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Independence - the why and how

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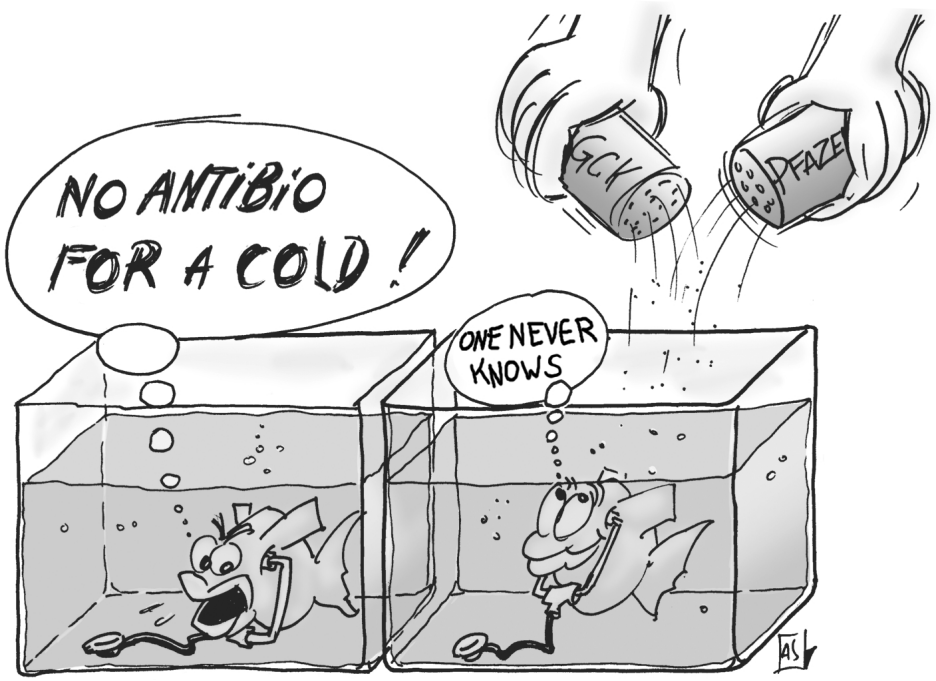
INDEPENDENCE: WHAT'S THE POINT?
Or "How to choose an acceptable dependence?"



I-FOREWORD

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The International Society of Drug Bulletins (ISDB) was created on 2 August 1986 in Stockholm after a preparatory meeting in Madrid in May 1985. Contemporary reports show that the independence of member bulletins was a central issue right from the outset (1,2).

The funding sources were defined as follows: "*Bodies sponsoring independent drug information bulletins have variously included government agencies, professional organizations, university departments, philanthropic foundations and consumer organizations*" (1,2). During the preparatory meeting in Madrid, "independent" information was defined thus: "*Independent information comprises both data and interpretations which attain the highest possible degree of objectivity and which are provided by bodies having no commercial or other interest in the promotion of particular patterns of drug treatment, their sole aim being to optimise such treatment in the interests of the patient and society at large*" (1).

Even if the trendy words "conflict of interest" do not figure in the documents from that period, the relationships between drug bulletins and their environment were clearly described. The section on Allegiance stipulates that: "*A drug bulletin must be independent of the pharmaceutical industry, advertisers, advertising agencies, pressure groups and governmental agencies insofar as the latter are supervising the economics of prescribing. Its links with regulatory agencies should be purely scientific, without a regulatory agency having the power to influence the content of a Bulletin, even if the latter is sponsored by a Department of Health*" (1). The key notion of allegiance, or dependence, is there, right from the outset. For both practical and political reasons, we will discuss this issue in terms of "dependence".

Choosing one's dependence

All human enterprises are undertaken on behalf of "someone and something". All editorial teams of drug bulletins depend at the very minimum on those who control and fund their publications. The philosophy underlying ISDB member bulletins has always been to refuse dependence on the pharmaceutical industry and to opt for the most acceptable form of dependence, i.e. that which allows one to generate comparative, updated and operational information on therapeutics with the maximum of freedom. ▶▶

► The choice of an acceptable degree of dependence depends on the local context. It can also evolve over time: certain ties that were necessary at a given period may later be shed. At the 1985 Madrid meeting, bulletin representatives discussed the advantages and disadvantages of the different options: *"There is no singly ideal solution to the question as to how a drug bulletin should be financed. For some the ideal proves to be a form of financing which ensures free distribution to a large number of prescribers; others have shown that a good bulletin can command a fair price and win a wide audience. There is clearly a risk on the one hand that a "free" bulletin may be ignored because it has not been asked for, and on the other hand that a bulletin available only on subscription will not reach the physicians who need it most… Financing by a government department, a health insurance organization or a professional body (through direct subsidies or bulk subscription) can be a means of securing wide readership without major problems of expense, provided the arrangement does not render the bulletin editorially dependent upon the sponsor's policies (e.g. as determined by a regulatory body). There is also a risk that a bulletin which has become too dependent upon such support may collapse if the sponsor's policies change"* (1).

All players have a part

In all countries, whether rich or poor, small or large, rational use of therapeutic and diagnostic tools depends on the balance of forces and commitments of four players: patients (or consumers) and their organisations; health professionals and their organisations; 'regulators' (governments, regulatory agencies, social security organisations); and health product companies (3). The first three players represent the market that companies attempt to exploit.

Pharmaceutical firms, and especially multinationals, wield considerable power in all countries. But they can only go as far as the government, regulatory agencies, health professionals and consumers allow them to, for better or for worse (4). The *de facto* deregulation that has occurred in developed countries over the last two decades, and the increasing financial dependence of regulatory agencies on drug companies, have strengthened bigPharma's global clout (5).

The independence of health professionals is an essential condition for quality health care and for a trustful relationship with the public. The need for free and rigorous thought and action should be a cornerstone of both initial and continuous medical training. Yet the pharmaceutical industry has succeeded in penetrating every aspect of medical practice, starting in medical schools. Drug companies are now omnipresent, in research, initial and continuous training, award-giving ceremonies, computer logistics, conferences and seminars, and even health professionals' leisure activities. It is illusory to imagine that, in such conditions, health professionals can maintain autonomous thought and action, whether in their daily practice, training, or research activities (6-8).

The refusal of ISDB Bulletins to "swear allegiance" to drug companies is an essential condition, though not sufficient by itself, for the regular production of high-quality comparative information. How else could member bulletins be in a position to point out that only 10 to 15% of the new drugs marketed each year represent a true therapeutic advance, or to recommend optimal therapeutic choices?

When ISDB was created in 1986, most regulatory agencies were often an integral part of national health authorities and were funded directly by the taxpayer. Companies paid small fees to have their marketing applications processed, and this money returned to the public coffers rather than being collected by the agencies themselves. Now, users fees account for around 70%, and sometimes up to 100%, of regulatory agencies' funding. This has transformed them into little more than service providers to pharmaceutical firms, and has undermined their original public health mission (9). The Industry has become the client rather than Public Health.

This transformation of the regulatory landscape has had significant implications for those ISDB Bulletins that are financially dependent on regulatory agencies. Whatever their integrity, professionalism and commitment, Bulletin editors and managers can find themselves in a difficult position when, for example, they need to denounce an unjustified marketing authorisation or the authorities' failure to withdraw a dangerous drug in due time.

Björn Beerman, head of the Swedish regulatory agency bulletin, didn't sign the ISDB Declaration on therapeutic advance, despite having made a substantial contribution to the discussions. ►►

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► The bulletin of the Swedish regulatory agency has indeed maintained a strictly editorial policy, even though the agency is funded entirely by company fees. Furthermore, Björn and his team managed to carry out and publish some remarkable studies on unpublished trials and the impact of advertising, for example (10). But the Swedish situation is unique and is likely to remain so.

What is important for individual ISDB Bulletins is just as important for ISDB itself. The fact that WHO accounted for more than 50% of ISDB finances in 2005 poses a threat to our long-term political independence.

Dependence on WHO carries two major dangers for ISDB: the first is a loss of credibility, and the second is the abrupt termination of WHO's financial support if ISDB criticises its actions or publications.

In 1999, ISDB signed a letter, together with other organisations, underlining the risk of conflicts of interest inherent in the way WHO now functions, and the threats these conflicts pose to WHO's public health mission (11). Can ISDB bite the hand that feeds it?

II-PRACTICAL CONSEQUENCES OF DEPENDENCE ON HEALTH INDUSTRY

All players in the health sector are at risk of being dependent on health industry. This dependence should be examined with respect to its practical implications.

Patients and consumers "under the influence"

Several trends have increased over the last 20 years in many countries:
– direct-to-consumer advertising, even for prescription-only drugs; and so called "health information" provided by industry-dependent sources;
– the increasing number of over-the-counter drugs;
– legitimate demands for greater public information and participation in decisions concerning their health.

One result of these changes is that consumers are playing an increasingly active role, but this also makes them more receptive to advertising disguised as "information". A new market trend is therefore the direct targeting of patients, thereby bypassing prescribers. Some companies are now using patient and consumer organisations to their own commercial ends.

Many patient organisations are dependent on drug companies, but the financial links are often disguised. Health Action International (HAI) has investigated such links for several years (6,12,13).

In a recent report, HAI examined the case of the umbrella organisation *European Patients' Forum*, a favorite partner of the European Commission (especially Health & Consumer Protection DG) and the European Medicines Agency (EMEA) (13). The HAI report shows that this organisation was artificially created at the instigation of the European Commission, and highlights the carefully disguised financial links between the Forum and drug companies.

Many other organisations are in bed with drug companies; they include the Global Alliance of Mental Illness Advocacy Networks (GAMIAN), created many years ago by Novartis; and the International Alliance of Patient Organisations (IAPO), created by a group of 30 drug companies.

In Europe, these so-called patient organisations are official partners of European institutions. Worse, representatives of these organisations are about to be appointed to the EMEA management board.

Health professionals "under the influence"

The detrimental effects of health professionals' dependence on drug companies are all pervading. They can be seen in initial and continuous education, research, and daily practice (14). Here are a few examples:
– funding of initial medical education by drug companies seeking to 'format' young prescribers;
– post-marketing seeding-trials, in which practitioners are paid to prescribe a particular brand under the guise of "scientific survey";
– the influence of medical reps, as reported by Prescrire's surveillance network for 15 years (15), and by the organisation No Free Lunch (16); ►►

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► – continuing education is largely funded by drug companies; many general practitioners and specialists obtain their training exclusively from medical reps, sponsored conferences, free reprints and leaflets and throaway journals, free journals supplements to satellite symposias. Many Bulletins denounced the abusive prescription of SSRI antidepressants and Cox-2 inhibitors (17,18, etc.), as highlighted in the British parliamentary report entitled "The influence of the pharmaceutical industry" (4);
– health professionals have less and less control over the agenda of clinical research topics, and are becoming little more than service providers to drug companies. Clinical research is now mainly funded by drug companies and is designed to reap a short-term profit; health professionals no longer participate in the definition of research priorities or in clinical trial design. Their independence is also threatened when company sponsors censor negative clinical trial findings.

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Regulatory agencies "under the influence"

The increasing dependence of rich nations' regulatory agencies on the fees paid by drug companies for marketing applications and advice on drug development means that their original mission of protecting public health is being downgraded to second place (4,19,20). The Vioxx° scandal illustrated the disastrous effects of agencies' failure to apply the precautionary principle, either when granting initial marketing authorisation or when examining post-marketing pharmacovigilance data.

Regulatory agencies' subservience to their principal clients, i.e. drug companies, leads to a lack of transparency, especially with regard to pharmacovigilance data.

The World Health Organisation "under the influence"

The WHO comes under pressure from the pharmaceutical companies, both indirectly, when member states seek to defend their national industries, and also directly, in the form of public/private partnerships.

Many WHO-sponsored studies and guidelines have been influenced by drug companies. They include:
– the guidelines on hypertension, compiled in partnership with the International Society of Hypertension (ISH) in 1999 (21); the 2003 version is also flawed by conflicts of interest (22);
– the guidelines on osteoporosis;
– the ARIA workshop report on allergic rhinitis, written in collaboration with WHO and drug companies; this report twists the vocabulary of allergic rhinitis, therefore widening the potential market for antihistamines (23);
– recommendations on maternal breast-feeding (24);
– work on antibiotic resistance;
– the methods used to choose INNs are highly opaque. For example, the initial, highly evocative name "amfebutamone", a reminder of the amphetamine family was replaced by the mild "bupropion", for reasons that WHO has declined to explain;
– the "Report on priority medicines for Europe and the world" written by WHO in 2005 at the instigation of the Dutch Presidency of the European Union: its content virtually reproduces the wish-list of the European Federation of Pharmaceutical Industries and Associations (EFPIA), a body that represents European drug companies (25,26);
– the essential drugs list is open to criticism, not least for the way in which it was selected. For example, the ofloxacin isomer levofloxacin was recently included on the list, a move that implicitly endorsed the manufacturer's anti-generic manœuvering.

The International Conference on Harmonisation for technical requirements of registration of pharmaceuticals for human use: his Master's Voice...

The ICH process started in 1990, at the instigation of American, European and Japanese pharmaceutical firms and the corresponding regulatory agencies. Its stated objective is to harmonise drug registration procedures by adopting recommendations for the assessment of their quality, efficacy and safety.

ICH functions as a private club for drug companies and regulatory agencies in rich countries, to the exclusion of health professionals, the public, and poor countries. WHO and Canada (Health Canada) both have observer status.

The desire to harmonise regulatory requirements is perfectly laudable. But experience shows that the ICH process leads to the adoption of guidelines that correspond to the lowest common denominator in drug evaluation. For example, ICH advocates the acceptance of simple placebo-controlled trials instead of head-to- ►►

► head comparisons with existing alternatives. Therefore, comparative trials versus standard treatments have now become the exception. Likewise, irrelevant surrogate markers are recommended in many areas instead of morbidity and mortality endpoints.

III-FIRM ACTION NEEDED ON CORRUPTION AND CONFLICTS OF INTEREST

Corruption in the health sector and conflicts of interest have become major issues in medicine and pharmacy worldwide.

Several measures can and must be taken.

By ISDB Bulletins

– promotion of ISDB Declarations by member Bulletins (e.g. the Paris Declaration on therapeutic advance and the Berlin Declaration on pharmacovigilance);
– collaboration among Bulletins in order to rank regulatory agencies according to their transparency ("WorstRegulators BestRegulators list");
– a call on member bulletins to support the Medicines in Europe Forum campaign for the use of INNs instead of trade names ("Think INN, prescribe INN, consume INN"). This is part of the campaign for rational drug use, in line with the recent Medicines in Europe Forum campaign aiming to ensure that European pharmaceutical legislation maintains the obligation to mention the INN on drug packaging. And WHO must be lobbied to ensure that INNs are chosen transparently and rationally, in order to prevent medical errors due to confusing INNs;
– promotion of the *No Free Lunch*, *No Grazie*, *Non Merci* Charters by all member Bulletins and in all countries;
– participation in an international study of pharma sales representative practices (Barbara Mintzes);
– disclosing member Bulletins' funding sources and publishing annual financial statements in order to promote the uniqueness of comparative information prepared independently from drug companies (27,28). Some Bulletins have been doing this for several years (BODHI, Prescrire, etc.). The subscription Bulletin WorstPills clearly announces its policy on its website: "*If you subscribe to worstpills.org, you will get completely independent, unbiased prescription drug information that might just save your life. Public Citizen refuses to accept contributions from corporations or the government, and we will never accept advertising on our site. This policy allows Public Citizen and its nationally renowned Health Research Group to remain a fierce advocate on behalf of consumers, without fear of offending a sponsor. As a nonprofit consumer advocacy organization, we must charge a modest fee to users of worstpills.org so that we can continue putting your health first. Many websites have information about drugs, but we are the only one that applies rigorous scientific analysis to identify drugs that consumers should not take under any circumstances*" (29).

By ISDB

– ISDB member Bulletins should jointly analyse guidelines from regulatory agencies and ICH, and first point out that they are not binding laws; we should denounce what is wrong in these guidelines and encourage regulatory agencies to be more demanding, in patients' best interests;
– assistance must be provided to Bulletins that have difficulties in achieving financial independence. It is advisable to diversify one's funding sources and thereby avoid being too dependent on a single organisation;
– a drastic cut must be made in the WHO contribution to the ISDB budget (by cutting down on non essential spending).

In Europe, a number of actions by the Medicines in Europe Forum are underway (see annex 2 for a description of the ongoing European Campaigns).

European Bulletins should monitor the application of the new European Directive at the national level and the new Regulation at EMEA level, especially regarding institutional transparency.

Collaboration with other organisations is possible and desirable within the Medicines in Europe Forum (30); these include HAI, the European Consumers' Organisation (BEUC), the Association Internationale de la Mutualité (AIM), and the European Public Health Alliance (EPHA). The aims are: ►►

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► – to counter the nomination to the EMEA management board of patient and physician representatives belonging to organisations funded by drug companies;
– to push for transparency on the funding sources of industry lobbyists (Corporate Europe Observatory petition);
– to combat creeping direct-to-consumer advertising of prescription drugs, including on the Internet.

Christophe Kopp
Prescrire Editorial Staff
16 August 2005

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