

ARON FARREL STEIN, Ph.D.

15036 El Camino Real
Del Mar, CA 92014
858-523-9219 (Home) 858-523-0280 (Fax)
E-Mail: afstein@sbcglobal.net

SUMMARY:

Over 18 years of pharmaceutical experience with demonstrated ability to lead, build, mentor, develop, and manage in both small and large organizations. Broad areas of management responsibilities include Regulatory and Medical Affairs, and Quality Assurance. Strategic FDA initiatives involved partnering with the Agency to develop CDER Guidance and reintroduction of marketed products. Project specific regulatory strategies have led to rapid registration for multiple drug products.

Initial Industry experience was as a Study Director conducting toxicology GLP studies in support of new therapeutics entering clinical trials. Utilized scientific training and expertise on early staged compounds to assume a broader role in drug development. Directed and/or supervised the management of FDA interactions for preclinical, CMC, and clinical activities in Phase 1 through 3 development programs. These responsibilities applied to as many as 40 INDs at a given time and across a variety of review divisions including Neuropharmacology, Cardio-Renal, Oncology, Dermatology, Anti-Infective, Anti-Viral, Gastrointestinal, Metabolic and Endocrine, Anesthesia and Rheumatology, and Cellular, Tissue, and Gene Therapy. Chemical classes of compounds include small molecules, natural products, oligonucleotides, and proteins.

Additional postmarketing support includes interactions with FDA DDMAC across numerous products including those approved under accelerated regulations. Built the infrastructure to support pharmacovigilance, scientific medical liaison, and Phase 4 postmarketing clinical trial activities.

Experience outside of the US includes key meetings held with Health Authorities to obtain agreements for two marketing applications. Directed the preparation and submission of clinical trial applications in Canada and the EU.

PROFESSIONAL EXPERIENCE:

Regulatory Consultant (April 2005 to present)

Provide regulatory consulting services for pharmaceutical companies. Services include the development of regulatory strategies, preparation and review of submissions, leadership on development and management teams, as well as functional oversight for employee development and department functions.

**ISIS PHARMACEUTICALS, INC, Regulatory Affairs and Quality Assurance,
Carlsbad, California**

Vice President and Corporate Officer (September 2002 to April 2005)

Responsible for the development and implementation of global regulatory strategies for all development programs including: Oncology, Metabolism, and Inflammation. Functional groups reporting to this position include; Regulatory Liaison, Operations, Quality Assurance (GMP), Pre-clinical (GLP) and Clinical Compliance (GCP). In addition, this position serves as a member of the Executive and Development Management Committees which are responsible for driving the corporate and development direction of the company.

This position ensures regulatory manufacturing compliance inclusive of pre-approval and ongoing inspections by regulatory authorities and corporate partners. Accomplishments in these areas include successful commissioning of new manufacturing suite, FDA district inspections, and hosting FDA review chemist visits under CDER's summer education initiative.

Isis Pharmaceuticals, and its partners, have Phase 1 through 3 development programs in the US, Canada, and the EU. Primary goals include the development of internal resources that provide regulatory and quality representation on project teams, establishment of preferred provider in the EU to meet recent requirements set forth in the Clinical Trial Directive for regulatory applications and pharmacovigilance, as well as senior regulatory influence on R&D direction and initiatives.

**ABBOTT LABORATORIES, Hospital Products Division, Medical and Regulatory
Affairs, Abbott Park, Illinois**

Divisional Vice President (September 1999 to September 2002)

Responsible for the development of strategy and organizational structure to ensure registration, safety, and appropriate use of division-wide products worldwide. Specific responsibilities include:

- Drug and Device Safety, and Postmarketing Clinical Research
- Regulatory Affairs and Clinical Compliance
- Device Medical Development and Postmarketing Research

Act as advisor/liaison to Division President and/or senior management in order to plan, evaluate, and recommend overall medical, regulatory, and compliance strategy.

The Hospital Products Division business focused on high acuity therapeutic areas for both pharmaceutical and device products. Key product areas were cardiovascular, renal, and pain management. Due to the success of the division, this department grew from 45 to 120 professionals. Primary goals were to build organizational infrastructure, drive key marketed product enhancements, and to closely collaborate with the Center of Biologics at FDA to negotiate the successful return of ABBOKINASE to the medical community.

SEQUUS PHARMACEUTICALS, INC., Regulatory Affairs, Menlo Park, California
Vice President and Corporate Officer (April 1997 to September 1999)

Responsible for providing worldwide regulatory strategy for developmental and marketed drugs, regulatory submissions, and all interactions with Health Authorities. Functional groups reporting to this position include Strategy, Operations, Quality Assurance (GMP), Clinical Compliance (GCP), Medical Safety, and Labeling.

Specific project oversight for DOXIL's solid tumor registration program which involved setting regulatory precedence on accelerated approval regulations in the U.S. and requirements in Europe. Additional registration activities include AMPHOTEC and liposomal-cisplatin.

Registration strategy, compliance audit, and preparation of marketing applications in U.S. and ex-U.S. were successfully completed for DOXIL and AMPHOTEC. Responsible for review of promotional materials, training of sales force, and interactions with DDMAC for these two marketed products.

Serve as a member of the Executive Management Committee. This committee formulates and implements Sequus vision, mission, and strategic planning to advance the business needs of the corporation.

PFIZER, INC Central Research, Drug Regulatory Affairs-Liaison, Groton Connecticut 1991-1997

Director (December 1995 to April 1997)

Responsible for the daily operations, management, and administration of a group of ten, including five Ph.D. level Associate Directors. Responsible for providing worldwide regulatory strategy for developmental drug candidate programs, regulatory submissions, and all Central Research interactions with the FDA and HPB. Therapeutic responsibilities are focused on cardiovascular, metabolic/endocrine, reproductive, and oncology. Oversight on registration programs and applications for VIAGRA, TIKOSYN, and NORVASC.

Senior Associate Director/Group Leader (January 1994 to December 1995)

Responsible for the daily operations, management, and administration of approximately thirty total staff, including nine Ph.D. level Associate Directors. Responsible for providing worldwide regulatory strategy for developmental drug candidate programs, regulatory submissions, and all Divisional interactions with the FDA and HPB across all therapeutic areas.

- Regulatory management for approximately 40 active IND programs including eight global Phase III development programs.
- Directed submission/approval of nine NDAs/sNDAs for significant supplemental programs for DIFLUCAN and ZITHROMAX.

- Member of Pfizer Senior Management Committee for oversight of all US Phase I and II drug candidate programs. Subcommittee member on internal initiatives to expedite early drug development programs.
- Authored PhRMA-RAC “Mock IND” which formed the basis of FDA’s Guidance for Industry on IND content and format.

Senior Associate Director (August 1993 to January 1994)

Responsible for providing worldwide regulatory strategy and oversight for Pfizer's late stage drug development portfolio. This included the management of Ph.D. level Associate Directors and the document submission group.

Associate Director II (January 1993 to August 1993)

Associate Director I (August 1991 to January 1993)

Responsible for coordination of internal activities related to the filing of the IND, NDA, and NDS. Act as liaison with FDA and HPB. Compile responses to regulatory questions, monitor progress IND programs and NDA review, maintain logs of interactions, review IND and NDA submissions, attend regular candidate management meetings and FDA Advisory Committee meetings.

DU PONT MERCK PHARMACEUTICALS, Wilmington, Delaware 1986-1991

Manager, Drug Regulatory Affairs (May 1989 to August 1991)

Responsible for the development of worldwide regulatory strategies, management of regulatory submissions, knowledge of clinical evaluation of investigational drugs and expertise in US drug regulations and guidelines for INDs/NDAs. This position requires a comprehensive understanding of pharmaceutical sciences through the review of current literature, attendance at FDA Advisory Committee meetings, and interaction with consultants to address regulatory issues as well as act as liaison with the FDA.

Specific project support was provided on ETHMOZINE NDA approval, CARDENE IV advisory committee meeting, and joint development team with Merck on COZAAR through the End of Phase II meeting.

Research Toxicologist, Drug Safety Department (January 1986 to May 1989)

Primary responsibility of this position was to serve as Study Director for acute and subchronic toxicity studies performed according to the FDA's Good Laboratory Practices. This included the evaluation and interpretation of all toxicology findings and for the preparation of final reports. Experience in preparing toxicology sections that were submitted to the FDA in support of safety claims. Significant interaction with contract laboratories for primate, chronic and reproductive studies. Represented the Toxicology department in the development of CNS active compounds at working group and management meetings.

EDUCATION/TRAINING:

1980 - B.S., Biomedical Science

Texas A&M University; College Station, Texas

1983 - Ph.D., Toxicology

Texas A&M University; College Station, Texas

1986 - NIH Fellow, Toxicology

University of Kansas Medical Center; Kansas City, Kansas

DISSERTATION:

Stein, A.F.: Toxic and biologic effects of ochratoxin A in the partially nephrectomized rat, Ph.D. Dissertation, Texas A&M University (Dr. Timothy D. Phillips - Advisor), 1983.

MANUSCRIPTS:

1. Phillips, T.D., Nechay, B.R., Kubena, L.F., Heidelbaugh, N.D., Shepherd, E.C., Stein, A.F., Neldon, S.L. and Hayes, A.W.: Vanadium induced inhibition of renal (Na⁺ -K⁺)-adenosine triphosphatase in the chicken after chronic dietary exposure. *J. Toxicol. Environ. Health* 9:651-661, 1982.
2. Phillips, T.D., Stein, A.F., Ivie, G.W., Kubena, L.F. and Heidelbaugh, N.D.: High performance liquid chromatographic analysis of an α -methyl, methylester derivative of ochratoxin A and its application in tissue detection and confirmation. *J. Assoc. Off. Anal. Chem.* 66:3, 1983.
3. Stein, A.F., Geerling, S., Mollenhauer, H.H., Heidelbaugh, N.D. and Phillips, T.D.: Effects of ochratoxin A in the partially nephrectomized rat. *J. Toxicol. Environ. Health*, 14:535-550, 1984.
4. Geerling, S., Mollenhauer, H.H., Stein A.F. and Phillips, T.D.: Effect of partial nephrectomy and ochratoxin A on renal structure: A light and electron microscope study. *TSEMJ* 15 (No. 3):20-24, 1984.
5. Mayura, K., Stein, A.F., Berndt, W.P. and Phillips, T.D.: Teratogenic effects of ochratoxin A in rats with impaired renal function. *Toxicology*, 32:277-285, 1984.
6. Stein, A.F., Phillips T.D., Kubena, L.F. and Harvey, R.B.: Renal tubular secretion and reabsorption as factors in ochratoxicosis: Effects of probenecid on nephrotoxicity. *J. Toxicol. Environ. Hlth.* 16(3-4):593-605, 1985.
7. Stein, A.F., Dills, R.L. and Klaassen, C.D.: High-performance liquid chromatographic analysis of glutathione and its thiol and disulfide degradation products. *J. Chromatog.* 381:259-270, 1986.

8. Gregus, Z., Stein A.F. and Klaassen, C.D.: Age-dependent biliary excretion of glutathione-related thiols in rats. Role of gamma-glutamyl transferase. *Am. J. Physiol.* 253:G86-G92, 1987.
9. Gregus, Z., Stein A.F. and Klaassen, C.D.: Effect of inhibition of gamma-glutamyltranspeptidase on biliary and urinary excretion of glutathione-derived thiols and methylmercury. *J. Pharmacol. Exp. Therap.* 242:27-32, 1987.
10. Stein, A.F., Bracken, W.M. and Klaassen, C.D.: Utilization of methionine as a sulfhydryl source of metallothionein synthesis in rat primary hepatocyte cultures. *Toxicol. Appl. Pharmacol.*, 87:276-283, 1987.
11. Stein, A.F., Gregus, Z. and Klaassen, C.D.: Species variations in biliary excretion of glutathione-related thiols and methylmercury. *Toxicol. Appl. Pharmacol.*, 93:351:359, 1988.
12. Gregus, Z., Stein, A.F., Varga, V. and Klaassen, C.D.: Effect of lipoic acid on biliary excretion of glutathione and metals. *Toxicol. Appl. Pharmacol.*, 114:88-96, 1992.

ABSTRACTS:

1. Phillips, T.D., Nechay, B.R., Kubena, L.F., Heidelbaugh, N.D., Shepherd, E.C., Stein, A.F., Neldon, S.L. and Witzel, D.A.: Effects of calcium orthovanadate on Na⁺-K⁺ adenosinetriphosphatase activities in the chicken. *Toxicologist* 1(1):119, 1981.
2. Phillips, T.D., Stein, A.F., Ivie, G.W., Heidelbaugh, N.D. and Hayes, A.W.: High performance liquid chromatographic analysis of a diazomethane reaction product of ochratoxin A and its application to tissue detection and confirmation. *Pharmacologist* 23(3):115, 1981.
3. Stein, A.F., Morgan, R.G., Geerling, S. Mollenhauer, H.H., Heidelbaugh, N.D. and Phillips, T.D.: The effects of ochratoxin A in the partially nephrectomized rat. *Toxicologist* 1(3):149, 1983.
4. Stein A.F. Berndt, W.O. and Phillips, T.D.: Ochratoxin A-induced nephrotoxicity: Comparative studies in the partially nephrectomized rat. *Toxicologist* 1(4):31, 1984.
5. Stein, A.F., Bracken, W.M. and Klaassen, C.D.: Methionine as a sulfhydryl source for Zn-induced metallothionein in cultured rat hepatocytes. *Toxicologist* 1(5):32, 1985.
6. Gregus, Z., Stein, A.F. and Klaassen, C.D.: Biliary excretion of glutathione (GSH) and related thiols in rats: Age-dependence and responsiveness to acivicin, an inhibitor of gamma-glutamyl transpeptidase (GGT). *Hepatology* 5(5):958, 1985.
7. Stein, A.F., Dills, R.L. and Klaassen, C.D.: High-performance liquid chromatographic (HPLC) analysis of glutathione (GSH) and its sulfhydryl (SH) degradation products. *Toxicologist* 1(6):597, 1986.

8. Stein, A.F., Gregus, A. and Klaassen, C.D.: Species variations in biliary excretion of glutathione-related sulfhydryls and methylmercury (MM). *Toxicologist* 1(6):444, 1986.
9. Gregus, Z., Stein A.F. and Klaassen, C.D.: Effect of inhibition of gamma-glutamyltranspeptidase (GGT) on biliary and urinary excretion of endogenous thiols and methylmercury (MM). *Toxicologist* 1(6):607, 1986.
10. Gregus, Z., Stein, A.F., and Klaassen, C.D.: Biliary excretion of Glutathione (GSH) and related thiols in rats: Age-dependence and responsiveness to acivicin, an inhibitor of gamma-glutamyltranspeptidase (GGT). *Toxicologist* 1(6):596,1986.
11. Gregus, Z., Stein, A.F., Varga, F. and Klaassen, C.D.: Paradoxical effect of lipoic acid on biliary excretion of metals. *Toxicologist* 1(7):1987.