Paul A. Harmon CURRICULUM VITAE

I. Personal

A. Name: Paul A. Harmon

B. Business Address: **Pharxmon Consulting, LLC**
P.O. Box 300
Eagleville, PA 19408

C. Work Phone: (267)-520-4693
D. website: https://pharxmonconsulting.com/

II. Education

School	Date	Major	Degree Received
University of Pittsburgh **Pittsburgh, PA**	**1984-90**	**Analytical Chemistry**	**Ph. D.**
University of Delaware **Newark, DE**	**1980-84**	**Chemistry**	**B.S.**

III. Employment and Academic History

PhaRxmon Consulting, LLC, Eagleville, PA **September 2016-current**
Owner and Chief Scientific Officer **https://pharxmonconsulting.com/**

Bringing 25 years of lab-bench experience in pharmaceutical analytical chemistry to a wide variety of virtual and brick-and-mortar pharmaceutical clients worldwide. Solving developmental problems with deep expertise in HPLC method development, oxidative drug degradation and inhibition, drug dissolution processes (including bio-relevant dissolution concepts), and the unique aspects of developing amorphous solid dispersion drug products. Recently, contributed to the mechanistic understanding of nitrosamine formation in drug products (authored publications 1 and 2).

Merck and Co. Inc. **1994-2016**

1997-2016 Senior *Research Fellow*, *Senior Investigator*, *Distinguished Senior Investigator*. (Analytical Sciences, Merck Research Laboratories, West Point)

Led small analytical groups responsible for development of Phase I/II programs, including development/validation of HPLC stability indicating methods, content uniformity, and dissolution methods. Provided critical analytical support for optimization of formulations as well as providing data to guide manufacturing process selection. Working in the laboratory in this analytical/formulation/process nexus for almost 20 years on nearly 100 compounds, Dr. Harmon had the opportunity to develop expertise and scientific publications in several areas other than HPLC method development:

*Understanding and predicting drug oxidation issues. Oxidation of drugs on stability appeared to be the least predictable and the least understood chemical transformation in Dr. Harmon's early experiences. As a result, Dr. Harmon took the opportunity to do research in that area while supporting developmental programs. Dr. Harmon published nine research articles (pub. 3, 6, 9, 11, 14, 16, 17 and 18) on this topic including a book Chapter on Oxidative Susceptibility testing (9). As a result, more predictive oxidative stress tests have since been employed by the industry, and a new peroxyl radical test has been developed and published by Dr. Harmon (16).

* Excipient driven degradation and API form changes: oxidation can often be enhanced by certain excipients which carry oxidizable impurities (see ref. 14). Crystal form changes can also be induced by excipient choice (8). Excipients themselves can have reactive impurities that form new degradation products (19). Dr. Harmon published four research articles demonstrating these various phenomena (pub. 8, 14, 19, 20) as well as a co-authoring a patent to prevent API form changes. Countless other examples of excipient induced phenomena were witnessed.

*Predictive dissolution and enhanced dissolution understanding. Dr. Harmon worked at the forefront within Merck in trying to understand dissolution processes of solid dosage forms as well as the relationship of those behaviors to drug exposures in animals and humans. Dr. Harmon co-authored a publication on understanding the variable hydrodynamics within USP II dissolution apparatus (ref. 13). Simple experimental ways to produce bio-relevant and more predictive dissolution data were studied and implemented. Dr. Harmon also recognized the slow dissolution certain very small (yet poorly soluble) drug particles even in surfactant media, which led to a publication which shows that micellar solubilization often will not increase small particle dissolution rates (ref. 4). This was a completely new concept and important when attempting to increase exposures of poorly soluble compounds.

*Amorphous solid dispersions-dissolution mechanisms and analytical challenges. While creating a molecular mixture of a poorly soluble drug and a water-soluble polymer often increases drug exposures, it does create risks and challenges. Dr. Harmon provided analytical support to development of numerous amorphous dispersion programs. Analytical challenges are numerous (see publication 10). Provided important insights into products, such that co-authored a patent on (a successful) amorphous dispersion formulation. Details of how the polymer and drug dissolve out of the dispersion in water, and the structures that are created can have significant impact on the resulting exposure increases. Dr. Harmon studied this in great detail in publication 5 which provided a general view of amorphous nanoparticle formation in the case of very low solubility drugs.

1994-1997 *Sr. Project Chemist, Research Fellow* (Analytical Methods and Support, Merck Manufacturing Division)

Applied modern HPLC to develop and validate scores of stability-indicating HPLC methods across entire Merck legacy product portfolio (tablets/creams/solutions /ointments/syrups). Identified products by isolation and purification (see publications 15, 21, 22 and 23). Developed deep technical understanding of HPLC methods and related trouble-shooting and problem-solving issues.

The Liposome Company, Princeton, NJ **1992-1994**

Research Scientist. Member of the Membrane Research group. Primary responsibilities were to understand the interactions between drug molecules and the liposomal bi-layer membrane in novel liposome-based drug formulations. Formulation candidates were typically characterized using fluorescence, circular dichroism, ESR, calorimetry, UV-vis spectrophotometry, HPLC, dialysis and various particle sizing techniques. Methodology for the detection of endotoxins in liposomal systems was also investigated and led to a novel patent and publication (pub. 24). Co-authored three other liposome related scientific research papers (25-27).

National Institutes of Health (NIH) **1990-1992**
IRTA Postdoctoral Fellow, National Institute of Diabetes and Digestive and Kidney Diseases, Laboratory of Chemical Physics, NIH

Designed and aided in the fabrication of a novel electrochemical-Raman spectroscopic sampling apparatus for vibrational spectroscopic monitoring of electron transfer events in proteins, working with R. W. Hendler (Mentor Dr. Ira Levin). Apparatus allowed for the precisely controlled input or removal of electrons in an anaerobic environment, while simultaneously acquiring both the vibrational Raman and optical absorption spectral signatures. The research led to three scientific publications (28-30) and contributed significantly to understanding of electron transfer events in cytochrome oxidase.

University of Pittsburgh, Pittsburgh, PA **1985 – 1990**
Andrew Mellon Predoctoral Fellow/Research Assistant, Department of Chemistry
Advisor: Professor Sanford A. Asher. Research involved the development of ultraviolet resonance Raman spectroscopy to probe biomolecular structure. The non-linear dependence of the aromatic amino acid resonance Raman intensities on the excitation source laser power was quantitatively measured and theoretically modeled. This offered a new way to probe the amino acid residue environment. Daily work involved maintaining, optimizing and upgrading a variety of spectroscopic instrumentation including Nd:YAG, argon, krypton, excimer and dye lasers; single, double and triple monochromators and photomultiplier, diode array and charge coupled device photon counting systems. Research resulted in authoring and co-authoring six scientific publications (31-36 below).

IV. SOCIETY MEMBERSHIPS

American Chemical Society

V. PUBLICATIONS and PATENTS

- **Publications below – PharmaRx Consulting, LLC**

1. Paul A. Harmon. "Trace aldehydes in solid oral dosage forms as catalysts for nitrosating secondary amines". *Journal of Pharmaceutical Sciences* On-line 04Nov 2022 doi:10.1016/j.xphs.2022.10.033. https://pubmed.ncbi.nlm.nih.gov/36336102/

2. Paul A. Harmon. Ranitidine: A proposed mechanistic rationale for NDMA formation and a potential control strategy". Journal of Pharmaceutical Sciences On-line 13Nov 2022 doi:10.1016/j.xphs.2022.11.011
https://jpharmsci.org/action/showPdf?pii=S0022-3549%2822%2900521-4

- **Publications below- Merck 1994-2016**

3. Kausik Nanda, William Blincoe, Leonardo Allain, W. Peter Wuelfing and Paul Harmon. "Iron III mediated oxidative degradation on the Benzylic carbon of drug molecules in the absence of initiating peroxides". *Journal of Pharmaceutical Sciences*. 2017, vol. 106, 5. 1347-1354. doi: 10.1016/j.xphs.2017.01.025.

4. Kendra Galipeau, Adam Socia, Michael Socki and Paul A. Harmon. "Incomplete loading of Fassif and Fessif micelles within the diffusion layers of dispersed drug particles during dissolution". *Journal of Pharmaceutical Sciences*. 2018, vol. 107, 1, 156-169. doi: 10.1016/j.xphs.2017.06.006.

5. Paul Harmon, Wei Xu, Kendra Galipeau, Chad Brown, W. Peter Wuelfing "Mechanism of dissolution induced nanoparticle formation from a copovidone based amorphous solid dispersion". *Mol. Pharmaceutics 2016, 13, 1467-1481*

6. Marcela Nefliu, Todd Zelesky, Patrick Jansen, Gregory Sluggett, Chris Foti, Steve Baerstchi, Paul Harmon "Artifacts generated during azoalkane peroxy radical oxidative stress testing of pharmaceuticals containing primary and secondary amines. *J. Pharmaceutical Sciences.* 2015, vol. 104, 12, 4287-4298

7. M. Watkins, S. Pitzenberger, P. A. Harmon. "Direct evidence of 2-cyano 2 propoxy radical activity during AIBN based oxidative stress testing in acetonitrile-water solvent systems". *Journal of Pharmaceutical Sciences.* 2013, vol 102, 1554-1568

8. Christopher John, Wei Xu, Lisa Lupton, Paul Harmon "Formulating weakly basic HCl salts: relative ability of common excipients to induce disproportionation and the unique deleterious effects of magnesium stearate". *J. Pharm. Research. 2013(30): 1628-1641*

9. P. Harmon and G. Boccardi *"Oxidative Susceptibility Testing", in Pharmacuetical Stress Testing, 2nd Edition (vol. 210), 2011. Ed. S. Baertschi, K. M. Alsante, R.A. Reed. Informa Healthcare.* Chapter 6, 168-191.

10. Paul Harmon, Li Li, Patrick Marsac, Narayan Variankaval, Wei Xu "Amorphous Solid Dispersions: Analytical Challenges and Opportunities", *AAPS Newsmagazine*, September 2009, 14-22.

11. Eric D. Nelson, Gina M. Thompson, Ye Yao, Holly M. Flanagan, Paul A. Harmon "Solvent Effects on the AIBN Forced Degradation of Cumene: Implications for Forced Degradation Practices" *Journal of Pharmaceutical Sciences.* 2009, vol. 98, 3, 959-969

12. A. Peresypkin, N. Variankaval, R. Ferlita, R. Wenslow, J. Smitrovich, K. Thompson, J. Murry, L. Crocker, D. Mathre, J. Wang, P. Harmon, M. Ellison, S. Song, A. Makorov, R. Helmy. Discovery of a Stable Molecular complex of an API with HCl: A long road to a conventional salt. *Journal of Pharmacuetical Sciences*, 2008, 97 (9), 3721

13. G. Bai, P. Armenante, R. Plank, M. Gentzler, K. Ford, P. Harmon. Hydrodynamic investigation of a USP Dissoluton Test Apparatus II -----*Journal of Pharmaceutical Sciences*, 2007, 96, (9), 2327

14. W. R. Wasylaschuk, P. A. Harmon, G. Wagner, A. B. Harman, A. C. Templeton, H. Xu, W. Peter Wuelfing and R. A. Reed "Evaluation of Hydroperoxides in Common Pharmacuetical Excipients" *Journal of Pharmaceutical Sciences*. 2007, vol. 96, 1, 106-115.

15. P. A. Harmon, "Challenges in Defining and Achieving Selectivity Requirements for Phase I Stability Indicating HPLC Methods", *AAPS Newsmagazine*, December 2006, 12-16.

16. P. A. Harmon, K. Kosuda, E. Nelson, M. Mowery and R. Reed "A Novel Peroxy Radical Based Oxidative Stressing System for Predicting Oxidative Instability of Active Pharmaceutical Ingredients" *Journal of Pharmaceutical Sciences,* 2006, vol. 95, 9, 2014-2028.

17. E. D. Nelson, P. A. Harmon, M. G. Teresk, R. C. Szymanik, Li Li, R. A. Seburg and R. A. Reed "Evaluation of Solution Oxygenation Requirements for Azonitrile-Based Oxidative Forced Degradation Studies of Pharmaceutical Compounds" *Journal of Pharmaceutical Science,* 2006, vol. 95, 7, 1527-1539.

18. P. A. Harmon, S. Biffar, S. M. Pitzenberger and R. A. Reed "Mechanism of the Solution Oxidation of Rofecoxib Under Alkaline Conditions" *Pharmaceutical Research*, 2005, Vol. 22, No. 10, 1716-1726.

19. D. Ma, W. Wasylaschuk, C. Beasley, Z. Zhao, P. Harmon, J. Ballard, S. Pitzenberger, S. Varga and R. Reed. "Identification and Quantitation of Extractables from Cellulose Acetate Butyrate and Estimation of their In Vivo exposure Levels" *Journal of Pharmaceutical and Biomedical Analysis*, 2004, 35, 779.

20. R. A. Reed, P. Harmon, D. Manas, W. Wasylaschuk, C. Galli, R. Biddell, P. Berquist, W. Hunke, A. Templeton and D. Ip "The Role of Excipients and Package Components in the Photostability of Liquid Formulations", *PDA Journal of Pharmaceutical Sciences and Technology,* 2003, 57 (5), 351.

21. C. Galli, P. Frey, P. Harmon, H. Hartman, R.A. Reed. "Modeling the effect of analyte and reference bandwidths on signal and noise magnitudes in spectrophotometic assays, *Journal of Pharma. Biomed. Analysis*, 2003, 32 (3) 401.

22. X. Xueguang, R. Bibard, S. Mayr, W. Yin, P. Harmon, J. McCafferty, J. Tyrrell, R. Reed. "Purification and Identification of an Impurity in bulk Hydrochlorothiazide". *Journal of Pharmacuetical Sciences,* 2001, 90 (11), 1800-1809.

23. P. A. Harmon, W. Yin, W. E. Bowen, R. J. Tyrrell and R. A. Reed "LC-MS and ^{1}H NMR Characterization of Trace Level Condensation Products Formed Between Lactose and the Amine Containing Diuretic Hydrochloride", *J. Pharmaceutical Sciences*, 2000, 89**(**7**)**, 920.

- **Publications below from The Liposome Company Inc. 1992-1994**

24. P. A. Harmon, D. Cabral-Lilly, R. A. Reed, F. P. Maurio, J. C. Franklin and A. Janoff "The release and Detection of Endotoxin from Liposomes"; *Anal. Biochem.* 1997, 250, 139.

25. W.R. Perkins, X. Li, J.L. Slater, P.A. Harmon, P.L. Ahl, S.R. Minchey, S.M. Gruner and A.S. Janoff "Solute Induced Shift of Phase Transition Temperature for Di-saturated PC Liposomes: Adoption of Ripple Phase Creates Osmotic Stress" *Biochem. Biophys. Acta* 1327 (1997) 41-51.

26. David F. Eierman, Machiko Yagami, Scotte M. Erme, Sharma R. Minchey, Paul A. Harmon, Kerri J. Pratt and Andrew S. Janoff "Endogenously opsonized particles divert prostanoid action from lethal to protective in models of experimental endotoxemia" *Proc. Natl. Acad. Sci. USA.* 92 (1995) 2815.

27. D. Eierman, M. Machiko, S. Erme, S. Minchey, P. Harmon, A. Janoff, "Synergistic prevention of endotoxin induced mortality in rats by PGE1 and particles" *Advances in Prostaglandin, Thromboxane, and Luekotriene Research* 23, 1995, 241-343.

- **Publications below from Post-Doc at NIH 1990-1992**

28. Paul A. Harmon, Richard W. Hendler, Walter S. Friauf and Ira W. Levin, " Combination of Potentiometry and Resonance Raman Spectroscopy for the Analysis of a Redox Protein" *Analytical Biochemistry* 224 (1995) 309.

29. Paul A. Harmon, Richard W. Hendler, and Ira W. Levin, "Resonance Raman and Optical Spectroscopic Monitoring of Heme A Redox States in Cytochrome Oxidase During Potentiometric Titrations" *Biochemistry* 33 (1994) 699.

30. Richard W. Hendler, Paul A. Harmon and Ira W. Levin, "Near Infrared Spectral Changes of Cytochrome aa_3 during Potentiometric Titrations" *Biophysical Journal* 67 (1994) 2493.

- **Publications below from Graduate School Ph.D. 1985-1990**

31. Joyce A. Sweeney, Paul A. Harmon, Sanford A. Asher, Cindy M. Hutnik, and Arthur G. Szabo, " UV Resonance Raman Examination of the Azurin Tryptophan Environment and Energy Relaxation Pathways" *J. Am. Chem. Soc*. 113 (1991) 7531.

32. Junji Teraoka, Paul A. Harmon, and Sanford A. Asher, "Ultraviolet Resonance Raman Saturation Spectroscopy of Tryptophan Derivatives: Photophysical Relaxation Measurements with Vibrational Band Resolution", *J. Am. Chem. Soc.* 112 (1990) 2892.

33. Paul A. Harmon, Junji Teraoka, and Sanford A. Asher, "Ultraviolet Resonance Raman Saturation Spectroscopy Measures Protein Aromatic Amino Acid Excited State Relaxation Rates" *J. Am. Chem. Soc.* 112 (1990) 8789.

34. Paul A. Harmon and Sanford A. Asher,"Environmental Dependence of Preresonance Raman Cross Section Dispersions: Benzene Vapor Phase Excitation Profiles", *J. Chem. Phys.* 93 (1990) 3094.

35. Paul A. Harmon and Sanford A. Asher,"Differentiation Between Resonance Raman Scattering and Single Vibrational Level Fluorescence 5100 cm^{-1} Above the B_{2u} Origin by Means of Excitation Profiles" *J. Chem. Phys.* 88 (1988) 2925.

36. Colleen M. Jones, Valentino L. Devito, Paul A. Harmon and Sanford A. Asher, "High Repetition Rate Excimer Laser Avoids Saturation in Resonance Raman Measurements of Tyrosinate and Pyrene" *Appl. Spectros.* 41 (1987) 1268.

Patents

1. Eric Mayhew, Craig Franklin, Suresh Bhatia, Paul Harmon and Andrew Janoff , "Hydrophobic Taxane Derivatives", U. S. Patent # 5,580,899 issued 12/3/96.

2. Paul A. Harmon, Donna J. Cabral-Lilly, J. Criag Franklin, Robert A. Reed and Andrew S. Janoff , " Detection of Endotoxin Levels in Liposomes, Lipid Bilayers and Lipid Complexes", U. S. Patent # 6,015,716 issued 8/2000.

3. Christopher John, Paul Harmon. "Pharmaceutical formulations that Inhibit disproportionation". Granted June 2016. US9339543B2.

4. Paul A. Harmon, Narayan Variankaval, Michael Lowinger, Chad David Brown, Francis Flanagan "Solid Dosage Formulations of an Orexin Receptor Antagonist" US patent # 10,098,892 issued October 16, 2018.