



US009220700B2

(12) **United States Patent**
Savarese et al.

(10) **Patent No.:** **US 9,220,700 B2**
(45) **Date of Patent:** **Dec. 29, 2015**

(54) **CYSTEINE FOR PHYSIOLOGICAL INJECTION**

(75) Inventors: **John J. Savarese**, Southbury, CT (US);
Paul M. Heerdt, Greenwich, CT (US)

(73) Assignee: **Cornell University**, Ithaca, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 771 days.

(21) Appl. No.: **13/391,154**

(22) PCT Filed: **Aug. 18, 2010**

(86) PCT No.: **PCT/US2010/045907**

§ 371 (c)(1),
(2), (4) Date: **May 7, 2012**

(87) PCT Pub. No.: **WO2011/022491**

PCT Pub. Date: **Feb. 24, 2011**

(65) **Prior Publication Data**
US 2012/0214873 A1 Aug. 23, 2012

Related U.S. Application Data

(60) Provisional application No. 61/235,191, filed on Aug. 19, 2009.

(30) **Foreign Application Priority Data**

Mar. 17, 2010 (WO) PCT/US2010/000796

(51) **Int. Cl.**
A61K 31/195 (2006.01)
A61K 31/198 (2006.01)
A61K 9/00 (2006.01)
A61K 9/06 (2006.01)

(Continued)

(52) **U.S. Cl.**
CPC **A61K 31/198** (2013.01); **A61K 9/0019** (2013.01); **A61K 9/06** (2013.01); **A61K 31/375** (2013.01); **A61K 47/22** (2013.01)

(58) **Field of Classification Search**
CPC **A61K 31/195**; **A61K 31/198**
USPC **514/562**
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,004,031 A 10/1961 Taylor et al.
4,036,959 A 7/1977 Green et al.
4,039,682 A 8/1977 Ausman et al.

(Continued)

FOREIGN PATENT DOCUMENTS

CN 101366695 A 2/2009
EP 0008824 A1 3/1980

(Continued)

OTHER PUBLICATIONS

"U.S. Appl. No. 13/257,214, Notice of Allowance mailed Jul. 19, 2013", 19 pgs.

(Continued)

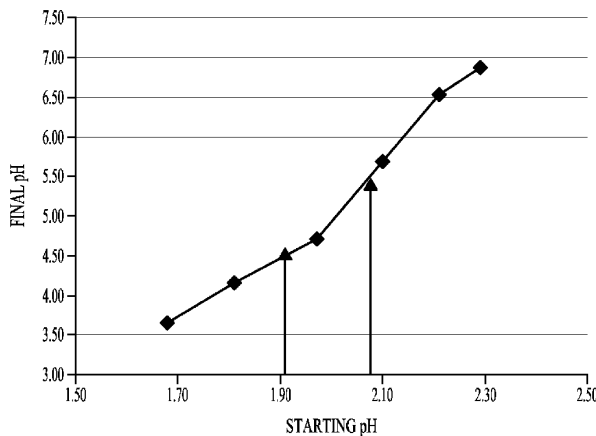
Primary Examiner — San-Ming Hui

(74) *Attorney, Agent, or Firm* — Schwegman Lundberg & Woessner, P.A.

(57) **ABSTRACT**

This application describes methods of making and using physiological cysteine solutions useful for reversing a neuromuscular blockade caused by a cysteine-reversible neuromuscular blockade agent, that overcomes problems of cysteine precipitation and dimerization.

6 Claims, 5 Drawing Sheets



- (51) **Int. Cl.**
A61K 31/375 (2006.01)
A61K 47/22 (2006.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,179,507	A	12/1979	Stenlake et al.	
4,192,877	A	3/1980	Savarese et al.	
4,235,906	A	11/1980	Savarese et al.	
4,491,665	A	1/1985	El-Sayad et al.	
4,556,712	A	12/1985	Rice	
4,666,918	A	5/1987	Ivanova et al.	
4,686,228	A	8/1987	Campbell et al.	
4,701,460	A	10/1987	El-Sayad et al.	
4,707,485	A	11/1987	Kaiser et al.	
4,727,146	A	2/1988	Rice	
4,727,147	A	2/1988	Wintermeyer et al.	
4,761,418	A	8/1988	Swaringen, Jr. et al.	
5,240,939	A	8/1993	Demko	
5,438,140	A	8/1995	Ofring et al.	
5,453,510	A	9/1995	Hill et al.	
5,556,978	A	9/1996	Hill et al.	
5,684,154	A	11/1997	Chamberlin	
6,177,445	B1	1/2001	Bigham et al.	
6,187,789	B1	2/2001	Bigham et al.	
6,194,421	B1	2/2001	Cohen et al.	
6,548,521	B1	4/2003	Cohen et al.	
6,562,836	B1	5/2003	Szarek et al.	
6,838,270	B1*	1/2005	Kurosawa et al.	435/189
6,858,750	B2	2/2005	Joshi	
7,037,489	B2	5/2006	Uchiwa et al.	
8,592,451	B2	11/2013	Savarese et al.	
2003/0149082	A1	8/2003	Makriyaannis et al.	
2003/0191115	A1	10/2003	Pinto et al.	
2004/0054001	A1	3/2004	Joshi et al.	
2004/0180925	A1	9/2004	Matsumo et al.	
2005/0192243	A1	9/2005	Savarese	
2006/0177408	A1	8/2006	Uchiwa et al.	
2006/0205659	A1	9/2006	Joshi et al.	
2008/0139482	A1	6/2008	Savarese	

FOREIGN PATENT DOCUMENTS

EP	1380573	A2	1/2004	
EP	1526130	A1	4/2005	
EP	1676580	A1	7/2006	
JP	54-055577	A	5/1979	
JP	61-087666	A	5/1986	
JP	5-017431	A	1/1993	
WO	WO-98/42674	A1	10/1998	
WO	WO-98/42675	A1	10/1998	
WO	WO 98/47534	A1	10/1998	
WO	WO-2004/035869	A1	4/2004	
WO	WO-2005/041960	A2	5/2005	
WO	WO-2007/074454	A2	7/2007	
WO	WO-2008/070121	A1	6/2008	
WO	WO-2010/107488	A1	9/2010	
WO	WO-2011/022491	A1	2/2011	

OTHER PUBLICATIONS

- "U.S. Appl. No. 13/257,214, Response filed May 9, 2013 to Restriction Requirement mailed Apr. 24, 2013", 52 pgs.
 "U.S. Appl. No. 13/257,214, Restriction Requirement mailed Apr. 24, 2013", 8 pgs.
 "Chinese Application Serial No. 201080047362.6, Office Action mailed Sep. 9, 2013", (w/ English Translation), 15 pgs.
 "Chinese Application Serial No. 201080047362.6, Response filed May 9, 2013 to Office Action mailed Dec. 25, 2012". (w/ English Translation of Amendments), 19 pgs.
 "Chinese Application Serial No. 201080047362.6, Response filed Nov. 25, 2013 to Office Action mailed Sep. 9, 2013", 4 pgs.
 "U.S. Appl. No. 11/951,114 Response filed Oct. 14, 2010 to Restriction Requirement mailed Jul. 16, 2010", 40 pgs.

- "Australian Application Serial No. 2007328210, Response filed Oct. 22, 2012 to Office Action mailed Apr. 13, 2012", 15 pgs.
 "Chinese Application Serial No. 201080047362.6, Office Action mailed Dec. 25, 2012", (w/ English Translation), 17 pgs.
 "Indian Application Serial No. 2432/KOLNP/2009 , Voluntary Amendment filed Nov. 22, 2010", 25 pgs.
 "Japanese Application Serial No. 2009-540280, Office Action mailed Nov. 16, 2012", (w/ English Translation), 5 pgs.
 "Japanese Application Serial No. 2009-540280, Response filed Jan. 30, 2013 to Office Action mailed Nov. 16, 2012", (w/ English Translation of Claims), 15 pgs.
 "U.S. Appl. No. 10/975,197, Advisory Action mailed Jan. 24, 2007", 3 pgs.
 "U.S. Appl. No. 10/975,197, Final Office Action mailed Oct. 18, 2007", 15 pgs.
 "U.S. Appl. No. 10/975,197, Final Office Action mailed Sep. 26, 2006", 16 pgs.
 "U.S. Appl. No. 10/975,197, Non-Final Office Action mailed Feb. 24, 2006", 9 pgs.
 "U.S. Appl. No. 10/975,197, Non-Final Office Action mailed May 2, 2007", 13 pgs.
 "U.S. Appl. No. 10/975,197, Response and Declaration filed Jul. 24, 2006 to Non-Final Office Action mailed Feb. 24, 2006", 23 pgs.
 "U.S. Appl. No. 10/975,197, Response filed Jan. 13, 2006 to Restriction Requirement mailed Dec. 27, 2005", 10 pgs.
 "U.S. Appl. No. 10/975,197, Response filed Jul. 30, 2007 to Non-Final Office Action mailed May 2, 2007", 17 pgs.
 "U.S. Appl. No. 10/975,197, Response filed Oct. 30, 2007 to Final Office Action mailed Oct. 18, 2007", 17 pgs.
 "U.S. Appl. No. 10/975,197, Response filed Dec. 22, 2006 to Final Office Action mailed Sep. 26, 2006", 13 pgs.
 "U.S. Appl. No. 10/975,197, Restriction Requirement mailed Dec. 27, 2005", 5 pgs.
 "U.S. Appl. No. 10/975,197, Non-Final Office Action mailed Feb. 4, 2008", 17 pgs.
 "U.S. Appl. No. 11/951,114, Restriction Requirement mailed Jul. 16, 2010", 7 pgs.
 "U.S. Appl. No. 11/951,114, Non Final Office Action mailed May 25, 2011", 7 pgs.
 "U.S. Appl. No. 11/951,114, Non Final Office Action mailed Dec. 15, 2010", 6 pgs.
 "U.S. Appl. No. 11/951,114, Notice of Allowance mailed Nov. 30, 2011", 9 pgs.
 "U.S. Appl. No. 11/951,114, Preliminary Amendment filed Jan. 7, 2009", 16 pgs.
 "U.S. Appl. No. 11/951,114, Response filed Mar. 15, 2011 to Non Final Office Action mailed Dec. 15, 2010", 12 pgs.
 "U.S. Appl. No. 11/951,114, Response filed Sep. 26, 2011 to Non Final Office Action mailed May 25, 2011", 15 pgs.
 "Canadian Application Serial No. 2,671,904, Office Action mailed Jun. 15, 2011", 3 pgs.
 "Canadian Application Serial No. 2,671,904, Response filed Sep. 14, 2011 to Office Action mailed Jun. 23, 2011", 30 pgs.
 "Chinese Application Serial No. 200780050532.4, Office Action mailed Sep. 20, 2010", (w/ English Translation), 10 pgs.
 "Chinese Application Serial No. 200780050532.4, Response filed Feb. 5, 2011 to Office Action mailed Sep. 20, 2010", (w/ English Translation of Claims), 15 pgs.
 "Chinese Application Serial No. 200780050532.4, Response filed Dec. 8, 2011 to Office Action mailed Sep. 26, 2011", (w/ English Translation of Claims), 22 pgs.
 "Chinese Application Serial No. 200780050532.4, Second Office Action mailed Sep. 26, 2011", (w/ English Translation), 11 pgs.
 "Database WPI Week 199309", *Thomson Scientific*, London, GB; AN 1993-071085, JP 5 017431 A (Seiko Epson Corp), (Jan. 26, 1993), 2 pgs.
 "Database WPI Week 200923", *Thomson Scientific*, London, GB; AN 2009-G02209, CN 101366695 A (Jiangsu Sihuan Biological Co Ltd), (Feb. 18, 2009), 2 pgs.
 "European Application Serial No. 07862551.4, Response filed Jun. 2, 2011 to Office Action dated Nov. 25, 2010", 9 pgs.
 "European Application Serial No. 07862551.4, Supplemental European Search Report mailed Oct. 29, 2010", 7 pgs.

(56)

References Cited

OTHER PUBLICATIONS

- "International Application Serial No. PCT/US07/24914, International Search Report mailed Apr. 17, 2008", 3 pgs.
- "International Application Serial No. PCT/US07/24914, Written Opinion mailed Apr. 17, 2008", 8 pgs.
- "International Application Serial No. PCT/US2004/035869, International Preliminary Report on Patentability and Written Opinion mailed May 11, 2006", 9 pgs.
- "International Application Serial No. PCT/US2004/035869, International Search Report mailed May 3, 2005", 3 pgs.
- "International Application Serial No. PCT/US2010/000796, International Preliminary Report on Patentability mailed Sep. 29, 2011", 12 pgs.
- "International Application Serial No. PCT/US2010/000796, International Search Report mailed Aug. 4, 2010", 2 pgs.
- "International Application Serial No. PCT/US2010/000796, Written Opinion mailed Aug. 4, 2010", 13 pgs.
- "International Application Serial No. PCT/US2010/045907, International Search Report mailed Nov. 10, 2010", 4 pgs.
- "International Application Serial No. PCT/US2010/045907, Written Opinion mailed Nov. 10, 2010", 8 pgs.
- "Le Chatelier's Principle", © Jim Clark 2002. Retrieved from the Internet: <URL: <http://www.chemguide.co.uk/physical/equilibria/lechatelier.html>>, (2002), 6 pgs.
- "Rate equation", 2006 Wikipedia® [online]. Retrieved from the Internet: <URL: http://en.wikipedia.org/wiki/rRate_equation>, From Wikipedia®, *Free Encyclopedia*, (2006), 6 pgs.
- Agoston, S., et al., "The Neuromuscular Blocking Action of Org NC 45, A New Pancuronium Derivative, in Anaesthetized Patients", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 53S-59S.
- Baird, W. L. M., et al., "A New Neuromuscular Blocking Drug, Org NC 45", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 61S-62S.
- Bedford, R. F., "From the FDA", *Anesthesiology*, 82, (1995), p. 33A.
- Belmont, M. R., "Succinylcholine/Suxamethonium", *Current Opinion in Anaesthesiology*, 8, (1995), 362-366.
- Bencini, A., et al., "Use of the Human "Isolated Arm" Preparation to Indicate Qualitative Aspects of a New Neuromuscular Blocking Agent, Org NC 45", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 43S-47S.
- Bevan, D. R., "Newer Neuromuscular Blocking Agents", *Pharmacology & Toxicology*, 74(1), (1994), 3-9.
- Boros, E. E., et al., "Neuromuscular Blocking Activity and Therapeutic Potential of Mixed-Tetrahydroisoquinolinium Halofumarates and Halosuccinates in Rhesus Monkeys", *Journal of Medicinal Chemistry*, 46, (2003), 2502-2515.
- Boros, E. E., et al., "Bis- and mixed-tetrahydroisoquinolinium chlorofumarates: New ultra-short-acting nondepolarizing neuromuscular blockers", *Journal of Medicinal Chemistry*, 42(2), (1999), 206-209.
- Boros, E. E., "Neuromuscular Blocking Activity and Therapeutic Potential of Mixed-Tetrahydroisoquinolinium Halofumarates and Halosuccinates in Rhesus Monkeys", *Journal of Medicinal Chemistry*, 46, (Jun. 2003), 2502-2515.
- Buckett, W. R., et al., "Pancuronium Bromide and Other Steroidal Neuromuscular Blocking Agents Containing Acetylcholine Fragments", *Journal of Medicinal Chemistry*, 16(10), (1973), 1116-1124.
- Buzello, W., "The New Non-Depolarizing Muscle Relaxant Org NC 45 in Clinical Anaesthesia: Preliminary Results", *British Journal of Anaesthesia*, 52 (Supplement 1), (1980), 62S-64S.
- Crul, J. F., et al., "First Clinical Experiences With Org NC 45", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 49S-52S.
- De Rosa, S. C., "N-acetylcysteine Replenishes Glutathione in HIV Infection", *European Journal of Clinical Investigation*, 30, (2000), 915-929.
- Dizdar, N., et al., "Comparison of N-acetylcysteine and i-2-oxothiazolidine-4-carboxylate as cysteine deliverers and glutathione precursors in Human Malignant Melanoma Transplants in Mice", *Cancer Chemother Pharmacol*, 45, (2000), 192-198.
- Durant, N. N., et al., "Suxamethonium", *British Journal of Anaesthesiology*, 54, (1982), 195-208.
- Fahey, M. R., et al., "Clinical Pharmacology of Org NC45 (Norcuron TM): A New Nondepolarizing Muscle Relaxant", *Anesthesiology*, 55(1), (1981), 6-11.
- Foldes, F. F., et al., "Influence of Halothane and Enflurane on the Neuromuscular Effects of Org NC 45 in Man", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 64S-65S.
- Huang, T. C., et al., "Mechanistic Studies on Thiazolidine Formation in Aldehyde/Cysteamine Model Systems", *J Agric Food Chem.*, 46(1), (Jan. 1998), 224-227.
- Kharkevich, D. A., "New Curare-Like Agents", *J. Pharm. Pharmac.*, 26, (1974), 153-165.
- Khromov-Borisov, N. V., et al., "Removal of a Curare-Like Effect by Direct Inactivation of the Myorelaxant Molecule by Disruption of the Disulfide Bond", *Doklady Biological Sciences, Proceedings of the Academy of Sciences of the USSR*, 186(1), (1968), 460-463.
- Kreig N., et al., "Preliminary Review of the Interactions of Org NC 45 With Anaesthetics and Antibiotics in Animals", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 33S-36S.
- Kulawska, et al., "Kinetics of the esterification of maleic anhydride with octyl, decyl or dodecyl 68-69 alcohol over dowex catalyst", (Abstract Only), *Reaction Kinetics and Catalysis Letters*, 85(1), (2005), 51-56.
- Lee, C., "Structure, Conformation, and Action of Neuromuscular Blocking Drugs", *British Journal of Anaesthesia*, 87(5), (2001), 755-769.
- Li, J., et al., "Dietary supplementation with cysteine prodrugs selectively restores tissue glutathione levels and redox status in protein-malnourished mice", *Journal of Nutritional Biochemistry*, 13, (2002), 625-633.
- Lien, C. A., "The Pharmacology of GW280430A: A New Nondepolarizing Neuromuscular Blocking Agent", *Seminars in Anesthesia: Perioperative Medicine and Pain*, 21(2), (Jun. 2002), 86-91.
- Mahajan, R. P., "Focus on: Controversies in Anaesthesia—Is Suxamethonium Now Obsolete?", *Current Anaesthesia and Critical Care*, 7, (1996), 289-294.
- Marshall, I. G., et al., "Pharmacology of Org NC 45 Compared With Other Non-Depolarizing Neuromuscular Blocking Drugs", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 11S-19S.
- Marshall, R. J., et al., "Comparison of the Cardiovascular Actions of Org NC 45 With Those Produced by Other Non-Depolarizing Neuromuscular Blocking Agents in Experimental Animals", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 21S-32S.
- McNulty, M., "The Ultra-Short Acting Nondepolarizing Relaxant GW280430A Undergoes Rapid Degradation by Chemical Mechanisms", *Anesthesiology Abstracts of Scientific Papers Annual Meeting—2002*, (2002), 1 pg.
- Miller, R. D., "Org NC 45", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 71S-72S.
- Morrison, R. T., et al., *In: Organic Chemistry* (Second Edition), Allyn and Bacon, Inc., Boston, MA, (1966), 290-293.
- Murphy, G. S., "Residual neuromuscular blockade: incidence, assessment, and relevance in the postoperative period", *Minerva Anestesiol*, vol. 72(3), (2006), 97-109.
- Naguib, M., et al., "Advances in Neurobiology of the Neuromuscular Junction", *Anesthesiology*, 96(1), (2002), 202-231.
- Nebergall, W. H., "Chapter 7—Molecular Structure and Hybridization", *in: General Chemistry* (6th Edition), D. C. Heath and Company, (1980), 149-152.
- Norman, J., et al., "Introduction", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), S1-S2.
- Rees, D. C., et al., "Chapter 5. Drugs in Anesthetic Practice", *Annual Reports in Medicinal Chemistry*, 31, (1994), 41-50.
- Reese, M. J., "Comparative Metabolic Profiles of the Neuromuscular Blocker GW280430 in Human, Monkey, and Dog, and Characterization of a Major Metabolite as an Unusual Cyclized Cysteine conjugate", (Abstract 282), Presented at the 9th North American ISSX Meeting (issx.org); Nashville, TN, (Oct. 1999), p. 142.
- Saitoh, Y., et al., "Infusion of Amino Acid Enriched Solution Hastens Recovery From Neuromuscular Block Caused by Vecuronium", *British Journal of Anaesthesia*, 86, (2001), 814-821.

(56)

References Cited

OTHER PUBLICATIONS

Sakuraba, H., et al., "Asymmetric Michael Addition of Aromatic Thiols to 2-Cyclohexenone and Maleic Acid Esters Via Formation of Crysatine Cyclodextrin Complexes", *Journal of Inclusion Phenomena and Molecular Recognition in Chemistry*, (1991), 195-204.

Savage, D. S., et al., "The Emergence of ORG NC 45, 1-[(2beta,3alpha,16beta,17beta)-3, 17-Bis(Acetyloxy)-2-(1-Piperidinyl)-Androstan-16-YL]-1-Methylpiperidinium Bromide, From the Pancuronium Series", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 3S-9S.

Savarese, J. J., et al., "Chapter 14. Pharmacology of Muscle Relaxants and Their Antagonists", in: *Anesthesia*, vol. 1, (Fourth Edition), Miller, R. D., et al., Editors, Churchill Livingstone Inc., (1994), 417-487.

Savarese, J. J., et al., "Rapid chemical antagonism of neuromuscular blockade by L-cysteine adduction to and inactivation of the olefinic (double-bonded) isoquinolinium diester compounds gantacurium (AV430A), CW 002, and CW 011.", *Anesthesiology*, 113(1), (Jul. 2010), 58-73.

Schaer, H., et al., "Preliminary Clinical Observations With Org NC 45", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 65S-67S.

Son, S. L., et al., "A Comparison of the Neuromuscular Blocking and Vagolytic Effects of ORG NC45 and Pancuronium", *Anesthesiology*, 55(1), (1981), 12-18.

Speight, T. M., et al., "Pancuronium Bromide: A Review of its Pharmacological Properties and Clinical Application", *Drugs*, 4(1-2), 163-226.

Sunaga, H., et al., "Cysteine reversal of the novel neuromuscular blocking drug CW002 in dogs: pharmacodynamics, acute cardiovascular effects, and preliminary toxicology", *Anesthesiology*, 112(4), (Apr. 2010), 900-909.

Van Der Veen, F., et al., "Pharmacokinetics and Pharmacodynamics of Org NC 45 in Man", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 37S-41S.

Viby-Mogensen, J., et al., "On Org NC 45 and Halothane Anaesthesia", *British Journal of Anaesthesia*, 52(Supplement 1), (1980), 67S-69S.

Zhang, L., et al., "Thiazolidine formation as a general and site-specific conjugation method for synthetic peptides and proteins", *Anal Biochem.*, 233(1), (Jan. 1, 1996), 87-93.

* cited by examiner

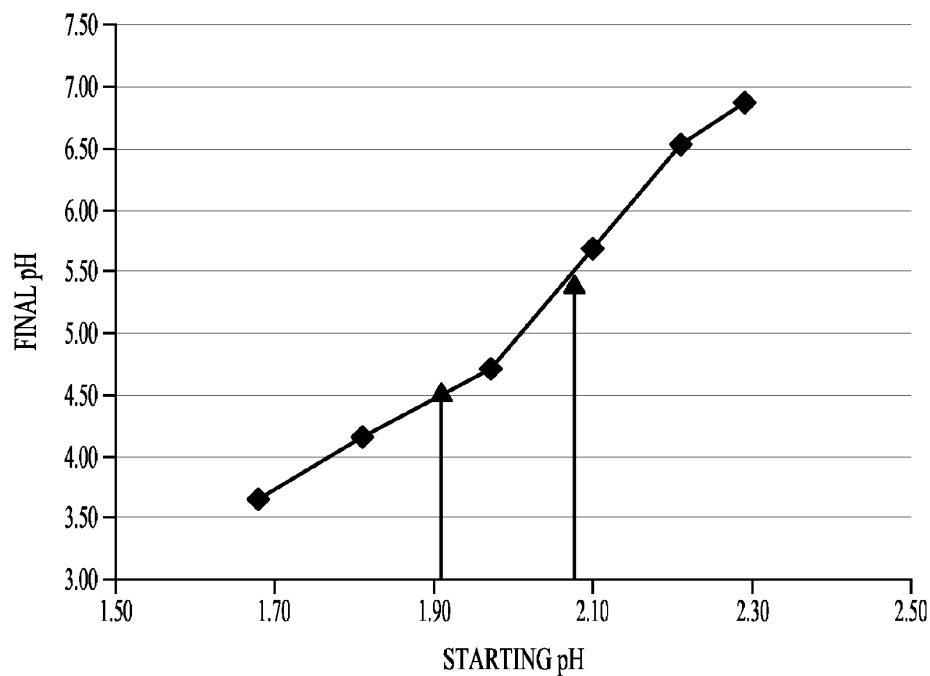


FIG. 1

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.