

EXPERT WITNESS REPORT

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I.

This expert witness report is authored by David J. Rothman. I am the Bernard Schoenberg Professor of Social Medicine at the Columbia College of Physicians & Surgeons, the medical school of Columbia University. I am also the director of the Center on Medicine as a Profession at the Columbia College & Surgeons. In addition, I am president of the Institute on Medicine as a Profession.

My qualifications for undertaking this assignment include substantial research and leadership in the field of medicine-industry relationships, in particular the pharmaceutical industry and the medical device industry. My vita (appended as Exhibit I) contains the list of my publications and activities relative to this area. Highlights include my serving as co-chair of a task force to define appropriate relationships with industry for academic medical centers, and co-chair of a task force to define appropriate relationships with industry for professional medical associations. Both of these reports were published in the Journal of the American Medical Association, one of the most prestigious journals in medicine, and are helping to establish standards for behavior among these centers and organizations. Over the past several years, I and my colleagues at the Center have published 8 articles in this area, all in peer reviewed and prominent journals. The most recent article that we published in this area appeared in the Archives of Internal Medicine (website prior to printed journal, September 13, 2010) and was discussed in a New York Times article of the same day, Wilson, "Medical Industry Ties Often Undisclosed in Journals." (B1) The impact of my work is also evidenced as well by the substantial grant support I receive from leading foundations.

In the past ten years, I have served once before as an expert witness. The case involved the ethics of human experimentation, prompted by the disclosure that investigators at a prominent medical school had fed radioactive iron to pregnant women in the late 1940s without informing them that they were receiving the substance or were subjects in a research project. (*Craft v. Vanderbilt*).

I have been hired as an expert witness in this case by the Texas Attorney General's office, and I submit this report for the Plaintiffs.

II.

I was asked to address the following questions:

- 1) Are appropriate safeguards necessary to guard against conflict of interest in relationships of medicine with the pharmaceutical industry? Was Johnson & Johnson (hereinafter J&J, which includes Janssen and other subsidiaries named as defendants in this lawsuit) aware of the need for such safeguards?
- 2) In the relationship between J&J and medical and state personnel, were there appropriate safeguards in place to prevent opportunities for undue influence in the activities of the Texas Medical Algorithm Project (TMAP)?
- 3) Were appropriate safeguards in place to prevent opportunities for undue influence in other marketing efforts for Risperdal?
- 4) Did Dr. Shon have any relationships with any Defendants that created conflicts of interest in his role as medical director of TDMHMR?
If so, was disclosure sufficient to resolve the problem?
- 5) Did Dr. Crismon have any relationships with any Defendants that created conflicts of interest in his role as a leading member of TMAP?
If so, was disclosure sufficient to resolve the problem?
- 6) Did Dr. Miller have any relationships with any Defendants that created conflicts of interest in his role as a leading member of TMAP?
If so, was disclosure sufficient to resolve the problem?
- 7) Is the ghostwriting of scientific research articles appropriate, and if not, why not?
- 8) Did Defendants engage in ghostwriting of scientific research articles?
- 9) Did Defendants disguise promotion of Risperdal through the use of advocacy and third party organizations?

To answer these questions, I drew on my substantial knowledge of the norms and ethical standards for the field, the literature in the field, and the standards set by medical and government bodies. I explored the documentary evidence in the case; I had access to all depositions, exhibits, and documents. I conducted my own searches of the online materials, assisted by Columbia Professor of Public Health, Sheila M. Rothman and by a research assistant. In addition, I reviewed the materials and the documents cited in my report.

My work is still ongoing and as discovery continues, I will supplement my report. The documents cited here to support my opinions are further supplemented by an extensive scholarly literature that addresses conflicts of interest and appropriate measures to reduce or eliminate them. Additional references may be used in support of my opinions.

1) Are appropriate safeguards necessary to guard against conflict of interest in relationships of medicine with the pharmaceutical industry? Was J&J aware of the need for such safeguards?

Yes. Appropriate safeguards are necessary to guard against conflicts of interest. Conflicts of interest in the relationships between physicians and industry arise because financial ties have the potential to subvert scientific integrity. Although some physicians and researchers think that they are not affected by industry, many studies have demonstrated that even gratuities as insignificant as drug samples and small gifts can compromise judgment about scientific evidence and influence prescribing practices. The power of the gift to prejudice decision-making, whether consciously or unconsciously, was and is fully appreciated.

The explicit need for appropriate standards to govern medical-pharmaceutical industry relationships were both fully appreciated and well established by the time Risperdal was introduced in 1994. (Here and below, references to "industry" are specific to the pharmaceutical industry.) Then and now, there is general recognition on the part of the leaders of academic medical centers, medical organizations, medical journals, foundations, government agencies, and within the industry itself that, unless properly managed, the marketing goals of industry pose both real and potential dangers to scientific and educational integrity.

Documents make clear that J&J was not only aware of and knowledgeable about compliance requirements, but also had enacted its own compliance policies that were consistent with general standards. The problems were that it was slow to do so and did not consistently live up to them in practice. Despite the widespread knowledge of the need for standards as detailed above, Janssen's then compliance officer (Mallegol) testified that Janssen did not have a formal compliance policy in place until 2000. The earliest regulatory guidelines that I could locate were those of J&J in late 1998.

Both the objective literature and J&J's own compliance documents show a widespread sensitivity among parties to the problems posed by conflicts of interest between medical researchers, authors, and practice guideline writers on the one hand, and drug companies on the other. Pharmaceutical influence is pervasive, but there are several distinct areas that are particularly troubling: 1) gifts, honoraria, and other types of financial support to those who prescribe drugs or who influence the prescribing behavior of others; 2) industry-funded continuing medical education courses (CME); and 3) biasing the medical literature through ghost-writing and strategic publication plans.

1. Gifts, honoraria, and other types of financial support to those who prescribe drugs or who influence the prescribing behavior of others.

It is well understood by all parties that honoraria, consulting agreements, travel, entertainment, and research grants provided by industry to medical professionals have the potential to bias research outcomes, educational materials, and practice guidelines. The power of the gift to prejudice decision-making, whether consciously or unconsciously, is fully recognized.

The medical literature reveals how influential the interactions between industry and physicians are. They affect:

1. Prescribing practices (See for example, A. Wazana, "Physicians and the Pharmaceutical Industry." JAMA (283) 2000, 373-380.)
2. Requests for addition of drugs to hospital formularies (See, for example, M. Chren et al., "Physicians' Behavior and their Interactions with Drug Companies..." JAMA (271) 1994, 684-689.)

3. The conclusions of industry sponsored research (See, for example,, J. Bekelman et al., "Scope and impact of Financial Conflicts of Interest..." JAMA (289) 2003, 454-465.)
4. The recommendations of clinical practice guidelines (See, for example, N. Choudhry, "Relationships between Authors of Clinical Practice Guidelines and the Pharmaceutical Industry," JAMA (287) 2002, 612-617.)

Although the issues in conflict of interest are intricate, there is extraordinary unanimity about the principles that should govern industry relationships. Several groups have issued guidance, including a committee of the American Board of Internal Medicine Foundation and the Institute on Medicine as a Profession (See Brennan, Rothman, et al., Health industry practices that create conflicts of interest, JAMA, 2006; 295: 429-433; and Institute of Medicine report, "Conflict of Interest in Medical Research, Education, and Practice" (2209). They recommend that gifts to physicians be eliminated; that honoraria and consulting arrangements be closely monitored and fully disclosed; that transparency and management of conflict of interest is especially crucial when it comes to the formation of clinical practice guidelines and publishing research results.

The Office of the Inspector General of the Department of Health and Human Services has also issued relevant guidance for ethical behavior. (See "OIG Compliance Program Guidance for Pharmaceutical Manufacturers.") Addressing fraud, abuse, and the False Claims Act, it cites several practices especially relevant to the issues on gifts and other financial support. First, "kickbacks:" The OIG is particularly concerned with the relationship between a manufacturer and persons "in a position to generate federal health care business for the manufacturer," citing specifically purchasers, benefit managers, and formulary committee members. It asks: "Does an arrangement or practice have a potential to interfere with or skew clinical decision-making? In still more particular terms: does it have a potential to undermine clinical integrity of a formulary process?" It is also especially sensitive to the quality of the information provided to "decision makers, prescribers, or patients." (Federal Register, vol. 68, May 5, 2003, p. 23734) Second, the Guidance addresses company relationships with physicians. It notes that "gifts, entertainment and personal services compensation ...have a high potential for fraud and abuse." (23737) Third, the Guidance

emphasizes the need for prompt reporting by a company of misconduct to state and federal authorities. (23742)

In addition, not only physicians but also state employees in positions to influence prescribers must guard against conflicts of interest. The Texas Ethics Commission, in an advisory opinion issued in March 1996, declared that an honorarium is not permissible if the public servant's official status was a deciding factor in the payor's decision to hire him to perform services. It cited the Texas Penal Code provision prohibiting state employees from accepting honoraria in such circumstances. (Hunt Exhibit, 1636) Finally, the Texas Government Code stipulates that a state employee may not have a financial interest or engage in a business or "professional activity" that is in "substantial conflict with the proper discharge or...duties in the public interest." (Texas Gov't Code ANN. §572.001(a))

J&J was fully cognizant of these principles. In December 1998, it issued "Health Care Regulatory Documents for Promotional and Marketing Practices." Noting recent government enforcement efforts and fines to companies, it aimed to "provide guidance to J&J companies and their employees and to facilitate employee training in appropriate marketing practices." (J-TXCID1336536) The document included materials on kickbacks, warning that payments were not allowed to induce "referrals or product recommendations." (.....6541) So too, consulting and service arrangements were not to be used to promote the purchases of J&J products. (.....6547) It went on to declare that advisory board meetings "should generally not be held in resort locations." (.....6557). Finally, it stated that "J&J companies may not provide clinical grants to customers in exchange for or based on referrals, purchases, or recommendations for J&J products." (.....6573) As we shall see below, J&J practices did not consistently meet these standards.

In 2000, Janssen produced a formal compliance policy document. (Mallegol Deposition, 20-24) The Health Care Compliance manual issued to its sales staff included such directives as: "Janssen employees must not provide any gifts, gratuities, or payments for meals, travel, or lodging to federal, state or local government employees." (J-TX2163186) The company policy declared: "Government employees are bound and responsible for complying with the Government Code of Ethics." It immediately added: "Janssen employees must be aware of these standards and avoid creating situations that compromise them." (Mallegol Exhibit, 40,

27) It went on to note that "special circumstances may apply with the written authorization from the government supervisor." (28) As we shall see below with Dr. Steven Shon, the company failed to fulfill its own standard.

2) Industry-funded continuing medical education courses

To attend CME courses is required for physicians. CME attendance is the primary method by which physicians fulfill their obligation to carry out life-long-learning and maintain professional competence. Accordingly, it is vital the CME courses conform to the highest standards of scientific integrity and reflect best practices for patient care. They must be free of bias and not allow pharmaceutical marketing to affect the content of the presentation.

Professional guidelines reflect how CME should be conducted so as to limit industry influence. The Accreditation Council of Continuing Medical Education (ACCME) promulgated guidelines in 1992 that set standards regarding the independence of CME activities. CME activities "must be free of commercial bias for or against any product; if the activities are concerned with commercial products, they must present objective information about those products, based on scientific methods generally accepted in the medical community." To this end, "Commercial supporters of such activities shall not control the planning, content or execution of the activity." (Standards for Commercial Support of Continuing Medical Education, Approved by ACCME March 20, 1992).

The ACCME further elaborated its Standards for Commercial Support in 2004. Among its most relevant and significant stipulations were:

"Standard 1: Independence

1.1 A CME provider must ensure that the following decisions were made free of the control of a commercial interest. (a) Identification of CME needs; (b) Determination of educational objectives; (c) Selection and presentation of content; (d) Selection of all persons and organizations that will be in a position to control the content of the CME.

Standard 2: Resolution of Personal Conflict of Interest

2.1 The provider must be able to show that everyone...has disclosed all relevant financial relationship with any commercial interest to the provider.

2.3 The provider must have implemented a mechanism to identify and resolve all conflicts of interests.

Standard 3: Appropriate Use of Commercial Support.

3.1 A provider cannot be required by a commercial interest to accept advice or services concerning teachers, authors, or participants or...content.

3.7 The provider must have written policies and procedures governing honoraria and reimbursement of out-of-pocket expenses for planners, teachers and authors.

Standard 5: Content and Format without Commercial Bias

5.1 The content...must promote improvement or quality in healthcare and not a specific proprietary business interest or a commercial interest.

5.2 Presentations must give a balanced view of therapeutic options. Use of generic names will contribute to this impartiality.

Standard 6: Disclosure Relevant to Potential Commercial Bias

6.1 An individual must disclose to learners any relevant financial relationship(s)"

Here, too, J&J demonstrated familiarity with existing standards. Its Health Care Regulatory Documents of 1998 made explicit reference to CME programs: "The sponsor must have complete discretion with respect to the use of funds" (J-TXCID1336544-45) and "J&J must remain largely 'hands off' with respect to influencing the content of the program." (.....6567)

3) Biasing the medical literature through ghostwriting and strategic publication plans.

Medical publications are at the heart of scientific progress and patient care. Investigators design their research projects based on prior findings. Physicians prescribe medications to their patients based on reports of

efficacy in medical journals. For these reasons, the integrity of publications is absolutely essential. Ghostwriting subverts this integrity by concealing information about who conducted the research, who authored the article, and who funded the research. It takes several guises: it omits the names of participants in the project, usually by omitting the names of industry employees. It includes the names of persons who had no role or a minimal role in the project, usually by including the names of key medical opinion leaders. It also omits the names of members of medical communication firms so as to further obfuscate the role of pharmaceutical companies. These companies through ghostwriting hide their role in defining the research project, in analyzing the data, and in editing and revising the manuscript. In all these ways, ghostwriting gives a veneer of objectivity to findings that may have been manipulated to serve the marketing interests of a drug company.

To counter such abuses of scientific integrity, medical journal requirements for publication and authorship set the appropriate standards. (See, "Uniform Requirements of the ICJMA," New England Journal of Medicine, January 23, 1997) The stipulations include:

Each author should have participated sufficiently in the work to take public responsibility for the content." (p. 311). The order of authorship should be a joint decision of the coauthors." (p. 311) Acknowledgments should include:

b) Acknowledgments of financial and material support which should specify the nature of the support; and (d) "Relationships that may pose a conflict of interest."

Although I saw no reference to ghostwriting standards in J&J documents prior to 2005, the company had to be aware of these principles, given the intensity of its involvement with the publication in medical journals of its in-house research. In August, 2005, in a "Guidance Document on the...Dissemination of Scientific Information," J&J stated that "J&J companies should not engage in or condone the "ghost writing" of articles, i.e., omitting from a publication the name of an individual that contributed materially or giving a misleading impression of the contribution made by an individual." J&J does not state that this is a new policy or a departure from previous practice. (J-TXCID1826155-6)

In addition, the 2005 document goes on to declare: "J&J companies must be particularly mindful when developing a 'publication plan' for a product to insure that the above principles are complied with. Thus, while it is appropriate to anticipate and plan for potential publication venues and scientific themes, the scientific results of the J&J company's research must govern the publication outcome." (J-TXCID1826156) As we shall see, J&J and the medical writing companies that it hired frequently and indisputably violated these principles.

As in the case of financial conflicts of interest, there is a rich and relevant medical literature setting out the principles for publication. See for example: D Rennie, "When Authorship Fails," JAMA (278), 1997, 579-585; JS Ross et al., "Guest Authorship and Ghostwriting..." JAMA (299) 2008, 1800-1812; S Sismondo, "Ghost management..." PLOS (4) 2007, e286.

Other areas of concern in medicine-industry relationships and the problems beyond undue influence have been well documented and fully analyzed in the medical literature. This literature makes eminently clear just how problematic and worrisome payments from industry are to medicine, and how such payments bias medical decision making. These issues have been so emphasized in the medical literature (and not surprisingly by the media) that J&J periodically issued a variety of compliance guidelines and policies. As we shall see, however, they did not enforce the stipulations or use them to guide their own behavior as evidenced by several activities discussed below.

Thus, a J&J Healthcare Compliance Policy Update of September 23, 2004, declared: "Grants must not be used to support promotional activities." (J-TX2204305) A J&J Healthcare Compliance Contracting Handbook (October 2004) also declared: "These programs cannot principally benefit the Company directly." (J-TX2774170) But these standards, as evidence on J&J-TMAP activities makes clear, were not adhered to by J&J or by the communication firms that it hired.

J&J compliance manuals stated unambiguously: "Janssen will not place Educational, Advisory, Consultant or Training programs at 'Resorts.'" (TXJAN 0079965) It declared: "Education must be modest in value and location." (Mallegol Exhibit, 40) Nevertheless, violations of this policy were frequent, as witness the events discussed below at the Mansion at Turtle Creek (Texas) and Amelia Island (Florida).

Another Janssen manual "Questions and Answers for Health Care Compliance," responding to "conviction of individuals and organizations engaged in activities that defraud Federal Health Care programs," set forth in the period 2000-2002 standards that should govern company activities. However, the standards were not upheld. (Mallegol Exhibit, 36, preface-1) In particular, the manual declared that in terms of advisory boards, speakers, and other consulting services, "interactions should not be used as a selling opportunity to physician." (1-3) J&J practice differed. So too, the manual stipulated that CME programs must give the provider "full control over program content, planning and speaker selection." (1) Again, J&J practice departed from the standard. The focus of the program was to be "free from commercial bias," (2) and yet J&J used the programs for marketing purposes. In terms of educational grants, J&J's stated policy was that such grants should not be "promotional," but again, practice did not follow policy. (3-1) Grants were to go to the provider, not the speaker, but J&J frequently circumvented the policy. (3-2)

Finally, a J&J "Commercial Compliance" manual demonstrated the depth of the company's knowledge of compliance standards, including anti-kickback and safe harbor provisions in the guidance issued from the Office of the Inspector General of Health and Human Services. (J-TX2204015). The J&J manual showed familiarity with these stipulations. (See, for example,...4020) It closed with a check list of questions that a prosecutor might pose to create a "Perfect Storm." Included are: "Who did the sales force target? Are there budgets for unapproved use? CME-Independence of provider?" (4033) Nevertheless, as will be discussed, J&J ignored the guidance and sailed straight into the perfect storm.

2) In the relationship between J&J and state of Texas medical and official personnel, were there appropriate safeguards in place to prevent opportunities for undue influence in the activities of the Texas Medical Algorithm Project (TMAP)?

A review of the documentary record demonstrates that adequate safeguards were not in place. In promoting its drug, Risperdal, in its oral and injectable forms, J&J exerted improper influence over potential payors and prescribers. Activities that it funded in medical education, research, and publication were, in fact, thinly disguised marketing activities. J&J's funding of these activities created conflicts of interest that subverted

scientific objectivity and professional medical integrity. J&J dispensed gifts, honoraria, speaking fees and meeting attendance payments to win favors from payors and prescribers; these activities represented a deliberate effort by J&J to influence payors and prescribers to favor Risperdal. J&J carefully targeted its efforts at physicians who were Key Opinion Leaders (KOLs) or in positions to influence the purchase of J&J products, with the goal of establishing relationships that would advance marketing.

Even before Risperdal received FDA approval, J&J understood that the dominant market for the drug would be in the public sector—mental hospitals, outpatient clinics, nursing homes, jails, and prisons. Its efforts were aimed, therefore, at payors, physicians, and advocates in a position to affect public spending, especially Medicaid spending.

The strategy was set forth early in the history of Risperdal. Already in September 1992, a consulting firm (State and Federal Associates) gave J&J a blueprint that it would subsequently follow. (J-TXCID 1513719-3849) The firm advised J&J that between 60 and 80 percent of schizophrenia medications were paid for by state mental health and Medicaid programs, and should be the prime target of promotional activity. (p. 2) The firm also recommended devoting special attention to issues of cost, on the grounds that Risperdal would be more expensive than the generic alternatives, such as Haldol, but cheaper than the competing drug, Clozaril. (81) It particularly advised J&J to identify state mental health officials because they would be essential to Risperdal's marketing success, including marketing in Texas. J&J should meet with the key state officials and establish relationships with them; (96) the company should be certain to interact with mental health program directors, make its case to them, and use research findings from pharmacoeconomics to buttress the argument. (83-84). So too, the firm urged J&J to work with such patient advocacy groups as the National Alliance on Mental Illness (NAMI) to expand mental health insurance benefits and thus gain more of a market for Risperdal. (95) Indeed, it recommended that J&J enlist support from NAMI to accompany the product launch. (97) J&J generally followed their advice, and undue influence frequently marked J&J's efforts to fulfill this agenda.

In 1993, GTFH Public Relations echoed what State and Federal Associates had recommended the year before. It, too, emphasized the need to cultivate state officials along with members of the psychiatric community. (J-TXCID1513850) GTFH also emphasized that J&J should be convening

Expert Task Force Meetings: "Formulate position and draft guidelines for consensus (J-TXCID 1513883) Use: "Personalized invitational campaign to maximize participation." (...1513885) Finally, it counseled J&J to "Form exclusive partnership with growing advocacy group," citing NAMI as one case in point. J&J should help establish chapters and co-sponsor educational programs on patient issues. (...892)

It is worth noting that J&J policies referred to physicians and other health care personnel (nurses, managed care employees) as "customers," defined as "any individual or company that has the ability to prescribe or influence the use of Janssen products." (Mallegol Exhibit, 40, J-TXCID0909360) Rather than conceptualize them as healers with responsibility to alleviate pain, suffering, and disease, they defined them as purchasers and customers. This mindset, as we will see, extended as well to advocacy groups, researchers, state officials and decision-makers. These, too, are all "customers." See Customer Interaction Strategic Plan November 6, 2003 J-TX4955228 which lists Shon, Crismon and others as customers. This orientation at once reflected and reinforced the priority of marketing over scientific integrity and medical professionalism.

As one of its first activities, and in disregard of professional medical ethics and principles of conflict of interest, in 1995 J&J funded a project led by three psychiatrists at three medical centers (Duke, Cornell, and Columbia) to formulate Schizophrenia Practice Guidelines. From the start, the project subverted scientific integrity, appearing to be a purely scientific venture when it was at its core, a marketing venture for Risperdal. In fact, the guidelines produced by this project would become the basis for the TMAP algorithms, giving a market edge to the J&J products in Texas.

Three psychiatrists, Dr. Allen Frances, Chairman of the Department of Psychiatry, Duke University, Dr. John P. Docherty, Professor and Vice Chairman of Psychiatry, Cornell University and Dr. David A. Kahn, Associate Clinical Professor of Psychiatry, Columbia University, took the lead in designing and developing the Tri-University guidelines. Dr. Frances negotiated the agreement with J&J (November 9, 1995), to set forth the Schizophrenia Practice Guidelines. (J-TXCID1722938-40) The project would employ three questionnaires to establish the guidelines: one went to academic experts, one to clinicians, and one to policy experts. Including the third group was in all likelihood J&J's idea as witness the fact that Frances

wrote J&J: "This is new to us and requires additional discussion. The panel members would include mental health commissioners, community mental health directors, state hospital directors, managed care medical directors, pharmacy directors, NAMI representatives, experts in pharmoeconomics, and so forth." These were precisely the constituencies that J&J was eager to influence. J&J was the exclusive supporter of the project, dividing an "unrestricted" grant of \$450,000 among the three schools. It further agreed to a \$65,000 bonus incentive payment if the team was timely with its product. The team met the requirement, requested the additional payment, and received it. (Anderson Deposition, 56)

The guideline team promised wide distribution of its product, including publication in a journal supplement. The team was prepared to have J&J participate in its work, not keeping the company even at arms length. With a disregard for conflict of interest and scientific integrity, the group shared its drafts with J&J. On June 21, 1996, Frances wrote Lloyd: "We are moving into the back stretch and thought you would be interested in seeing the latest draft of the guideline project.... *Please make comments and suggestions.* (Italics added) So too, the group was eager to cooperate with J&J in marketing activities. Frances wrote without embarrassment or equivocation: "We also need to get more specific on the size and composition of the target audience and *how to integrate the publication and conferences with other marketing efforts.*" (Italics added) (J-TXCID1722944) Indeed, from the start J&J had made it apparent to the team that this was a marketing venture. In a letter to Frances, Lloyd set forth what he called an "aggressive time line" for the project, and added: "There are a number of other Treatment and Practice Guidelines for schizophrenia being developed or published during this same period that may well serve our marketing and implementation needs at a substantial lesser cost." (J-TXCID 1722945)

Not only were Frances, Docherty and Kahn ready to violate standards of conflicts of interest in mixing guideline preparation with marketing for J&J, but also in publicizing the guidelines in coordination with J&J. The three men established Expert Knowledge Systems (EKS). The purpose of this organization was to use J&J money to market the guidelines and bring financial benefits to Frances, Docherty, and Kahn.

EKS wrote to Janssen on July 3, 1996 that it was pleased to respond to its request to "develop an information solution that will facilitate the

implementation of expert guidelines." (Anderson Exhibit 2247, p. 1) It assured the company: "We are also committed to helping Janssen succeed in its effort to increase its market share and visibility in the payor, provider, and consumer communities." Now that the "first phase" was completed, with the guidelines created, "EKS is now ready to move forward in a strategic partnership with Janssen." (p.2) The strategy will allow Janssen to "Influence state governments and providers.... Build brand loyalty and commitment with large groups of key providers around the country." (p.2) EKS also promised "rapid implementation," with particular attention to having an impact on Texas decision making. (p.3) "It is our intent to work with the State of Texas immediately in implementing this product in a select number of CMHC's with the assistance of A. John Rush, MD." (p.3) Again EKS emphasized: "It is essential for Janssen to distinguish Risperidone from other competitors in a timely and creditable way." (p.8) In its Summary of the document, EKS wrote: "Your investment in the development of state of the art practice guidelines for schizophrenia is already beginning to pay off in terms of positive exposure in the Texas implementation project." (p.9)

The costs for these various activities included: \$250,000 for "educational conferences;" and dissemination of publications at \$177,659. (Anderson Exhibit, 2244, 2245). J&J agreed to them. (Anderson Deposition, 56-67) So all told, J&J paid at least \$942,659 on the production and marketing of the Tri-University guidelines.

The framing of the inquiry, the sharing of the data, and the tie to marketing make it clear that J&J's use of the phrase "unrestricted educational grant" to describe its funding was misleading. Generally, the term "unrestricted" means that the company would exert no influence over any aspect of an educational program it supported (in keeping with ACCME Guidelines). In practice, J&J did not remain at arm's length from the choice of speakers or the content of the educational materials. Lloyd, J&J's lead contact with Frances, was "Director of Reimbursement Services." On July 18, 1996, as the project coming to a close, Lloyd wrote Frances to express his delight with the way the project had turned out: "How we work together as a team to insure their [guideline] delivery and implementation will be critical..." (J-TXCID1722936) Even more telling is the heading to the letter, which demonstrates how closely the company linked the Tri-University Guidelines to its product. It was entitled: "RE: RISPERDAL (risperidone) Treatment Guidelines." In official terminology, these were general guidelines supported by an unrestricted grant. In fact, to J&J, this was a

venture to help Risperdal expand its market. And so it was in all too many ways to the Tri-University leaders. As Frances wrote Lloyd: "We also need to get more specific on...how to integrate the publication and the conferences with other marketing efforts." (J-TXCID1722944)

J&J took great credit internally for the Tri-University guidelines. In the "Reimbursement 1996" report, the J&J team noted among its "Team Projects and Accomplishments:" "Tri-University Schizophrenia Guidelines, Design, development and implementation." (J-TXCID-1403148) So too, J&J's Reimbursement Team considered at length how it "can leverage the Expert Consensus Opinion to increase Risperdal sales by making atypical antipsychotics more widely available.... *We decided that a key would be presenting these at 'arms length' making sure that our customers realize that the protocols are not Janssen influenced but rather Janssen supported.*" (Italics added) Making this point suggests that J&J tried to conceal its true motives and active participation in the project. (J-TXCID1395263)

J&J turned the guidelines into a powerful marketing tool. The slides presented at a CNS National Sales Meeting in March 1997, instructed employees to use the guidelines to convince its "Primary customers: P& T members, Formulary Decision Makers and Psychopharmacologists"—those who made purchasing and reimbursement decisions— that they should use the guidelines to justify making Risperdal the drug of choice. (TXJAN0048073) J&J also wanted the guidelines to promote the product's use among "Secondary Customers," namely "Physicians who are not convinced of RISPERDAL's 1st line status." So although the front piece for the guidelines described them as "suggestions for clinical practice," from J&J's perspective, they provide "credibility; Reinforces RISPERDAL's 1st line status; Differentiates RISPERDAL from convention APS and other atypical APS." To make certain the customers got the message, the "Full Supplement [of the guideline publication] should be left behind." J&J also funded CME offerings to publicize the guidelines, including a "Free 1/2 Day Seminars, Earn Up to 8 Hours of CE/CME." The panel of experts included Frances, Doherty, and Kahn, and also John Rush (who would play a key role in TMAP).
(web.archive.org/web/19961106071503/www.ibh.com/expert1.htm)

The guidelines were published in the Journal of Clinical Psychiatry (1996) 57 Supplement 12B. The Journal, in a preface, acknowledged that the supplement was supported by an unrestricted educational grant from J&J.

Dr. Alan J. Gelenberg, the editor-in chief of the Journal, however, was sufficiently troubled by what he knew that he took a highly unusual step. He warned readers of the possibility of undue pharmaceutical company influence. "Pharmaceutical companies devote enormous sums to academic departments and individual faculty members who consult, conduct research, and teach under the auspices of the company. There then are the experts who create consensus guidelines. While few of us sell our opinions to the highest bidder, fewer still are immune from financial influence." (Crismon Exhibit, 559)

Tri-University was the first of the guideline strategies that J&J deliberately, and at substantial expense, pursued. J&J next gave funding to the Texas Medical Algorithm Project (TMAP), again looking to increase the sales of Risperdal by getting it well placed in the recommended sequence for the use of pharmaceutical agents. One J&J employee, Rob Kraner, explained J&J's approach to colleagues: *"One of the reasons Janssen committed substantial funding was to develop treatment guidelines/algorithms for schizophrenia that positioned atypicals as the first line agents (at the time atypicals were usually positioned after conventionals) and test it in a real world setting. The rationale was to develop this approach in Texas, find out the most effective way to roll it out, and then other states could replicate TMAP with minimal investment."* (Italics added) (Kraner Deposition, p. 255, citing Snyder Exhibit 75.)

Just as Kraner noted, J&J effectively applied both the substance of Tri-University and the tactics that worked so well there to TMAP. Its "substantial funding" accomplished its goals. TMAP members adapted themselves all too readily to the opportunity. Rather than maintain appropriate distance, TMAP was willing to take industry money if it was "technically" unrestricted. (Crismon Exhibit, 556) The record contains TMAP Minutes from June 6, 1996 (with Drs Crismon and Shon among the five participants present). (Crismon Exhibit, 556) It noted under item 12: "New Policy discussed: No drug company money for conferences. Drug company money can be used if donated as an unrestricted educational or research grant to a foundation- companies will not be able to change protocol or algorithm nor state how the money will be used. May be able to get multiple grants from the same company if donating to different foundations. The money will be used to support the protocol in Phase I and II." These qualifications ignored both the reality of conflicts of interest (the

conscious or unconscious need to reciprocate to industry for gifts) and the appearance of conflicts of interest (developing algorithms that had crucial implications for drug companies with drug company money).

The record continues with Minutes from July 18, 1996 (with Crismon one of the 6 participants present and with Minutes distributed to Drs. Miller and Shon). (Crismon Exhibit, 448) Section XI declared: "At this point in the project it is time to bring the researchers on board. They will be helpful in reviewing the protocol and making revisions to the protocol. These individuals will also be asked to assist in seeking unrestricted grants from the pharmaceutical industry to fund the project."

In short order, even these qualifications were ignored. On September 5, 1996, Dr. John Rush, a TMAP member, wrote to J&J (at the suggestion of John Lloyd, who led the J&J Tri-University initiative) about TMAP and J&J support for Phase I activities to pilot the administration of the TMAP drug algorithm. (Dr. Shon was copied on the memorandum.) (TXJAN0018178) The expectation was that J&J would contribute \$75,000. (J_J_DSHS 0085247)

Moreover, to ask researchers in a position to revise the TMAP protocol to assist in soliciting grants from industry violates standards governing the reality and appearance of conflicts of interest. From the very beginning of TMAP, its leaders gave only lip service to conflict of interest considerations, ignoring principles in their search for industry funds.

Two additional points suggest how serious this lapse was. First, in the design of the schizophrenia algorithm, great weight was given to the recommendations of the Tri-University committee (led by faculty from Duke, Columbia and Cornell) that emphasized the benefits of the atypical antipsychotics. (Miller Deposition, p. 281) As discussed above, the work of the Tri-University group was funded by J&J. (Crismon Exhibit, 559) Second, the schizophrenia guidelines were being developed in this very period—and the algorithms used in TMAP placed atypicals such as Risperdal into the first level of use, while typicals went into the third or fourth tier. (Crismon Deposition, pp. 351-360) This change had obvious benefits for the manufacturers of atypicals in general and J&J in particular.

Thus, J&J fingerprints were all over the TMAP algorithms. As Dr. Miller declared in his deposition, the creators of TMAP adopted the guidelines of Tri-University "wholesale." (Miller Deposition, pp. 279-281)

The result was to transform the order of drug preference in the algorithm. In the "initial version" of the TMAP schizophrenia guidelines (1996), "conventional antipsychotic or risperidone" were both in Stage 1. (Crismon Exhibit, 519). The March 6, 1997 TMAP Meeting Minutes note the receipt of the \$75,000 expected from J&J along with contributions from Wyeth (\$75,000), Lilly (\$25,000), and promises of \$175,000 from three other companies. (Crismon Deposition, pp. 345-356) Then in the revised version (1998), the atypicals moved to Stage 1, and the "typical" or conventional antipsychotics moved down to Stage 4. (Crismon Exhibit 519, the 1999 publication of the Texas Medication Algorithm Project in Psychiatric Services, vol. 50, pp. 69-74) To be sure, Risperdal was not alone in Stage 1 but as we shall see, J&J through the exercise of undue influence with TMAP leaders, notably Drs. Shon, Crismon, Miller, and Chiles, was able to position its drug favorably. To cite one example, on June 6, 2000, a J&J employee, Yolanda Roman, outlined the "PHS&R Business Plan." The document emphasized the need for working with Medicaid officials and "ongoing interaction with Advocacy," as well as focusing on "price as a key element in the decision tree," in light of the extent of public funding for psychiatric drugs. The Plan also called for promoting Treatment Guidelines to the psychiatric community so as to make Risperdal the "standard of care." (Roman Exhibit, 129) In sum, J&J had its script and it proceeded to follow it closely.

J&J aimed its efforts directly at selected physicians and state mental health decision makers who were in the best position to advance its marketing interests and its particular aim to affect guideline development in the TMAP deliberations. Its activities and funding were not undertaken for the purpose of enhancing professional knowledge but for promoting the sale of its products. In its exercise of undue influence, J&J closely tracked TMAP physicians, in particular, Steven Shon, Lynn Crismon, and Alexander Miller. It also paid close attention to John Chiles, John Rush, and Kenneth Altshuler.

The attention that J&J gave to these physicians is evident from its internal memoranda (Leech Exhibit, 825). They include such observations as: Dr. Miller: "He is an investigator in the RIS-112 trial.... I will use the concept of this trial to support the idea that Risperdal is the better drug [than olanzapine]." Dr. Chiles: "My goal with Dr. Chiles is to keep him informed of advances with Risperdal research data and neutralize the influence of our competitors.... As we get new data and slides into his hands, I believe he