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Surgeons, companies and scientific societies: an ethical challenge

Dr Antonio Amato
Unità di Colonproctologia - Reparto Chirurgia - Ospedale Sanremo

"If all men were angels, no government would be necessary", James Madison

Time has passed from the age of the physician of "The imaginary invalid" by Molière, who worked hand in hand with the apothecary – the ancient pharmacist – in preparing different drugs for his hypochondriac patient. The relationships between the physicians and the biomedical industry has dramatically changed over the last 20 years.

There is no question that during the past decades companies have discovered, developed and marketed many new drugs and devices, increasing the potentials of medicine and improving the lives of millions of people. Obviously, industry has never been philantropic. It always makes products with the aim to getting a return on investment. It is uninterested in developing drugs for those areas of "market failure" - tropical diseases that afflict millions of people with low income or orphan diseases[1]. It has the responsibility to increase sales and to maximise profits for his shareholders.

The global pharmaceutical market and investments are rising: in 2008 the whole sales has been estimated to be worth US$ 735 billion. Annual global investment towards research and development of new therapies was US$ 98 billion (13.4%), with US$ 38.5 billion for human testing of new products[2-4].

Yearly, the life-science industry requires to identify 95,000 study sites for the recruitment of 1,282,000 subjects[5].

Furthermore, industry has became dominant in funding and performing clinical research, shifting decisively the balance between the public and private sector in its favour. In 2007, companies in the US provided 21% more research grants than National Institute of Health, a situation comparable in the most of developed countries where grants for sponsored clinical trial are higher than governmental funding in the medical area[6-10].

Drugs and devices are designed, manufactured, tested in clinical trial and ultimately presented to the US Food and Drug Administration (FDA) for approval, a notoriously expensive and time-consuming process. It has been estimated that, by 2010, an investment of almost 2 US$ billion will be required to bring a new product to the market[11,12].

On the other side, the physicians have the unique responsibility, based on the "fiduciary" nature of the patient-physician relationship, to provide the best care with clinical decisions free of undue influences. There is a growing concern for the mounting number of links between clinical investigators and industry, that range from honoraria to consulting fees, grants, direct payments, stock options.

The opportunity to be involved in a study is extremely desirable to an investigator, but it is ethically wrong to profit directly or indirectly from a company, whose products the physician is testing as a part of an allegedly "objective" clinical trial.

A potential conflict of interest exists: it is defined as a condition where an opinion concerning a primary interest is under the undue influence of secondary interests. It cuts across the heart of our perception of science: how it works and the role that the scientific research plays in the society[13].

FDA regulations require clinical trial sponsor – usually the company developing or licensing the drug or device under evaluation – to disclose for marketing approval any financial information from investigators about potential conflicts of interest. Is this an adequate measure to minimize one of the sources of bias? In 2007, only 1% (206 of 29,691) of clinical investigators disclosed a financial interests, whereas the Journal of the American Medical Association reported that 23-28% of academic researchers had financial interests in medical companies. Moreover, 42% of FDA-approved marketing applications lacked financial information and in 20% of applications with disclosed financial conflicts no action was taken[14].

From 1997 to 2008, FDA has conducted 3818 site inspections to verify clinical trial data and human subjects protection. An official action for submission of false information, a violation that is always virtually related to financial benefits, was carried out in five cases[15].

Unfortunately, FDA is unable to identify all ongoing clinical trials and their associated sites

because it does not maintain a clinical trial registry and it has been estimated that FDA are able to inspect only 1% of trial sites[16].
It has been reported that papers in which the authors disclosed some financial relationship significantly more frequently discuss a non-FDA-approved use of a commercial product. Many industry-sponsored clinical trials are designed more to get the approval of a drug/device or to investigate minor variants of established products or to find small advantages that can be highlighted in promotional campaigns than to test a scientific hypothesis or to verify clinically meaningful effects. That supports marketing may drive research[17,18]. On the other hand, an FDA survey showed that companies carried out only 34% of 2701 post-marketing studies they promised to make after registration, raising suspicion that industry's interest in research was over after approval[19].

From October 2005 to June 2009, 1017 industry-sponsored medical device trials were registered in the US trial register[20]. Medical devices are not regulated by the FDA in the same way as drugs and biologics, which are developed, tested and approved through a formal structured system. They are not necessarily evaluated by means of randomized clinical trials, the aim is often to study efficacy and safety or to observe device failures, with no need for a control arm. When a trial is needed, it is not required to register it publicly, the sample size is usually smaller and the duration shorter than drug trials[21]. Moreover, throughout the history of surgery, innovations and new procedures, including more recently laparoscopic cholecystectomy and laparoscopic assisted colectomy, became the standard of care with only minimal formal research concerning their safety, effectiveness and efficacy, before being subjected to formal controlled clinical trials. So, human subjects' protection are no formalized and rely mainly on the surgeon's competence and integrity. This approach has worked for more than one century, but nowadays as stated by Reitsma "the current system of definitions, ethical theories and voluntary professional guidelines may be inadequate to meet the challenge of surgical innovation"[22,23].
The inventor of a medical device might receive royalty income and might also be compensated by manufacturer for training other surgeons and for researching. The minimum condition to minimize the potential conflicts of interest, in addition to a full disclosure, must include that the research be overseen by a monitoring board and informed consent be obtained by a clinician with no financial ties.

The extensive links between industry and the authors of clinical practice guidelines may generate potential conflicts, because it can influence the practice of a large number of physicians. A survey among 192 authors of 44 guidelines endorsed by North American and European scientific societies reported that 87% of authors had some form of interaction with an average of 81% of authors per guideline, and 59% had relationships with companies whose drugs were considered in the guideline they authored. In published versions, a specific disclosure of the personal financial interactions with the industry were made in only 2 cases[24]. A survey about clinical trials and editorials on anticancer drugs and supportive care published in the Journal of Clinical Oncology over a 1-year period showed that industry partially or totally funded 44% of clinical trials and at least one conflict of interest was disclosed in 69% and 51% of clinical trials and editorials, respectively[25].
The influence of industrial funding over the conclusions of published articles have been reported. Sponsored studies were more likely to report outcomes in favour of the sponsor than comparable ones not funded by that sponsor[26,27,28,29]. The manufacturer has the control over the drug / device, the design of the trial, the sites, the analysis and publication of the results. Furthermore, almost 20 years after under-reporting research was first identified as scientific misconduct and after recent accusations that important trial data were hidden from public view, there is a growing evidence that some physicians have been discouraged from publishing negative results[30,31,32]. These positive result bias could be misleading for the scientific debate and the meta-analytic methodology, weakening the core of the evidence based medicine[33].
Guest authorship and ghostwriting were also well documented: manuscripts were written by unacknowledged sponsor-employees authors and then the authorship was falsely attributed to supposedly independent academically affiliated investigators[34].

A regulation of the financial associations of the authors has become a main key-point in the editorial policy of the most relevant journals. Their mission is to publish up-to-date, objective, unbiased and authoritative information. The increasing expansion of sponsorships of the studies and of relationships between authors and biomedical companies makes difficult to keep the balance:

a strict policy can affect the recruitment of the best possible authors but if they publish nothing the silence helps neither readers nor patients, leaving the companies as the chief source of information. On the other side, the management of the conflicts by means of more flexible guidelines is suspected of being ambiguous and of producing bad science and betraying readers' confidence[27,35,36].
In the last years, many journals have revised their policy adopting more stringent rules[37,38,39]. Nevertheless, these strategies missed the target and Richard Smith, former editor of the BMJ, argued that journals are little more than extensions of pharmaceutical marketing departments[40]. In 2009, an editorial written by all the editors of the journals of the International Committee of the Medical Journal Editors (which includes NEJM, The Lancet, BMJ, JAMA) was published at the same time, introducing a new disclosure form. The goal was to make the disclosure's process uniform and easier, but also to provide the reader with a more detailed and comprehensive information to understand the relationships between authors and various commercial entities. The authors are required to disclose 4 types of information concerning the work under consideration for publication, any relevant financial activities outside the submitted work, financial relationships involving the partner and the children over eighteen, non-financial associations[41]. A clear sign of the will to adopt an unambiguous strategy. Unfortunately, editors alone cannot solve the heart of the problem: industry can always holds its influence through the advertisement and the reprints of papers that are the main income of the publishing houses[42].

Drugs and devices makers fund about half of all postgraduate medical education and commercial support has grown steadily over the last years. In 2006, it provided about 60% ($ 1.5 billion) of the income for educational programmes in the US[43,44,45]. These activities are funded by their marketing budgets and a survey presented in 2009 by the UE Committee reported that annually industry invests more in marketing activities addressed to the physicians than in research (23% vs. 17%)[46].
In the last 30 years interventional procedures became more and more depending upon devices and technology. To remain competitive, the companies have been required to educate and train the physicians to perform new procedures with the new products. So education progressively shifted from academic medical centers to industry. Doctors are paid by manufacturers to learn about their products and companies have the obligation to make a profit: can we expect they will always be objective when assessing benefits, risks and effectiveness? They provide information for educational or commercial purposes? Neutrality and independence is what is needed in continuing education and an inescapable conflict of interest exists.
Wazana demonstrated the influence on prescribing habits, showing that the attendance to a sponsored meeting is significantly related to an increasing prescription of the sponsor's products[47]. It has been also reported how sponsors of allegedly independent educational events got special privileges to recommend speakers and align messages and that unfavourable information were suppressed or distorted[48,49].
Key opinion leaders are one of the most contradictory global phenomenon: influential experts recruited and paid for lectures largely based on slides supplied by the companies and delivered at sponsored educational events, or for working on sponsored clinical trials. They become an integral part of an aggressive marketing strategy, influencing thousands of specialists also through their participation to committees, boards, societies, guidelines/consensus documents, etc. Industry continuously monitors their performances and the return on investment[50]. Ray Moynihan pragmatically defined 'key opinion leader' an 'Orwellian term used to describe the senior doctors who help drug companies sell drugs[51].

Still exists an antidote for this uneasy alliance? The key to the future is culture: transparency and communication can promote a more independent and cooperative exchange of ideas. Medical colleges and institutions have adopted policies for monitoring and regulating the potential conflicts of interest, making recommendations on patient care, professional education, research and relationships, but their effectiveness is not proven yet[52].
Scientific societies are informed but not always disinterested parties since they often have an high-level of interaction with the industry, receiving support for annual conference, research, travel, continuing medical education, official journal, newletters, etc.[53]. However, they have to take their own responsibility and play an active role, firstly acting as a catalyst to promote a cultural framework for the creation of new patterns of cooperation. Relationships with industry should relate to information exchanged, not to gifts received, but undergraduate and postgraduate course

do not adequately prepare doctors for managing them. The General Medical Council has produced strict guidance, stating that doctors 'must not ask for or accept any inducement, gift or hospitality which may affect the way you prescribe for, treat or refer patients'[54].Small gifts seem innocuous but cognitive psychologists well know their indirect influence and samples and advertisements are intended to create demand than to provide educational value[55,56].

Medical associations need to adopt clear policies and guidelines covering at least some basic issues. All companies' payments for congresses, lectures, presentations, guidelines, journals, research, etc. should be routinely disclosed as well as the interactions with industry of the members of governing councils, editorial boards, educational committees, etc. All financial arrangements should be declared and publicly accessible. Even if disclosure it is not enough to ensure an ethical conduct, it can inhibit embarrassing or questionable ones and warns the audience[57].
They should emphasize the role of independent expert for producing clinical practice guidelines and assessing effectiveness and safety of new drugs and technologies; they should promote independent research and protection of patients' rights. The intellectual property and the publication rights belong to the investigators: they have to take a more active role in trial design and may analyze, interpret and publish the data independently, supervised by a data safety monitoring board. Payments that are conditioned upon a given research result or a successful research outcomes must be prohibited as well as ghostwriting and ghostauthorship.
Education is one of the most debated areas but colleges and societies cannot abdicate it to companies. It has been claimed that sponsorship by industry must stop because financial support can compromise integrity and objectivity of teaching, the credibility is threatened regardless of its quality and no "firewall" can eliminate the potential for substantial bias[43,52,58]. We have to solve the problem, avoiding that the care of our patients could be influenced, even subconsciously, by marketing interests[58]. Unfortunately, no government, health authority or academic institution could assume the financial role of the continuing education and, probably, in many cases industry have simply filled a vacuum left in the training needs of the professionals. A balanced solution could allow the companies to support medical education through an independent body that collects the money to unlink financing from a single one, diminishing the perception of undue commercial influence. Obviously, industry should have no role in the design and content of the education.
Finally, any medical society is recommended to form a Conflict of Interest Committee to appropriately review every specific situation.

In conclusions, patients are well served when industry, investigators and clinicians work together, generating new knowledge and appropriate spread of effective diagnostic and therapeutic products. They have the right to expect that physicians have no other motive than their opinion in assessing the beneficial effects of a drug or a device.
Industry deserves recognition for the extraordinary developments it has achieved. It is understandable it primarily looks after its financial interest, but a so crucial role for the public health includes social responsibilities that should not be totally overshadowed by its drive for profit. It needs a better balance between the interests of the shareholders and those of the society at large.
At the same time, our profession has been at least colluded or have had acquiescence in promoting advertising in guise of science as investigators, ghostauthors, paid opinion leaders, recipients of grants, honoraria and gifts. Doctor Knock by Jules Romains has not been a merely literary character lived in the imaginary village of St. Maurice during the past century.
The experience and the evidence tell us that all parties have lessons to learn and changes to make.
The words of the joint declaration of the Standing Committee of European Doctors and the European Federation of Pharmaceutical Industries Associations contain an uncontroversial statement: "*Cooperation between the medical profession and the pharmaceutical industry is important and necessary at all stages of the development and use of medicines to secure safety of patients and efficacy of therapy*".
We cannot impose restrictions on industries but there must be an ethical common ground in a climate of mutual respect and fruitful partnership. We have no hostility, simply different purposes. History has largely demonstrated, especially in surgery, that innovation requires ideas and training rather than promotion.

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