IRA PAUL KREFTING, MD

Krefting Consulting, LLC

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PROFESSIONAL EXPERIENCE

Owner, Krefting Consulting, LLC: consultant to the pharmaceutical industry on regulatory and safety issues with specific expertise on diagnostic imaging agent development.

Positions at the Food and Drug Administration, Center for Drug Evaluation and Research, Office of New Drugs, Silver Spring, Md

- Deputy Director for Safety, Division of Imaging and Radiation Medicine**,** 2007-2023 *(Retired)*
  - Responsible for the post-marketing safety of imaging agents; supervises one project manager
  - Organized 2 Medical Imaging Drug Advisory Committees (MIDAC) meetings on gadolinium-based contrast (GBCA) safety issue: Nephrogenic Systemic Fibrosis (NSF) and gadolinium retention
  - Organized and led multiple cross disciplinary teams reviewing newly identified safety issues related to: Iodinated contrast media, ultrasound contrast agents, GBCAs, and Positron Emission Tomography (PET) drugs
  - Point of contact for: GBCA manufacturers' performance of post marketing required (PMR) studies and Iodinated Contrast Media manufacturers PMR studies performance
  - Managed FDA response to excess radiation exposure from rubidium generators – interacted with NRC and state radiation control agencies
  - Collaborated with OSE and other review divisions to review a Citizens' Petition for revised recommendations related to iodinated contrast imaging studies in patients prescribed Metformin. Recommendations were then incorporated into Metformin prescribing information

- Supervisory Medical Officer, Radioactive Drug Research Committee, 2010 -2023 *(Retired)*
  - Oversight of basic research on experimental radioactive agents performed at centers throughout the United States; supervises one nuclear pharmacist
  - Managed adverse reaction reporting and subsequent mitigation

- Provide direction to RDRCs on cumulative radiation exposure from RDRC studies and clinical treatments
- Fostering the development of multi-institutional RDRCs
- Hired new staff

- Team Leader, Division of Medical Imaging Products, April 2016 – April 2018
  - Supervised two medical officers in their reviews of INDs, NDAs and other regulatory filings
  - Managed the regulatory review process
  - Organized meetings with CDRH on combination products
  - Improved a medical officer's performance

- Manager of Critical Path Project: (Completed) Title: Establish a Patient-Based Registry to Evaluate the association of Gadolinium Based Contrast Agents (GBCAs) exposure and Nephrogenic Systemic Fibrosis (NSF). Performed at the University of Pittsburg Medical Center FDA Cooperative Agreement U01 FD004713
  FDA principal investigator:
  - Organized research program with the University of Pittsburgh Medical Center leading to a publication

- CDER Project Lead National Center for Toxicological Research (NCTR) joint project:
  CONCEPT: Functional Correlates of Gadolinium Deposition in the Rat Brain
  - Collaboration with pre-clinical pharmacologists to develop a research protocol
  - Interacted with NCTR researchers
  - Moderated joint meetings between DIRM and NCTR
  - Manuscripts in preparation for publication

Private Practice, Adult Pulmonary & Internal Medicine, Silver Spring, MD, 1980-2006
Part-time disability reviewer, University Disability Consortium, Newton, MA. 2005 - present

Medical Staff Positions

Member, Medical Executive Committee, Suburban Hospital, Bethesda, MD, 2004-2006
Member, Hospital Patient Safety Committee, Suburban Hospital, Bethesda, MD, 2004-2006 (Medication and Other Safety Issues)
Chairman, Pulmonary Medicine Department, Suburban Hospital, Bethesda, MD, 1997-2000
Chairman, Pulmonary Medicine Department, Holy Cross Hospital, Silver Spring, MD, 1988-1992
Secretary, Department of Medicine, Montgomery General Hospital, Olney, MD, 1992-1994

Director, Continuing Medical Education, Holy Cross Hospital, Silver Spring, MD, 1990-1992

EDUCATION

B.A., Chemistry, with Honors, New York University, Bronx, 1970
M.D., Downstate Medical Center, State University of New York, Brooklyn, 1974

Post-Graduate Medical Training

Internship: Medicine, Kings County Hospital, Brooklyn, NY, 1974-1975
Residency: Medicine, Kings County Hospital, Brooklyn, NY, 1975-1977
Pulmonary Fellowships: National Institutes of Health, Bethesda, MD, 1977-1979, George Washington University Medical School, Washington, DC, 1979-1980

Medical Licenses

Maryland, [District of Columbia, New York, California, Virginia (Voluntarily Inactive)]

Certifications

National Board of Medical Examiners, Parts I-III, completed 1975
American Board of Internal Medicine, 1978
American Board of Internal Medicine, Pulmonary Diseases, 1986

Courses Completed
American Course on Drug Development and Regulatory Sciences Certificate Program, 2011

Core Course in Clinical Research, National Institutes of Health, Clinical Center, 1996 and 1997

FACULTY APPOINTMENTS

Associate Clinical Professor Medicine, 1997 to 2002, Department of Medicine, George Washington University School of Medicine. Faculty member since 1982

PUBLICATIONS

Liachenko S, Sadovova N, Tripp A, Ghorai S, Patri A, Hanig J, Cohen J, Krefting I. Optimization of Detection of Gadodiamide Brain Retention in Rats Using Quantitative T2 Mapping and Intraperitoneal Administration. *J. Magn. Reson. Imaging (*2022): 56(5): 1499-1504

Kanal M, Patton T, Krefting I, Wang C, Nephrogenic Systemic Fibrosis Risk Assessment and Skin Biopsy Quantification in Patients with Renal Disease following Gadobenate Contrast Administration. *Am J Neuroradiol.* (2020) Mar;41(3):393-399

Bird ST, Gelperin K, Sahin L, Bleich KB, Fazio-Eynullayeva E, Woods C, Radden E, Greene P, McCloskey C, Johnson T, Shinde M, Krefting, I. First-Trimester Exposure to Gadolinium-based Contrast Agents: A Utilization Study of 4.6 Million U.S. Pregnancies. *Radiology. (*2019) Oct;293(1):193-200. doi: 10.1148/radiol.2019190563. Epub 2019 Aug 20

Yang L, Krefting I, Gorovets A, Marzella L, Kaiser J, Boucher R, Rieves D, (2012) Nephrogenic Systemic Fibrosis and Class Labeling of Gadolinium-based Contrast Agents by the Food and Drug Administration, *Radiology.* 265(1): 248-53

Honchel R, Carraway J, Gopee N, Callicott R, Chen J, Ratton R, Xu Q, Zalkkar J, Laniyonu A, Krefting I, Cato M, Robie-Suh K, Rieves R (2011). A dose-response study in animals to evaluate the anticoagulant effect of the stage 2 unfractionated heparin USP monograph change. *Regulatory Toxicology and Pharmacology.* 60(3): 318-22.

Krefting I, (1996). The Challenge to Solo Practice. *Today's Healthcare,* 17.

Krefting I, P. et al. (1994). Pleomorphic Carcinoma (spindle and giant cell) of the Lung. *Maryland Medical Journal,* 43, 787-790.

Poster

Hypersensitivity Reactions with Ultrasound Contrast Agents in Patients with a History of Polyethylene Glycol Allergy Presented at: International Society for Pharmacoepidemiology, Halifax, Nova Scotia, Canada, August 23 to 27, 2023
Authors: Cotter S. Jones C. Coquia S. Krefting I. Mundhur M.

CLINICAL RESEARCH PROJECTS (While in private practice)

Centoxin in Sepsis, Phase III, sponsored by Centocor, Principal Investigator for Holy Cross and Suburban Hospitals

Pulmozyme: Chronic Obstructive Pulmonary Disease Mortality Endpoint Trial, sponsored Genentech, Principal Investigator for Holy Cross and Suburban Hospitals

E-5 in Sepsis, sponsored by Pfizer, Principal Investigator for Holy Cross and Suburban Hospitals

Accolate in Asthma, sponsored by Astra-Zeneca, in-office post-marketing trial

LECTURES & TEACHING CONFERENCES

Gadolinium Based Contrast Agents: Safety Considerations, Global Summit on Regulatory Science, September 2020

Gadolinium Based Contrast Agents – FDA's Perspective, American Heart Association, November 2019

Gadolinium Retention from Gadolinium Based Contrast Agents: Implications for Public Health and FDA Regulation, moderator, CDER Scientific Rounds, September 2018

Extending Imaging Applications to Pediatric Patients, Society of Nuclear Medicine Molecular Imaging, June 2016

Ultrasound Contrast Agent Approval Complexity: FDA Experience, American Institute for Ultrasound in Medicine, March 2015

FDA Approval of Diagnostic Radiopharmaceuticals: Major Considerations, American Society of Nuclear Cardiology, September 2012

FDA Safety Update Adverse Event Reporting: Clinical Investigator Responsibilities, Society of Nuclear Medicine and Molecular Imaging, June 2012

FDA GBCA Regulatory Update, Yale NSF Symposium, May 2011

FDA Perspective on Ultrasound Contrast Agent Safety, American Institute for Ultrasound in Medicine, April 2009

Safety Considerations for Ultrasound Contrast Agents, American Society of Echocardiography, June 2008

Safety Initiatives at the FDA, Society of Nuclear Medicine, June 2007

Mycoplasma Infections, Pulmonary Subspecialty Rounds, Holy Cross Hospital Teaching Program (affiliated with George Washington University Medical School), January 1992

Artificial Airways (presented with the Speech Pathology Department), Respiratory Care Group, Holy Cross Hospital, August, 1992

New Treatments of Chronic Obstructive Pulmonary Disease, Pulmonary Rehabilitation Program, October 1995

Intensive Care Unit Teaching Rounds, Holy Cross Hospital, 1987-1996

Aspiration Pneumonia, Speech Pathology Department, Holy Cross Hospital May 1998

Ward Teaching Rounds, Holy Cross Hospital, December 1999, 2003

AWARDS

Group Recognition Award: For excellence in the investigation of possible adverse effects from gadolinium in the body September 24, 2018

Group Recognition Award: For outstanding efforts to investigate excessive radioactive contamination associated with the PET medical isotope Rubidium-82 resulting in a global recall

PHARMACEUTICAL COMPANY-SPONSORED MEETINGS

Physician speaker, Singulair (for practicing physicians in Montgomery County, MD), February 1999
Physician speaker, Xopenex (for practicing physicians in Montgomery County, MD), March 2000

PROFESSIONAL MEMBERSHIPS

Fellowship, American College of Chest Physicians, 1987 (Inactive)