

EXPERT REPORT
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I. QUALIFICATIONS

1. Since August 1995, I have been President and founder of MD Assist, Inc., a regulatory and medical consulting firm specializing in matters involving the United States Food and Drug Administration's regulation of products. I received my Medical Degree (M.D.) from the University of South Florida in 1978 and Board Certification in Anatomic and Clinical Pathology since 1989. I have been a general practitioner and President of Mountain Emergency Physicians. I received a Masters in Biology from the University of Central Florida. I am the author of FDA Inside and Out, a text about the FDA.

2. From 1991 to 1995, I served as a Commissioned Officer in the United States Public Health Service and achieved the rank of Lt. Commander. During the time period, I was primarily assigned to the Center for Devices and Radiological Health ("CDRH") at the Food and Drug Administration ("FDA"). Concurrently, I was also assigned clinical responsibilities at the Armed Forces Institute of Pathology ("AFIP"), Office of the Medical Examiner for the Armed Forces, Washington, D.C.

3. From 1991 to 1993, I was a FDA Medical Officer in the Office of Health Affairs (OHA), a staff office within the Center for Devices and Radiological Health (CDRH), FDA. In OHA, I provided regulatory support to both the FDA's Office of Compliance and Office of Device Evaluation. My responsibilities in OHA included health hazard and health risk assessment, Safety Alerts and physician and layperson communications, review of adverse event reports and medical literature and review of product labeling, promotions, advertising, and

corporate records as to compliance with the Food, Drug and Cosmetic Act. I was responsible for the review of mandatory adverse event reports submitted by manufacturers, as well as the review of voluntary reports submitted by health care providers, patients and others. I presided over 162 health risk assessments convened to advise the FDA on overall health risk issues for the public and made recommendations to the FDA regarding the subsequent regulatory actions, which should be undertaken by the FDA, health care providers, users groups and manufacturers to help protect the public's welfare. My assignment at OHA specifically included identification of safety issues. I participated in mandatory recalls and participated in an administrative hearing as the FDA's expert witness.

4. An example of a drug safety issue that I helped identify and manage for the FDA as its medical officer occurred in 1992. The FDA had received reports in its databases from the medical literature of serious adverse events and deaths occurring in patients taking ACE Inhibitor (ACEI) drugs for regulation of blood pressure. From reviewing the AERs, both CDER's and CDRH's, the patients shared a common precipitating event such as blood exposure to certain types of membrane surfaces shortly after taking a dose of ACEI. As an example, it had been reported that patients taking ACEI drugs followed by recent exposure to surface-treated AN69 membrane during hemodialysis had an increased risk for anaphylactoid reactions. ACEI had been a class of drugs that had been first approved by the FDA for marketing in the 1980s. There had been relatively little safety information about these drugs. When a patient would take an ACEI and then had blood exposed to specific types of membrane surfaces, whether as hemodialysis or LDL apheresis, a sudden life-threatening anaphylactoid reaction could be triggered that did not respond to antihistamines such as benadryl. As the FDA's medical officer, I reviewed both drug and device adverse event reports, perform a health risk assessment as

described per 21 CFR Part 7, and then made a clinical recommendation to FDA as a reasonable degree of medical certainty. Health care providers needed to be quickly informed by the FDA of the ACEI membrane association and the Agency and industry needed help to identify the etiology of the reaction and physicians needed recommendations for emergency treatment. No other FDA medical officer was assigned involvement in the work-up or handling of this drug/device safety issue. Working with an FDA epidemiologist, I helped design and issue the Agency's epidemiologic study to quickly obtain additional data for FDA and the involved drug and device industry. The epidemiology study was in the form of a questionnaire contained in the Agency's Safety Alert and designed to help capture the overall risk for the public, raise awareness of the issue, define the pharmacological mechanisms involved and trigger the appropriate label changes for both the drugs and devices involved in the issue in order to protect the public. As a result, I helped draft the current ACEI class drug warning about the risks of membrane surface exposure and anaphylactoid reaction.

5. From March 1993 to December 1993, I was a Medical Officer in the Office of Device Evaluation (ODE), Division of Reproductive Abdominal, Ear, Nose and Throat, and Radiology (DRAERD), FDA, January 1994 through June 1995; I was one of two Chief Medical Officers in ODE. ODE, in contrast to OHA, is primarily responsible for pre-marketing evaluation of new product applications and clinical trials to support safety and effectiveness to begin legal marketing within the United States. In ODE, I participated in the review of proposed clinical trial, pre-marketing applications, including review of animal toxicology and biocompatibility data, in addition to the assigned responsibility of training new medical officers and scientific reviewers in application, clinical trial and labeling evaluation. I was the primary reviewing medical officer in charge of pre-marketing approval applications required for

adherence to CDER's Drug Guidances, and for presentation at the FDA Advisory Panel with members from CDRH and Center for Drug Evaluation and Research (CDER). I was a primary author for FDA's guidance for Hemodialyzer Reuse labeling. I consulted as a medical officer on INDs for combination products including drugs and biologics. While in ODE, I conducted an additional 100 health risk assessments and was required to train medical officers as to methods for health risk assessments, health hazard evaluations, annual report, adverse event and labeling review.

6. I was an initial instructor in the FDA's Staff College for training FDA reviewers in the design and evaluation of clinical data in investigational and pre-marketing applications. I had primary responsibility for review of marketing applications, labeling and was required to teach medical officers the process for evaluation and review required by the Food, Drug and Cosmetic Act for support of product marketing. I was charged with training medical officers on the process for health risk assessment and health evaluation per 21 CFR Part 7.

7. Regarding post-market surveillance of marketed products, I participated with the FDA's District Offices, Office of General Counsel, and the Office of Compliance in the review of manufacturing records, labeling, product complaints and adverse event reports obtained by the FDA. I was the primary clinician involved in several of the FDA's Major Corporate-Wide Actions for which I received various citations and honors for my services to the FDA. My awards have included Department of Health and Human Services and the Food and Drug Administration Employee of the Month.

8. I was sent by the FDA to serve as an official Agency representative to medical meetings and seminars to help identify and monitor conduct of manufacturers for potential

deviations from regulations governing promotional activities. At those interactions, I was required to provide official guidance as to the FDA's interpretation of Food and Drug Laws as they pertain to all medical products and the roles of manufacturers and health care providers.

9. While at the FDA, I helped draft agency documents, guidance documents regarding requirements for obtaining FDA's marketing approval, FDA Safety Alerts, provided the FDA comments for voluntary warnings and physician and user notifications, and agency comments on voluntary industry standards. I was a FDA liaison with the National Institutes of Health (NIH) for issues involving ENT, Renal, Respiratory, Women's Health, and Alternative Medicine. I was required to provide support to Health Care Financing Agency (HCFA now CMS) regarding the FDA's approval of product and issues involving hemodialysis. I was assigned responsibility for product adverse event reporting to the Department of Defense (DOD) and Veterans Administration.

10. One of my assigned responsibilities at the FDA, based on my clinical training and experience, was to review facts contained in product marketing applications, clinical trials, medical literature, reports of post-marketing experience, and available manufacturing documents gathered by the FDA or provided to the FDA by the manufacturer or other regulatory agencies, and then to use those facts to 1) make a clinical determination to a reasonable degree of medical certainty for FDA per the FDCA and; 2) recommend the next courses of action available to FDA to protect the public health. I was also required by the FDA to advise and train other FDA employees regarding the review of facts of a case or issue, the requirements of the Food, Drug and Cosmetic Act, and making a determination to a reasonable degree of medical certainty regarding the clinical impact of the agency's actions to the public. This was a process I was trained in and required to perform for the FDA. The health risk assessment process is further

described in 21 CFR Part 7. During my tenure at the FDA, I reviewed hundreds of marketing applications for safety and efficacy as well as proposed draft labeling. In this capacity, I worked with industry scientists and academic clinical investigators for evaluation, marketing and labeling review of new products. I organized national conferences with industry and physicians to discuss and obtain expert consensus regarding the development of new products and labeling as well as evaluating existing products on the market for safety and efficacy.

11. At the Armed Forces Institute of Pathology (AFIP), Office of the Medical Examiner, I was required, again based on my clinical training and experience in pathology, to take all available facts surrounding a patient's death and any involved adverse events and make a final determination: 1) to a reasonable degree of medical certainty, as to the cause of death, and 2) to recommend the next steps that should be taken by the military or another agency of the federal government. In that capacity as a Medical Examiner, I provided support to the various legal staff of the armed services, as well as the FBI and CIA. While a medical examiner at the AFIP, I determined that a cause of civilian patient deaths, occurring in military hospitals, to a reasonable degree of medical certainty, appeared to have been associated with unanticipated drug/device effect. I then reported my findings as a MedWatch report to the FDA. As an AFIP Medical Examiner, I was able to trigger the FDA to investigate a major drug regulatory safety action which resulted in the protection of public health.

12. After leaving the FDA, and founding MD Assist, Inc., I have continued to provide information to individuals, manufacturers, and organizations of the FDA's requirements, Adverse Event Reporting, and labeling of FDA-regulated products. Those products have included INDs, NDAs, IDEs, PMAs, and 510(k)s for devices, biologics and drugs. I was requested by the FDA to participate in a 1997 panel of experts convened by the FDA to comment

on changes proposed in the requirements for medical device labeling. I continue to consult for manufacturers, lecture at conferences and seminars regarding FDA, pre-market clearance, design of clinical trials, product labeling, Corrective and Preventive Action (CAPA) and Quality Systems.

13. I have attached a list of my last 5 years of deposition and court testimony Appendix 1. A copy of my most recent Curriculum Vitae is attached as Appendix 2. I receive \$400/hr for study and \$600/hr for deposition and trial testimony.

II. OPINIONS:

14. All opinions are rendered to a reasonable degree of profession, scientific and regulatory certainty. My expert opinions have been developed using the same methodology I was first trained to use while at FDA as well as my education, professional training and experiences since leaving FDA. With ongoing discovery, I also reserve the right to amend my opinions.

OPINION #1:

15. On February 16, 1984, the FDA's Paul Leber, MD, Director, Division of Neuropharmacological Drug Products, wrote to defendants ("GSK") regarding its IND 23,280 and request to begin human investigations of paroxetine hydrochloride tablets, 10 and 30 mg for the treatment of depression. The letter followed the FDA's completion of a review of the 11 volume IND submission dated December 21, 1983. From the initial IND communications with the FDA for human investigation of paroxetine and based on the limited safety data, the defendant's ("GSK") IND clinical trial for treatment of depression was to exclude enrollment of

all women of child-bearing potential. The preclinical studies provided also had not been adequately designed by GSK to elucidate the qualitative “differences” in cardiovascular effects produced by paroxetine.

16. The proposed IND study was titled: “Phase II Placebo Controlled Double Blind Study of Paroxetine in Depressed Outpatients” (PAR060011223-7; pxfdacor00000005-9). The FDA’s letter stated the following (underlining added for emphasis):

During a telephone conversation on January 27, 1984 between Mr. Lawrence Olon and Joyce Creamer of this agency we informed you that pharmacokinetic studies, both clinical and preclinical may proceed with the condition that you exclude women of childbearing potential until there is documented evidence of efficacy in a placebo controlled trial. Even, then, preclinical reproduction studies suggest that paroxetine adversely affects reproductive parameters at rather low doses. Only postmenopausal and surgically sterile females may be included at present. During that telephone conversation, you agreed to these conditions.

In addition, we have the following comments and recommendations:

3. Preclinical studies should be designed to elucidate the mechanism of cardiovascular effects of paroxetine since they are qualitatively different from the well known effects of tricyclics...

17. The FDA’s letter concluded reminding GSK of its own responsibilities to ensure compliance with the Federal Food, Drug and Cosmetic Act:

You are responsible for compliance with the Federal Food, Drug and Cosmetic Act and Regulations. This includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

18. When paroxetine was approved by FDA with a benefit (efficacy) shown when compared to treatment with placebo in the enrolled population of depressed patients, excluding all women of child-bearing potential. At the time of FDA’s approval, there was no evidence provided to FDA’s reviewers which suggest a teratogenic effect associated with use of

paroxetine for a pregnant female. The GSK NDA was approved with Use in Pregnancy as pregnancy category B.

19. In 1995, when GSK sought to expand its indications for paroxetine, based on the animal data that had been provided in the initial NDA and the agency's concern and increased awareness about the risk of SSRI drugs, paroxetine was requested by FDA as a condition of NDA approval to be changed from pregnancy category B to pregnancy category C. The change in pregnancy category for paroxetine was discussed internally at GSK in a series of emails (PAR041224019-20) beginning September 4, 1995 with an email sent from Martina Dempsey to Gwyn Morgan, et al. titled "Re: SSRIs and pregnancy category". Dr. Dempsey wrote:

...The paroxetine OCD review is almost complete in the US and we anticipate receiving an action letter before the end of the year. To date we have not received any request with regard to a change in pregnancy category nor are our USRA colleagues aware of any 'rumblings' in this regard. Prozac as you know is approved for both OCD and depression and currently still retains it's (*sic) category B pregnancy statement. Again, the US are not aware of any FDA requests to Lilly in this regard. I have asked that USRA see if there is anything further they can find out on this issue...

20. A follow-up email was sent October 16, 1995 again from Dr. Dempsey to Gwyn Morgan, Joyce Cole and Diane Macklestone still titled "Re: SSRIs and pregnancy category". In this email she wrote:

Further to my note in September (below), just to let you know that we have now received an approvable letter from the FDA on our paroxetine OCD sNDA. One of the conditions of approval is that we change our pregnancy warning from Class B to C which we understand is a class labeling change for all SSRIs.

21. An additional email was sent on February 22, 1996 from GSK toxicologist, Patrick Wier, PhD to Gwyn Morgan, Dennis Meyer and Bill Kearns still titled "Re : SSRIs and pregnancy category". Dr. Wier wrote:

In a rat Segment II study paroxetine caused embryo-fetal death and reduced fetal weight which indicates FDA Use in Pregnancy Category C (effects in animals, no human data). Category B applies when animal studies are negative and human studies are lacking or when animal studies are positive and there are well-controlled human studies showing no risk (current paroxetine label states "There are no adequate and well-controlled studies in pregnant women.")

The current paroxetine label was written to suggest Category B ("...revealed no evidence of teratogenic effects."), but in fact the FDA Guideline for Category B is "...animal findings are negative." In the science of developmental toxicology it is universally appreciated that embryo-fetal death, malformation, growth retardation and functional deficits are equally important manifestations; any prioritization of these outcomes is purely subjective.

Despite the original labeling (see below), all SSRIs should be Category C.

venlafaxine (Cat. C)- labeling reports no teratogenic effects but stillborn pups and reduced pup weight.

The above is yet another example of why informed obstetricians and clinical teratologists find the FDA Use in Pregnancy categorization scheme to be flawed and useless. None of these labels provide the caretaker and patient with information necessary to understand the hazards and put them into a clinically-relevant risk assessment.

These drugs produce similar developmental toxicity in rats and differences in the labeling are the result of different labeling strategies (in that light it is particularly interesting to compare paroxetine with venlafaxine, which got the label 'right').

22. On February 27, 1996, Dr. Wier sent an email now to Michael Brennan with copy to C. Nigel Toseland, Bill Kerns, Henk Solleveld and Gwyn Morgan titled "Paxil® Re-labeling proposed by FDA" (PAR000056279-80). Dr. Wier wrote:

1. Change from FDA Use in Pregnancy Cat. B to Cat. C. This is expected because Paxil caused rats embryo-fetal death, reduced fetal weight and pup deaths which indicates Cat. C (effects in animals, no human data). Category B applies when animal studies are negative and human studies are lacking or when animal studies are positive and there are well-controlled human studies showing no risk (current paroxetine label states "There are no adequate and well-controlled studies in pregnant women"). All the SSRIs should be Cat. C because they produce similar effects in rats:...

23. In 2005, based on FDA's receipt of human data showing an association of paroxetine use during pregnancy with congenital malformations, paroxetine's labeling was once

again changed in terms of pregnancy category. Paroxetine was changed from pregnancy category C to pregnancy category D.

OPINION #2:

24. The Paxil® Controlled Release (“CR”) product insert (“PI”) available to Dr. Jackie Snell prior to January 2005 and before she prescribed Paxil CR to Ms. Lisa Collins for treatment of symptoms of anxiety and Irritable Bowel Syndrome (IBS) failed to adequately describe and warn about the increased risks associated with *in utero* exposure of Paxil in a pregnant women during the first trimester. The labeling also did not provide adequate warnings regarding the increased risk for major cardiovascular birth defects associated with first trimester use of Paxil CR. Such failure to adequately warn physicians by GSK prior to January 2005 about the risk of *in utero* exposure denied physicians, including Dr. Snell, the information necessary to make a meaningful risk versus benefit decision for their patients about whether or not to prescribe Paxil to a female patient and to warn about the risk of pregnancy. This failure of GSK to adequately warn about the risks of Paxil for a developing fetus prior to January 2005, directly contributed to the subsequent major cardiac birth defect and neurodevelopmental outcome of Chase Steele.

OPINION #3

25. GSK deviated from its duty and the conduct of a responsible pharmaceutical manufacturer when it failed to ensure its own compliance with the federal Food Drug and Cosmetic Act and disregarded public safety by not voluntarily providing adequate warnings in its paroxetine labeling prior to December 2005 about the risks of prescribing paroxetine to women during pregnancy. GSK did not provide communications to health care professional prior to

