

# JAMES VINCENT McARDLE, Ph.D.

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## PROFESSIONAL EXPERIENCE

### McARDLE & ASSOCIATES

Present

#### *President*

Provide CMC consulting service to the pharmaceutical industry for both small molecules and oligonucleotides, particularly in CMC development strategy, worldwide CMC regulatory strategy, GMP, synthesis and scale up, analytical development, stability, preparing applications for clinical trial or marketing authorization, due diligence, out-of-specification investigations, and implementing 21<sup>st</sup>-century quality systems. Assist clients with outsourcing decisions and placement.

### ARCHEMIX CORPORATION, CAMBRIDGE, MA

2006 - 2008

#### *Vice President, Chemistry, Manufacturing, and Controls*

Provide scientific and managerial leadership to the analysts, chemists, and formulators. Establish CMC regulatory strategy. Supervise contract laboratories and manufacturers. Contribute to management committees.

### McARDLE & ASSOCIATES

2006

#### *President*

As above.

### ISIS PHARMACEUTICALS, Carlsbad, CA

1999 – 2005

#### *Vice President, Quality Assurance*

2005

Provided strategic and managerial leadership to the Quality Assurance department. Ensure all development operations are performed under appropriate standards of GLP, GMP, and GCP.

- Hosted FDA project managers for three-day visit to Isis; assisted in organizing oligonucleotide workshop at FDA; presented at workshop a tutorial on CMC of oligonucleotides.
- Led team in assessment of risk in drug substance synthesis, resulting in a more reliable process.
- Investigated thoroughly a clinical trial that revealed anomalous data and presented findings to senior management resulting in confidence in interpreting the data.

#### *Vice President, Analytical Development and Quality Control*

1999 – 2005

Provided scientific and managerial leadership to members of Analytical Development and Quality Control Department within the Development Chemistry and Pharmaceuticals group.

- Replaced all important analytical methods with new technology, resulting in a more efficient operation that enabled a 28% reduction in staff.
- Led effort to characterize impurities and degradation products, enabling a series of process improvements that increased purity of drug substances from 80% to 90%.
- Proposed and implemented a new process to reduce time to first clinical trial while reducing risk resulting in overall cost savings and competitive advantage.
- Transferred technology to our development partners, thus conserving in-house resource for new projects.
- Supervised preparation of numerous regulatory documents in support of worldwide regulatory submissions, permitting on-time start of planned clinical trials.

**SMITHKLINE BEECHAM PHARMACEUTICALS, Upper Merion, PA****1992 – 1999*****Group Director, Analytical Sciences***

Provided scientific and managerial leadership to the worldwide Analytical Sciences Department within Chemical Development, maintained department's state-of-the-art capabilities in analysis of small molecules and recombinant proteins, and supervised the environmental research lab.

- Supervised submission of our data for numerous successful INDs, CTXs, NDAs, and MAAs, including those for *Requip*<sup>TM</sup>, *Hycamtin*<sup>TM</sup>, *Kredex*<sup>TM</sup>, *Teveten*<sup>TM</sup>, and *Augmentin*<sup>TM</sup> IV.
- Reorganized department from function-based to project-based, enabling direct support of project teams and building depth of experience with individual compounds.
- Assembled and led *ad hoc* team to investigate specification failure of US launch supplies of major product, culminating in saving US launch supplies and minimizing delay to launch.
- Led the introduction of new technology including NIR and LC-NMR resulting in more efficient operations.

**SMITHKLINE BEECHAM PHARMACEUTICALS, Tonbridge, England****1988 – 1992*****Director, Analytical Chemistry-UK*****1990 - 1992**

Performed functions similar to those of next position, but without responsibility for analytical development of protein products or the environmental research lab.

***Assistant Director, Analytical Chemistry*****1988 – 1990**

Accepted this position to help expand the Tonbridge site and assist in its conversion from a manufacturing operation to a center for drug development.

**SMITH KLINE AND FRENCH LABORATORIES, Philadelphia and Upper Merion, PA****1983 – 1988*****Senior Investigator, Analytical, Physical, and Structural Chemistry***

Principal duties were to characterize and analyze drug substances and to serve on drug-development project teams.

**EDUCATION**

- **National Institutes of Health Postdoctoral Fellow**  
Department of Chemistry, University of California, Berkeley, CA.  
Research Director: Kenneth N. Raymond  
Research Topic: Microbial Iron Transport Compounds
- **Ph.D.**  
Department of Chemistry, California Institute of Technology, Pasadena, CA.  
Research Director: Harry B. Gray  
Research Topic: Electron Transfer Kinetics of Redox Proteins
- **Sc.B. (Honors)**  
Department of Chemistry, Brown University, Providence, RI.  
Research Director: Richard Eisenberg  
Research Topic: Active Species Bound to Metal Complexes

**AWARDS**

- “**Simply the Best**” award for leading the launch supplies analysis team, SmithKline Beecham.
- **Alan Berman Research Publication Award**, Department of the Navy, Naval Research Laboratory.

## ADDENDUM

## SELECTED AFFILIATIONS

- **Member**, ICH Expert Working Group on Quality. Pharmaceutical Research and Manufacturers of America (PhRMA), 1994 – 2005
  - Topic Leader for development of ICH guideline Q3C, Residual Solvents
  - Deputy Topic Leader for development of ICH guideline M4Q, the Quality Section of the Common Technical Document (CTD-Q)
  - Deputy Topic Leader for development of ICH guideline Q8, Pharmaceutical Development
- **Deputy Coordinator** of all ICH Quality Topics for Pharmaceutical Research and Manufacturers of America, 1998-2003.
- **Member**, Quality Technical Group, Pharmaceutical Research and Manufacturers of America, 2005
- **Chairman**, Manufacturing and Marketing section, Asia Pacific Economic Cooperation (APEC) initiative, Life Sciences Innovation Forum (LSIF), 2003-2004
- **Member**, Analytical R&D Steering Committee, Pharmaceutical Research and Manufacturers of America, 1993-2001. **Chairman**, June, 1997 through December, 1999.
- **Member**, Technical Steering Committee, Pharmaceutical Research and Manufacturers of America. Liaison to Regulatory Affairs Coordination Committee, 1998-2000.
- **Member**, Preclinical Drug Safety Steering Committee, Pharmaceutical Research and Manufacturers of America. 1997-1998
- **Chairman**, Compound and Products Specifications Committee (R&D Worldwide), SmithKline Beecham 1993-1999
- **Member**, Compendial Standards Committee (Worldwide Technical Operations); SmithKline Beecham 1997-1999

**SELECTED COURSES, SYMPOSIA AND PRESENTATIONS**

- DIA and FDA co-sponsored conference, “Third Conference on Oligonucleotide-Based Therapeutics;” member of planning committee, invited speaker “Reporting, Identification, and Qualification Thresholds,” panel member, and session chair; Bethesda, MD, March, 2010
- “Sequencing Synthetic Oligonucleotides” presentation; IBC Conference on Oligonucleotide and Peptide Technology and Product Development; Boston, MA; invited speaker, April 2010
- DIA and FDA co-sponsored conference, “Second Conference on Oligonucleotide-Based Therapeutics;” member of planning committee, invited speaker “What Constitutes Proof of Structure?”, panel member, and session chair; Falls Church, VA, September, 2008
- “Do We Really Have to do All this Work?” presentation; IBC Conference on Oligonucleotide and Peptide Technology and Product Development; Las Vegas, NV; invited speaker, May 2007
- DIA and FDA co-sponsored conference, “Oligonucleotide-Based Therapeutics;” member of planning committee and session chair; Washington, DC; April, 2007
- “Chemistry, Manufacturing, and Control of Oligonucleotides” presentation; FDA Center for Drug Evaluation and Research (CDER) course on "Antisense and Oligonucleotide Therapeutics;” Bethesda, MD; invited speaker, November, 2005
- “The Comprehensive Quality Overall Summary” presentation; FDA AAPS Pharmaceutical Quality Assessment Workshop; Bethesda, MD; invited speaker, October 2005
- Introduction to Good Clinical Practices; DIA Training Course, San Francisco, CA, March 2005
- APEC LSIF II; Manufacturing and Marketing session chair, Penang, Malaysia, September 2004
- “Risk-based Approaches to Laboratory Systems” presentation; GMP by the Sea Conference; invited speaker and workshop moderator, Cambridge, MD, August 2004
- “Quality by Design” presentation; Drug Information Association (DIA) Annual Meeting; invited speaker, Washington, DC, June 2004
- APEC LSIF Expert Group Meeting; invited participant, Washington, DC, June 2004
- APEC LSIF Expert Group Meeting; invited participant, Khon Kaen, Thailand, February 2004
- “ICH Guidelines and ‘Tides” presentation; EuroTIDES Oligonucleotide and Peptide Technology Conference; Berlin, Germany; invited speaker, November 2003
- APEC LSIF; invited speaker and workshop leader, Phuket, Thailand, August 2003
- “Characterization of Synthetic Oligonucleotides” presentation; Conference on Pharmaceutical Analysis (University of Wisconsin-Madison); invited speaker, August 2002
- GMP by the Sea Conference; session moderator for laboratory issues, Hilton Head Island, SC, August 2002
- AAPS/FDA Workshop: Drug Substance and Drug Product Specifications; session moderator and invited speaker, Arlington, VA, March 2002
- Q7A Training Workshop; Newport Beach, CA, February 2002
- AAPS/FDA Specification Workshop; Washington, D.C.; December 2001
- ICH 5 International Conference; invited speaker; San Diego, CA; November 2000
- PhRMA Bulk Pharmaceuticals Committee Technical Symposium; invited speaker; Braselton, GA, June 1999
- Analytical Biochemistry in Process Monitoring and Validation; Massachusetts Institute of Technology, Cambridge, MA; August 1994
- Analytical Methods for Proteins; ACS Short Course, Atlanta, GA; March 1993
- Creative Leadership for R&D Managers; Manchester Business School, Manchester, England; June 1991

## PUBLICATIONS

1. Matthias Kretschmer, Gary Lavine, James McArdle, Satya Kuchimanchi, Veeravagu Murugaiah, and Muthiah Manoharan, "An Automated Algorithm for Sequence Confirmation of Chemically Modified Oligonucleotides by Tandem Mass Spectrometry," *Analytical Biochemistry*, 2010, 405(2), 213-23.
2. Kurata C., Bradley, K., Gaus, H., Luu, N., Cedillo, I., Ravikumar, V.T., Van Sooy, K., McArdle, J.V., Capaldi, D.C., "Characterization of High Molecular Weight Impurities in Synthetic Phosphorothioate Oligonucleotides," *Bioorganic & Medicinal Chemistry Letters*, 16, (2006), 607-614.
3. Claus Rentel, Xiaojing Wang, Michael Batt, Christine Kurata, Jay Oliver, Hans Gaus, Achim Krotz, James V. McArdle and Daniel Capaldi, "Formation of Modified Cytosine Residues in the Presence of Depurinated DNA," *Journal of Organic Chemistry*, 70, 7841-7845, 2005.
4. Hans Gaus, Phil Olsen, Kent Van Sooy, Claus Rentel, James V. McArdle and Daniel Capaldi, "Trichloroacetaldehyde Modified Oligonucleotides," *Bioorganic & Medicinal Chemistry Letters*, 15, 4118-4124, 2005.
5. Daniel C. Capaldi, Hans J. Gaus, Recaldo L. Carty, Max N. Moore, Brett J. Turney, Stella D. Decottignies, James V. McArdle, Anthony N. Scozzari, Vasulinga T. Ravikumar and Achim H. Krotz, "Formation of 4,4'-dimethoxytrityl-C-phosphonate Oligonucleotides," *Bioorganic & Medicinal Chemistry Letters*, 14, 4683-4690, 2004.
6. Alex M. Hoinowski, Sol Motola, Richard J. Davis, and James V. McArdle, "Investigation of Out-of-Specification Results," *Pharmaceutical Technology*, January, 2002.
7. J.C. Connelly, R. Hasegawa, J.V. McArdle and M.L. Tucker, "ICH Guideline – Residual solvents," *Pharmeuropa* Vol. 9, No. 1 – Supplement, 1997.
8. Usha V. Nair, Samuel S.C. Chang, Daniel W. Armstrong, Yasir Y. Rawjee, Drake S. Eggleston and James V. McArdle, "Elucidation of Vancomycin's Enantioselective Binding Site Using Its Copper Complex," *Chirality* 8:590-595, 1996.
9. E. McCafferty and James V. McArdle, "Corrosion Inhibition of Iron in Acid Solutions by Biological Siderophores," *Journal of the Electrochemical Society*, 142, No. 5, 1995.
10. Sean D. McCrossen, Robert G. Giles, Paul W. Oxley and James V. McArdle, "High-performance Liquid Chromatography Procedure for the Determination of Purity of di-N-n-propylamine," *Journal of Chromatography A*, 623, 229-235, 1992.
11. James V. McArdle and Gerald E. Bossard, "Electrochemical Studies of Gold(I) and Gold (III) Complexes of Bis(diphenylphosphines)," *J. Chemical Society, Dalton Trans.*, 2219-2224, **1990**.
12. James V. McArdle, Gerald E. Bossard and Drake Eggleston, "Redox and Structural Studies of Gold (I) and Gold (III) Complexes of bis(diphenylphosphines)," *Journal of Inorganic Biochemistry*, 36, Issues 3-4, 161, 1989.
13. Glen D. Hoke, Glenn F. Rush, Gerald E. Bossard, James V. McArdle, Bruce D. Jensen, and Christopher K. Mirabelli, "Mechanism of Alterations in Isolated Rat Liver Mitochondrial Function Induced by Gold Complexes of Bidentate Phosphines," *The Journal of Biological Chemistry*, 263, 11203-11210, 1988.
14. Drake S. Eggleston, James V. McArdle, and Gary E. Zuber, "Synthesis and Structure of u-[trans-1,2-bis(diphenylphosphino)ethylene]bis[chlorogold(I)]," *J. Chem. Soc., Dalton Trans.*, 677-679, 1987.

15. S. Arif Kazmi, A. Lee Shorter, and James V. McArdle, "Mechanism of Iron Release from Microbial Iron Transport Compounds," Studies in Organic Chemistry, Vol. 26, New Trends in Natural Product Chemistry, A. U. Rahman and P.W. Le Quesne, Eds., Elsevier, The Netherlands, 1986.
16. S. Arif Kazmi, A. Lee Shorter, and James V. McArdle, "Kinetics of Reduction of Ferrichrome and Ferrichrome A by Chromium (II), Europium(II), Vanadium(II), and Dithionite," Inorganic Chemistry, 23, 4332-4341, 1984.
17. Jeffrey P. Robinson, E.F. Wawrousek, James V. McArdle, George Coyle and Isadore Adler, "X-Ray Photoelectron and Electron Spin Resonance Spectra of Iron(III) Parabactin," Inorganica Chimica Acta, 92, L19-L21, 1984.
18. James V. McArdle and Michael R. Hoffman, "Kinetics and Mechanism of the Oxidation of Aqueous Sulfur Dioxide by Hydrogen Peroxide at Low pH," Journal of Physical Chemistry, 87, 5425-5429, 1983.
19. James V. McArdle, review of Advances in Inorganic and Bioinorganic Mechanisms, Volume 1, edited by A.G. Sykes, Academic Press, London, 1982. Invited book review, Journal of the American Chemical Society, 105, 6200, 1983.
20. James V. McArdle, Eric de Laubenfels, A. Lee Shorter, and Herman L. Ammon, "The Synthesis and Structure of trans-Bis(methylnicotinate)aquatrifluorochromium(III)," Polyhedron, 1, 471-474, 1982.
21. S. Arif Kazmi, A. Lee Shorter, and James V. McArdle, "Kinetics of Reduction of Ferrioxamine B by Chromium(II), Vanadium(II), and Dithionite," Journal of Inorganic Biochemistry, 17, 269-281, 1982.
22. E.F. Wawrousek and James V. McArdle, "Spectroelectrochemistry of Ferrioxamine B, Ferrichrome, and Ferrichrome A," Journal of Inorganic Chemistry, 17, 169-183, 1982.
23. S. Arif Kazmi and James V. McArdle, "Kinetics of Formation of Ferrioxamine B," Journal of Inorganic Biochemistry, 15, 153-162, 1981.
24. S. Arif Kazmi and James V. McArdle, "Kinetics of Formation of Bis- and Tris(acetohydroxamato)Fe(III)," Journal of Inorganic and Nuclear Chemistry, 43, 3031-3034, 1981.
25. Jeffrey P. Robinson and James V. McArdle, "Electrochemistry of Ferric Complexes of Parabactin and Parabactin A," Journal of Inorganic and Nuclear Chemistry, 43, 1951-1953, 1981.
26. James V. McArdle, "Iron Compounds," Encyclopedia of Chemical Technology. Vol 13, Third Edition, Wiley and Sons, New York, 764-788, 1981. Invited Contribution.
27. Wesley R. Harris, Carl J. Carrano, Stephen R. Cooper, Stephen R. Sofen, Alex E. Avdeef, James V. McArdle, and Kenneth N. Raymond, "Coordination Chemistry of Microbial Iron Transport Compounds. 19. Stability Constants and Electrochemical Behavior of Ferric Enterobactin and Model Complexes," Journal of the American Chemical Society, 101, 6097-6104, 1979.
28. James V. McArdle, Stephen R. Sofen, Stephen R. Cooper, and Kenneth N. Raymond, "Coordination Chemistry of Microbial Iron Transport Compounds. 13. Preparation and Chirality of the Rhodium(III) Enterobactin Complex and Model Tris(catecholato)rhodium(III) Analogues," Inorganic Chemistry, 17, 3075-3078, 1978.
29. Stephen R. Cooper, James V. McArdle, and Kenneth N. Raymond, "Siderophore Electrochemistry: Relation to Intracellular Iron Release Mechanism," Proceedings of the National Academy of Science (USA), 75, 3551-3554, 1978.

30. Harry B. Gray, Catherine L. Coyle, David M. Dooley, Paula J. Grunthaner, Jeffrey W. Hare, Robert A. Holwerda, James V. McArdle, David R. McMillin, Jill Rawlings, Robert C. Rosenberg, N. Sailasuta, Edward I. Solomon, P.J. Stephens, Scot Wherland, and James A. Wurzbach, "Structure and Electron Transfer Reactions of Blue Copper Proteins," Bioinorganic Chemistry, Kenneth N. Raymond, Ed., American Chemical Society, Washington, D.C., 145-155, 1977.
31. James V. McArdle, Kathryn Yocum, and Harry B. Gray, "Kinetic Studies of the Oxidation of Horse Heart Ferrocycytochrome *c*, *Pseudomonas aeruginosa* Ferrocycytochrome  $c_{551}$ ,  $\text{Co}(\text{terpy})_2^{2+}$ , and  $\text{Ru}(\text{NH}_3)_5\text{py}^{2+}$  by  $\text{Tris}(1,10\text{-phenanthroline})\text{cobalt(III)}$  Ions," Journal of the American Chemical Society, 99, 4141-4145, 1977.
32. James V. McArdle, Catherine L. Coyle, Harry B. Gray, Gerald S. Yoneda, and Robert A. Holwerda, "Kinetics Studies of the Oxidation of Blue Copper Proteins by  $\text{Tris}(1,10\text{-phenanthroline})\text{cobalt(III)}$  Ions," Journal of the American Chemical Society, 99, 2483-2489, 1977.
33. James V. McArdle, Harry B. Gray, Carol Creutz, and Norman Sutin, "Kinetic Studies of the Oxidation of Ferrocycytochrome *c* from Horse Heart and *Candida krusei* by  $\text{Tris}(1,10\text{-phenanthroline})\text{cobalt(III)}$ ," Journal of the American Chemical Society, 96, 5737-5741, 1974.
34. Arthur J. Schultz, James V. McArdle, Gyaneshwari P. Khare, and Richard Eisenberg, "Carbene Precursors and Metal Complexes. The Synthesis and Structure of Dichloro(difluoromethyl)carbonylbis(triphenylphosphine)iridium(III),  $\text{IrCl}_2(\text{CHF}_2)(\text{CO})(\text{PPh}_3)_2$ ," Journal of Organometallic Chemistry, 72, 415-423, 1974.
35. James V. McArdle, Arthur J. Schultz, Brian J. Corden, and Richard Eisenberg, "Coordination of the Arylazo Group. Molecular Structure of Trichloro(*p*-tolylazo)bis(triphenylphosphine)ruthenium(II)-Acetone,  $\text{RuCl}(\text{pN}_2\text{C}_6\text{H}_4\text{Me})(\text{PPh}_3)_2\text{Me}_2\text{CO}$ ," Inorganic Chemistry, 12, 1676-1681, 1973.
36. Arthur J. Schultz, Gyaneshwari P. Khare, James V. McArdle, Richard Eisenberg, "Metal Complex Promoted Decomposition of the Carbene Precursor Chlorodifluoroacetate," Journal of the American Chemical Society, 95, 3434-3436, 1973.