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Leah E. Appel* PhD

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Education

Ph.D. in Pharmaceutics, University of Utah, Salt Lake City, UT, 1988
Dissertation: Characterization of a Self-Regulating Insulin Delivery System
Advisor: Sung Wan Kim Ph.D.

B.S. in Chemical Engineering, University of California - Los Angeles, Los Angeles, CA, 1982

Areas of Specialization

Development and application of drug delivery technology. Extensive experience in formulation and process development for oral solid dosage forms including controlled and sustained release formulations, poorly soluble compounds, fixed dose combinations and pediatric formulations for oral delivery. Strong expertise in tablets, capsules, osmotic systems, multiparticulates, and amorphous solid dispersions.

Employment

Managing Partner, 2007 - present
Green Ridge Consulting, Bend, OR
Responsible for formulation, process development, CRO/CMO management and expert witness work for >100 clients. Project areas encompass NCE development, product enhancement, fixed dose combinations. Experienced in formulation development and scale-up, transfer and troubleshooting. Specific technology expertise in oral controlled release technologies (osmotic, matrix, multiparticulates) and amorphous solid dispersions.

Director, Controlled Release, 1996 - 2006
Bend Research, Bend, OR

Responsible for formulation, process development and technology transfer for a wide range of drug delivery technologies including oral osmotics and multiparticulates. Led team to commercialize Zmax sustained release microsphere product with Pfizer. Extensive experience in formulation and process development of hot melt and spray dried dispersion-based IR and CR dosage forms.

Project Leader, 1995 - 1996
Sarcos Research Corporation, Salt Lake City, UT
Responsible for project planning management and development of electro-mechanical topical drug-delivery systems.

Research Fellow 1993 - 1995
Sr. Research Chemist 1988 - 1993
INTERx Research Corporation/Merck & Co., Lawrence, KS
Responsible for design and evaluation of erodible injectable systems for bone-growth promotion. Led electromechanical drug-delivery effort. Developed oral osmotics aqueous-based coatings.

Publications: 14 publications (see attached addendum)

Patents: 15 Patents issued, 29 pending (see attached addendum)

Presentations: 20 presentations (see attached addendum)

Scientific Appointments: Advisor for the Journal of Pharmaceutical Sciences July 2013 - 2016

* Formerly known as Leah Appel Seminoff

Publications

- Seminoff, L.A., G.B. Olsen and S.W. Kim, "A Self-Regulating Insulin Delivery System I. Characterization of a Synthetic Glycosylated Insulin Derivative," *Intl. J. Pharm.*, 54(1989)241-249.
- Seminoff, L.A., J.M. Gleeson, J. Zheng, G.B. Olsen, D. Holmberg, S.F. Mohammad, D. Wilson and S.W. Kim, "A Self-Regulating Insulin Delivery System II. In Vivo Characteristics of a Synthetic Glycosylated Insulin," *Intl. J. Pharm.*, 54(1989)251-257.
- Kim, S.W., C.M. Pail, K. Makino, L.A. Seminoff, D.L. Holmberg, J.M. Gleeson, D.E. Wilson and E.J. Mack, "Self-Regulated Glycosylated Insulin Delivery," *J. Controlled Rel.*, 11(1990)193-201.
- Seminoff, L.A. and S.W. Kim. "A Self-Regulating Insulin Delivery System Based on Competitive Binding of Glucose and Glycosylated Insulin." *Pulsed and Self-Regulated Drug Delivery*. Ed. Joseph Kost. Boca Raton: CRC Press, 1990. 187-199.
- LeCluyse, E.L., L.E. Appel and S.C. Sutton, "Relationship Between Drug Absorption Enhancing Activity and Membrane Perturbing Effects of Acylcarnitines," *Pharm. Res.*, 8(1991)84-87.
- Appel, L.E. and G.M. Zentner, "Use of Modified Ethylcellulose Lattices for Microporous Coating of Osmotic Tablets," *Pharm. Res.*, 8(1991)600-604.
- Appel, L.E., J.H. Clair and G.M. Zentner, "Formulation and Optimization of a Modified Microporous Cellulose Acetate Latex Coating for Osmotic Pumps," *Pharm. Res.*, 9(1992)1664-1667.
- Appel, L.E., R. Balena, M. Cortese, E. Opas, G. Rodan, G. Seedor and G.M. Zentner, "In Vitro Characterization and In Vivo Efficacy of a Prostaglandin E₂/Poly (Ortho Ester) Implant for Bone Growth Promotion," *J. Controlled Rel.*, 26(1993)77-85.
- Appel, L.E. and L. Witchey-Lakshamanan, "Oncologic, Endocrine & Metabolic Overview: Recent Advances in Implants for Bone Growth Promotion," *Expert Opinion on Therapeutic Patents*, 4 (1994)1461-1469.
- Jensen, J.L., L.E. Appel, J.H. Clair and G.M. Zentner, "Variables That Affect the Mechanism of Drug Release from Osmotic Pumps Coated with Acrylate/Methacrylate Copolymer Latexes," *J. Pharm. Sci.*, 84(1995)530-533.
- Thombre, A.G., L.E. Appel, M.B. Chidlaw, P.D. Daugherty, F. Dumont, L.A.F. Evans and S.C. Sutton, "Osmotic Drug Delivery Using Swellable-Core Technology," *J. Control. Release*, 94(2004)75-89.
- Ray, R., L. Graham, R. Falk, J.R. Shockey, L.E. Appel, K. Dhanasekharan and L. S. Mohan, "Understanding Fluid-Bed Coating," *Fluent News*, Spring 2006, S14.
- Lo, J.B., L.E. Appel, S.M. Herbig, S.B. McCray and A.G. Thombre, "Formulation Design and Pharmaceutical Development of a Novel Controlled Release Form Of Azithromycin For Single Dose Therapy," *Drug Dev Ind Pharm*, 35(2009)1522-1529.
- Appel, L.E., J.R. Shockey, M.J. Shaffer and J. Chu. "Process Design and Development for Novel Pharmaceutical Dosage Forms." *Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing*. Ed. David J. am Ende. Hoboken: John Wiley & Sons, Inc., 2011. 663-672.

Patents / Patent Applications

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Appel, L.E. and G.M. Zentner, "Process for Producing a Tablet Core Aperture," U.S. Patent No. 5,256,440 (1993).

Appel, L.E., G.M. Zentner and G.A. Rodan, "Implant Therapy for Bone Growth Stimulation," published as World Intellectual Property Organization Publication No. WO 93/15767 A1 (1993).

Appel, L.E., D.T. Friesen, W.J. Curatolo, J.A.S. Nightingale and A.G. Thombre, "Matrix Controlled Release Device," U.S. patent pending, published as European Patent Application No. 00300546.9 (2000).

Curatolo, W. J., S.C. Sutton and L.E. Appel, "Controlled Release Pharmaceutical Dosage Forms of a Cholesteryl Ester Transfer Protein Inhibitor," U.S. patent pending Application No. 10/349,600 (2003), published as World Intellectual Property Organization Publication No. WO 03/063868 A1 (2003).

Appel, L.E., W.J. Curatolo, S.M. Herbig, J.A.S. Nightingale and A.G. Thombre, "Controlled Release By Extrusion of Solid Amorphous Dispersions of Drugs," U.S. Patent No. 6,706,283 B1 (2004), continued in U.S. Patent No. 7,550,158 B2 (2009).

Curatolo, W.J., K.C. Waterman, A.G. Thombre, M.B. Fergione, M.C. Roy, L.E. Appel, D. Supplee, D.T. Friesen, M.B. Chidlaw and R.A. Beyerinck, "Hydrogel-Driven Layered Drug Dosage Form," U.S. Patent No. 6,899,896 B2 (2005).

Appel, L.E., M.D. Crew, D.T. Friesen, D.K. Lyon, S.B. McCray, R.J. Ray and J.B. West, "Azithromycin Multiparticulate Dosage Forms By Liquid-Based Processes," U.S. patent pending Application No. 11/004,453 (2004), published as World Intellectual Property Organization Publication No. WO 2005/053640 A2 (2005).

Appel, L.E., R.J. Ray, D.D. Newbold, D.T. Friesen, S.B. McCray, J.B. West, D.K. Lyon, M.D. Crew, S.R. Lemott, S.M. Herbig and J.B. Lo, "Azithromycin Multiparticulate Dosage Forms By Melt-Congel Processes," U.S. Patent pending Application No. 11/003,856 (2004), published as Publication No. US 2005/0158391 A1 (2005).

Appel, L.E., M.D. Crew, D.T. Friesen, D.D. Newbold and R.J. Ray, "Controlled Release Dosage Forms of Azithromycin," U.S. patent pending Application No. 11/003,855 (2004), published as World Intellectual Property Organization Publication No. WO 2005/053654 A1 (2005).

Appel, L.E., M.D. Crew, D.T. Friesen, J.B. Lo, D.K. Lyon, S.B. McCray, D.D. Newbold, R.J. Ray and J.B. West, "Controlled Release Multiparticulates Formed with Dissolution Enhancers," U.S. patent pending Application No. 11/003,853 (2004), published as World Intellectual Property Organization Publication No. WO 2005/053639 A2 (2005).

Appel, L.E., M.D. Crew, D.T. Friesen, S.M. Herbig, J.B. Lo, D.K. Lyon, S.B. McCray, R.J. Ray and J.B. West, "Multiparticulate Crystalline Drug Compositions Containing a Poloxamer and a Glyceride," U.S. patent pending, published as World Intellectual Property Organization Publication No. WO 2005/053652 A1 (2005).

Hagen, T.A., S.M. Herbig, J.B. Lo, A.G. Thombre, L.E. Appel, M.D. Crew, D.T. Friesen, K.D. Lyon, S.B. McCray and J.B. West, "Azithromycin Dosage Forms With Reduced Side Effects," published as World Intellectual Property Organization Application No. WO 2005/053650 (2005).

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Ahmed, I., L.E. Appel, W.C. Babcock, D.T. Friesen, S.M. Herbig, D.K. Lyon, S.L. Shamblin, R.M. Shanker, D.T. Smithey, S.C. Sutton, A.G. Thombre and K.C. Waterman, "Sustained Release Dosage Forms of Ziprasidone," U.S. patent pending Application No. 10/931,143 (2004), published as World Intellectual Property Organization Publication No. WO 2005/020929 A2 (2005).

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Appel, L.E., D.T. Friesen, S.M. Herbig and A.G. Thombre, "Controlled Release Dosage Forms Combining Immediate Release and Sustained Release of Low-Solubility Drug," U.S. patent pending Application No. 11/748,134 (2007), published as World Intellectual Property Organization Publication No. WO 2006/024949 A2 (2006).

Appel, L.E., W.C. Babcock, D.T. Friesen, R.J. Ray, S.L. Shamblin, R.M. Shanker and D.T. Smithey, "Pharmaceutical Dosage Forms Comprising A Low-Solubility Drug and Polymer," U.S. patent pending Application No. 11/747,468 (2005), published as World Intellectual Property Organization Publication No. WO 2006/024944 A2 (2006).

Appel, L.E., W.J. Curatolo, D.T. Friesen, S.M. Herbig, S.R. LeMott, J.B. Lo, D.K. Lyon, S.B. McCray and J.B. West, "Enteric Coated Azithromycin Multiparticulates," U.S. patent pending Application No. 11/722,364 (2005), published as World Intellectual Property Organization Publication No. WO 2006/067576 A1 (2006).

Appel, L.E., D.T. Friesen, D.K. Lyon, S.B. McCray and J.R. Shockey, "Multiparticulates Comprising Low-Solubility Drugs and Carriers that Result in Rapid Drug Release," U.S. patent pending Application No. 11/920,468 (2006), published as World Intellectual Property Organization Publication No. WO 2006/131806 A3 (2006).

Appel, L.E., C.A. Brown, J.S. Burton, H. Huatan, N. Loggia and D. Supplee, "Osmotic Bi-Layer Tablet," U.S. patent pending, published as World Intellectual Property Organization Publication No. WO 2007/057762 A3 (2007).

Friesen, D.T., L.E. Appel, J.R. Shockey, S. Konagurthu and E.D. LaChapelle, "Multiparticulates of Spray-Coated Drug and Polymer on a Melttable Core," U.S. Patent No. 10,357,462 (2007).

Appel, L.E., W.J. Curatolo, S.M. Herbig, J.A.S. Nightingale and A.G. Thombre, "Osmotic System for Delivery of Solid Amorphous Dispersions of Drugs," European Patent No. EP1027888 B1 (2009).

Ray, R.J., L.E. Appel, D.D. Newbold, D.T. Friesen, S.B. McCray, D.K. Lyon, J.B. West, M.D. Crew and J.R. Shockey, "Extrusion Process For Forming Chemically Stable Drug Multiparticulates," U.S. Patent No. 7,625,507 B2 (2009).

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Ray, R.J., L.E. Appel, D.T. Friesen, M.D. Crew and J.R. Shockey, "Multiparticulate Compositions With Improved Stability," U.S. Patent No. 7,736,672 (2010).

Tidmarsh, G. and L.E. Appel, "NSAID Dose Unit Formulations With H₂-Receptor Antagonists and Methods of Use," U.S. patent pending, published as World Intellectual Property Organization Publication No. WO 2010/009432 A1 (2010).

Friesen, D.T., M.D. Crew, R.J. Ray and L.E. Appel, "Method of Making Pharmaceutical Multiparticulates," U.S. Patent No. 7,951,403 (2011).

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Appel, L.E., D.T. Friesen, E.D. LaChapelle, S. Konagurthu, R.F. Falk and J.P. Reo, "Taste-Masked Drugs In Rupturing Multiparticulates," U.S. Patent No. 8,236,349 (2012).

Hagan, J.P., P.N. Roberts, M.D. Booth, D. Supplee and L.E. Appel, "Methods and Compositions for Treating Obesity, Blood Glucose Conditions and Improving Glycemic Control," U.S. patent pending Application No. 62/021,886 (2014).

Hagan, J.P., P.N. Roberts, M.D. Booth, D. Supplee and L.E. Appel, "Methods and Compositions for Treating Obesity, Blood Glucose Conditions and Improving Glycemic Control," U.S. patent pending Application No. 62/021,892 (2014).

Hagan, J.P., P.N. Roberts, M.D. Booth, D. Supplee and L.E. Appel, "Methods and Compositions for Treating Obesity, Blood Glucose Conditions and Improving Glycemic Control," U.S. patent pending Application No. 62/021,895 (2014).

Hagan, J.P., P.N. Roberts, M.D. Booth, D. Supplee and L.E. Appel, "Methods and Compositions for Treating Obesity, Blood Glucose Conditions and Improving Glycemic Control," U.S. patent pending Application No. 62/021,896 (2014).

Hagan, J.P., P.N. Roberts, M.D. Booth, D. Supplee and L.E. Appel, "Methods and Compositions for Treating Obesity, Blood Glucose Conditions and Improving Glycemic Control," U.S. patent pending Application No. 62/021,902 (2014).

Hagan, J.P., P.N. Roberts, M.D. Booth, D. Supplee and L.E. Appel, "Methods and Compositions for Treating Obesity, Blood Glucose Conditions and Improving Glycemic Control," U.S. patent pending Application No. 62/021,904 (2014).

Hagan, J.P., P.N. Roberts, M.D. Booth, D. Supplee and L.E. Appel, "Methods and Compositions for Treating Obesity, Blood Glucose Conditions and Improving Glycemic Control," U.S. patent pending Application No. 62/021,912 (2014).

Hagan, J.P., P.N. Roberts, M.D. Booth, D. Supplee and L.E. Appel, "Methods and Compositions for Treating Obesity, Blood Glucose Conditions and Improving Glycemic Control," U.S. patent pending Application No. 62/021,919 (2014).

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Appel, L.E., R.A. Beyerinck, M.B. Chidlaw, W.J. Curatolo, D.T. Friesen, K.L. Smith and A.G. Thombre, "Hydrogel-Driven Drug Dosage Form," U.S. Patent No. 9,028,870 (2015).

Appel, L.E., J.E. Byers, M.D. Crew, D.T. Friesen, B.C. Hancock and S.J. Schadtler, "Immediate Release Dosage Forms Containing Solid Drug Dispersions," U.S. Patent No. 9,211,261 (2015).

Appel, L.E., J.R. Shockey and D. C. Schelling, "Palatable Compositions Including Sodium Phenylbutyrate and Uses Thereof," U.S. Patent No. 11,154,521 (2021).

Presentations

Seminoff, L.A., S.Y. Jeong, and S.W. Kim, "A Self-Regulating Insulin Delivery System—A Novel Approach," paper presented to the Basic Pharmaceutical Section, 37th National Meeting of the American Pharmaceutical Association Academy of Pharmaceutical Sciences, Philadelphia, Pennsylvania, October 28-November 1, 1984.

Seminoff, L.A., and S.W. Kim, "*In Vitro* Characterization of a Self-Regulating Insulin Delivery System," paper presented to the Pharmaceuticals and Drug Delivery Section, First National Meeting of the American Association of Pharmaceutical Scientists, Washington, D.C., November 2-6, 1986.

Seminoff, L.A., G. Olsen, J. Zheng, D. Wilson, and S.W. Kim, "Self-Regulated Insulin Release," paper presented to the Insulin Delivery Minisymposium at the 15th International Symposium on Controlled Release of Bioactive Materials, Basel, Switzerland, August 15-19, 1988.

Seminoff, L.A., G. Olsen, J. Fox, J. Zheng, D. Wilson, and S.W. Kim, "Self-Regulated Insulin Release," presentation to the Regulated Drug Delivery Systems Session, Pharm Tech Conference '88, East Rutherford, New Jersey, September 26-28, 1988.

Seminoff, L.A., J.L. Fox, and S.W. Kim, "A Mathematical Model for the Competitive Binding of Glucose and Glycosylated Insulin on a Con A Column," paper presented to the Pharmaceuticals and Drug Delivery Section, Third National Meeting of the American Association of Pharmaceutical Scientists, Orlando, Florida, October 30-November 3, 1988.

LeCluyse, E.L., J.A. Fix, L.A. Seminoff, and S. Sutton, "Relationship Between Drug Absorption Enhancing Activity and Membrane Perturbing Effects of Acylcarnitines," paper presented at the Fourth National Meeting of the American Association of Pharmaceutical Scientists, Atlanta, Georgia, October 22-26, 1989.

Appel, L.E., and G. Zentner, "Release from Osmotic Tablets Coated With Modified Aquacoat™ Lattices," paper presented at the 17th International Symposium on Controlled Release of Bioactive Materials, Reno, Nevada, July 22-25, 1990.

Appel, L.E., and G. Zentner, "Utilization of Statistical Experimental Design in the Formulation of Modified Cellulose Acetate Latex Coating," paper presented to the Pharmaceuticals and Drug Delivery Section, Sixth National Meeting of the American Association of Pharmaceutical Scientists, Washington, D.C., November 17-21, 1991.

Presentations (continued)

Appel, L.E., "Novel Approaches to Insulin Delivery," invited lecture before the Kansas City Discussion Group of the American Association of Pharmaceutical Scientists, Kansas City, Missouri, October 27, 1992.

Appel, L.E., R. Balena, M. Cortese, G. Rodan, G. Seedor, and G. Zentner, "Prostaglandin E₂/Poly (orthoester) Implant for Bone Growth Promotion," paper presented to the Pharmaceutics and Drug Delivery Section of the Seventh National Meeting of the American Association of Pharmaceutical Scientists, San Antonio, Texas, November 15-19, 1992.

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Appel, L.E., L. Rajewski, P. Leppert, and G. Zentner, "*In Vivo* Evaluation of Monoolein Cubic Phase Gels in a Mouse Model," paper presented to the Pharmaceutics and Drug Delivery Section of the 11th National Meeting of the American Association of Pharmaceutical Scientists, Seattle, Washington, October 27-31, 1996.

Appel, L.E., and D.T. Smithey, "Solubilization For Enhanced Colonic Absorption," presentation at the 30th International Symposium and Exhibition of the Controlled Release Society, Glasgow, Scotland, July 24-25, 2003.

Appel, L.E., E. Eisenhart, and J. Lo, "Melt-Congel Multiparticulates," presentation at the 30th International Symposium and Exhibition of the Controlled Release Society, Glasgow, Scotland, July 24-25, 2003.

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Chu, J., L.E. Appel, and J.R. Shockey, "Development of Adipiplon Immediate Release and Delayed Release Multiparticulate Formulation for the Treatment of Insomnia," poster for the FDD Section of the AAPS Annual Meeting 2009.

Appel, L.E., "Amorphous Solid Dispersions", invited presenter by Pharmatek for the Pharmatek U Seminar Series, San Diego, CA, July 30, 2009.

Appel, L.E., "Formulation Design Considerations", invited presenter by Colorcon for the webinar titled Design and Performance of Oral Osmotic Technology, November 15, 2011.

Appel, L.E., "Industry and Consulting Perspectives on Early Development," invited presenter by Patheon at the seminar titled Moving from Molecule to Clinical Trial — Overcoming Challenges in the Early Development of Small Molecules, San Diego, CA, December 13, 2011.