

Anything to declare? Border stories on the conflict of interest

Giancarlo Sturloni

ISC - Innovations in Science Communication, ISAS, Trieste, Italy ste

On September 15, 2001, a joint editorial simultaneously published in thirteen medical journals, pointed an accusing finger at the increasing pressures coming from the pharmaceutical industry. During past decades, a key role in trial design and conduct was played by independent clinical investigators working in academic medical centres. They were also able to vouchsafe the quality of their research, which might not, however, be the case in the future.¹

The editorial also reveals that new treatments are proving to be less beneficial, in spite of increasingly sophisticated and expensive trials. Today, marketing a new drug in the US costs an average \$500 million.² In order to reduce costs, the pharmaceutical industry prefers investing in private research groups, the so-called CRO's (Contract Research Organizations), who received, in 2001, 60 percent of all US research grants. Companies may thus decide upon the terms and conditions of recruitment, and investigators may have little say in the design of trials and may not have access to raw data or data interpretation. In addition, more and more frequently companies impose binding contract conditions which forbid researchers to publish trial results when these are unfavourable to the sponsor. There are well documented cases.³

¹ *Op.cit.* (1)

² *Op.cit.* (2)

³ *Op.cit.* (3), (4)

Not all members of the International Committee of Medical Journals subscribe to the article. The *British Medical Journal*, for instance, prefers to publish a separate, more moderate editorial.⁴ This journal does not ignore the problem posed by the conflict of interest, and dedicates to it the May 13 2003 monographic issue, titled “Time to untangle doctors from drug companies”. Inside, there is an interesting systematic review, made by North American researchers, showing that, compared to public funded research, studies sponsored by drug companies have a lower frequency of publication and a four times higher probability of reporting results favourable to the sponsor’s product.⁵ The authors stress the fact that it is not a question of lacking rigour. Considering the methods, industry funded research is no less reliable than other research. Rather, the authors suggest that in some cases trials are expressly designed to favour the tested product (for example, by choosing to compare a new drug with a placebo, even though another drug of proven efficacy already exists, or by administering an incorrect dosage of the comparator). Furthermore, industry funded studies appear more often in the proceedings of conferences, known for their lack of peer review and for being partial to sponsors. Finally, unfavourable studies may even vanish into thin air.⁶

The snake and the staff

In 1990, Betty Dong, researcher at the University of California at San Francisco, handed to the pharmaceutical firm Boots the results of a study comparing Synthroid (a levothyroxine-based drug produced by Boots to replace thyroid hormones in case of thyroid dysfunction) with three generic drugs containing the same active principle and marketed at a much lower price. The company had always claimed the superior efficacy of Synthroid, which earned them \$600 million every year. However, Dong’s results indicated that this drug had the same efficacy as the other three. Considering their lower prices, American taxpayers could have saved around \$360 million a year.⁷

⁴ *Op.cit.* (5)

⁵ *Op.cit.* (6)

⁶ *Op.cit.* (7), (8)

⁷ *Op.cit.* (9)

The company did its utmost to prevent the study from being published. Initially, it held that it was biased by methodological faults and called on the University of California for an inquiry. Later on, in 1994, when the internal investigation had proved Dong's correctness and she announced that she was going to publish her work, Boots manipulated the data and published a study with opposite conclusions in a journal whose editor was one of the company's researchers. The *JAMA* accepted Dong's study, but a week before going to press, in January 1995, the journal received a letter from the author saying that she was withdrawing the article because of a legal problem. She had realized that she had signed a contract not allowing her to publish any result without the company's approval. The article eventually appeared in the *JAMA*, but only in 1997⁸, seven years after being originally written. A journalist of the *Wall Street Journal* had opened Pandora's box and revealed the whole story to the public. Knoll, who in the meantime had bought the trademark from Boots, had to pay \$83 million in compensation.⁹

In the following years, concerns about the conflict of interest kept growing. In a long article, recently published by the *BMJ* and titled "Who pays for the pizza?", the American journalist Ray Moynihan shows that US drug prescriptions have vertically increased (a business that has nearly doubled between 1997 and 2001, and today is worth \$154 billion) while at the same time relationships between physicians and the drug industry have become closer and more generalized. Moynihan talks of them as being "twisted together like the snake and the staff", with an obvious reference to the symbol of medicine.¹⁰

Disclosure

Consequently, there is a growing number of initiatives, specially in the US, demanding a greater distance between physicians and industry investigators. The University of California in San Francisco is one of the most active: it has already put a stop to company-paid lunches and is planning to ban drug representatives from its clinic.¹¹ The American Medical Student Association (with around 30,000 members) has

⁸ *Op.cit.* (10)

⁹ *Op.cit.* (9)

¹⁰ *Op.cit.* (11)

¹¹ *Op.cit.* (12)

included in the Hippocratic Oath a commitment not to accept “money, gifts or hospitality that might create a conflict of interest with education, clinical practice, teaching or medical research”.¹² And, though on different sides, both the American Medical Association¹³ and Pharmaceutical Research and Manufacturers of America¹⁴ have adjusted their codes of conduct.

On the other hand, what international journals propose is disclosure. As early as 1989 the *JAMA* had begun asking authors to submit, together with their paper, a signed statement indicating conflicts of financial interest.¹⁵ It was an attempt at giving the readers the opportunity to judge by themselves if, and to what extent, the published study may have been distorted. Also the September 2001 editorial insists on the importance of disclosure, but it takes it a step further by considering, for the first time, researchers’ independence as the basis for future editorial policy: “Many of us will ask the responsible author to sign a statement indicating that he or she accepts full responsibility for the conduct of the trial, had access to the data, and controlled the decision to publish”.¹⁶

And, elsewhere: “As editors, we strongly oppose contractual agreements that deny investigators the right to examine the data independently or to submit a manuscript for publication without first obtaining the consent of the sponsor. Such arrangements not only erode the fabric of intellectual inquiry that has fostered so much high-quality clinical research but also make medical journals party to potential misrepresentation, since the published manuscript may not reveal the extent to which the authors were powerless to control the conduct of a study that bears their names. [...] We will not review or publish articles based on studies that are conducted under conditions that allow the sponsor to have sole control of the data or to withhold publication”.¹⁷

Dancing with the porcupine

¹² *Op.cit.* (13)

¹³ *Op.cit.* (14)

¹⁴ *Op.cit.* (15)

¹⁵ *Op.cit.* (16)

¹⁶ *Op.cit.* (1)

¹⁷ *Op.cit.* (1)

Aim of all these initiatives is obviously not that of demonizing pharmaceutical companies. After all, the whole sector, from basic research to specialized journals, relies largely on private funding. The codes of conduct and the guidelines of medical associations, as well as the new rules on transparency adopted by major international journals, are to be seen more as a sign of the public's awareness of the conflict of interest, rather than an attempt to solve it. In other words -quoting a recent article on the subject- they are instructions for "learning how to dance with the porcupine" without getting hurt too much.¹⁸

Besides, scientific journals are themselves not free from conflicts of interest.¹⁹ British physicians and their American colleagues are entitled to free copies of the *BMJ* or the *JAMA* thanks to the money paid by drug companies for advertising in these journals. There is evidence that these advertisements are misleading²⁰ and almost certainly influence physicians, who will tend to prescribe advertised drugs (otherwise, why would companies invest so much money?). Furthermore, in their search for sponsors, international journals have to compete with the glossy publications distributed for free by pharmaceutical companies, and an advertising space is often bought only on condition that the journal publish one or more articles favourable to the sponsor's product.²¹

And that is not all: today, three quarters of all drug trials published in the main international journals are funded by the pharmaceutical industry.²² Many trials are expressly designed to show the supposed advantages of one drug over its competitors, a step that is necessary to turn a drug into a blockbuster drug. Sometimes marketing considerations prevail over scientific motivations: "Many clinical trials are performed to facilitate regulatory approval of a device or drug rather than to test a specific novel scientific hypothesis", editors admit.²³ Journals may thus become party to this process, also considering that, when a favourable trial is published, sponsors order large numbers of reprints, with earnings as high as a million dollar for the editor.²⁴ These reprints are

¹⁸ *Op.cit.* (17)

¹⁹ *Op.cit.* (18)

²⁰ *Op.cit.* (19), (20), (21)

²¹ *Op.cit.* (18)

²² *Op.cit.* (22)

²³ *Op.cit.* (1)

²⁴ *Op.cit.* (18)

then used by drug representatives to show potential clients the quality of their products. Finally, many specialized journals only survive thanks to the publication of supplements, often paid for by a company. These contain studies of lower quality and in general are more favourable to the sponsor.²⁵

Biomedical communication and marketing

Major international journals like the *JAMA*, *The Lancet* or the *BMJ*, though very authoritative, account for only a fraction of the information flow reaching general practitioners. Other important sources include journals published by the companies, drug sales representatives (an army of 80,000 men and women in the US alone, accounting for the bulk of the \$19 billion invested yearly by drug firms in self promotion and defined by *Pharmaceutical Executive* as the industry's favourite marketing tool)²⁶, conferences and Continuing Medical Education courses paid by sponsors (over 300,000 events every year in the US alone). Recently, new companies have emerged catering for drug firms' public relations, and sometimes hiring apparently independent opinion leaders or patients associations as spokespersons²⁷ The information that reaches the public through the mass media often has the same origin: luxurious conferences sponsored by drug companies, beautifully presented press releases and, where allowed, even advertisements on drugs packagings.²⁸

As may now be seen, in daily practice, medical communication flows through the ramifications of a complex network. Much more complicated than the linear scheme whereby, on one side there is basic and applied research, on the other, the general media (newspapers and magazines), and in the middle, acting as a filtre, the specialized journals. It is also clear that communication channels have increased mostly because of marketing needs, and, considering the interests at stake, companies are unlikely to agree to lower the pressure. John Kelly, Vice President of Pharmaceutical Research and Manufacturers of America, declared to the *BMJ* that sponsored medical education is in

²⁵ *Op.cit.* (23)

²⁶ *Op.cit.* (24), (25)

²⁷ *Op.cit.* (26)

²⁸ *Op.cit.* (27)

the patients' interest, since it gives physicians access to "the best available information" (but then failed to explain why medical education is in the sponsors' interest).²⁹

Admitting that the conflict of interest exists implies admitting that the production of scientific knowledge, at least in the biomedical sector, may no longer be considered as being independent from the logics of economic interest dominating our society. The attempts made by international journals to solve the problem through disclosure seem to have had a limited effect. They also appear to be aimed at preserving the journals' privilege of watching over the quality of the science being produced. A privilege that they are progressively losing. However, with reference to the conflict of interest, there might be much more at stake than the credibility of scientific journals. "The very credibility of clinical medicine is at stake –writes Giovanni Fava in *Il Sole 24 Ore* -, and if this is lost, the healing power of the physician is also lost".³⁰

Translated by **Andrea Cavatorti**, Scuola Superiore di Lingue Moderne per Interpreti e Traduttori, Trieste, Italy

²⁹ *Op.cit.* (12)

³⁰ *Op.cit.* (28)

Bibliography

- 1) F. Davidoff et al., *Sponsorship, authorship, and accountability*, "Ann Intern Med", n. 135, 2001, p. 463-6
- 2) M.P. Mathieu, *Parexel's pharmaceutical R&D statistical sourcebook*, 1998. M.A. Waltham, *Parexel International Corporation*, 1999
- 3) J.O. Kahn, D.W. Cherng, K. Mayer, H. Murray, S. Lagakos for the 806 Investigator Team, *Evaluation of HIV-1 immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549 x 10⁶/L CD4 cell counts*, "JAMA", n. 284, 2000, p. 2193-202
- 4) D. Blumenthal, E.G. Campbell, M.S. Anderson, N. Causino, K.S. Louis., *Withholding research results in academic life science: evidence from a national survey of faculty*, "JAMA", n. 277, 1997, p. 1224-28
- 5) R. Smith, *Maintaining the integrity of the scientific record*, "BMJ", n. 323, 2001, p. 588
- 6) J. Lexchin, L.A. Bero, B. Djulbegovic, O. Clark, *Pharmaceutical industry sponsorship and research outcome and quality: systematic review*, BMJ, n. 326, 2003, p. 1167-70
- 7) D. Rennie, *Thyroid storm*, "JAMA", n. 277, 1997, p. 1238-43
- 8) M. McCarthy, *Company sought to block paper's publication*, "Lancet", n. 356, 2000, p. 1659
- 9) <http://www.epicentro.iss.it/archivio/16-5-2002/conflitto.htm>
- 10) B. Dong, *Bioequivalence of generic and brand-name lvothyroxine products in the treatment of hypotoroidism*, "JAMA", n.277, 1997, p.1205-1213
- 11) R. Moynihan, *Who pays for the pizza? Redefining the relationship between doctors and drug companies. 1: Entanglement*, "BMJ", n. 326, 2003, p. 1189-92
- 12) R. Moynihan, *Who pays for the pizza? Redefining the relationship between doctors and drug companies. 2: Disentanglement*, "BMJ", n. 326, 2003, p. 1193-6

- 13) American Medical Students Association, *PharmFree campaign*, “AMSA”, 2002, www.amsa.org/prof/pharmfree.cfm
- 14) American Medical Association, *Ethical guidelines for gifts to physicians from industry*, 2001, www.ama-assn.org/ama/pub/category/5689.html
- 15) Pharmaceutical Research and Manufacturers of America, *PhRMA code on interactions with healthcare professional*, 2002, www.phrma.org/publications/policy//2002-04-19.391.pdf
- 16) G.D. Lundberg, A. Flanagin, *New requirements for authors: signed statements of authorship responsibility and financial disclosure*, “JAMA”, n. 262, 1989, p. 2003-2004
- 17) E. Wager, *How to dance with porcupines: rules and guidelines on doctors’ relations with drug companies*, “BMJ”, n. 326, 2003, p. 1196-8
- 18) R. Smith, *Medical journals and pharmaceutical companies: uneasy bedfellows*, “BMJ”, n.326, 2003, p. 1202
- 19) S. Gottlieb, *Congress criticises drugs industry for misleading advertising*, “BMJ”, n. 325, 2002, p. 137
- 20) M.S. Wilkes, B.H. Doblin, M.F. Shapiro, *Pharmaceutical advertisements in leading medical journals: experts’ assessments*, “Ann Intern Med”, n. 116, 1992, p. 912-9
- 21) P. Villanueva, S. Peiro, J. Librero, I. Pereiro, *Accuracy of pharmaceutical advertisements in medical journals*, “Lancet”, n. 361, 2003, p. 27-32
- 22) M. Egger, C. Bartlett, P. Jüni, *Are randomised controlled trials in the BMJ different?*, “BMJ”, n. 323, 2001, p. 1253
- 23) P.A. Rochon, J.H. Gurwitz, M. Cheung, J.A. Hayes, T.C. Chalmers, *Evaluating the quality of articles published in journal supplements compared with the quality of those published in the parent journal*, “JAMA”, n. 272, 1994, pp.108-13
- 24) A. Brichacek, L. Sellers, *Flexing their budgets: big pharma spend trends*, “Pharmaceutical Executive”, settembre 2001 (Reprint), http://www.imshealth.com/vgn/images/portal/cit_759/7696bigPharmaSpendTrends.pdf

- 25) United States General Accounting Office, *Prescription drugs: FDA over-sight of direct-to-consumer advertising has limitations*, ottobre 2002, www.gao.gov
- 26) B. Burton, A. Rowell, *Unhealthy spin*, “BMJ”, n. 326, 2003, p. 1205-7
- 27) Nico Pitrelli, *La strada pubblica della peer-review*, “Jekyll.comm”, n. 8, marzo 2004
- 28) Giovanni Fava, *È in gioco la credibilità della Medicina*, “Il Sole 24 Ore”, 25 settembre-1° ottobre 2001