structure and Analysis of Therapeutic Peptides and Proteins" in Therapeutic Peptides and Proteins: Formulation, Processing, and Delivery Systems, Chapter 2 (2006) ("Banga")

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1045	Graf, *et. al.*, "Iron-catalyzed Hydroxyl Radical Formation," 259 J. Bio. Chem. 3620 (1984) ("Graf")
1046	U.S. Patent No. 6,238,664 to Hellerbrand et al. ("Hellerbrand")

Maia Pharmaceuticals, Inc. ("Petitioner" or "Maia") requests *inter partes* review of claims 1-19, 21-38, 40-55, 77-102, and 104-105 ("Challenged Claims") of U.S. Patent No. 6,803,046 ("the '046 patent," MAIA1001), purportedly owned by Bracco Diagnostics Inc. ("Patent Owner" or "Bracco").

I. SUMMARY OF ISSUE PRESENTED

The claims of the '046 patent generally recite a formulation for sincalide, a peptide drug that is administered by injection. Independent claim 1, for example, claims a sincalide formulation that includes the following standard classes of excipients, defined by their function: at least one stabilizer, a surfactant/solubilizer, a chelator, a bulking agent/tonicity adjuster, and a buffer. The other independent claims are insubstantial variations of this basic formulation, claiming the formulation as a kit (claim 40), or as a method of making the formulation by mixing the excipients (claim 21), or as a method of imaging a patient by first administering the formulation (claims 77, 104). The dependent claims narrow the extremely broad excipient classes to common subclasses and common compounds, or list common techniques for administering the drug, or imaging a patient.

The '046 patent admits that old sincalide formulations had *various drawbacks*. Indeed, sincalide's potency and stability drawbacks were well-known and well-documented in the art. The '046 patent explains the obvious need resulting from the drawbacks to make "sincalide formulations having improved

stability and/or potency over previous formulations." MAIA1001, 3:37-39. The inventors of the '046 patent purportedly solved the known drawbacks with the simple and obvious "selection of excipients that provide certain desired functions." *Id.*, 3:35-36.

But selecting these broad excipient classes for their desired and known functions was not patentable when Bracco filed its patent application in August 2002. By that time, using functional classes of excipients according to their desired function—to stabilize unstable injectable drug products and improve potency—was well known. For example, Wang in 1980, and Nema in 1997, published lists of the functional classes of excipients to use in injectable formulations—the exact excipient classes claimed in the '046 patent. MAIA1016, 453-458 (Table I); MAIA1017, 167-169 (Tables II-VII). DeLuca instructed that these same excipient classes be used to "provide safe, efficacious, and elegant parenteral dosage forms." MAIA1014, 192.

Sato, in particular, disclosed all the excipient classes claimed in the '046 patent for use in peptide formulations, and expressly taught using these excipients in unstable cholecystokinin formulations. MAIA1007, 7-11. Sincalide is a cholecystokinin peptide. MAIA1010, 1:18-32.

Sato was not before the Examiner during examination. Had Sato, and the other highly relevant—and invalidating—prior art references, been applied by the

Examiner, Bracco's claims would not have issued. The '046 patent slipped through the PTO with only a later-retracted restriction requirement, followed by a Notice of Allowance. The Board should rectify this error by canceling the Challenged Claims. Additional support for this Petition is included in the Declaration of Christian Schöneich, Ph.D. MAIA1003.

II. INTRODUCTION AND STATE OF THE ART

A. The Sincalide Peptide

Sincalide is the sole active ingredient in Bracco's reformulated Kinevac product, which Bracco gained FDA approval to market in 2002. MAIA1033, 22.[1] The reformulated Kinevac product is the subject of the '046 patent. Sincalide was also the sole active ingredient in Bracco's old Kinevac formulation, first marketed in 1976, that exhibited the potency and stability drawbacks. MAIA1001, 1:17-20, 1:27-28.

Sincalide is an eight-amino acid peptide having the following sequence:

Asp—Tyr(SO_3H)—Met—Gly—Trp—Met—Asp—Phe—NH_2.

MAIA1001, 1:11-16; MAIA1010, 1:25-32. Sincalide's two methionine residues and its sulfated-tyrosine residue (highlighted above) are essential for biological

[1] The citations to MAIA1033 are to new page numbers added to the document, in light of the document's inconsistent internal page numbering.

activity, but they are also susceptible to chemical degradation, resulting in sincalide's instability. Section II.C.1, *infra*.

Sincalide is sometimes called "CCK-8" because it is the sulfated C-terminal octapeptide of cholecystokinin (CCK). MAIA1001, 1:11-16. Sincalide is one of many peptide molecules in the cholecystokinin (CCK) family. MAIA1010, 1:18-32. CCK peptides vary in amino acid chain length, but all biologically-active CCK peptides share the same eight-amino acid C-terminal sequence that makes up sincalide. MAIA1010, 1:18-32; MAIA1012, 903; MAIA1003, ¶¶33-34.

Sincalide has been used for decades to stimulate gall bladder contraction, which allows a physician to more easily image the patient's gallbladder with x-ray imaging or another imaging modality in order to diagnose gallbladder conditions. MAIA1005, 154 (1977/78 Kinevac PDR entry); MAIA1015, 1:14-17, MAIA1029, 1-3 (1994 Kinevac Package Insert). Sincalide is administered to the patient as a parenteral drug (i.e., by injection). MAIA1005, 154; MAIA1029, 1. It is often accompanied by separate administration of an imaging agent that further enhances gall bladder visibility during imaging. MAIA1030, 126-127 (describing administration of radiopharmaceutical agents with sincalide to enhance visibility of the hepatobiliary system, including the gall bladder).

B. The Old Kinevac Formulation Had Known Drawbacks

Like most peptide and protein molecules, sincalide is prone to instability and loss of biological activity in aqueous solution, making it difficult to formulate as a shelf-stable liquid formulation. Section II.C, *infra;* MAIA1003, ¶¶37-39. Unstable peptides and proteins have been historically formulated as lyophilized (freeze-dried) powders in an attempt to stabilize the active ingredient and retain biological activity. MAIA1014, 217 ("Substances that degrade in solution become candidates for freeze-drying."); MAIA1013, 146 (majority of commercial and clinical protein drug products are freeze-dried powders); MAIA1003, ¶31.

In 1976, E.R. Squibb ("Squibb") patented a method of purportedly "enhancing the stability" of sincalide during storage by lyophilizing it with sodium chloride. MAIA1015, 2:60-4:2, Abstract. That same year, Squibb began marketing this two-ingredient lyophilized sincalide product under the tradename Kinevac. MAIA1001, 1:17-20; MAIA1005, 154. Bracco acquired Kinevac from Squibb in 1994. MAIA1033, 39.

This Kinevac formulation (herein "the old Kinevac formulation") was packaged in vials containing the lyophilized powder in amounts of 5 micrograms of sincalide and 45 milligrams of sodium chloride. MAIA1005, 154. The user was instructed to reconstitute the lyophilized powder with 5 mL of sterile water prior to administering the sincalide solution to the patient via injection. MAIA1030, 154;

MAIA1015, 2:57-58. The reconstituted sincalide solution could also be diluted in a physiological acceptable fluid (for example Sodium Chloride Injection USP, 0.9%) prior to administration. MAIA1029, 3.

But simply lyophilizing the formulation with sodium chloride did not solve sincalide's instability problems. The '046 patent recognizes that since its introduction in 1976, the old Kinevac formulation suffered from "***various drawbacks***" related to sincalide's instability. MAIA1001, 1:27-28 (emphasis added). It describes the potency variability and loss of bioactivity in the old Kinevac formulation due to sincalide degradation. *Id.*, 1:29-30 ("the two-ingredient formulation suffers from potency variability"); 1:34-36 ("This bioassay was unable to distinguish between bioactivity of sincalide and bioactivity of sincalide degradants."). To compensate for this degradative loss, the '046 patent acknowledges that the old Kinevac formulation required a "***20% overage*** of sincalide" to maintain its required potency and bioactivity. *Id.*, 1:35-37 (emphasis added).

Before Bracco ever filed for the '046 patent, it was well documented that sincalide's potency variability and loss of bioactivity—that is, its drawbacks—were due to its chemical and physical instability. Section II.C, *infra*. Likewise, the obvious solutions to these drawbacks were well documented in the literature, also before Bracco ever filed for the '046 patent. Section II.D, *infra*. Bracco simply

claimed in the ’046 patent the broad functional excipient classes that the prior art instructed a POSA to use for stabilizing unstable peptides, like sincalide.

C. Sincalide’s Known Chemical and Physical Instability

Like most peptides and proteins, sincalide is susceptible to chemical and physical instability that, if left unchecked, leads to sincalide’s degradation, potency variability, and loss of bioactivity. MAIA1019, S4-S8 (identifying protein and peptide degradation pathways); MAIA1024, 187-203 (same); MAIA1003, ¶¶37-54. The specific causes of sincalide’s chemical and physical instability were well known before August 2002.

1. Sincalide’s Chemical Instability

In 1983, Wünsch reported that CCK had been studied for years “because of its well-known instability.” MAIA1020, 503. Wünsch’s analysis via HPLC found that most of the sincalide in the old Kinevac formulation had been destroyed due to sincalide chemical instability: “HPLC of ampuled CCK-PZ-octapeptide (***Scincalide***) [sic], as well as of the bulk material (***Squibb Laboratories***), clearly revealed that in the ampule form, ***most of the active material was destroyed***.” *Id.* (emphasis added).

Wünsch taught that the two main factors contributing to sincalide’s chemical instability were hydrolysis of its sulfated tyrosine residue and oxidation of its methionine residues:

> The ***instability*** of the CCK-PZ-tritriacontapeptide amide, as well as of its C-terminal fully active octa- and decapeptides [sincalide] with concomitant ***loss of biological activity***, is mainly due to two factors: (1) facile hydrolysis of the tyrosine-O-sulfate moiety and (2) the strong tendency of the two methionine residues to oxidize.

Id. (emphasis added).[2] These factors are discussed below.

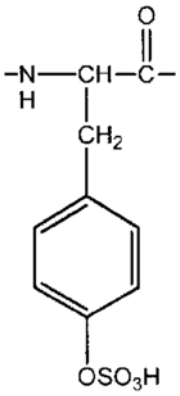
a. Hydrolysis of the Sulfated Tyrosine Residue

The first main factor contributing to sincalide's chemical instability is hydrolysis of sincalide's sulfated tyrosine residue. MAIA1020, 503; MAIA1003, ¶¶40-43. Sincalide's sulfated tyrosine residue is at the two amino acid position in the peptide, highlighted below:

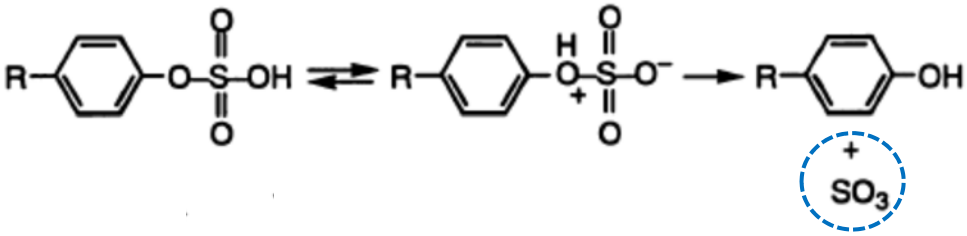
Asp—Tyr(SO_3H)—Met—Gly—Trp—Met—Asp—Phe—NH_2.

An excerpt of Fig. 1 from the '046 patent shows the sulfated tyrosine residue:

[2] The peptide family that researchers more recently have called cholecystokinin, had historically been called pancreozymin (PZ) or pancreozymin-cholecystokinin (CCK-PZ). *See* MAIA1027, 221; MAIA1020, 503. Thus, the peptide that Wünsch calls the "C-terminal fully active octa-[]peptide" of CCK-PZ is sincalide. MAIA1020, 503; MAIA1003 ¶¶34, 37.



MAIA1001, Fig. 1 (excerpted). Hydrolysis of the sulfated tyrosine simply means that the tyrosine-O-sulfate ester bond is broken by reaction with water and the sulfate (-SO_3, circled) moiety is cleaved from the tyrosine residue:



MAIA1021, Figure 1 (excerpted, annotated); MAIA1003, ¶41.

Hydrolytic reactions are highly pH dependent, where a more acidic environment drives the reaction. *See* MAIA1019, S4 ("The formulation factor that most influences the hydrolytic rate is solution pH."); MAIA1003, ¶42. Yagami explained that "[i]t is well known that Tyr(SO_3H) residues tend to rapidly desulfate to Tyr under acidic conditions." MAIA1021, 240. Huttner also stated "[o]ne of the most remarkable properties of tyrosine sulfate is the lability of the ester bond in acid and its stability in alkali." MAIA1022, 203. Tyrosine desulfation is catalyzed

by protons and accelerated under nonpolar conditions. MAIA1021, 240. Yagami disclosed that shorter CCK peptides are more susceptible to tyrosine desulfation in acidic conditions than longer chain CCK peptides, making CCK-8 (sincalide) the most susceptible among biologically-active CCK peptides to hydrolytic degradation. *Id.*, 243; MAIA1003, ¶¶40-43.

Not all tyrosine residues in peptides or proteins are sulfated, but sincalide's tyrosine residue must be sulfated for it to be biologically active. MAIA1012, 903 ("Sulfation of the tyrosine residue at position seven from the carboxyl terminus of CCK is critical for biological activity."). Marseigne reported the biological activity of cholecystokinin is "dependent on the sulfation of tyrosine since the sulfated form was about 250 times more potent than the unsulfated one." MAIA1025, 445. Liddle likewise reported that sulfation "is critical for biological potency of CCKs" and found that the "unsulfated form of CCK is ~1000-fold less active than its sulfated counterpart." MAIA1027, 224. Wang 1988 explained that "hydrolysis of the tyrosine-O-sulfate moiety was responsible for ***inactivation of cholecystokinin***." MAIA1019, S5 (emphasis added); MAIA1003, ¶40.

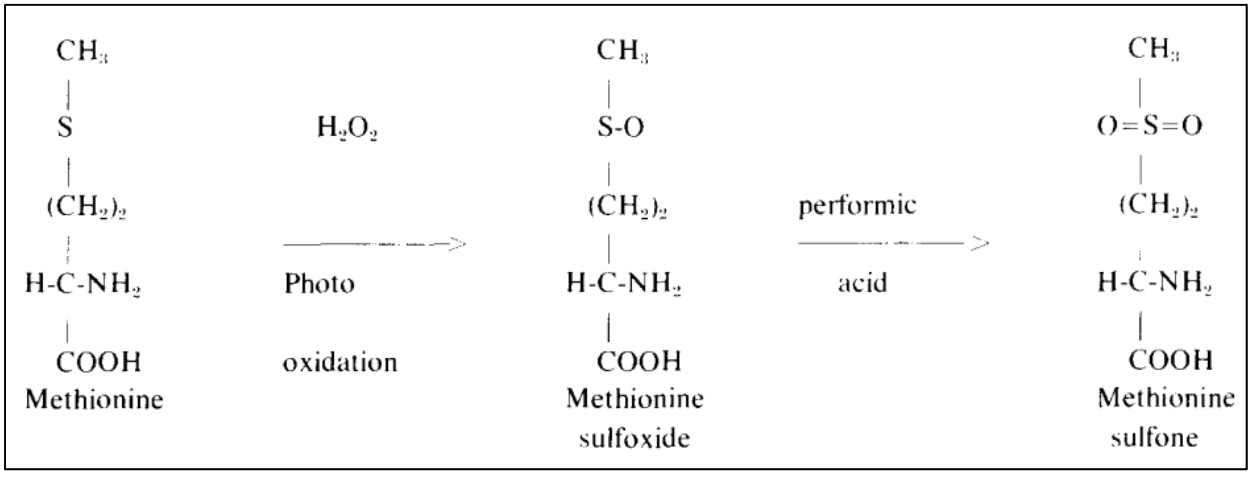
b. Oxidation of the Methionine Residues

The second main factor contributing to sincalide's chemical instability is oxidation of its methionine residues. MAIA1020, 503. MAIA1003, ¶¶44-50.

Sincalide's methionine residues at the three and six amino acid positions are highlighted below:

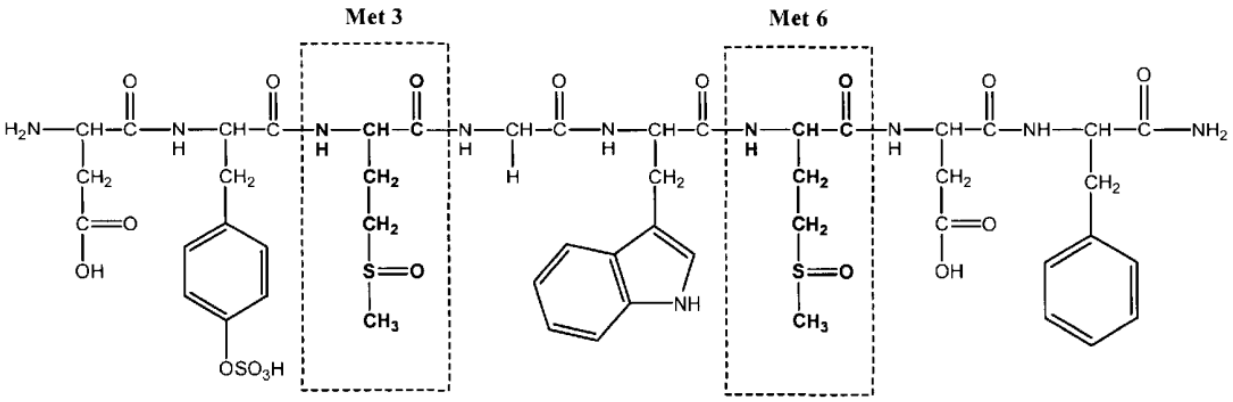
Asp—Tyr(SO_3H)—**Met**—Gly—Trp—**Met**—Asp—Phe—NH_2.

Although methionine residues in any peptide or protein can be susceptible to degradation (*see, e.g.*, MAIA1019, S4, MAIA1013, 153), Bacarese-Hamilton I indicated in 1985 that "[c]holecystokinin (CCK) is particularly susceptible to oxidation of its methionine residues (of which CCK-33 has three, and CCK-8 two)." MAIA1008, 571. Also in 1985, Bacarese-Hamilton II illustrated the mechanism of methionine oxidation in CCK and explained that the methionine degradation byproducts on the methionine residue are methionine sulfoxide and methionine sulfone:



MAIA1009, 18. The '046 patent acknowledges that sincalide's methionine oxidation was well understood: "Methionine has been identified as one of the most

easily oxidizable amino acids, which degrades to its corresponding sulfoxide and, under more strenuous oxidation conditions, its sulfone." MAIA1001, 10:12-15. Figure 4 of the '046 patent shows the methionine residues oxidized to the sulfoxides:



Id., Fig. 4.

Akers stated that the oxidation of methionine to the sulfoxide occurs with peptide exposure to "the solvent and environmental conditions such as the presence of oxygen, light, high temperature, metal ions, and various free radical initiators." MAIA1013, 153; *see also* MAIA1014, 200; MAIA1024, 192; MAIA1003, ¶48. Again, the '046 patent acknowledges the mechanisms of sincalide's methionine oxidation were known in the art: "The mechanisms of oxidation appear to be highly dependent on the reactive oxygen species under consideration: peroxide, peroxyl radicals, singlet oxygen, and hydroxyl radical have all been shown to oxidize methionine residues to sulfoxides and other products." MAIA1001, 10:15-20.

Any oxidation at sincalide's methionine residues is problematic because the resulting sulfoxide is highly polar, which "alters the non-polar characteristic of the side chain thereby ***interfering with (or even destroying) biological activity***." MAIA1009, 18 (emphasis added); *see also* MAIA1012, 903 ("Oxidation of CCK reduces its biological activity 100- to 1000-fold."); MAIA1008, 571 (oxidation of methionine in CCK-8 "can cause loss both of immunoreactivity and biological potency"); MAIA1003, ¶49.

Thus, in 2002 a POSA would have known that sincalide is chemically unstable due to hydrolysis of its sulfated tyrosine residue and oxidation of its methionine residues, and that this instability leads to loss of potency and a reduction in biological activity. MAIA1003, ¶50. A POSA would have been motivated to develop a sincalide product formulated to address these instability issues. *Id.*; Section II.D, *infra*.

2. Sincalide's Physical Instability

Peptides and proteins may experience physically instability due to, for example, denaturation, aggregation, adsorption, or precipitation. MAIA1024, 193; MAIA1013, 159-163. Larger peptides and proteins are generally susceptible to denaturation, aggregation, and precipitation, whereas smaller peptides may be less so. MAIA1024, 187, 193; MAIA1003, ¶¶51-52. Proteins and peptides alike are susceptible to loss of potency and biological activity due to surface adsorption:

"Adsorption of peptides and proteins onto the walls of containers has been reported for various formulations." MAIA1024, 194. Wünsch reported that peptides in the secretin and CCK families, including sincalide ("CCK-PZ-octa-[]peptide"), were observed to undergo surface adsorption on glassware. MAIA1020, 503-504; *see also* MAIA1042, 1146 (explaining need for special measurement technique due to CCK-8 adsorption losses in syringes and tubing); MAIA1043, 1015 (adding excipient to prevent CCK-8 adsorption); MAIA1003, ¶¶52-54.

As with chemical instability, surface adsorption diminishes the peptide's biological activity. MAIA1013, 162. ("biological activity may be either reduced or totally lost if such adsorption occurs during manufacturing, storage, or use of the final product."). Wünsch found that CCK's surface adsorption resulted in an "unpredictable loss of material" and called it "a real problem in establishing the right dosages in human medicine." MAIA1020, 504.

The problem of surface adsorption for a sincalide drug product is exacerbated by the small amount of sincalide present in the lyophilized formulation—just 5 micrograms per vial. MAIA1005, 154; MAIA1029, *1. Losing even a small amount of sincalide to surface adsorption could be detrimental to the drug's potency and biological activity. MAIA1003, ¶54.

Given the well-documented loss of potency and biological activity due to sincalide's chemical and physical instability, it is unsurprising that "***a 20% overage***

of sincalide was required in previous sincalide formulations to compensate for the limitations." MAIA1001, 1:35-37 (emphasis added). But oversupplying sincalide in the old Kinevac formulation was a crude and inefficient "fix" for sincalide's instability, especially considering the drug product was frequently in short supply nationwide due to Bracco's manufacturing troubles. MAIA1031, 16N-19N. The 20% overage of sincalide also failed to address the underlying instability. By August 2002, the scientific community already understood that adding functional excipient classes to the formulation would stabilize an unstable peptide like sincalide.

Bracco eventually updated its sincalide formulation in August 2002. MAIA1033. Bracco submitted its revamped formulation to the FDA for approval (*id*.) and submitted its patent application to the PTO for examination. Unfortunately, the examiner failed to substantively examine the patent application and it slipped through to issue as the '046 patent.

D. Stable Lyophilized Parenteral Formulations

By the time Bracco revamped its sincalide formulation and filed for the '046 patent in 2002, the knowledge and expertise for creating stable lyophilized parenteral peptide and protein drug formulations was already well-established. MAIA1003, ¶¶55-59. In 2002, one commentator declared "[o]ur understanding of the basic requirements for obtaining a stable lyophilized protein formulation is

relatively well developed." MAIA1011, 188; *id.*, 110 ("[D]eveloping stable lyophilized protein formulations should be a rational, straightforward process, which for most proteins should be rapid.); *id.* ("[A] properly lyophilized formulation can maintain adequate physical and chemical stability of the protein during shipping and long-term storage even at ambient temperatures.").

Formulators understood making stable, physiologically acceptable parenteral dosage forms required adding certain functional excipients to the formulation:

> Added substances such as antioxidants [stabilizers], buffers, bulking agents, chelating agents, antimicrobial agents, solubilizing agents, surfactants, and tonicity adjusting agents must frequently be incorporated into parenteral formulas in order ***to provide safe, efficacious, and elegant parenteral dosage forms***.

MAIA1014, 192 (emphasis added) (underlining indicates excipient classes claimed in the '046 patent independent claims).[3] These classes of excipients were ubiquitous in the literature and had been used in parenteral formulations for decades prior to 2002. *See, e.g.*, MAIA1016, 453-458 (Table I); MAIA1017, 167-169 (Tables II-VII); MAIA1003, ¶56.

[3] Claims 1 and 21 recite a surfactant/solubilizer, which would be an excipient class that acts as at least a surfactant, and may have solubilizing properties.

In 1980, Wang published a list of parenteral-administered drugs that used these classes of excipients to solve formulation problems, indicating the frequency of use for each FDA-approved compound under each excipient class. MAIA1016, 453-458, Table I. The reason Wang and others published such lists is because they understood "[t]o avoid uncertainty, most formulators tend to employ compounds used in existing parenteral products." *Id.*, 452. Nema published an update to Wang's list in 1997, explaining that "a knowledge of which excipients have been deemed safe by the FDA or are already present in marketed product provides increased assurance to the formulator that ***these excipients will probably be safe for their new drug product***." MAIA1017, 166 (emphasis added).

Certainly, a POSA understood that adding "[a]ny additive to a formulation must be justified by a clear purpose and function." MAIA1014, 192; MAIA1003, ¶58. And while the ideal formulation is the one without any excipients at all (*see* MAIA1016, 462), in 2002 a POSA would have been motivated and justified in adding well-understood functional excipients to a sincalide formulation to solve its instability problems. MAIA1003, ¶58.

As detailed below, a POSA had a clear purpose and function in adding the following excipient classes—recited in the independent claims—to a sincalide formulation in order to stabilize it: stabilizers, surfactant/solubilizer, chelator, bulking agent/tonicity adjuster, and buffer. The claimed formulation is nothing

more than a combination of known excipients for a predictable result of stability as confirmed by routine testing. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367 (Fed. Cir. 2007) ("[O]ur conclusion here relies on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation.").

1. Stabilizers

A POSA would have known to add stabilizers to the unstable, old Kinevac formulation. MAIA1003, ¶¶60-68. Antioxidants and amino acids were well-known classes of stabilizers used prior to 2002 to prevent oxidative and hydrolytic degradation of peptides and proteins. *Id.*

Antioxidants are a class of stabilizer used to successfully stabilize parenteral formulations by acting as "reducing agents or may serve as free radical scavengers" to prevent oxidation. MAIA1017, 168; MAIA1013, 154-156; MAIA1003, ¶¶61-62. Because sincalide's methionine oxidation is a major factor contributing to its instability (Section II.C.1, *supra*), a POSA would have sought to prevent such oxidation by adding antioxidants to the formulation. MAIA1013, 154-156; MAIA1003, ¶¶61-62. Antioxidants "are added to parenteral solutions either alone or in combination with a chelating agent or other antioxidants." MAIA1014, 201.

Wang and Nema listed a variety of commonly-used antioxidants in FDA approved products. MAIA1016, 455-456; MAIA1017, 168. Nema disclosed "[s]ulfite, bisulfite, and metabisulfite constitute the majority of antioxidants used in parenteral products." MAIA1017, 168. Among these, Table IV showed sodium metabisulfite was one of the most commonly used antioxidant. *Id.* Akers also reported that in protein formulations "salts of sulphurous acid (sodium bisulphite, sodium metabisulphite or sodium thiosulphate)" are among the antioxidants used most frequently. MAIA1013, 154-155; *see d.*, 155, Table 8.3. Swadesh demonstrated that stabilizing a protein in solution with sodium sulfite was "regular and predictable" and improved stability of oxidizable cystine, methionine, and tyrosine residues. MAIA1038, 398-401.

Amino acids are another class of stabilizer used to successfully stabilize protein and peptide parenteral formulations that are prone to both oxidative and hydrolytic degradation. Takruri explained that "[c]ertain amino acids and various combinations thereof and surfactants, such as polysorbate and poloxamer and the like have been used to stabilize peptide and protein compositions." MAIA1032, 2:44-47. Wang 1988 included Table II, titled "Patents Citing Amino Acids as Stabilizers," which lists over a dozen patents disclosing amino acids used as stabilizers in parenteral formulations. MAIA1019, S14. Wang 1988 also provided the specific example of arginine and lysine as stabilizers in a protein immune

globulin G formulation. *Id.*, S12 ("[A]dded arginine or lysine as stabilizers" to protein formulation); MAIA1003, ¶63.

For methionine-containing peptides such as sincalide, Sato taught adding free methionine to the formulation to prevent oxidation of the peptide's methionine residues. MAIA1007, 10.[4] The free methionine added to the formulation acts a sacrificial agent and is oxidized in place of the methionine residue in the peptide. *Id.* Sato's formulation strategy is applicable to a variety of proteins and peptides, including cholecystokinin (CCK). *Id.*, 11. A POSA would have understood that Sato's disclosure of "cholecystokinin" encompasses sincalide (i.e., CCK-8) because cholecystokinin is a family of peptides and the biological activity of CCK peptides resides in the CCK-8 C-terminal octapeptide. MAIA1003, ¶64; *see* MAIA1010, 1:18-32 (patent assigned to Bracco teaching same).

Through a series of experiments, Sato successfully confirmed that adding methionine to the G-CSF formulation inhibited the protein's methionine oxidation and improved long-term shelf stability. MAIA1007, 19 (Examples 4 and 5). Sato concluded that "the content of Met-oxidized G-CSF could be completely

[4] Sato originally published in Japanese on September 8, 2000 as PCT Publication No. WO 00/51629. *See* MAIA1006. All citations to Sato are to the certified English translation provided as MAIA1007.

suppressed by adding 0.1 mg or more of methionine." *Id.* Sato similarly showed in Example 6 that adding free methionine to a parathyroid hormone (PTH) formulation had an inhibitory effect on oxidation of PTH's methionine residues. *Id.* Sato concluded that "addition of methionine to the formulations can specifically improve exclusive[] suppression of oxidation of the protein at the methionine residues without influencing other chemical decomposition reactions." *Id.*, 20. Thus, Sato successfully inhibited methionine oxidation in two protein formulations by addition of free methionine, and did so without adverse interaction with the active compound, or other components in the formulation. *Id.*; MAIA1003, ¶65.

Other experiments in Sato demonstrated the value of adding multiple amino acids to the peptide or protein formulation. *Id.*, 11-20 (providing experimental data indicating long-term stability improvements for G-CSF and PTH formulations with the addition of amino acid combinations); MAIA1003, ¶66. Sato explained that when, in addition to methionine, "one or more *other* amino acids are added" to the formulation, the protein or peptide is stabilized "as well as inhibited from decomposition, aggregation or the like." MAIA1007 at 10 (emphasis added). Amino acids that can be added for this purpose include, among others, lysine and arginine (*id.*), which are basic amino acids. For reasons explained below, basic

amino acids were known to prevent hydrolytic degradation of sincalide's sulfated tyrosine residue.

Yagami taught that adding basic amino acids to a formulation increases stability of a sulfated tyrosine by protecting against hydrolytic degradation. MAIA1021, 247-248 ("intermolecular conjugation between sulfated peptides and highly basic peptides was [] demonstrated"); MAIA1003, ¶67. In particular, Yagami found that arginine, which has the highest-proton affinity among the 20 biologically important amino acids (MAIA1026, 3987, Table I), was effective in stabilizing CCK sulfate groups by forming conjugate acid-base pairs. MAIA1021, 248 (Arg "assume[s] a primary role in stabilizing Tyr(SO_3H) residues."). Having high proton affinity is important in stabilizing the sulfated tyrosine because protons catalyze the hydrolytic degradation. MAIA1021, 240. Like arginine, lysine is also a basic amino acid and has the second highest proton affinity behind arginine. MAIA1026, 3987, Table I. Yagami taught that lysine, though a "weaker conjugate base[]," would be useful in stabilizing peptides containing sulfated tyrosine residues. MAIA1021, 248; MAIA1003, ¶67.

Additionally, the art taught "[c]ertain amino acids can be used as cryoprotectants and/or lyoprotectants" to stabilize a lyophilized drug product. MAIA1040, 13. The '046 patent acknowledges this was known: "Amino acids ***have [] been used as stabilizers*** or co-stabilizers of peptides to: act as

cryoprotectants during freeze drying. . . ." MAIA1001, 10:42-44 (emphasis added); *Id*., 10:47-49 ("[Amino acids] can also increase the product glass transition temperature (T_g) and thereby increase process stability."). Mattern determined that lysine and arginine were among the four basic amino acids with an observable glass transition temperature (T_g) during freeze-drying. *See* MAIA1039, 201. With the increased T_g, it would have been expected that lysine and arginine would be effective lyoprotectants for sincalide during lyophilization. MAIA1040, 16; MAIA1003, ¶68.

2. Surfactants/Solubilizers

Surfactants are "surface active agents" that "reduce the concentration of proteins in dilute solutions at the air-water and/or water-solid interfaces where proteins can be adsorbed and potentially aggregated." MAIA1013, 163; *see also* MAIA1024, 194 ("surfactants appear to be effective in reducing drug binding to surfaces."); MAIA1003, ¶69. A POSA would have been motivated to include a surfactant in the sincalide formulation to prevent surface adsorption, such as adherence to the walls of a glass vial, and the resulting loss of biological activity. MAIA1013, 162 (describing loss of protein's biological activity due to adsorption); MAIA1020, 504 (reporting an "unpredictable loss of material" due to CCK and secretin surface adsorption); MAIA1003, ¶70.

Nema reported that polysorbate 80 and polysorbate 20 were the most commonly used surfactants (categorized under "Solublizing, Wetting, Suspending, Emulsifying or Thickening Agents") in parenteral drug formulations. MAIA1017, 167. Akers likewise reported that "[p]olysorbate 20 and 80 and sodium dodecyl sulphate are effective and acceptable surfactant stabilizers used in marketed protein formulations." MAIA1013, 163. Under the heading "Surfactants as Solubilizers," DeLuca explained that surfactants can also have solubilizing effects because of their "wetting properties." MAIA1014, 189. Sato disclosed use of surfactants in its formulations. MAIA1007, 8; MAIA1003, ¶¶71-72.

3. Chelators

Chelators are "added to complex, and thereby inactivate, trace amounts of metals such as copper, iron, and zinc which catalyze a variety of reactions, e.g., ***oxidation***, ***hydrolysis***, and deiodination." MAIA1016, 460 (citations omitted). Nema found that "[o]nly a limited number of chelating agents are used in parenteral products," these include DTPA (pentetic acid) and three salt forms of EDTA. *See* MAIA1017, 167-168, Table III; MAIA1003, ¶72.

Because many oxidation reactions are catalyzed by transition metals, "a proper chelating agent often ***enhances the effectiveness of [the] antioxidant***." MAIA1016, 460 (emphasis added); *see also* MAIA1017, 167-168 (chelators "serve

to complex heavy metals and therefore can improve the efficacy of antioxidants or preservatives.").

Li reported that when formulating the methionine-containing protein NESP, adding methionine and other stabilizing agents provided a more stable formulation, even in extreme conditions. MAIA1018, ¶[0011]. Although the presence of methionine alone reduced the oxidation of NESP's Met-54 residue, the combination of methionine with a chelator (EDTA) "was more effective in inhibiting the oxidation than individual additives." *Id.*, ¶¶[0048]-[0049], Fig. 3; MAIA1036, 191 (demonstrating prevention of methionine oxidation on BDNF protein by addition of EDTA); MAIA1037, 688 (same); MAIA1003, ¶¶73-74. Sato also disclosed use of chelating agents in its formulations. MAIA1007, 9.

4. Bulking agents/tonicity adjusters

For lyophilized drug products in which the active ingredient is offered in a relatively small quantities like sincalide (formulated with only 5 micrograms), a bulking agent is needed to provide solid content, or "bulk," to the finished drug product. MAIA1014, 218; MAIA1003, ¶¶75-76. The old Kinevac formulation employed sodium chloride as a bulking/tonicity agent. MAIA 1029, 1. Mannitol is the most commonly used bulking agent in freeze-dried formulations. MAIA1013, 158. Mannitol was known to act as both a bulking agent and tonicity modifier in parenteral formulations. MAIA1011, 126. Sato disclosed the use of

tonicity agents in its formulations, with mannitol being especially preferred. MAIA1007, 8. Thus, a POSA would have been motivated to use a bulking agent/tonicity adjuster, such as mannitol, in a stable sincalide formulation. MAIA1003, ¶¶75-76.

5. Buffers

Buffers are added to parenteral formulations to provide pH stability. MAIA1014, 195 ("[B]uffers are added to many products to resist change in pH."); MAIA1003, ¶77. "For simple peptides, consideration should be given to identifying a pH at which overall degradation reactions are minimal." MAIA1019, S22. As explained above, sincalide is prone to hydrolytic degradation of its sulfated tyrosine residue under acid conditions. Section II.C.1.a, *supra*. MAIA1003, ¶¶40-43. Sato disclosed the use of buffers in its formulations. MAIA1007, 9. Thus, a POSA would have been motivated to add a buffer to a sincalide formulation to maintain the formulation pH above acidic conditions, preferably near neutral pH. MAIA1003, ¶77.

A POSA understood that a suitable buffer system "should have an adequate buffer capacity to maintain the pH of the product at a stable value during storage, while permitting the body fluids to adjust the pH easily to that of the blood following administration." MAIA1014, 195. "Phosphate, citrate, and acetate are the most common buffers used in parenteral products." MAIA1017, 168; *see also*

MAIA1014, 197 (noting acetates, citrates, phosphates, and glutamates are buffer systems commonly used for injectable products). Phosphate buffers were demonstrated to have no adverse effects on the stability of sulfated phenols, and thus would have been suitable buffers for sincalide with its sulfated tyrosine residue. MAIA1034, 3853-3854, Fig. 2, Fig. 3, and Table II (indicating successful use of 0.01 M KH_2PO_4 and K_2HPO_4 buffer in nitrophenyl sulfates across pH range of 4-11). MAIA1003, ¶78.

The prior art taught using the claimed excipient classes to solve the chemical and physical instability problems plaguing the old Kinevac formulation. MAIA1003, ¶79. Using the claimed excipient classes to develop a stable, physiologically acceptable sincalide formulation was "nothing more than routine application of a well-known problem-solving strategy, . . . the work of a skilled artisan, not an inventor." *Coalition For Affordable Drugs II LLC v. NPS Pharmaceuticals, Inc.*, IPR2015-00990, Paper 68 at 28 (PTAB Oct. 21, 2016) (*quoting Pfizer*, 480 F.3d at 1368).

E. Person of Ordinary Skill in the Art ("POSA")

A POSA is a hypothetical person of ordinary creativity who is presumed to be aware of all pertinent prior art. A POSA in the technical field of the '046 patent would have had knowledge of the scientific literature concerning methods of formulating stable peptide compositions. MAIA1003, ¶¶23-27.

Here, a POSA would typically have had (i) a Ph.D. in Chemistry, Biochemistry, or Pharmaceutical Chemistry, or in a related field in the chemical sciences, and have at least about two years of experience in formulating peptide or protein pharmaceutical compositions; or (ii) a Master's degree in the same fields with at least about five years of the same experience. MAIA1003, ¶24. Also, a POSA may have worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but of others on the team, including, for example a molecular biologist and a clinician specializing in hepatobiliary imaging. *Id.*, ¶24.

III. THE '046 PATENT

A. The '046 Patent Specification

The '046 patent purports to solve the known stability, potency, and overage issues of the old Kinevac formulation by selecting excipients "that provide certain desired functions." MAIA1001, 3:30-37. The '046 patent then lists categories of excipients that were well-known and commonly used to address the stability problems associated with parenteral protein and peptide formulations. MAIA1003, ¶80. To illustrate, the '046 patent includes the following headings:

- "Chelators" (9:20)
- "Buffering Agents" (9:41)
- "Stabilizers" (10:10)
    - "Antioxidants/Reducing Agents" (10:23)

- "Amino Acids" (10:42)

- "Cryoprotectants/Lyoprotectants" (11:5)
- "Surfactants/Solubilizers/Surface Active Agents" (11:26)
- "Bulking Agents/Tonicity Adjustors" (11:64) and
- "Other Excipients" (12:15).

Under each heading, Bracco provides a simple explanation of each excipient class and a laundry list of excipients that were to known fulfill the desired function. These excipient classes reflect nothing more than the common knowledge in the prior art, and track exactly the excipient classes that the prior art literature instructed a formulator to use in stabilizing parenteral formulations. Section II.D, *supra*; MAIA1003, ¶81. The remainder of the '046 patent provides examples of routine experimentation which show that the functional excipients performed as expected in sincalide formulations. *Id.* Dr Schöneich provides a table summarizing the admissions in the '046 patent. MAIA1003, ¶93.

Under the heading "**Chelators,**" the '046 patent explains what was known in the art, that "[e]xcipient impurities and/or stopper extractables can introduce trace metals into pharmaceutical formulations" and that "[s]incalide contains two methionine residues (Met 3 and Met 6) that are susceptible to oxidation by free metals." MAIA1001, 9:20-23. To address this known problem, the '046 patent describes adding either of two well-known "preferable" chelating agents, pentetic

acid (DTPA) and edetic acid (EDTA). *Id.*, 9:26-27. Example 2 describes experiments showing the effects of DTPA as a chelator. *Id.*, 18:16-19:51. These experiments show nothing more than the expected result, that the well-known chelator DTPA was effective at inhibiting oxidation of Met 3 and Met 6 residues. MAIA1003, ¶82.

Under "**Buffering Agents**," the '046 patent states that "Buffering agents are employed to stabilize the pH of sincalide formulations of the invention, and consequently, reduce the risk of chemical [in]stability at extreme pH values." MAIA1001, 9:45-47. The '046 patent states that no pH-dependent related trends in sincalide recovery were observed within the pH range of 5.5-8.5. The '046 patent lists a preferred pH range of 6.0-8.0. *Id.*, 10:8-9; MAIA1003, ¶83.

The '046 patent describes two experiments "to determine the effect of pH on the chemical stability of sincalide." *Id.*, 16:47-48. The '046 patent describes the well-known degradation pathways of peptides and proteins—"chemical instability, or degradation, may be caused by, for example, ***oxidation***, reduction, deamidation, ***hydrolysis***, imide formation, racemization, isomerization, and/or β-elimination." *Id.*, 16:48-51 (emphasis added). The only buffer studied was dibasic potassium phosphate. *Id.*, 16:52-67. The '046 patent concludes that phosphate is the buffering agent of choice due to its lack of interaction with sincalide, and an ideal buffering capacity in the physiological pH range. *Id.*, 17:18-20.

Under "**Stabilizers,**" the '046 patent recognizes sincalide's known instability at the methionine residues, and states "based on the potential for oxidation of this peptide, it was necessary to identify functional additives for peptide stabilization." *Id.*, 10:20-22; MAIA1003, ¶85. Then, the '046 patent includes two subsections describing different categories of known stabilizers: "Antioxidants/Reducing Agents" and "Amino Acids." *Id.*, 10:23-11:4.

Under the subheading "**Antioxidants/Reducing Agents**," the '046 patent lists well known antioxidants and reducing agents which can stabilize protein and peptide formulations through well-known mechanisms. *Id.*, 10:23-41. The preferred antioxidant stabilizer listed is sodium metabisulfite (*id.*, 10:39-40), which is one of the most commonly-used antioxidant in parenteral formulations. MAIA1017, 168; MAIA1013, 154; MAIA1003, ¶86. Example 4 only confirmed what a POSA would have anticipated—that sodium metabisulfite improved sincalide recovery and inhibited sincalide oxidation. MAIA1001, 24:15-18; MAIA1003, ¶86. Example 4 also confirmed a POSA's expectation that the antimicrobial agents benzalkonium chloride and benzethonium chloride would not have had the same stabilizing effect. *Id.*, 23:10-15; MAIA1003, ¶86.

Under the subheading "**Amino Acids**," the '046 patent admits that "[a]mino acids have also been used as stabilizers or co-stabilizers of peptides to: act as cryoprotectants during freeze drying, stabilize against heat denaturation, inhibit

aggregate formation, improve solubility or rehydration, inhibit isomerization, reduce surface adsorption, or act as chelating agents." MAIA1001, 10:42-47. The '046 patent notes the well-known problem of "reduced potency [as] a result of surface adsorption/denaturation resulting from exposure of sincalide to air, and yielding degradants via oxidation" and "thermal stress during lyophilization result[ing] in degradation and reduced recovery of sincalide." *Id.*, 31:8-13; MAIA1003, ¶87.

The '046 patent describes adding methionine to improve the processing stability of sincalide by "being preferentially oxidized." *Id.*, 31:28-31. The experimental results show the predictable outcome that adding methionine to a formulation improved sincalide recovery. *Id.*, 32:17-22. The '046 patent also describes adding lysine and arginine as stabilizers for a lyophilized formulation. *Id.*, 32:48-55, 33:23-25.

Under "**Cryoprotectants/Lyoprotectants**," the '046 patent states the well-known fact that cryoprotectants/lyoprotectants can provide stability by affecting the glass transition temperature (T_g) of a formulation to be lyophilized. *Id.*, 11:6-11. Lysine and arginine are the preferred cryoprotectants/lyoprotectants. *Id.*, 11:24-25; MAIA1003, ¶89.

Under "**Surfactants/Solubilizers/Surface Active Agents**," the '046 patent indicates "[t]o minimize sincalide degradation associated with surface adsorption,

surfactants are added as formulation excipients in bulk and lyophilized formulations of sincalide." MAIA1001, 20:5-9. The '046 patent lists standard, well-known surfactants as preferred "surfactants/solubilizers," and lists the commonly used TWEEN® 20 as the most preferred surfactant in the invention. *Id.*, 11:51-63. Example 3 of the '046 patent tests the effects of surfactants in formulations. The experiments tested sincalide recovery of sincalide with and without TWEEN® 20 and TWEEN® 80. *Id.,* 20:26-22:42. The experiments show that the surfactants TWEEN® 20 and 80 performed as expected, improving sincalide recovery. MAIA1003, ¶90.

Under "**Bulking Agents/Tonicity Adjusters**," the '046 patent recognizes that due to "the small amount" of sincalide in the formulation, "bulking agents/tonicity adjusters are useful to provide structure and support for the active ingredient, sincalide, as well as to provide tonicity." *Id.*, 11:65-12:1. The '046 patent admits that "[b]ulking agents/tonicity adjusters (also called lyophilization aids) useful in the preparation of lyophilized products of the invention ***are known in the art***, and include mannitol, lactose, potassium chloride, sodium chloride, maltose, sucrose" and others. *Id.*, 12:2-12 (emphasis added). Of those bulking agents/tonicity adjustors known in the art, the '046 patent identifies the common bulking agent mannitol as the most preferred bulking agent/tonicity adjustor. *Id.*, 12:12-14; MAIA1003, ¶91.

The ’046 patent describes routine experiments that simply confirmed what was already known—that “[m]annitol, a common excipient for freeze-dried pharmaceuticals” was often used in lyophilized formulations “because of the high melting temperature of the mannitol/ice eutectic mixture (about -1.5° C) and its tendency to crystallize from frozen aqueous solutions.” *Id.*, 27:50-28:3. The ’046 patent also describes further experiments which were conducted merely to “optimize the mannitol concentration and lyo-cycle time.” *Id.*, 28:45-47; MAIA1003, ¶92.

Finally, under the heading “**Other Excipients**,” the ’046 patent lists other classes of excipients which “may optionally be used” in the formulation, including preservatives, osmolality adjustors, lyoprotectants, solubilizers, tonicity adjusters, cake forming agents, complexing agents, and dissolution aids. *Id.*, 12:15-21. The specification assigns no criticality to any of these excipients. This section also lists 13 different prior art publications related to parenteral formulations that contain “[a] listing of various excipients that can be used in sincalide formulations for parenteral administration.” *Id.*, 12:21-63.

B. The Independent Claims

The challenged independent claims all recite the same sincalide formulation containing the same functional classes of excipients. Claim 1 is representative:

A stabilized, physiologically acceptable formulation of sincalide comprising:

(a) an effective amount of sincalide,

(b) at least one stabilizer,

(c) a surfactant/solubilizer[5][,]

(d) a chelator,

(e) a bulking agent/tonicity adjuster, and

(f) a buffer.

MAIA1001, 37:41-49. Other independent claims differ only immaterially from claim 1: claim 21 recites a method of making the formulation by mixing the excipients; claim 40 recites a kit containing the formulation; claim 77 recites a method for imaging by administering the formulation, along with an imaging agent; and claim 104 recites a method for imaging by administering the formulation.

C. The Dependent Claims

The majority of the '046 patent dependent claims simply reflect specific chemical compounds a POSA would have selected for various of the functionally-claimed excipients classes recited in the independent claims. For example, claims 3, 23, 41, and 87 depend from their respective independent claims and recite that

[5] Claims 1 and 21 recite "a surfactant/solubilizer," whereas claims 40 and 104 recite "a surfactant."

the claimed buffer is selected from among 31 different compounds or classes of compounds. Similarly, claims 6, 26, 44, and 90 depend from their respective independent claims and recite that the surfactant is selected from among 16 different compounds or classes of compounds.

Other dependent claims in the '046 patent simply recite the obvious method of administering the formulation (claims 19 and 78, respectively reciting the formulation "is suitable for parenteral formulation" and "is administered by injection"). Still other dependent claims recite using known imaging agents (claims 81 and 82, respectively reciting "a ^{99m}Tc-IDA (Iminodiacetic acid) analog" and "^{99m}Tc-mebrofenin") or using known imaging devices (claim 85 reciting "a gamma camera").

D. Prosecution History

The prosecution history of the '046 patent is relatively short, having passed through the Patent Office without serious examination. *See* MAIA1002.

The '046 patent issued from U.S. Application No. 10/222,540 (the '540 application), filed on August 16, 2002. The '540 application was filed with 108 claims. MAIA1002, 64-79. On August 1, 2003, a restriction requirement was issued which required election between three inventions. *Id.*, 97. Following a telephone interview on August 25, 2003, the Examiner agreed to withdraw the restriction requirement as between two of the claim groups. *Id.*, 102-103.

On October 3, 2003, a Notice of Allowance was mailed in which the withdrawn claims were rejoined. *Id.*, 105. The Notice of Allowance included a Statement of Reasons for Allowance, identifying the closest prior art as Wang (US 5,011,678), and noting that the sincalide composition of Wang "does not contain additional ingredients as claimed by application such as a stabilizer, surfactant/solubilizer or chelator." *Id.*, 111.

On December 19, 2003, Applicant filed an RCE with an IDS listing 9 patent documents and 26 non-patent literature references. *Id.*, 114-117. On July 27, 2004, the Patent Office mailed a second Notice of Allowance which incorporated the statement on Reasons for Allowance from the October 3, 2003 Notice of Allowance. *Id.*, 122-127. The '046 patent issued on October 12, 2004.

IV. CLAIM CONSTRUCTION

Petitioner has considered the claim terms according to their plain and ordinary meanings, consistent with the specification. Petitioner does not believe that any claim construction is necessary. However, in the event Bracco raises proposed constructions of any claim terms, Petitioner reserves the right to respond to such proposed constructions.

V. STATEMENT OF PRECISE RELIEF REQUESTED

Petitioner requests that claims 1-19, 21-38, 40-55, 77-102, 104, 105 be cancelled for the following reasons:

A. Grounds

Ground 1. Claims 1-4, 6-11, 13, 15, 16, 19, 21-24, 26-31, 33, 35, 36, 40-42, 44-49, 51, 53, 55, and 104 are unpatentable under 35 U.S.C. § 103(a) in view of the Physicians' Desk Reference ("PDR") in combination with Sato.

Ground 2. Claims 5, 12, 14, 17, 18, 25, 32, 34, 37, 38, 43 50, 52, and 54 are unpatentable under 35 U.S.C. § 103(a) in view of the PDR in combination with Sato and Nema.

Ground 3. Claims 77-88, 90-95, 97, 99, 100, and 105 are unpatentable under 35 U.S.C. § 103(a) in view of the PDR in combination with Sato and Essentials of Nuclear Medicine Science ("ENMS").

Ground 4. Claims 89, 96, 98, 101, and 102 are unpatentable under 35 U.S.C. § 103(a) in view of the PDR in combination with Sato, ENMS, and Nema.

Additional support for this Petition is included in the Declaration of Christian Schöneich, Ph.D. MAIA1003. Dr. Schöneich received his Ph.D. in Chemistry from the Technical University Berlin, Germany in 1990 and is currently the Takeru Higuchi Distinguished Professor for Bioanalytical Chemistry and Chair of the Department of Pharmaceutical Chemistry at The University of Kansas. *Id.* ¶¶8-10. Dr. Schöneich focuses his research on peptide and protein stability, specifically the mechanisms of oxidation and free radical reactions. *Id.* ¶13.

B. Status of References as Prior Art

The PDR, Sato, Nema, and ENMS are prior art to the '046 patent under § 102(b) because they were published in 1977, 2000, 1997, and 1987, respectively, all of which were published more than one year before the earliest priority date of the '046 patent, August 16, 2002.

VI. THE CHALLENGED CLAIMS ARE UNPATENTABLE

A. Ground 1: Claims 1-4, 6-11, 13, 15, 16, 19, 21-24, 26-31, 33, 35, 36, 40-42, 44-49, 51, 53, 55, and 104 Are Unpatentable as Obvious Over the PDR in Combination with Sato

1. Overview of the PDR

The Physicians' Desk Reference ("PDR") is a published compilation of prescribing information (i.e., package inserts) for prescription drugs. The 1977/78 PDR entry for sincalide describes the two-ingredient drug product that Squibb first marketed in the 1970s and Bracco acquired rights to in the 1990s. MAIA1005, 154; MAIA1033, 39.

2. Overview of Sato

The primary protein described in Sato is G-CSF (granulocyte colony-stimulating factor), which, like sincalide suffers from physical and chemical instability unless appropriately formulated. MAIA1007, 4. Like sincalide, G-CSF contains methionine residues susceptible to oxidation. *Id.* Also like sincalide, G-

CSF is employed "in extremely small quantit[ies]" and similarly suffers from surface adsorption. *Id.*

As shown below, Sato disclosed all excipient classes recited in the challenged independent claims. Sato's use of these excipients was successful in stabilizing G-CSF formulations, "showing little loss of the active ingredient even after long-term storage" and exhibiting low methionine oxidation. *Id.* Sato disclosed using excipients to stabilize lyophilized peptide and protein formulations suffering from chemical and physical instability, thereby maintaining the drug's biological activity and potency even after long-term storage. *Id.*

Sato expressly disclosed using these excipients to stabilize other "physiologically active peptides," including "cholecystokinin." *Id.*, 11. Sincalide is a physiologically active cholecystokinin peptide, and therefore Sato's disclosure encompasses sincalide formulations. *See* Section II.A, *supra*; MAIA1003, ¶33-35, 98. Thus, a POSA would have relied on Sato and a POSA's general knowledge of the art to develop a sincalide formulation that solves sincalide's known stability problems; Sato successfully solved the same stability problems in G-CSF, and also expressly applied the teachings to cholecystokinin peptides, such as sincalide. *Id.* Accordingly, a POSA would have been motivated to apply the teachings of Sato to the sincalide formulation taught in the PDR, and would have had a reasonable expectation of success in doing so. *Id.*

3. Independent Claim 1

The preamble to claim 1 recites, "A stabilized, physiologically acceptable formulation of sincalide." As set forth below, a stabilized, physiologically acceptable formulation of sincalide would have been the obvious and direct result of the prior art's instructions to add functional excipient classes to an unstable formulation, such as the old Kinevac formulation. MAIA1003, ¶100.

a. An Effective Amount of Sincalide

The PDR disclosed an effective amount of sincalide. MAIA1005, 154; MAIA1003, ¶101. The PDR specifically disclosed that Kinevac is provided as a "lyophilized, white powder of the synthetic C-terminal octapeptide of cholecystokinin" and that "[e]ach vial provides 5 mcg. sincalide with 45 mg. sodium chloride as a carrier." MAIA1005, 154. The PDR instructed one to reconstitute the lyophilized powder with "5 ml. of Sterile Water for Injection U.S.P." *Id.* The PDR then instructed one to inject intravenously "a dose of 0.02 mcg. sincalide per kg" in order to stimulate "prompt contraction of the gallbladder." *Id.* The 5 micrograms of sincalide disclosed in the PDR is "an effective amount of sincalide," and is also the amount used in Bracco's updated Kinevac formulation. MAIA1033, 15 ("5 μg/vial").

Sato likewise expressly disclosed that the "physiologically active peptides" of its invention include cholecystokinin. MAIA1007, 11. As explained above, the

term "cholecystokinin" was, and is, understood by a POSA to include various forms of cholecystokinin, including sincalide (CCK-8). Section II.A, *supra*.

It therefore would have been obvious to develop a stabilized, physiologically acceptable formulation of sincalide that contains an effective amount of sincalide. MAIA1003, ¶¶101-103.

b. At Least One Stabilizer

The '046 patent recognizes what was already known in the art—that sincalide's instability is due in part to its easily oxidizable methionine residues. MAIA1001, 10:12-15 ("Methionine has been identified as one of the most easily oxidizable amino acids."). It was well known before Bracco filed for the '046 patent that sincalide suffers from both oxidation of its methionine residues *and* hydrolysis of its sulfated tyrosine residue. *See* MAIA1020, 503 (attributing sincalide's instability and loss of biological activity to two main factors: (1) "facile hydrolysis of the tyrosine-O-sulfate moiety" and (2) "strong tendency of the two methionine residues to oxidize."); Section II.C.1, *supra*. Thus, a POSA would have been motivated to include stabilizers in a sincalide formulation to prevent oxidative and hydrolytic degradation of the sincalide molecule. MAIA1003, ¶¶104-110. Amino acids and antioxidants were well-known classes of stabilizers available prior to 2002 that would have been obvious to use in preventing sincalide's oxidative and hydrolytic degradation. Section II.D.1, *supra*.

Sato disclosed adding amino acids as stabilizers to prevent oxidative degradation of peptides and proteins. MAIA1007, 2. In particular, Sato disclosed adding free methionine to formulations of a methionine-containing peptide, such as sincalide, to "suppress[] the formation of the methionine-oxidized variant." *Id.* Sato also disclosed adding other amino acids, including lysine, histidine, arginine, and others, to peptide and protein formulations to further stabilize the formulations. *Id.*, 5. Sato found that adding a combination of amino acids resulted in high recovery "even after long-term storage." *Id.*; MAIA1003, ¶105.

Moreover, amino acids have been used as lyoprotectants and/or cryoprotectants to stabilize lyophilized peptide formulations, such as those disclosed in Sato. MAIA1040, 13; MAIA1039, 201; MAIA1003, ¶106. The '046 patent admits that using amino acids as stabilizers was known in the art: "Amino acids ***have [] been used as stabilizers*** or co-stabilizers of peptides to: act as ***cryoprotectants*** during freeze drying. . . ." MAIA1001, 10:42-44 (emphasis added).

Furthermore, basic amino acids, such as arginine and lysine, were known to stabilize sincalide against hydrolytic degradation of its sulfated tyrosine residue. *See* MAIA1021, 247-248 (demonstrating that arginine and lysine are effective in stabilizing CCK's sulfated tyrosine against hydrolysis). Sato taught that arginine and lysine would be used in peptide and protein formulations, including

cholecystokinin, to stabilize the drug product. MAIA1007, 6, 11; MAIA1003, ¶107.

Sato also disclosed adding antioxidants as stabilizers to prevent oxidative degradation of peptides and proteins:

> Antioxidants include erythorbic acid, dibutylhydroxytoluene, butylhydroxyanisole, α-tocopherol, tocopherol acetate, L-ascorbic acid and salts thereof, L-ascorbyl palmitate, L-ascorbyl stearate, ***sodium bisulfite***, sodium sulfite, triamyl gallate, propyl gallate or chelating agents such as disodium ethylenediamine tetraacetate (EDTA), sodium pyrophosphate, or sodium metaphosphate.

MAIA1007, 9. Antioxidants were known to stabilize peptide formulations prone to oxidation by removing the oxidants and free-radicals in the formulation that initiate oxidation of sincalide's methionine residues. *See* MAIA1017, 168; MAIA1013, 154-156; MAIA1003, ¶108. Akers reported that in protein formulations "salts of sulphurous acid (sodium bisulphite, sodium metabisulphite or sodium thiosulphate)" are among the antioxidants used most frequently. MAIA1013, 154-155; *see id.*, 155, Table 8.3.

A POSA would have had a reasonable expectation of success in using stabilizers to stabilize a sincalide formulation against oxidative and hydrolytic degradation. MAIA1003, ¶109. For example, Sato provided experimental data showing "[m]arked improvement in long-term storage stability" for G-CSF

formulations by adding various amino acids as stabilizers. MAIA1007, 18-19. Moreover, Sato concluded the experimental data indicates "addition of methionine to the formulations can specifically improve exclusively suppression of oxidation of the protein at the methionine residues ***without influencing other chemical decomposition reactions***." *Id.*, 20 (emphasis added). That is, free methionine in the formulation prevented oxidation at the methionine residue, and importantly, did not negatively influence the active ingredient or other formulation components. *Id.*; MAIA1003, ¶109.

Furthermore, Swadesh successfully demonstrated that the antioxidant, sodium sulfite, was "regular and predictable" in its protection of a protein against oxidation in solution and it improved the stability of oxidizable amino acids cystine, methionine, and tyrosine in the protein. MAIA1038, 398-401. Thus, a POSA would have had a reasonable expectation of success in using an antioxidant to stabilize a sincalide formulation. *Id.*; MAIA1003, ¶110.

c. A Surfactant/Solubilizer

Prior to 2002, it was known that sincalide is susceptible to surface adsorption, e.g., adsorption to the inner wall of a glass vial, when reconstituted as a liquid formulation, resulting in loss of biological activity. Section II.C.2, *supra* (describing sincalide's physical instability due to surface adsorption); MAIA1020, 503-504; MAIA1003, ¶111. Sato disclosed that G-CSF, like sincalide, "is

employed in extremely small quant[ities]" and it "tends to be adsorbed on the wall of the container, such as for example the injection ampoule or syringe." MAIA1007, 4. A POSA would have been motivated to add a surfactant/solubilizer to a sincalide formulation to prevent surface adsorption of sincalide to the container. Section II.D.2, *supra*; MAIA1003, ¶¶111-113.

Sato disclosed adding surfactants to the formulations of its invention, and disclosed that preferred surfactants are non-ionic surfactants, most preferably polysorbate 20 and 80. MAIA1007, 9. Non-ionic surfactants act as solubilizers for small quantity compounds like sincalide and G-CSF that tend to adsorb to surfaces. *See* MAIA1014, 189; MAIA1003, ¶112.

Sato demonstrated successful use of polysorbate 20, a non-ionic surfactant, in Samples 1-36, where each sample also contained the protein G-CSF, amino acids as stabilizers, mannitol as a bulking agent/tonicity adjuster, and a phosphate buffer. *See* MAIA1007, 11-16. In view of Sato's disclosure, a POSA would have had a reasonable expectation of success in adding a surfactant/solubilizer disclosed in Sato to a sincalide formulation to prevent sincalide's physical instability due to surface adsorption. *Id.*; MAIA1003, ¶113.

d. A Chelator

It was known prior to 2002 that oxidation of sincalide's methionine residues is initiated, in part, by exposure of the peptide to trace metals in the formulation.

MAIA1013, 153; MAIA1014, 200; Section II.C.1.b, *supra*; MAIA1003, ¶114. The '046 patent admits this: "Excipient impurities and/or stopper extractables can introduce trace metals in pharmaceutical formulations" and "[s]incalide contains two methionine residues (Met 3 and Met 6) that are susceptible to oxidation by free metals." MAIA1001, 9:21-24. By 2002, it was also well known that chelating agents serve to complex metals and eliminate them as oxidants, thereby improving efficacy of antioxidants in the formulation. MAIA1016, 460; MAIA1017, 168; Section II.D.3, *supra*. Thus, a POSA would have been motivated to add a chelator to a sincalide formulation to complex the trace metals and aid stabilizers (e.g., antioxidants) in preventing oxidation of sincalide's methionine residues. MAIA1003, ¶114.

Sato disclosed using EDTA as a chelating agent in its formulations. MAIA1007, 9. Li also taught the addition of both a chelator (EDTA) and free methionine to a formulation of methionine-containing NESP, and disclosed that the combination EDTA and methionine was more effective in inhibiting oxidation of the methionine residue on the protein than using free methionine alone. MAIA1018, ¶¶[0048]-[0049], Fig. 3; MAIA1036, 191; MAIA1037, 688. Thus, a POSA would have had a reasonable expectation of success in using a chelator as disclosed in Sato in stabilizing a methionine-containing peptide, such as sincalide. MAIA1003, ¶115.

e. A Bulking Agent/Tonicity Adjuster

The PDR disclosed that sincalide is formulated in small quantities of 5 micrograms of the active ingredient with 45 mg of sodium chloride "as a carrier" (i.e., bulking agent). MAIA1005, 154. When reconstituted, each mL of the sincalide solution contained 9 mg of sodium chloride, which results in an isotonic solution. *Id.* Sincalide by itself would not provide the solid content or tonicity necessary for a finished drug product; thus, as explained above in Section II.D.4, a POSA would have been motivated to include a bulking agent to the formulation to provide the necessary "solid content" or "bulk" to the finished drug product, or to render the product isotonic. *See* MAIA1014, 218; MAIA1003, ¶116. Mannitol is the most commonly used bulking agent in freeze-dried formulations. MAIA1013, 158. It serves as both a bulking agent and a tonicity modifier in parenteral formulations. MAIA1011, 126.

Sato disclosed that G-CSF, like sincalide, "is employed in extremely small quant[ities]." MAIA1007, 4. Sato teaches adding "diluents" (i.e., bulking agents) to the disclosed formulations (MAIA1007, 9) and specifically disclosed mannitol as a preferred isotonizing agent. *Id.*, 8; MAIA1003, ¶117. Sato demonstrated successful use of mannitol as a bulking agent/tonicity adjuster in Samples 1-36, where each sample also contained the protein G-CSF, amino acids as stabilizers, polysorbate 20 as a surfactant/stabilizer, and a phosphate buffer. MAIA1007, 11-

16. In view of Sato's disclosure, a POSA would have had a reasonable expectation of success in adding mannitol as a bulking agent/tonicity adjuster to a stabilized, physiologically acceptable formulation of sincalide. *Id.*; MAIA1003, ¶118.

f. A Buffer

Prior to 2002, a POSA knew that a buffer would need to be added to an unstable parenteral formulation to establish pH stability. MAIA1014, 195; Section II.D.5, *supra*; MAIA1003, ¶119. This holds true for sincalide, which is prone to hydrolytic degradation of its sulfated tyrosine residue under acid conditions. MAIA1021, 240 (explaining "[i]t is well known that Tyr(SO_3H) residues tend to rapidly desulfate to Tyr under acidic conditions."); Section II.C.1.a, *supra*; MAIA1003, ¶119. Thus, a POSA would have been motivated to add a buffer to a sincalide formulation to maintain the formulation pH above acidic conditions, preferably near neutral pH, in consonance with blood pH upon injection of the formulation. MAIA1003, ¶119.

Sato disclosed using a buffer in the stabilized protein and peptide formulations. MAIA1007, 9. Sato disclosed that its lyophilized formulations are prepared by first dissolving the disclosed excipients "in an aqueous buffer known in the art of solution formulations such as ***phosphate buffers***," then "***lyophilizing*** or spray drying a thus prepared solution formulation by standard procedures." *Id.* Phosphate, citrate, and acetate buffers are the most commonly used buffers in

parenteral formulations. MAIA1017, 168. Among these, a POSA would have selected a phosphate buffer for the sincalide formulation because of its effective buffering range around its pKa of 7.2. MAIA1014, 198. Figure 11 of DeLuca showed the effective range of several common pharmaceutically acceptable buffers, including phosphate:

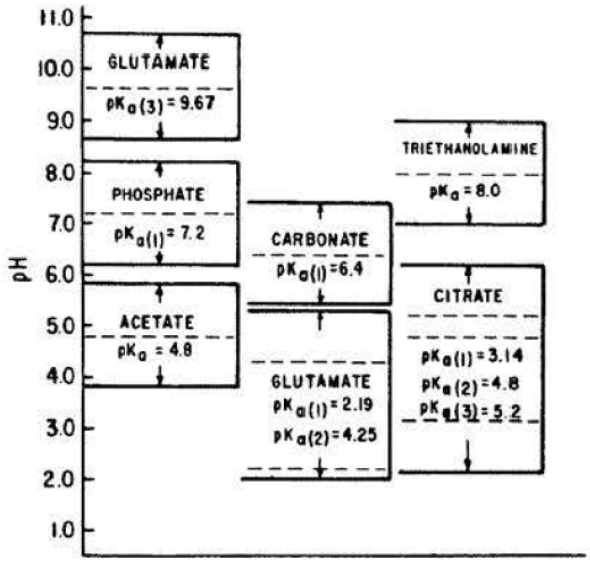


Figure 11 Effective range of pharmaceutical buffers, indicated by the arrows The dashed line represents the pK_a values.

MAIA1014, 198. The figure shows that phosphate is effective as a buffer in the range of approximately 6-8. *Id.*; *see id.,* 194 (Table 5, listing the pH buffering range of phosphoric acid salts as 6.0-8.2); MAIA1003, ¶¶120-121.

Furthermore, Sato provides experimental data showing successful use of a phosphate buffer at pH 7.4 or 6.5 in Samples 1-36 for G-CSF formulations and in Samples 37-39 for PTH formulations. MAIA1007, 11-20. Thus, a POSA would

have understood that a phosphate buffer would have provided the needed pH stability in a sincalide formulation without negatively affecting oxidation of sincalide's methionine residue. *Id.*; MAIA1003, ¶122. Indeed, phosphate buffers had no adverse effect on the stability of sulfated phenols, and thus would have been suitable buffers for a sincalide formulation and would not have adversely affected sincalide's sulfated tyrosine residue. MAIA1034, 3853-3854, Fig. 2, Fig. 3, and Table II (indicating successful use of 0.01 M KH_2PO_4 and K_2HPO_4 buffer in nitrophenyl sulfates across pH range of 4-13); MAIA1003, ¶122. Thus, a POSA would have had a reasonable expectation of success in using a phosphate buffer to stabilize the pH of a sincalide formulation. MAIA1003, ¶122.

For the reasons above, a POSA would have been motivated to add excipients from the claimed excipient classes recited in claim 1 to a sincalide formulation. MAIA1003, ¶123. Moreover, a POSA would have had a reasonable expectation of success in developing a stabilized, physiologically acceptable sincalide formulation using these excipient classes. *Id.*

4. Independent Claim 21

Claim 21 recites a method of making the formulation (rather than the formulation itself), but otherwise differs from claim 1 only by reciting "the step of mixing" the excipients and reciting "(f) an aqueous solution."

For the reasons explained above with respect to claim 1, it would have been obvious to a POSA to develop a sincalide formulation containing the claimed classes of excipients. Section VI.A.3, *supra*. Furthermore, it would have been obvious to a POSA to mix the claimed sincalide formulation in an aqueous solution prior to either filling into vials and/or lyophilization. MAIA1003, ¶¶125-126. Sato, for example, disclosed preparing the formulations "by dissolving these components in an ***aqueous buffer***." MAIA1007, 9 (emphasis added). In the Examples, Sato also disclosed that the "***[f]ormulated solutions*** containing various components" were "prepared and ***aseptic-filtered***, and then precisely 1 mL each was aseptically packed in a vial and lyophilized." *Id.*, 11 (emphasis added). Thus, Sato disclosed a method of making the formulated solution by dissolving the excipients in an aqueous buffer and then filtering the solution before lyophilization; such dissolution and filtering the aqueous solution involves mixing the excipients in the formulation. *Id.*, 9, 11; MAIA1003, ¶126.

5. Independent Claim 40

Claim 40 differs from claim 1 by reciting a kit comprising a powder mixture of the same formulation recited in claim 1, and by also reciting "(ii) a container to hold said powder mixture" and "(iii) optionally, a physiologically acceptable fluid."

For the reasons explained above with respect to claim 1, it would have been obvious to a POSA to develop a sincalide formulation containing the claimed classes of excipient. Section VI.A.3, *supra*. Furthermore, it would have been obvious to lyophilize the formulation and store the powdered mixture in a vial, as a kit. MAIA1003, ¶129. The PDR disclosed that the old Kinevac formulation was formulated as a lyophilized powder of sincalide and sodium chloride, which was stored in a container, i.e., a vial. MAIA1005, 154. Sato likewise disclosed lyophilizing its disclosed formulations and storing the resulting powder in vials. MAIA1007, 9, 11.

Claim 40 recites that the "physiologically acceptable fluid" is an optional limitation; it therefore need not have been disclosed in the prior art for the claim to be held unpatentable. Even so, it would have been obvious to include such a fluid in the claimed kit. The PDR disclosed that the lyophilized powder is reconstituted with 5 mL of water prior to administration. MAIA1005, 154. The package insert for the old formulation of Kinevac disclosed that reconstituted sincalide solutions may be further diluted in a physiologically acceptable fluid (Sodium Chloride Injection USP, 0.9%) for infusion. MAIA1029, 3. Sato also disclosed that after storing the formulations in vials for various lengths of time, the "formulations were dissolved in precisely 1 mL of pure water to prepare test samples for the assays." MAIA1007, 16. Thus, it would have been obvious in view of the PDR and Sato to

develop a kit that includes the claimed formulation as a lyophilized powder in a container, and optionally includes a physiologically acceptable fluid in which to reconstitute the powder mixture and/or dilute the reconstituted solution prior to administration of the drug to the patient. MAIA1005, 154; MAIA1007, 16; MAIA1029, 3; MAIA1003, ¶130.

6. Independent Claim 104

Claim 104 recites a method for imaging the hepatobiliary system of a subject by "a) administering to a subject a sincalide formulation comprising" the same excipient classes recited in claim 1 and "b) scanning the subject using a diagnostic imaging modality."

Again, for the reasons explained above with respect to claim 1, it would have been obvious to a POSA to develop a sincalide formulation containing the claimed classes of excipient. Section VI.A.3, *supra*. It would have also been obvious to administer the sincalide formulation to a subject in order to image the hepatobiliary system, because this is precisely what sincalide has long been used for and what the PDR instructs for sincalide's usage. MAIA1005, 154 (indicating that sincalide is "a diagnostic agent which may be used . . . (3) for postevacuation cholecystography" and that "roentgenograms [x-rays] are usually taken at five-minute intervals after the injection."). The gall bladder is part of a patient's hepatobiliary system. *See* MAIA1001, 2:39-47 (describing imaging the

hepatobiliary system as including gall bladder imaging); MAIA1030, 125-127 (listing cholecystokinin agents (including sincalide) for imaging the gall bladder under the heading, "Hepatobiliary System"); MAIA1003, ¶133. Thus, the PDR disclosed administering sincalide to a patient, followed by imaging the patient's gall bladder for diagnostic purposes, using the imaging modality cholecystography. MAIA1005, 154; MAIA1003, ¶133. Claim 104 would have been obvious over the PDR in view of Sato. MAIA1003, ¶133.

7. Claims 2, 22

Claims 2 and 22 depend from claims 1 and 21, respectively, and each recites the formulation has "a pH from 6.0 to 8.0." The PDR taught a pH within this range, disclosing that the pH of the sincalide formulation is adjusted prior to lyophilization to between pH 5.5 and 6.5. MAIA1005, 154. The PDR also taught reconstituting the lyophilized formulation with Sterile Water for Injection USP (*id.*), which has a pH of 5-7; MAIA1003, ¶¶134-135.

Additionally, Sato disclosed maintaining the G-CSF formulations in Samples 1-36 at pH 7.4 or 6.5 by adding a phosphate buffer to the solution. MAIA1007, 11-16. Thus, Sato and the PDR taught this limitation. MAIA1003, ¶¶134-135.

8. Claims 3, 4, 23, 24, 41, 42

Claims 3, 23, and 41 depend respectively from independent claims 1, 21, and 40 and recite that the claimed buffer is selected from among 31 different compounds or classes of compounds, including "phosphate." Claims 4, 24, and 42 also depend from independent claims 1, 21, and 40, and recite "wherein said buffer is a phosphate buffer."

For the reasons explained above with respect to claim 1, it would have been obvious to a POSA to use a phosphate buffer in a sincalide formulation to stabilize the formulation pH. Section VI.A.3.f, *supra*. Therefore, these claims are unpatentable as obvious over the PDR in view of Sato. MAIA1003, ¶¶136-137.

9. Claims 6-9, 26-29, 44-47

Claims 6-9, 26-29, and 44-47 depend directly or indirectly from independent claims 1, 21, and 40, and recite, with varying scope, different classes of surfactants or specific surfactants. The surfactant polysorbate 20 is within the scope of each of these claims.

For the reasons explained above with respect to claim 1, it would have been obvious to a POSA to use polysorbate 20 as a non-ionic surfactant in a sincalide formulation to prevent surface adsorption of the sincalide in the formulation. Section VI.A.3.c, *supra*. Therefore, these claims are unpatentable as obvious over the PDR in view of Sato. MAIA1003, ¶¶138-139.

10. Claims 10, 11, 13, 30, 31, 33, 48, 49, 51

Claims 10, 11, 13, 30, 31, 33, 48, 49, 51 depend directly or indirectly from independent claims 1, 21, and 40. Claims 10, 30, and 48 recite that the stabilizer "is selected from the group consisting of antioxidants and amino acids," and claims 11, 31, and 49 further narrow the claim scope to recite "wherein said stabilizer is an antioxidant." Claims 13, 33, and 51 recite "wherein said formulation comprises a plurality of stabilizers."

For the reasons explained above with respect to claim 1, it would have been obvious to a POSA to use a plurality of stabilizers in a sincalide formulation, including an antioxidant and amino acids, to stabilize sincalide against oxidation of its methionine residues. Section VI.A.3.b, *supra*. It would have been additionally obvious to use amino acids to stabilize sincalide against hydrolysis of sincalide's sulfated tyrosine residue and act as cryoprotectants and/or lyoprotectants in the lyophilized formulation. *Id*. Sato expressly disclosed using antioxidants and amino acids to stabilize such unstable peptides, including cholecystokinin. MAIA1007, 9, 11. Therefore, these claims are unpatentable as obvious over the PDR in view of Sato. MAIA1003, ¶¶140-141.

11. Claims 15, 16, 35, 36

Claims 15, 16, 35, and 36 depend directly or indirectly from independent claims 1, 21, and 40. Claims 15 and 35 recite that the claimed bulking

agent/tonicity adjuster is selected from among 16 different excipient compounds, including mannitol. Claims 16 and 36 recite "wherein said bulking agent/tonicity adjuster is D-mannitol."

For the reasons explained above with respect to claim 1, it would have been obvious to a POSA to use mannitol in a sincalide formulation as a bulking agent/tonicity adjuster. Section VI.A.3.e, *supra*. The Handbook of Pharmaceutical Excipients stated that "[m]annitol is D-mannitol," thus a POSA would have understood that Sato's disclosure of mannitol is disclosure of D-mannitol. MAIA1035, 324; MAIA1003, ¶¶142-143.

12. Claim 19

Claim 19 depends from claim 1 and recites "wherein said formulation is suitable for parenteral administration." This claim would have been obvious to a POSA, as the PDR expressly disclosed the sincalide formulation is "injected intravenously." MAIA1005, 154; *see* MAIA1029, 1 (Kinevac 1994 Package Insert indicating that sincalide is a drug product "for parenteral administration"); MAIA1003, ¶144.

13. Claim 55

Claim 55 depends from claim 40 and recites that the container is a vial. This claim would have been obvious to a POSA, as the PDR expressly disclosed the

sincalide formulation is a "lyophilized, white powder" stored in vials. MAIA1005, 154; MAIA1003, ¶145.

B. Ground 2: Claims 5, 12, 14, 17, 18, 25, 32, 34, 37, 38, 43 50, 52, and 54 are unpatentable under 35 U.S.C. § 103(a) over the PDR in combination with Sato and Nema

1. Claims 5, 25, 43

Dependent claims 5, 25, and 43 depend from dependent claims 4, 24, and 42, respectively, which in turn depend from independent claims 1, 21, and 40. Claims 5, 25, and 43 recite that the claimed phosphate buffer is dibasic potassium phosphate.

Nema disclosed this limitation. Nema included a "List of Excipients from 1996 FDA 'Inactive Ingredient Guide'" in Table IX and expressly disclosed "Potassium phosphate, dibasic" as an inactive ingredient for use in parenteral formulations. MAIA1017, 170. Sato disclosed use of a "phosphate buffer" in Samples 1-36. MAIA1007, 11-16. It would have been obvious to select a potassium phosphate buffer instead of a sodium salt buffer because the potassium phosphate is preferred to sodium phosphate for a lyophilized formulation, given the sodium salt shows a much larger change in pH during freezing compared to the potassium salt. MAIA1046, 6:21-31 (indicating that in "NaCl-containing phosphate buffers the pH value greatly decreases during the freezing process due to precipitated disodium hydrogen phosphate."); MAIA1003, ¶¶147-148.

Furthermore, it would have been obvious to choose among different phosphate buffers because doing so represented a simple design choice. MAIA1003, ¶¶147-148. Regardless of the associated salt (e.g., potassium or sodium) or the hydrogen/salt ratio (e.g., monobasic or dibasic), the phosphate ion in solution is the same and provides the same buffering effect. *Id.*, ¶148. The '046 patent fails to convey any distinction between different phosphate buffers. *See* MAIA1001, 1:66-67 ("Phosphate buffers, such as dibasic potassium phosphate, are preferred."); *see id.*, 9:48-51 ("Buffering agents useful in the preparation of formulation kits of the invention include, but are not limited to . . . phosphate (e.g. monobasic or dibasic sodium phosphate, monobasic or dibasic potassium phosphate, etc.)"). Thus, it would have been obvious to select dibasic potassium phosphate as the phosphate buffer used in the sincalide formulation. MAIA1003, ¶148.

2. Claims 12, 32, 50

Dependent claims 12, 32, and 50 depend from dependent claims 11, 31, and 49, respectively, which in turn depend from independent claims 1, 21, and 40. Claims 12, 32, and 50 recite "wherein said stabilizer is sodium metabisulfite."

Nema disclosed this limitation. Table IV in Nema is titled "Antioxidants and Reducing Agents" and lists antioxidants and reducing agents commonly used in parenteral formulations. MAIA1017, 168. Nema listed "Metabisulfite sodium"

as one of the most frequently used antioxidant/reducing agent among the excipients listed. *Id.*

As discussed above with respect to claim 1, a POSA would have been motivated to use an antioxidant in the sincalide formulation to prevent oxidation of sincalide's methionine residues. Section VI.A.3.b, *supra*. Sato disclosed adding sodium bisulfite as an antioxidant to prevent oxidative degradation of peptides and proteins. MAIA1007, 9. Selecting sodium metabisulfite instead of Sato's disclosed sodium bisulfite would have been obvious in view of Nema's express disclosure, and doing so represented a simple design choice between salts of sulphurous acid (sodium bisulphite, sodium metabisulphite or sodium thiosulphate). *See* MAIA1013, 154-155; MAIA1003, ¶151. Furthermore, the active antioxidant species generated by metabisulfite in solution is simply an equilibrium of the bisulfite and sulfite species. MAIA1041, 192; MAIA1003, ¶151. Thus, whether a POSA selected sodium metabisulfite or sodium bisulfite, the antioxidant species in solution is the same, further evidence it would have been obvious to select sodium metabisulfite as an antioxidant in view of Sato and Nema's disclosure. MAIA1003, ¶151.

A POSA would have had a reasonable expectation of success in using sodium metabisulfite in a sincalide parenteral formulation. MAIA1038, 398-401 MAIA1003, ¶152. Swadesh demonstrated that a related sulfurous acid salt,

sodium sulfite, successfully stabilized a methionine-containing protein against oxidation. MAIA1038, 398-401 (calling sodium sulfite's use "regular and predictable"). Given that the sulfite and bisulfite species exist in equilibrium in solution, and that metabisulfite generates these species (MAIA1041, 192), a POSA would have expected metabisulfite to also successfully stabilize a methionine-containing peptide, like sincalide, against oxidation. MAIA1003, ¶152.

3. Claims 14, 34, 52

Claims 14, 34, and 52 depend from dependent claims 13, 33, and 51, respectively, which in turn depend from independent claims 1, 21, and 40. Claims 14, 34, and 52 recite "wherein said stabilizers comprise L-arginine monohydrochloride, L-methionine, L-lysine monohydrochloride, and sodium metabisulfite."

As discussed above with respect to claim 1, Sato disclosed using arginine, methionine, and lysine as stabilizers. Section VI.A.3.b, *supra*. A POSA would have been motivated to use methionine in the formulation to prevent oxidation of sincalide's methionine residues, and would have had a reasonable expectation of success in doing so. *See id*.; MAIA1003, ¶154. Sato disclosed that free methionine acts as a sacrificial species in solution to prevent oxidation of the methionine residue on the peptide or protein. MAIA1007, 10.

Furthermore, a POSA would have been motivated to include arginine and lysine in a sincalide formulation to stabilize sincalide against hydrolysis of its sulfated tyrosine residue, and would have had a reasonable expectation of success in doing so. Section VI.A.3.b, *supra*. Moreover, a POSA would have been motivated to use arginine and lysine as lyprotectantants and/or cryoprotectants to stabilize a lyophilized sincalide formulation. *Id.* Sato also disclosed that its formulations "may contain D-, L- and DL-variants of these amino acids, ***more preferably L-variants and salts thereof***." MAIA1007, 8 (emphasis added). Thus, it would have been obvious to use L-arginine monohydrochloride, L-methionine, L-lysine monohydrochloride as the amino acid stabilizers in the sincalide formulation. MAIA1003, ¶155.

A POSA would have been motivated to add sodium metabisulfite to the formulation, and would have had a reasonable expectation of success in doing so, for the reasons discussed above with respect to claims 12, 32, and 50. Sato disclosed sodium bisulfite and Nema expressly disclosed sodium metabisulfite as an antioxidant for use in a parenteral formulation. MAIA1017, 168; MAIA1003, ¶156.

4. Claims 17, 37, 54

Claims 17, 37, and 54 depend from independent claims 1, 21, and 40 and recite "wherein said chelator is pentetic acid (DTPA)."

As discussed above with respect to claim 1, it would have been obvious to include a chelator in a sincalide formulation. Section VI.A.3.d, *supra*. Sato disclosed adding a chelating agent to stabilize the formulation and lists EDTA as an example. MAIA1007, 9; MAIA1003, ¶158.

It would have been obvious to use DTPA as a chelator, in view of Nema's express disclosure of DTPA as a chelating agent for parenteral formulations. MAIA1017, 168. Nema found that "[o]nly a limited number of chelating agents are used in parenteral products," including DTPA (pentetic acid) and three salt forms of EDTA. *See* MAIA1017, 167-168, Table III.

Other prior art references taught successful use of DTPA as a chelator. Bracco's own prior art patent, for example, shows that DTPA is compatible with CCK in various formulations. MAIA1010, 2:13-17 ("CCK8 derivatives containing the chelating agents DTPA or DOTA which complex radioactive metals like ^{111}In and ^{90}Y, and their application to identify and treat tumours that over express type B cholecystokinin receptor, have been reported."); MAIA1003, ¶160. Furthermore, Graf taught that DTPA is more effective than ETDA in many instances. MAIA1045, 3622 (showing formaldehyde (HCHO) formation is 31.1 nmol/30 min. in the absence of a chelator, which is reduced to 16.1 in the presence of EDTA, and completely eliminated in the presence of DTPA). Additionally, the '046 patent does not distinguish between DTPA and EDTA as chelators, calling

them both "preferred chelators." MAIA1001, 9:26-28. Thus, it would have been obvious to a POSA to use DTPA as a chelator in the claimed sincalide formulation. MAIA1003, ¶¶160-161.

5. Claims 18, 38

Claims 18 and 38 depend from dependent claims 17 and 37, respectively, which in turn depend from independent claims 1 and 21. Claims 18 and 38 recite "wherein said chelator is pentetic acid, said surfactant is polysorbate 20, said buffer is dibasic potassium phosphate, and said bulking agent/tonicity adjuster is D-mannitol."

It would have been obvious to select the claimed compounds for the chelator, surfactant, buffer and bulking agent/tonicity adjuster for the reasons described above with respect to claims 17 (Section VI.B.4), 9 (Section VI.A.9), 5 (Section VI.B.1), and 16 (Section VI.A.11); MAIA1003, ¶163.

C. Ground 3: Claims 77-88, 90-95, 97, 99, 100, and 105 are unpatentable under 35 U.S.C. § 103(a) in view of the PDR in combination with Sato and ENMS

1. Independent Claim 77

Claim 77 recites a method for imaging the hepatobiliary system of a subject by:

"(a) administering a hepatobiliary imaging agent to said subject;

"(b) before or after step (a), administering to a subject a sincalide formulation comprising [sincalide and the same excipient classes recited in claim 1]; and

"(c) detecting said imaging agent in said subject with a detection device."

For the reasons explained above with respect to claim 1, it would have been obvious to a POSA to develop a sincalide formulation containing the claimed classes of excipient. Section VI.A.3, *supra*. It would have also been obvious to administer the sincalide formulation to a subject in order to image the hepatobiliary system, because this is precisely what sincalide has long been used for and what the PDR instructs for sincalide's usage. MAIA1005, 154 (indicating that sincalide is "a diagnostic agent which may be used . . . (3) for postevacuation cholecystography" and that "roentgenograms [x-rays] are usually taken at five-minute intervals after the injection."). The hepatobiliary system includes the gall bladder. MAIA1001, 2:39-47 (describing imaging the hepatobiliary system as including gall bladder imaging); MAIA1030, 125-127 (listing cholecystokinin agents (including sincalide) for imaging the gall bladder under the heading, Hepatobiliary System); MAIA1003, ¶166. Thus, the PDR disclosed administering sincalide to the patient, followed by imaging the patient's gall bladder for

diagnostic purposes, using cholecystography as the imaging modality. MAIA1005, 154; MAIA1003, ¶166.

ENMS disclosed administering a hepatobiliary imaging agent to a patient in conjunction with administering sincalide. MAIA1030, 126-127. ENMS disclosed, in one approach, that "patients are premedicated with sincalide prior to injection of the radiopharmaceutical." *Id.*, 127. In another approach, patients are administered sincalide "followed by another injection of ^{99m}Tc-IDA," a radiopharmaceutical imaging agent. *Id.* Thus, ENMS disclosed two different approaches of administering the sincalide formulation, i.e., before *and* after administering the hepatobiliary imaging agent. *Id.*; MAIA1003, ¶167.

ENMS also disclosed detecting an imaging agent with a detection device, namely using a gamma camera to scan the patient's body to detect the imaging agent during scintigraphic imaging. MAIA1030, 145-160; *id.*, 159 ("The scintigraphic computer system is ideally suited to provide the processing necessary for tomographic reconstruction of gamma camera images."); *id.*, 126-127 (describing use of cholescintigraphic imaging to detect radiotracer (i.e., imaging agent, ^{99m}Tc-IDA) in patient in conjunction with sincalide administration); MAIA1003, ¶168.

Thus, claim 77 would have been obvious over the PDR in view of Sato and ENMS. MAIA1003, ¶164-169.

2. Claim 78

Claim 78 depends from claim 77 and recites "wherein said sincalide formulation is administered by injection." The PDR expressly disclosed this limitation, stating: "When injected intravenously, sincalide produces a substantial reduction in gallbladder size by causing this organ to contract." MAIA1005, 154; MAIA1003, ¶170.

3. Claims 79-80

Claims 79 depends from claim 77 and recites that the sincalide formulation is "administered to said subject before administration of said hepatobiliary imaging agent." Claim 80 also depends from claim 77 and recites that the sincalide formulation is "administered to said subject after administration of said hepatobiliary imagining agent."

As discussed above with respect to claim 77 (Section VI.C.1, *supra*) ENMS disclosed both of these limitations, disclosing two different approaches of administering the sincalide formulation—before *and* after administering the hepatobiliary imaging agent. MAIA1030, 127; MAIA1003, ¶¶171-172.

4. Claims 81-82

Claims 81 and 82 depend from claim 77 and respectively recite that the imaging agent is "^{99m}Tc-IDA (Iminodiacetic acid) analog" and "^{99m}Tc-mebrofenin."

ENMS disclosed these well-known imaging agents. MAIA1030, 184 ("most nuclear medicine hepalobiliary studies are performed with use of ^{99}mTc-iminodiacetic acid analogs"), 38 (describing ^{99}mTc-mebrofenin as a "compound with excellent properties as a cholescintigraphic agent"); MAIA1003, ¶¶173-174.

5. Claim 83

Claim 83 depends from claim 77 and recites "wherein said method further comprises, after administration of said sincalide formulation, measuring said the gallbladder ejection fraction (GBEF) of said subject."

ENMS expressly disclosed measuring the gall bladder ejection fraction after administering sincalide. MAIA1030, 127 ("Sincalide has been used as an adjunct to the examination of these patients . . . . Patients with acute acalculous cholecystitis will have a distinctly abnormal response, usually with a gallbladder ejection fraction of much less than 20%."); MAIA1003, ¶175-176.

6. Claims 84-85

Claims 84 depends from claim 77 and recites that the detection device "scans the body of said subject for radioactivity." Claim 85 depends from claim 84 and recites that the detection device is a gamma camera.

As discussed above with respect to claim 77 (Section VI.C.1, *supra*) ENMS disclosed both of these limitations, disclosing a gamma camera that scans the

patient's body for radioactivity of the radiotracer imaging agent. *See* MAIA1030, 126-127, 145-160; MAIA1003, ¶178.

7. Claims 86-88, 90-95, 97, 99, 100

Claims 86-88, 90-95, 97, 99, and 100 depend directly or indirectly from claim 77 and are identical to the excipient claims 2-4, 6-11, 13, 15, and 16 depending from 1, discussed above in Ground 1. Thus, for the reasons explained in Ground 1, claims 86-88, 90-95, 97, 99, and 100 are also unpatentable as obvious over the PDR, Sato, and ENMS:

Claims depending from claim 77	Corresponding claims	Previous section addressing claims
86 [pH]	2	*Supra* VI.A.7
87, 88 [buffer]	3, 4	*Supra* VI.A.8
90-93 [surfactant]	6-9	*Supra* VI.A.9
94, 95, 97 [stabilizer]	10, 11, 13	*Supra* VI.A.10
99, 100 [bulking agent/ tonicity adjuster]	15, 16	*Supra* VI.A.11

MAIA1003, ¶179.

8. Claim 105

Claim 105 depends from claim 104 and recites that the imaging modality "is selected from the group consisting of magnetic resonance imaging, scintigraphic imaging and ultrasound imaging." The PDR expressly disclosed imaging the gall

bladder by "cholecystography." MAIA1005, 154. ENMS further disclosed that sincalide is used to prepare the gall bladder for "cholescintigraphy," which is scintigraphic imaging of the hepatobiliary system. MAIA1030, 126 ("The rationale for use of sincalide with cholescintigraphy is to empty the gallbladder . . ."). The Kinevac 1994 Package Insert also indicated that the patient's gall bladder contraction is assessed by "contrast agent cholecystography or ultrasonography."). MAIA1029, 1. Thus, this claim would have been obvious over the PDR in view of Sato and ENMS. MAIA1003, ¶180.

D. Ground 4: Claims 89, 96, 98, 101, and 102 are unpatentable under 35 U.S.C. § 103(a) in view of the PDR in combination with Sato, ENMS, and Nema

Claims 89, 96, 98, 101, and 102 depend directly or indirectly from claim 77 and are identical to the excipient claims 5, 12, 14, 17, and 18 depending from 1, discussed above in Ground 2. Thus, for the reasons explained in Ground 2, claims 89, 96, 98, 101, and 102 are also unpatentable as obvious over the PDR, Sato, ENMS, and Nema:

Claim depending from claim 77	Corresponding claim	Previous section addressing claim
89	5	*Supra* VI.B.1
96	12	*Supra* VI.B.2
98	14	*Supra* VI.B.3

Claim depending from claim 77	Corresponding claim	Previous section addressing claim
101	17	*Supra* VI.B.4
102	18	*Supra* VI.B.5

MAIA1003, ¶181.

VII. SECONDARY CONSIDERATIONS

Where a strong *prima facie* obviousness showing exists, as here, secondary considerations may not dislodge the obviousness conclusion. *Leapfrog Enters. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). Should Bracco raise secondary considerations, Maia will respond.

VIII. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(A)(1)

A. Real Parties-In-Interest (37 C.F.R. § 42.8(b)(1))

Petitioner Maia, along with investors Shilpa Medicare Limited and BS&H Investors LLC, and development partner Gland Pharma Ltd., are the real parties-in-interest.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Bracco asserted the '046 patent against Maia in co-pending litigation captioned *Bracco Diagnostics Inc. v. Maia Pharmaceuticals, Inc.*, 3:17-cv-13151-PGS-TJB (D. N.J. Dec. 15, 2017).

C. Lead and Back-up Counsel Under 37 C.F.R. § 42.8(b)(3)

Maia provides the following designation of counsel:

Lead Counsel	Back-up Counsel
Benjamin B. Anger (Reg. No. 62,207) 2bba@knobbe.com Postal/Hand-Delivery Address: Knobbe, Martens, Olson, & Bear, LLP 2040 Main St., 14th Floor Irvine, CA 92614 Telephone: (949) 760-0404 Facsimile: (949) 760-9502	Peter J. Law (Reg. No. 72,722) 2pxl@knobbe.com Postal/Hand-Delivery Address: Knobbe, Martens, Olson, & Bear, LLP 2040 Main St., 14th Floor Irvine, CA 92614 Telephone: (949) 760-0404 Facsimile: (949) 760-9502

Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney from Maia accompanies this Petition, and the above identified Lead and Back-up Counsel are registered practitioners associated with Customer No. 20,995 identified in Maia's Power of Attorney.

D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Please address all correspondence to the addresses above. Petitioner also consents to service by email to BoxMaia@knobbe.com.

IX. PAYMENT OF FEES

The undersigned authorizes the PTO to charge the fee set forth in 37 C.F.R. § 42.15(a) for this Petition and any additional fees to Deposit Account No. 11-1410. Review of 81 claims is requested.

X. REQUIREMENTS FOR REVIEW

Maia certifies that the ’046 patent is available for IPR and that Maia is not barred or estopped from requesting this IPR.

XI. CONCLUSION

For the reasons provided, claims 1-19, 21-38, 40-55, 77-102, 104-105 of the ’046 patent are unpatentable and should be cancelled.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: November 19, 2018

By:/Benjamin Anger/

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CERTIFICATE OF TYPE-VOLUME LIMITATIONS UNDER 37 C.F.R. § 42.24

Pursuant to 37 C.F.R. § 42.24(d), Counsel for Petitioner Maia Pharmaceuticals, Inc. certifies that this document complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1)(i). According to Microsoft Office Word 2016's word count, this document contains approximately 13,995 words, including any statement of material facts to be admitted or denied in support, and excluding the table of contents, table of authorities, mandatory notices under § 42.8, exhibit list, certificate of service or word count, or appendix of exhibits or claim listing.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: November 19, 2018

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CERTIFICATE OF SERVICE

I hereby certify that true and correct copies of the foregoing **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT 6,803,046** and **MAIA EXHIBITS 1001-1046** are being served on November 19, 2018, via FedEx Priority Overnight service on counsel of record for U.S. Patent 6,803,046 patent owner **BRACCO DIAGNOSTICS INC.** at the address below:

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