

**Ethical Implications of Relationships between  
Psychiatrists and the Pharmaceutical Industry**

Proposal of Recommendations  
of the WFSBP

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## **Summary**

Relationships between psychiatrists and the pharmaceutical industry have increased in frequency and intensity, both on the individual level and particularly on the institutional level. They extend from necessary and desirable co-operation through questionable practices to unacceptable misconduct. Especially the latter has provoked a lively discussion and has initiated recommendations as well as guidelines. Their aim is to safeguard the integrity of physicians as well as the industry and to avoid endangering the relationship between the physician and the patient. They will do this by establishing clear norms, unequivocal documentation, and disclosure of relevant relationships, in order to build up more mutual trust. Based on a detailed review of the literature 25 recommendations are put forward for discussion. Psychiatric associations should be encouraged to develop explicit guidelines for the relationships between psychiatrists and the pharmaceutical industry.

*key words:* relationships – psychiatrists – pharmaceutical industry – misconduct – guidelines – continuing medical education – research – developing countries – trust

## Introduction

The growing size and intensity<sup>1</sup> of relationships between medicine and industry as well as an increasing frequency of reports of questionable, incorrect or even unacceptable behaviour of both individuals and institutions call for norms to regulate behaviour and for measures to enforce these norms in reality. This also implies the question of the relationship between the ethical norms for individuals and the rules that regulate the behaviour of and the atmosphere in institutions, i.e. of corporate culture<sup>2</sup>.

In the following realistic answers will be sought. They come from the assumption that human behaviour in general is based on more than one motive or goal, being more aware of some, less of others, some only declared, others effective, some perceived differently by other persons than by oneself, and that they may also be weighted differently. The following considerations should provoke a discussion in order to develop conditions for transparent interactions of all legitimate interests and motives of all who care for ill people.

The core question of relationships<sup>3</sup> between physicians<sup>4</sup> and industry<sup>5</sup> is: to what extent and by what means does industry *exert influence* on the patient-physician relationship? What are the *effects* of such possible influence with regard to 1) the gain of scientifically valid new knowledge, 2) the physician's clinical judgement, 3) the medical education and distribution of medical knowledge, 4) the process and quality of care, 5) the perception of physicians by patients, colleagues and the general public with regard to their trust in both the individual physician and in medicine as a whole?

The answers will be investigated in a threefold manner: 1) The interests and conflicts of interests of the participants in these relationships: the patient, the physician, industry, society.<sup>6</sup> 2) The modes of these relationships, both those of mutual interests and particularly those that

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<sup>1</sup> In the USA about 20 million people are reported to have participated in clinical drug trials. A Boston Information Company watches the clinical trial industry and issues information about more than 41,000 clinical studies ([www.centerwatch.com](http://www.centerwatch.com), accessed Apr 1, 2003). An international central register in the UK has registered 14,525 clinical studies, which is only an unknown small portion of all clinical studies performed world-wide ([www.controlled-trials.com](http://www.controlled-trials.com), accessed Apr 1, 2003).

<sup>2</sup> "Corporate Culture" (Schein EH 2001), „Psychological Climate in the Work Setting“ (Baltes BB 2001), "Merging Bioethics with Corporate Interests" (Dhanda RK 2002).

<sup>3</sup> Relationship means both co-operation, mainly with regard to drug (and other innovative device) developments, and influence of industry on the physician as an active participant in the market. A special aspect is that physicians also work in industry, particularly in the pharmaceutical industry.

<sup>4</sup> Publications on relationships between physicians and industry deal mainly with physicians in general, not specifically with psychiatrists. Therefore, in the following only the term physician will be used.

<sup>5</sup> Drug development and drug marketing is a major field of this relationship, whereas other aspects of it (such as e.g. that of radiologists with manufacturers of medicinal machines/products [CT, MRT, SPECT, PET, radiopaque material etc], or of laboratory physicians with manufacturers of diagnostic substances or lab-procedures, or, more broadly, with emerging industries such as biotechnology or information technology, or with the hotel industry building hospitals, or even with the alcohol industry promoting drinks, or the tobacco industry's engagement in campaigning in schools against smoking ) are at present of less relevance for psychiatrists. Therefore this text is limited to the pharmaceutical industry.

<sup>6</sup> A further relationship is that between the physician and the patient's insurance company. It is not dealt with here, although it may also exert influence on the patient-physician relationship, e.g. by closed budgets which may force the physician to prescribe not the best but the cheapest drug. Sometimes industry or pharmacy benefit management companies or health insurance companies may try to influence patient's drug regimes, e.g. by "positive lists", sometimes to reduce costs and sometimes to favour a manufacturer. "Cost savings are certainly encouraged, especially as a matter of justice and equity in health care. However, any agreement to change drugs should be evidence-based, not company-based" (Coyle SL 2002, Part I).

may allow industry to exert influence on the decisions of clinical researchers and physicians and their effects on the independence and objectivity of the physician's clinical judgement and his responsibility for care in the best interests of his patients. 3) Perceptions of these influences by and their possible effects on patients, physicians, industry, and the public.

These analyses will be based mainly on the present lively discussion<sup>7</sup> and background material of various guideline proposals that have been published recently by professional bodies in some countries.<sup>8</sup> The conclusions will be condensed into recommendations for the protection of the integrity of the patient-physician-relationship.

## 1. Interests

Among the multitude of declared or real interests, motives, and reasons that are relevant for the relationship of the physician to his patients on the one hand, and to industry on the other hand, at least the following are of major significance: The declared interests of industry are to promote scientific knowledge and to improve care and by that to support its real interests, which are profitability by having the best selling drugs, i.e. either the most efficient and safest drugs for the most frequent and most severe diseases, and/or the most persuasively advertised drugs, by supporting the physician's daily work mainly by serving as medical informants, by co-operating with the best physicians (i.e. clinical researchers and opinion-leaders), and by being perceived as serving patients most competently and innovatively. The interests of physicians are the patient's best interests by having, among other aspects, the best, i.e. the most efficient and safest drugs for their patients' diseases, and/or participating in the development of efficacious and safe drugs, running their offices economically successfully<sup>9</sup>, and/or gaining academic recognition by scientific success, being perceived as serving the individual patient's best interests by competence and personal engagement, and therefore, being much sought after. The interests of patients are to receive the best treatment, to be adequately informed, and

<sup>7</sup> see the last years in BMJ, CMAJ, JAMA, Lancet, NEJM

<sup>8</sup> - American College of Physicians (ACP) (1990) Physicians and the Pharmaceutical Industry

- Association of American Medical Colleges (AAMC) (1990) Guidelines for Dealing with Faculty Commitment and Conflicts of Interest in Research.
- Royal College of Psychiatrists (RCP) (1999) Guidelines on the sponsorship of college activities
- World Psychiatric Association (WPA) (1999) Guidelines concerning support from external sources for activities of the World Psychiatric Association
- Lewis S et al (2001) Rules for governing the university-industry relationship. *Criticisms in CMAJ 166 (5): 580 – 582 (Koehler, Pater et al, Lewis)*
- Harvard Medical School (2000) Faculty Policies on Integrity in Science
- American Society of Gene Therapy (ASGT) (2000) Policy on Financial Conflict of Interest in Clinical Research
- International Committee of Medical Journal Editors (ICMJE) (1997/2001): Uniform requirements for manuscripts submitted to biomedical journals. Davidson F et al (1997) Davidoff F et al (2001) *Reactions: CMAJ 166 (5): 579 – 580 (Loschiavo, Kuebler et al, Holmer); N Engl J Med 2002, 346 (4): 290 – 292 (Holmer, Landow, Peddicord, Reidenberg, Relman)*
- Editors of Neurological Journals (2002) Reporting clinical trials: full access to all of the data. Rosenberg RN et al (2002)
- The Royal Australian and New Zealand College of Psychiatrists. The relationship between psychiatrists and the pharmaceutical industry. Ethical Guideline. RANZCP. 1-12. 2003.

<sup>9</sup> and/or by having financial interests in companies potentially affected by their work, mainly their research or consultations (Cech TR et al 2001), or to earn more money by prescribing and selling drugs as is the case in many countries, e.g. in Japan.

formed, and to be involved in decisions (i.e. being respected for their autonomy) – and also altruism. These interests may also be influenced by the interests of government (for example, in saving money by opting for the cheapest medications) and of various non-governmental organisations (e.g. families, or former patients).

All of these interests are, of course, legitimate. However, they have the potential for conflict, perhaps more on the side of physicians and their institutions than on the side of industry, and particularly between physicians/academic institutions and industry<sup>10</sup>. Such conflicts of interest may threaten the independence and objectivity of physicians/clinical researchers in finding the most valid results with regard both to research and to the practice of patient treatment and the necessary confidence of patients and the public trust.

The common interests of all actors in these relationships are to provide or to receive the best drugs<sup>11</sup>. Accordingly “collaborations in pharmaceutical development are often effective spearheads for advancing therapies and patient care” (Coyle 2002, Part 1)<sup>12</sup>, and the industry can help to keep the physician informed of the present state of the art of drug therapy. The industry needs access to patients via physicians,<sup>13</sup> and physicians need the industry because only the pharmaceutical industry has the means to develop new drugs. However, although “pharmaceutical companies know that faulty or dishonest research leads down a long and costly road to drug withdrawals and lawsuits” (Editorial 2001), they have to be profitable, particularly in view of the immense costs of drug development; e.g., it was estimated in 1999 that it can cost up to more than \$ 600 million to bring a new drug into the market (Kettler H 1999). Therefore, conflicts of interests may arise if the industrial interest of profitability biases information on drugs, e.g. by overemphasising the qualities of drugs (efficacy, safety, indications, economic efficiency, etc.), or by having (uncontrollable) control of study data and

<sup>10</sup> Conflicts of interest are “ubiquitous and inevitable in academic life, indeed, in all professional life” (Korn D 2000), and they “represent the potential for biased judgement, but are not an indicator of the likelihood or certainty that such judgements or compromises will occur” (DeAngelis et al 2001). Among the different definitions of ‘conflicts of interest’ one of the simplest seems to be “situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigator’s professional judgement in conducting or reporting research” (AAMC 1990). WHO recently introduced for its consultants three different aspects of conflicts of interest: real, apparent, and potential conflict of interest in relationship to the tobacco industry (note by N. Sartorius).

<sup>11</sup> Cf. statements of A. F. Holmer (2002), President, Pharmaceutical Research and Manufacturers of America; this statement seems important insofar as it accepts that the data of studies are not only the property of the sponsor but also of the researchers. Cf. also the statement of Clinical Research Organisations (CROs) by C. Kübler et al. (2002). It is important to take note of the fact that the word “best” is understood by the parties in different contexts: easiest to use, least dangerous regardless of effectiveness, cheapest etc. (comment by N. Sartorius N).

<sup>12</sup> “Related Benefits of Entrepreneurial Activity: public benefits of new technology, economic development – jobs in new business, opportunities for student projects, jobs, incentives for faculty to produce results, allows universities to compete for/retain talent, increased support from industry for research” (NIH 2002). “According to the Association of University Technology Managers, corporate licensing of university inventions in 1999 accounted for US \$ 40 billion in economic activity in the United States, which, in turn, supports 270 000 private sector jobs. In the fiscal year 1999, the top 10 universities alone received US \$ 250 million in product royalties, with total royalties paid to universities of US \$ 862 million” (Moses H et al 2002). “World wide, pharmaceutical companies spend over US \$ 40 billion annually on research and development” (Editorial 2001); in 2000 the Canadian pharmaceutical industry spent \$ 900 million on research and development, i.e. “43% of gross domestic expenditures on research and development in the health field” and “\$ 161 million...in universities and teaching hospitals” which was “over half the amount received from federal sources (Lewis S et al 2001). Thus the pharmaceutical industry is a strong contributor to scientific development and is a job machine. Its relationships with academic research and teaching have become manifold and are increasing: “over the past two decades, governments have strongly encouraged the commercialisation of discoveries by academics” (Moses H et al 2002).

<sup>13</sup> and to the talent of “the best and brightest physician-scientists across all clinical disciplines” (C. Kübler et al 2002)

data interpretation (by keeping unfavourable findings of industry-sponsored studies confidential); or if the industry influences physicians by various kinds of support in order to induce them to prefer some drugs not based on evidence but on the sponsor<sup>14</sup>, or if it even threatens them by various actions<sup>15</sup>. The physician's economic or academic interests as well as those of his institution may make him receptive for such biased information or support and thus may impair his independent judgement at the cost of the best care of his patients or of the best interests of study subjects or of the scientific validity of the results of therapeutic clinical drug research<sup>16</sup>. Such negative aspects of the relationships between industry and physicians will impair the patients' interest in receiving valid and unbiased information as well as their trust in physicians.

## 2. Modes

The relationships between industry and physicians and their inherent risks of exerting inadmissible influence on the physician's decisions are manifold. There are at least two major modes: the more apparent influence by disseminating information on drugs by supporting educational activities, and a sometimes more hidden (and perhaps more far-reaching) influence by supporting both individual physicians and academic institutions in research.

### Sponsoring of educational activities:

Physicians will be informed about drugs either directly by advertisements in scientific journals or by pharmaceutical representatives, or indirectly by support for educational activities such as grand rounds, CME-events, symposia, and so on. These activities have a detectable impact on the prescription of drugs, i.e. an increase of prescription of the advertised drugs. On the one hand this influence is neglected or not recognised by physicians, on the other hand it is intensified demonstrably by gifts, hospitality, amenities, services, subsidies for travel, grand rounds, symposia, etc.. This influence may lead to non-rational prescriptions if the informa-

<sup>14</sup> In the 90ies American pharmaceutical companies "spent approximately \$11 billion each year in promotion and marketing, \$ 5 billion of which goes to sales representatives" (Wolfe SM 1996, cit. Wazana A 2000a). Analyses of published empirical material supply evidence that these expenditures influenced prescription or even clinical practice guidelines in favour of the advertised drugs (Wazana A 2000a; Collier J et al 2002; Dieperink ME et al 2001; Choudry NK et al 2002). A vivid example of the inattention to the change of culture in academic medical centers is given by Kassirer JP 2000. Recently in the Netherlands the public prosecutor's office started investigations against 70 physicians suspecting of having taken bribes (e.g. a course in car safety training for participants of a marketing meeting for a drug of the sponsor) (Koch K 2001). However, the tightening up of the German law against corruption (from 1997) overshot its mark and led to uncertainty and some demotivation (Clade H 2001). In November 2003 a symposium "research grants – criminal duty?" (in Heidelberg, Germany) showed a fairly controversial legal discussion and pointed out that researchers should meet the four principles documentation, transparency, equivalence, and separation (sponsoring from supply) in order to protect themselves against inquiries by the public prosecutor. These principles have been adopted on August 12, 2003 by the Federal Board of Physicians (Bundesärztekammer) as part of the professional rules for German physicians (Bundesärztekammer 2003).

<sup>15</sup> e.g. a lawsuit against the Canadian Coordinating Office of Health Technology Assessment to suppress a statin report (Skolnick 1998), loss of academic position - the Healy case (Silversides 2001), withdrawal of corporate funding of The Hastings Center following critical articles on antidepressant prescribing practices in its journal (Kaebnick 2001, cit. Lewis S et al 2001), legal threats against informing the community about unexpected new risks of a clinical trial - the Olivieri-case (Gibson et al 2002).

<sup>16</sup> Recent reports on misconduct of researchers can be taken as a particularly bad sign of such misleading personal interests.

tion is not scientifically sound and well balanced but selected, skewed, or inaccurate. The latter seems to be particularly effective if the specific information is more or less hidden in an interesting or demanding context, and if a speaker or informant although speaking or writing on behalf of industry seems to be independent and competent<sup>17</sup>.

### Sponsoring of clinical trials and research

Financial and material support of research by pharmaceutical companies, either specific drug-related research or other research, may influence the relationship between physicians and patients directly in clinical drug trials or indirectly by biasing the production and publication of new knowledge about drugs. Problems in receiving and evaluating all and unbiased preclinical data and difficulties in the full and comprehensive informing of patients as research subjects about randomisation, placebo-controls, and possible risks – even during an ongoing trial – indicate areas in which physicians must be aware of their primary responsibility towards the patients. The physician researcher must also be aware that his objectivity can be affected in a subtle way by a sponsor's influence on “framing the questions and the design of studies”, which may “increase the probability of a positive result” (Lewis S et al, 2001)<sup>18</sup>. Particularly in postmarketing studies (interventional phase IV trials and noninterventional surveillance) physicians need to consider the scientific validity of the research and its potential to enhance medical progress, in order to avoid participation in industrial promotional schemes (Coyle SL 2002, Part I; Foy R et al 1998; Linden M et al (1997)). The assumption of the latter is the stronger the more no unequivocal research question and corresponding clear study design

<sup>17</sup> A MEDLINE based study found 538 published studies with key words *conflicts of interest*, and *drug industry*. Analysis of 29 studies with control groups and quantitative data on the “extent of physician-industry interaction, the attitudes of physicians toward the interaction, and the effect of interaction” revealed that “meetings with pharmaceutical representatives were associated with requests by physicians for adding the drugs to the hospital formulary and changes in prescribing practice, drug-company-sponsored CME preferentially highlighted the sponsor's drug(s) compared with other CME programs, attending sponsored CME-events and accepting funding for travel or lodging for educational symposia were associated with increased prescription rates of the sponsor's medication. Attending presentations given by pharmaceutical representative speakers was also associated with nonrational prescribing” (Wazana A 2000a). An illustrating but – due to insoluble methodological flaws (Lohiya GS 2001) - not evidential example: “a psychiatry grand rounds had addressed the topic of atypical antipsychotic agents, and ... the speaker was sponsored by the manufacturer of quietapine. Of the 19 new prescriptions for quietapine 2 were written before the grand rounds and 17 after it” in the following 3 weeks. “The title of the grand rounds was ‘Psychotic features and the comorbidity of posttraumatic stress disorder’ ” (Dieperink ME et al 2001a). One of the uncontrolled factors was supposed to be the possible influence of local opinion leaders (Gilbody S et al 1999, cit. Dieperink ME et al 2001b). A further influential factor is apparently the commercial advertising in scientific journals: in a study “surveying physicians on their perception of 2 drugs for which commercial messages about efficacy differed substantially from scientific sources”,...it was “found that, although most physicians report paying little attention to drug advertising and pharmaceutical representatives, their answers revealed their receptivity to commercial sources.” (Avorn J et al 1982, cit. Wazana A 2000b). In another case 2 CME events were examined “on the same drugs but with different sponsors and found the content to be biased each time in favour of the sponsor's drug” (Bowman MA et al 1988, cit. Wazana A 2000b). Correspondingly Stryer D et al 1996 found: „ Little of the material distributed by pharmaceutical companies to physicians conveys information about important therapeutic breakthroughs; some of it fails to comply with FDA regulations. The material contains both educational and promotional characteristics.” Moreover, in a systematic analysis of 106 statements on drugs in 13 presentations of pharmaceutical representatives “11% contradicted information readily available to them. Physicians generally failed to recognise the inaccurate statements.” (Ziegler MG et al 1995).

<sup>18</sup> Bekelman et al (2003) in a recent systematic review report that industry sponsored clinical trials use inactive/placebo controls more often and that they increased the likelihood of positive study results, or that differences in dosages or gastrointestinal absorption between study and control group were in favour of the investigational drug.

exist, and payment of participating physicians is only for enrolment of patients (“finder's fee”), is high, and is figured per capita (Rao N et al 2002).

In view of an increasing number of critical reports about biasing industrial influences on scientific publications the editors of leading medical journals “are concerned that the current intellectual environment in which some clinical research is conceived, study subjects are recruited, and data are analysed and reported (or not reported) may threaten this precious objectivity”. They conclude that “contracts should give the researchers a substantial say in trial design, access to the raw data, responsibility for data analysis and interpretation, and the right to publish – the hallmarks of scholarly independence and, ultimately, academic freedom.”<sup>19</sup>

The legitimate industrial interest in patent protection raises some open questions such as on the independence of governmentally based research institutions if “in return for expending patent protection, the government exacted a commitment from industry to invest 10% of sales in Canadian-based research” (Lewis et al 2001). Other questions of patent protection and confidentiality of data are raised by a conflict of interests between the freedom of researchers to publish all data of studies in which they participate and the natural interest of industry to protect its products<sup>20</sup>. The problem of inadmissible influence from industry on the physician researcher's academic freedom in thinking independently and judging objectively is growing because of an increasing interweaving of industry and medicine<sup>21</sup>, and is stressed by the present decrease of public financing of academic institutions in many countries, which in turn encourages these institutions<sup>22</sup> and their employees to apply for sponsorships.

<sup>19</sup> Davidoff et al 2001: “As CRO's (contract research organisations) and academic medical centres compete head to head for the opportunity to enroll patients in clinical trials, corporate sponsors have been able to dictate the terms of participation in the trial, terms that are not always in the best interests of academic investigators, the study participants or the advancement of science generally. Investigators may have little or no input into trial design, no access to the raw data, and limited participation in data interpretation...the results of the finished trial may be buried rather than published if they are unfavourable to the sponsor's product.... There have been a number of recent public examples of such problems\*, and we suspect that many more go unreported. ...research sponsored by governmental\*\* or other agencies may also fall victim to this form of censorship, especially if the results of such studies appear to contradict current policy....”. \*(Blumenthal D et al 1997, Campbell ES et al 2003), \*\*(Meyer MA (2002). “in addition, editors will retain the right to review the study protocol as well as funding contracts for the study before accepting the paper for publication” (Editorial 2001). In a health policy report Bodenheimer T (2000) came to the conclusion: “An essential ingredient of any solution is increasing the independence of investigators to conduct and publish their research....drug trials should be funded by industry but the design, implementation, data analysis, and publication should be controlled entirely by academic medical centres and investigators.”

<sup>20</sup> “The right to publish is protected, with at most a 90-day delay allowed for patenting“ say the rules of the Howard Hughes Medical Institute (HHMI) (Cech TR et al 2001)

<sup>21</sup> “... profoundly changing relationships with the world of commerce” by an increasing “transfer of academic scientific discoveries into practice. In so doing it has increased the flow of revenues from patenting and licensing activity into research institutions and their faculties, thereby creating a positive feedback loop that drives the interest of both toward a more vigorous commercialisation of their intellectual property, while arguably creating a new and perhaps dangerous dependency on it. The result has been deepening entanglement of research universities with industry and progressive blurring of the boundaries that once reasonably, albeit not perfectly, demarcated academic interests and values from those of the world of commerce.” (Korn D 2000). In one article of the New England Journal of Medicine (NEJM) the editor decided merely to summarise because “the author's ties with companies that make antidepressant drugs were so intensive that it would have used too much space to disclose them fully” (Angell M 2000). In 2000 and 2001 the editors of the NEJM could publish only one Drug Therapy article on a novel form of treatment due to the very restrictive requirements for disclosure of financial interests: “Because the essence of reviews and editorials is selection and interpretation of the literature, the *Journal* expects that authors of such articles will not have any financial interest in a company (or its competitor) that makes a product discussed in the article.” This constraint was thought to deprive the readers of the *Journal* from “authoritative review articles written ...by the best possible authors”, and would make physicians find “that pharmaceutical companies become their chief source of information about new therapies. Therefore, the editors modified the above cited statement by adding the one word “significant” between “any” and “financial” (Drazen JM et al 2002).

<sup>22</sup> The developing relationships between academic institutions and industrial companies is a fairly unclear area, a “totally unexplored terrain” (Korn D 2002), with almost no explicit rules for institutional relationships to industry (Korn D (2000), Shalala D 2000). Although the vast majority (89%) of 89 biomedical research institutions receiving the most NIH funding in 1998 at least had a mechanism for disclosure to

Publication bias has become a major problem: the results of at least half of all clinical trials will not be published (Scherer et al 2002, Pich et al 2003), probably more among those that are undecided or, even more dangerous<sup>23</sup>, that are negative. Restrictions by funding agencies can be found among the reasons as well as the tendency of editors to not publish negative results (Blackledge G 2002), or the belief of investigators that a manuscript would not be accepted for publication (Weber EJ et al 1998)<sup>24</sup>. The effect may be a skewed basis for evaluation of the pros and cons of an intended clinical trial. This violates Principle 27 of the Declaration of Helsinki<sup>25</sup>, and, worse, the right of the patient to expect that the design of a clinical trial “has been informed by a scientifically defensible review of what is known already” (Antes G et al 2003), i.e. a comprehensive, “credible and relevant systematic review” (Mann 2002). Therefore, publication of all results of clinical trials is an obligation of clinical investigators as well as of funding agencies, not the least because such “public dissemination recognises the altruistic motivation of patients who agree to participate” (Mann 2002). Accordingly, underreporting of research is deemed to be a form of scientific as of ethical misconduct (Antes et al 2003, Chalmers 1990).

### Lobbying towards legislative bodies and governmental agencies

A further mode of influence is directed towards the legislative and governmental agencies controlling drugs, mainly but not only by the industry. For example, it is not in the interest of patients and their physicians if the access to centralised European data of unwanted drug effects will be restricted, or if the medical position of the director of a clinical trial will be dropped in European law<sup>26</sup>.

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the institution, “only 19% had specific prohibitions or limitations of activities related to research or teaching, and 38% had institutional committees to review conflicts of interest” (Cho MK et al 2000, cit. DeAngelis 2000). Examples of guidelines are: Association of American Medical Colleges (AAMC) 1990: “Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research”, Faculty of Medicine Harvard University 1996/2000: “Faculty Policies on Integrity in Science”, American Society of Gene Therapy (ASGT) 2000 on “Financial Conflicts of Interest in Clinical Research”, “or a seminar by NIH 2002 on “Conflicts of interest: An Overview for Administrators”.

<sup>23</sup> „Failure to publish can lead to unacceptable delays in uncovering harmful therapies. For example, the use of class 1 antiarrhythmics after myocardial infarction received FDA approval in the early 80s, despite the lack of evidence that these drugs reduced mortality. By 1993, evidence had accumulated that they actually increased mortality (Teo KK et al 1993), prompting the first publication of a negative trial conducted 13 years earlier (Cowley AJ et al 1993). The increased mortality was originally thought to be a chance finding, but thousands died in the resulting interim before publication (Moore T 1995).” (Jull et al 2002).

<sup>24</sup> Furthermore, on the other side a difference in peer-review process between industry-sponsored supplements and parent journals may lead to less quality of sponsored supplements (Bekelman et al 2003).

<sup>25</sup> „Negative as well as positive results should be published or otherwise available“.

<sup>26</sup> Müller-Oerlinghausen 2003

### Research in developing countries<sup>27</sup>

Some of these problems may be much more serious in developing countries, mainly due to lack of resources and lack of specific experience, e.g. lack of ethical committees controlling research or service reforms. A problem rather on the surface of sponsoring clinical trials in countries with a poor infrastructure may sometimes be in keeping a separation between (or avoiding the risks of) taking advantage (“exploitation”) by low grants and dubious influence (“corruption”) by high grants. However, there are more specific and probably more important questions of clinical trials in developing countries:

Sponsors of clinical trials in developing countries have to consider at least the following challenges: “The existence of alternative belief systems regarding the causes and treatment of mental illness; difficulty in implementing the results of successful research in resource-poor countries; providing for adequate prior ethical review in the host country of the proposed study and problems in ensuring that voluntary, informed consent is properly obtained from research subjects or their legally authorised representatives.” And “global justice demands that we not adopt one ethical standard for rich countries and another for resource-poor countries” (Macklin R (2001)). This is all the more valid as the problem of “informed” consent is also more or less relevant for all the countries of the world<sup>28</sup>.

One aspect of justice is to provide the results of research to those who participated in such research in a broader sense: “...the basic ethical principle of distributive justice<sup>29</sup>...requires that studies should benefit, not only participants in a trial, but also the class of persons they represent.” (Coovadia 1999). US bioethicists took up a similar position (Glantz et al 1998). The National Bioethics Advisory Commission in the US “agreed that sponsors of research should provide successful products of the research to the individuals who participated in a

<sup>27</sup> The most recent and comprehensive review of the field has been published by the Nuffield Council on Bioethics, 2002. In preparing the revision of the Declaration of Helsinki 2000 and with regard to the CIOMS statement that “persons in underdeveloped communities will not ordinarily be involved in research that could be carried out reasonably well in developed communities” Zion et al 2000 proposed a much stronger definition of the admissibility of research in vulnerable populations insofar as “the research is specifically related to inherent characteristics of that group (and not, for example, to the need or preferences of the researchers), and these characteristics are crucial to the internal research design (that is, the research only makes sense when the participants have these characteristics)”.

<sup>28</sup> “My personal experience in losing a son in a gene therapy trial exposed many very serious flaws in the informed consent process.” wrote Paul Gelsinger, an American, in his ‘Foreword’ in “Informed Consent” ( by Getz K & Borfritz D, Centerwatch 2003)

<sup>29</sup> The more general question of distributive justice cannot be dealt with here. However at least a hint will be given: one problem is the enormous discrepancies of the global distribution of resources. To give only two examples: Countries without own production of medical drugs depend on imports, e.g. Ethiopia, which had to spend all of its small funds for antibiotics alone, leaving no funds for psychotropic drugs, or Somalia, where the same reason, i.e. the lack of antipsychotic drugs, forces psychiatrists to chain psychotically aggressive patients. Such serious lack of medical care (in the majority of countries in the world) contrasts with the right of every human being to receive the best available psychiatric care, as declared by UN declaration 46/119 in 1991, and contradicts the ethical principle of distributive justice. Therefore, the problem of unequal distribution of resources is also valid for psychiatry, and some aspects of the growing international discussion on research in developing countries should be considered for psychiatry too.

Ruth Macklin (2001) mentioned in her Presidential Address to the 5<sup>th</sup> World Congress of Bioethics that the US offer of \$ 1 billion in annual loans to finance the purchase of anti-AIDS drugs in sub-Saharan Africa had been rejected by South Africa and Namibia. 12 other African countries expressed doubts about the offer and would prefer the US to pressure American drug companies to reduce prices and to support countries that seek to produce generic drugs more cheaply. Macklin concluded: “Interest-bearing loans cannot be the answer to the problem. That is a market solution, not one that stems from consideration of justice.” An extensive review of the issue resulted in recommending that “better access to essential drugs may be achieved through voluntary licensing arrangements between international pharmaceutical companies and manufacturers in developing countries” (Henry D et al 2002).

study if they still need those products after the study has ended, and also that sponsors should assist in capacity building in those countries.” (cit. Macklin et al 2001). As a first step in the right direction Macklin considered agreements in advance of beginning research such as is stated in the CIOMS-Guidelines for biomedical research (1993/2002) and as WHO promotes in a collaborative work with international groups against HIV/AIDS.

In a more general way ethical implications of medical research in developing countries were discussed for the first time at the 13<sup>th</sup> International World Aids-Congress in Durban, SA (Jäger H 2000): 1) The question remained open whether and how concepts such as “informed consent”, “placebo”, “randomisation” can be imparted to people with a high rate of illiteracy and without corresponding words in their language. 2) Research was criticised that is done in highly developed countries with material, e.g. blood, sent by physicians from developing countries without taking them into consideration for scientific publications, so-called “Federal Express Research”. 3) The idea to export parts of research done in industrialised countries into third world countries was rejected as paternalistic.

### 3. Perception

The perception and judgement of relationships of physicians with industry are apparently different among physicians and patients. “Patients feel pharmaceutical gifts are more influential and less appropriate than do their physicians” (Gibbons RV et al 1998) and believe that personal gifts have a negative effect on both the cost and quality of health care (Mainous AG et al 1995). More patients than physicians consider that a fee for recruiting patients for postmarketing studies is not acceptable and that it is also unacceptable that they, as study patients, are not to become informed about the payment (LaPuma et al 1995)<sup>30</sup>.

“Companies gain access to research talent and an affiliation with a prestigious institutional” or personal name (Moses H et al 2002). The strength of prestige in supporting dissemination of information by leading clinical scientists or opinion leaders depends upon the perception that their information is independent and valid. This strength will diminish if ties with industry or other influences from external sources to academia seem to impair this independence.

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<sup>30</sup> Gibbons RV et al (1998) compared attitudes of 286 (of 392) physicians and of 196 patients toward pharmaceutical gifts. The result was that “about half of the patients were aware of the gifts; of those unaware, 24% responded that this knowledge altered their perception of the medical profession.” In a random-digit dialing telephone survey Mainous AG et al (1995) asked 694 adults about their awareness of office-used and of personal gifts and attitudes toward physician acceptance of them and found: “Individuals with at least a high school education were 2.4 times as likely to believe that personal gifts have a negative effect on the cost of health care and 2.3 times as likely to believe that personal gifts would have a negative effect on the quality of health care”. Based on a self-report questionnaire on attitudes about financial disclosure about and participation in postmarketing research (answered by 54% of 733 doctors, and 74% of 269 outpatients) LaPuma et al. (1995) established that “most doctors (64%, 240) found it acceptable to be paid a fee, while most patients (56%, 110) found a fee unacceptable. Proportionally fewer doctors (75%, 282) than patients (86%, 171) believed that a physician should inform a patient if the physician is paid for enrolling the patient.”

The perception of the public is perhaps even more negatively influenced if physicians are engaged in research and give reason to the assumption that they “use their patients as if they were guinea pigs”.

Public confidence and trust demands the very high standard that “even the perception that faculty investigators or their institutions have financial interests that might compromise their independence and credibility cannot be tolerated” (Korn D 2000). Loss of confidence is not only detrimental for the individual patient-relationship, but also provokes the question of the taxpayer whether the very high public grants<sup>31</sup> for biomedical research are justified, and urges the government to institutionalise new controls of “financial relationships in clinical research”, e.g. by an Office for Human Research Protection (OHRP) or Office of Research Integrity (ORI)<sup>32</sup>, or even their own independent control by “a few key tests”<sup>33</sup>. Voluntary organisations are encouraged to represent society’s public health interests by calling publicly for correction of promotional malpractice and undesirable developments<sup>34</sup>.

#### 4. Recommendations

These recommendations aim for transparent procedures for recognising and avoiding (sometimes hidden) conflicts of interest that may affect adversely the integrity of physicians as well as of industry<sup>35</sup>.

##### a. General recommendations

Co-operation between physicians and industry is needed with regard to developing new treatments for patients, and, in addition, it is legally required by the licensing authorities. Furthermore, industry may play an important part in keeping the physician informed about new drug developments. And, conversely, industry needs access to patients and information about the experiences of physicians in practice, particularly on unwanted drug effects in the post-marketing phase.

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<sup>31</sup> “...including a likely fiscal year 2001 congressional appropriation to the National Institutes of Health of approximately \$ 20.5 billion” (Mervis J 2000, cit Korn D 2000)

<sup>32</sup> The response of the academic community to this draft of guidelines for “institutional financial relationships – which represent totally unexplored terrain – where we believe the guidance was, in fact, premature.” (Korn D 2001). Objections were raised against a data-collection-instrument proposed by the Office of Research Integrity (ORI), particularly against the federal definition of scientific misconduct, “which can lead only to confusion” (Korn D 2002).

<sup>33</sup> “The present drug regulatory systems are insufficiently robust in their political relations with the pharmaceutical industry, because they prevent proper public accountability, are highly vulnerable to industrial capture, and permit the industry’s scientific experts to have extensive conflicts of interest while providing their expert advice. A regulatory system capable of delivery of publicly defensible assessments, which are uncompromisingly in the interest of public health, is needed.” (Abraham J 2002).

<sup>34</sup> Dukes MNG (2002) names industrial practices that do not consider society such as “excessive or inappropriate pricing of drugs, an interference to the needs and limitations of the developing world, an imbalance between true innovation and promotional activity, interference with clinical investigations, and efforts to mould medical thinking and priorities as a means to enlarge the market \*.” \* (Moynihan R et al 2002). « The boundaries between knowledge as a good and knowledge as a commodity, have become blurred » (Editorial 2002).

<sup>35</sup> “The challenge for academic medicine is not to eradicate conflicts of interest, which is fanciful and would be inimical to public policy goals, but to recognise and manage them sensibly and effectively” (Korn D 2000). “The medical profession and industry must take seriously their obligation ...to develop industry-wide standards for the interactions between physicians and the health care technology industry company representatives” (Tenery RM 2000).

However, published experiences show some risks in the relationship between physicians and industry. Risks arise if on the side of industry legitimate profitability interests adversely affect the scientific *gain* of knowledge or the *distribution* of knowledge or even the physician's choice of drugs for his patient, and if on the side of the physician (or his institution) economic or scientific or personal reasons may influence his clinical judgement or his care for patients. Therefore<sup>36</sup>,

it is recommended that

1. the physician should evaluate all relationships, ties, affiliations, support, particularly financial ties between himself and industry with regard to possible conflicts with his ethical obligations to act in the best interest of the patient (beneficence), to withhold harm from his patient (non-maleficence), to respect the dignity and autonomy of his patient, and to consider justice with regard to chances, e.g. the equal access of all who are equally in need to medical resources.
2. the physician should also include in his evaluation possible perceptions of such relationships by his patients, his colleagues, and the public.
3. the physician should keep himself away from such relationships if his evaluation indicates ethical problems or even only doubts about some aspects of this relationship.
4. the physician should collaborate with industry only on the basis of a clearly formulated contract in advance to prevent abuse on any side, e.g. possible conflicts of interests between his integrity and his need for sponsorship, particularly with regard to educational or research activities.
5. the physician should disclose all relationships, ties, affiliations, support, particularly financial ties between himself and industry to patients, research subjects, review boards, editors, audiences, institutions and others to whom his actions may be influenced or by whom they may only be perceived as influenced by such relationships.

#### **b. Specific recommendations for educational activities**

In order to remain current with the state of the art physicians are obliged to take part in continuing medical education (CME). However, they should be aware of the quality of information, and of possibly biased information conveyed in a commercial context. Particularly, they should know that gifts and other subsidies will bias them in favour of the sponsor's product. And they should also consider how such relationships with industry will be perceived by their

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<sup>36</sup> The recommendations follow a basic principle of the Royal College of Psychiatrists: „Psychiatrists need to recognise that, while commercial organisations (and their representatives) may have similar goals to their own, the primary responsibility of such organisations towards their shareholders/sales targets may result in conflicts of interest.”

patients and the public, and the possible effects such perceptions will have on their confidence and trust. In order to avoid such negative effects

it is recommended that

6. physicians should be trained in and make use of evaluating critically all information; they should be careful in using educational material (slides, reference material etc.) produced by industry, in order to ensure their objectivity. It is unethical for physicians to publish articles which are ghostwritten by industry.
7. correspondingly officers of physicians' organisations<sup>37</sup>, societies, etc., must retain control of the title, educational and/or scientific content of any event or product, the level of advertising, and in the case of meetings, the level of hospitality.
8. physicians should not accept major gifts, e.g. free meals or free travel without their own work; sponsorship may not be purely for hospitality or social events. They may accept subsidies at best only if they are commensurate with the extent of their services, e.g. consultation fee or reasonable travel expenses for participation in a meeting to which they contribute.
9. physicians must disclose any industry sponsorship or affiliation and other potential conflicts of interest to formal lecture audiences and publication editors.
10. physicians, when in doubt, should have the opportunity to ask an authoritative body, which also will supervise behaviour of all concerned and be able to punish misbehaviour.

### **c. Specific recommendations for research**

In order to safeguard the scientific independence of physicians who participate in industry-sponsored research (and ultimately, the interests of patients)

it is recommended that

11. the physician should be aware of the goal of research, which is to gain new knowledge. Therefore, he should understand clearly the purpose for which the results of his studies will be used, by whom and when, and should consider all possible influences from sponsors of such research, either industrial or governmental or other agencies that may affect adversely this goal. The physician should also clarify whether his own interests in the study interfere with his ethical obligations. The application for consultation of an ethics committee should include considerations on the ethical acceptability of a relationship between the physician researcher and the (industrial) sponsor.

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<sup>37</sup> Royal College of Psychiatrists 1999: NB These guidelines apply to all College meetings and activities including those of Faculties, Sections, Special Interest Groups and Divisions. The 'relevant College Officer' may be an Honorary Officer, or an Officer of a Division, Faculty, Section, Special Interest Group, Standing or Special Committee.

12. the physician must provide full information to the research subject not only on goal, design, performance of the study, particularly on possible discomforts and risks, but also on unforeseen new risks arising during the study and also on relationships with a sponsor that may be relevant to the study.
13. the physician should agree in advance with the sponsor that he will have essential influence on study design and subject recruitment, and, in particular, full access to all raw data as well as control of both data analysis and interpretation, and, finally, no restrictions with regard to publishing the data. Contracts should be signed only after prior review and approval of consulting agreements by respective bodies such as review boards of academic institutions or boards of physicians (Cech TR et al 2001)<sup>38</sup>.
14. the physician as an author must disclose all relationships with industry, and particularly with a sponsor of a study, that may have an influence on his publication. He must state explicitly whether potential conflicts of interests do or do not exist<sup>39</sup>.
15. the physician should participate in postmarketing studies only if their scientific validity and expected potential for medical progress are evident. Participation in marketing studies is not acceptable.
16. the Research Ethical Committees (RECs) should guarantee the dissemination of information on all clinical research by some measures<sup>40</sup>.

Some of these aspects may be exaggerated in clinical studies with samples of subjects in developing countries<sup>41</sup>. Therefore, for industry-sponsored clinical research in developing countries

it is recommended that

17. research physicians as well as sponsors from developed countries should consider the specific cultural and social contexts of participants in developing countries, particularly the existence of alternative belief systems regarding the causes and treatment of mental illness and how concepts such as “informed consent”, “placebo”, “randomisation” can be im-

<sup>38</sup> Choudry NK et al 2002: “The study highlights the need for appropriate disclosure of financial conflicts of interest for authors of Clinical Practice Guidelines and a formal process for discussing these conflicts prior to CPG development.”

<sup>39</sup> The editors of leading journals require the following financial disclosure statement: “I certify that all my affiliations with or financial involvement (e.g. employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending royalties) with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed”. (International Committee of Medical Journal Editors (ICMJE) (1997/2001): “Uniform requirements for manuscripts submitted to biomedical journals)

<sup>40</sup> mainly to “establish the investigator(s) assuming responsibility for results dissemination, scrutinise any sponsor-imposed contractual impediments, and mandate trial registration” and “do continuing review until primary outcome data are reported” and “assess failure to report results as a possible research misconduct” (Mann 2002). The establishment of publicly (or privately) funded central registers for all clinical trials with unrestricted access of the public is in progress, e.g. the initiative of the European Science Foundation [www.efs.org](http://www.efs.org), the British [www.controlled-trials.com](http://www.controlled-trials.com), the American [www.clinicaltrials.gov](http://www.clinicaltrials.gov) or [www.centerwatch.com](http://www.centerwatch.com).

<sup>41</sup> Sartorius N (2001)

parted to people with a high rate of illiteracy and without corresponding words in their language. Therefore,

18. research physicians as well as sponsors from developed countries should give co-workers from the developing country a share in all stages of the study, from the development of the study design through the performance of the study to the publication of results. It should be a non-paternalistic (although sometimes expensive) contribution to the development of a scientific infrastructure in these countries.
19. research physicians should ensure an adequate prior ethical review in the host country of the proposed study and that voluntary, informed consent is properly obtained from research subjects.
20. research physicians as well as sponsors should participate only in studies that deal with specific characteristics of these probably vulnerable populations, and benefit not only participants in a trial but also the class of persons they represent.
21. research physicians should formulate agreements with the sponsor in advance of beginning research in order to provide successful products of the research to the individuals who participated in a study if they still need those products after the study has ended.

#### **d. Recommendations to be considered**

The increase of interweaving between industry and universities demands clarification and monitoring of these relationships on the organisational and institutional level<sup>42</sup>. One indication for this is that rules for disclosure are considered as to be no longer sufficient; therefore some further reaching proposals have been made (Moses H et al 2001) and should be considered:

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<sup>42</sup> (Korn D 2003) "the universities and their academic medical centers have failed to respond sufficiently or credibly to the profound transformation of their research culture in the past two decades, which has witnessed a dramatic increase in the privatization of historically public biomedical research, and in the financial self-interests of investigators and institutions in the research they conduct". "While university oversight of individual conflicts of interest demands strengthening, the issues are long debated and well understood. In contrast, the financial interest of institutions in the medical research they conduct is recent, more complicated, poorly understood, and highly sensitive, involving investment decisions that lie at the heart of university autonomy. The author argues that institutions and professional societies must promulgate and enforce transparent standards of conduct, and strengthen oversight and management of financial self-interests, to avoid burdensome federal intervention and corrosive public skepticism."

McCrary SV et al (2000): "Conflicts of interest pose a threat to the integrity of scientific research. The current regulations of the U.S. Public Health Service and the National Science Foundation require that medical schools and other research institutions report the existence of conflicts of interest to the funding agency but allow the institutions to manage conflicts internally. The regulations do not specify how to do so." We surveyed all medical schools (127) and other research institutions (170) that received more than \$5 million in total grants annually from the National Institutes of Health or the National Science Foundation; 48 journals in basic science and clinical medicine; and 17 federal agencies in order to analyze their policies on conflicts of interest." "There is substantial variation among policies on conflicts of interest at medical schools and other research institutions. This variation, combined with the fact that many scientific journals and funding agencies do not require disclosure of conflicts of interest, suggests that the current standards may not be adequate to maintain a high level of scientific integrity."

Hasselmo N (2003) discusses "efforts to manage real and potential conflicts of interest in university research in the United States. The focus is on the report by an Association of American Universities (AAU) task force that addresses both individual and institutional conflict of interest issues."

22. veracity of results of research should not be compromised, for example, by isolating research from economic pressure in commercially supported research institutes that are separated from other research facilities.
23. supervision by a disinterested party should be strengthened, for example, by broadening IRB's primary task of protection of research subjects to monitoring of conflicts of interest.
24. proprietary rights and control of intellectual property ought to be acknowledged at the outset, for example, by a new entity separate from the university to hold equities and receive royalties<sup>43</sup>.
25. financial and non-financial incentives should be designed to address the needs of institutions, senior investigators and junior faculty.

This proposal of recommendations had been discussed at the MEC Symposium of the WFSBP Congress in Sydney in 2004. All National Societies of Biological Psychiatry and interested pharmaceutical companies as well are invited to comment on it.

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<sup>43</sup> corresponding to the threshold at which the NIH deems an investigator's interest to be "significant": "a 5% limit on the equity a scientist can hold in a company for which he or she consults (Cech TR et al 2001)

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