



Vol. 14, N°1, May 2000

NEWSLETTER

WARNING!

ISDB MAIL ADDRESS HAS CHANGED

Please note that all correspondence to ISDB should be sent to the secretary:

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ANDREW HERXHEIMER'S 75TH BIRTHDAY

A *Drug and Therapeutics Bulletin* seminar is to be held to celebrate Andrew Herxheimer's 75th Birthday. The seminar, entitled "Info-kinetics: information collection, collation, interpretation and distribution" will take place on the afternoon of Wednesday 8 November 2000 in central London.

Talks will include:

- Designing clinical trials to meet patients' interests (*Iain Chalmers, Cochrane Centre*)
- Using data from individuals (*Ann McPherson, Oxford GP*)
- Exchanging information with government and industry (*Charles Medawar, Social Audit*)
- International levers for improving the use of medicines (*Ellen t'Hoën, Holland*)
- Conveying a just evaluation of benefit & harm (*Graham Dukes, Norway*)

For further information, contact the Seminar Administrator at *Drug and Therapeutics Bulletin*, 2 Marylebone Road, London NW1 4DF; tel +44 20 7770 7571; fax: +44 20 7770 7665; e-mail: dtb@which.net.

COLUMN

FOUR ACTORS

In every country or region, whether rich or poor, the rational use of medicines depends on the balance of power and commitment of four actors: regulatory authorities; health professionals (particularly doctors and pharmacists), their organisations and media; consumers and their media; and the pharmaceutical industry.

Truly reliable regulatory authorities should be in control of drug marketing authorisation and distribution, and should provide comparative evaluation data. If they don't, even well intentioned and organised health professionals, not to mention consumers, cannot do much to clear the market jungle and distinguish the drugs that benefit patients from gimmicky products.

Yet without well-educated and well-organised doctors and pharmacists who fully accept their responsibilities, without adequately informed and empowered consumers, health authorities are practically powerless to implement the rational use of drugs.

The pharmaceutical industry is a key actor with an impressive capacity to adapt. For better or for worse, it will eventually do whatever health authorities, health professionals and consumers allow it to do. Each country or each region has the pharmaceutical industry, the quality of drugs, and the marketing claims they deserve. In the long term, the momentum and competitiveness of the industry are directly linked to the requirements laid down by the three other actors.

In this context, independent drug bulletins are needed to provide unbiased and comparative information. They should also stimulate health authorities, contribute to inform the public, and act as a balancing factor with regard to the pharmaceutical industry. Their sustainability and independence are crucial.

Christophe Kopp

[This editorial is a rewriting of a version first published in 1987 in an ISDB newsletter. It was written by Gilles Bardelay, then Chief Editor of *la revue Prescrire*.]

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LA LETTRE DU GRAS - BELGIUM

For its tenth anniversary, the "Groupe de Recherche et d'Action pour la Santé" (Health Research and Action Group, GRAS, for its acronym in French) has completed an evaluation of the ideas, actions, and results obtained from its drug advertising watch (publivigilance).

GRAS is made up of general practitioners and pharmacists who keep a watch on drug advertising. The objective is to reduce the adverse effects caused by deceitful and misleading, or medically unethical marketing campaigns.

These campaigns frequently result in irrational prescriptions and a substantial incidence of side effects. They are detrimental to the good faith of the prescriber, the patient's health, and the health care provider.

The work carried out by the "Groupe de Recherche et d'Action pour la Santé" was initiated following our indignation as health practitioners confronted with some openly misleading advertisements (1,2,3). These unethical promotional practices led us to undertake a more systematic watch of the quality of drug advertising. Our network, independent and free of outside grants, is made up of practitioners. We do not pretend to step into the field of competence of the Belgian regulatory authorities. Our particular line of action consists in reporting abuses observed in drug promotional campaigns, leading to irrational prescribing.

GRAS studies the scientific references of the ads and formally questions the firms concerned and competent authorities in cases of persistent abuse. GRAS gives priority to promotional messages on products of particular importance, whether economically (potentially big markets such as osteoporosis or hypercholesterolaemia), pharmaceutically (new quinolones, new macrolides, statins), or illustrating a problem (direct-to-consumer (DTC) advertising, unethical studies). We deal mainly with prescription drugs, but there are also many questionable direct-to-consumer advertisements for over-the-counter products, phytotherapy and food supplements.

Other initiatives, similar to GRAS, have originated in several countries, with similar

results: in France, the "Réseau de Surveillance de la Visite Médicale" (4), and internationally, the Medical Lobby for Appropriate Marketing. Practitioners can also react quickly through the Internet. The World Organization of Family Doctors' site (<http://www.uib.no/isf/letter/français.htm>) was used recently by many practitioners sharing the same view on the hypertension guidelines published by the World Health Organization and sponsored by Astra.

We have studied in detail approximately 50 ads and found several types of problematic ads with:

- Minimised adverse effects
- Off-label indications – Indirect to consumer advertising (DTC advertising is not authorised in Europe)
- Pricing manipulation
- Misleading interpretation of clinical trials results
- Unethical clinical trials

The first two problems are usually due to lack of precision or omissions in the data sheet, skillfully exploited by promoters.

For example, in 1990, when quinolones were released on the market, ofloxacin was advertised as the "definite antibiotic therapy", and "first choice for respiratory infections". This drug is actually not very active against pathogens generally involved in respiratory infections, such as pneumococci. GRAS formally questioned the company and the regulatory authorities. We did not receive an official reply, but the data sheets were nevertheless reformulated and the advertisement at issue was modified. The danger of this type of publicity was unfortunately confirmed by reports describing several serious cases, sometimes fatal, of pneumococcal infections treated with quinolones (10,11,12). In spite of this, the French medicines agency in 1998 had to prohibit a similar advertisement for ciprofloxacin (13).

Prescribers received information minimising the adverse effects of new nonsteroidal anti-inflammatory drugs (NSAIDs): proglumetacin was described as the "first NSAID that does not affect the stomach" (June 1991), ketoprofen was claimed "for totally secure action" (June 1994), and meloxicam

for its "improved safety" (July 1997). In each case, a critical appraisal of the literature fails to confirm these claims.

In 1996, the pneumococcal vaccine was promoted to the general population through "humanitarian" campaigns that proposed the vaccine to underprivileged adults and children (off-label indications) despite call to order by the Health Ministry.

TV media are also involved. In October 1992 sumatriptan was put live on the air on RTBF's news broadcast and was also featured on television news in France, as reported by *la revue Prescrire* in its January 1993 issue.

In November 1997, it was reported on TV news that salmeterol "had received worldwide recognition by lung specialists as the sovereign remedy against asthma and also for treating asthma attacks", in clear conflict with the data sheet. The latter states, in bold characters, that salmeterol is not appropriate for the treatment of asthma attacks. If not rectified, such claims could be dangerous for the patients. A complaint filed by GRAS prompted an investigation by the Belgian judiciary, but it was not followed up.

Confronted with these irrational promotional practices GRAS has developed a strategy of formal questioning.

Regarding the pharmaceutical companies, we rarely had a constructive dialogue with those responsible for the questionable

THE BELGIAN DRUG FORMULARY ON THE INTERNET

As of March 2000 the Belgian Drug Formulary (1) is available on the Internet at <http://www.cbip.be> or <http://www.bcfi.be> in French and Dutch.

Information on preparations shall be updated every month and a complete revision of the print and electronic versions is done once a year and shall be available around October each year.

The site will become interactive in the future, with links to the Formulary, other publications of the Belgian Centre for Pharmacotherapeutic Information and other drug information sources.

(1) See ISDB Newsletter December 1999 page 9 for presentation of the Belgian Drug Formulary.

advertisement. However, the misleading advertisement was sometimes modified or withdrawn. On the other hand, our contacts with *investigators* involved in interviews or clinical trials proved to be much more productive in terms of claim modification.

Occasionally we were allowed to present our arguments to the Ethics commission of the Drug Industry but that was never followed by formal denials nor letters to practitioners clarifying the situation.

We have never received official replies from the Belgian regulatory authorities but we believe we should keep them informed.

The Health ministry only reply upon parliamentary request.

The ads control Commission, recently created within the Public Health Ministry, deny being competent in this matter and transfers the file to the prosecutor's office.

The Pharmacy Inspectorate reacted on several occasions to some questionable advertisements, but its surveillance activity remains unknown due to the confidentiality of investigations. Making sanctions public and imposing publication of a corrected version of the advertisement would be a valuable counter-information for prescribers and would be more dissuasive for the offenders than current practices involving administrative fines or simple withdrawal of the advertisement.

These abuses being recurrent we think that misleading promotional practices are not merely fortuitous, but the result of a deliberate policy of unscrupulous marketing departments. In practice, the legal means available in Belgium are either burdensome (litigation) or inefficient to combat these kinds of excesses (failure of post-release control in France (5), complications of pre-release control). Every practitioner should therefore carry out his/her own drug advertising watch and become skilled in the critical appraisal of drug advertisements and the clinical trials supporting them.

Tools are being developed, and medical schools are starting to train future doctors in this regard, for example through seminars on critical-appraisal of articles. The Local Groups for Medical Evaluation, (peer-review type groups) could well become privileged organisations for this activity. GRAS provides dossiers on different topics comparing drug advertisements with principles clinical trials and the international guidelines related to the subject.

Scientific societies could play a major role

in the promotion of this initiative and information exchange between Local Groups.

- 1- Fletcher RH. - Pharmaceutical Advertisements in Medical Journals *Ann Intern Med* 116 (11): 951-952, 1992.
- 2- Lexchin J - What information do physicians receive from pharmaceutical representatives *Canadian Family Physician* 43: 941-945, 1997.
- 3- Ziegler MG - The accuracy of drug information from pharmaceutical sales representatives *JAMA* 273 (16): 1296-1298, 1995.
- 4- Prescrire Rédaction - Visite médicale : bilan de 8 ans d'observation *La revue Prescrire* 193 (19): 226-229, 1999.
- 5- Prescrire Rédaction - La publicité pharmaceutique destinée aux professionnels de la santé est-elle vraiment contrôlée? *La revue Prescrire* 139 (14): 224-227, 1994.
- 6- Prescrire Rédaction - Les biais de publication *La revue Prescrire* 146 (14): 718-720, 1994.
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- 9- *En Marche*, 6 mai 1999, p.20
- 10- Frieden TR, Mangi RJ - . Inappropriate use of oral ciprofloxacin. *JAMA* 264: 1438-1440, 1990.
- 11- Lee BL, Kimbrough RC, Jones SR, Chaisson RE, Mills J - Infectious complications with respiratory

pathogens despite ciprofloxacin therapy *New Engl J Med* 325:520-521, 1991.

12- Kömer RJ, Reeves DS, MacGowan AP - Dangers of oral fluoroquinolone treatment in community acquired upper respiratory tract infections *Br Med J* 308:191-192, 1994.

13- Journal Officiel de la République française du 11.09.98 (p.13865-66).

14- National Health and Medical Research Council - A guide to the development, implementation and evaluation of clinical practice guidelines - http://www.ausinfo.gov.au/general/gen_hottobuy.htm 1999.

15- Bucher HC, Weinbacher M., Gy K - Influence of method of reporting study results on decision of physicians to prescribe drugs to lower cholesterol concentration *Br Med J* 309, 761-764, 1994.

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17- Bouvy ML, Egberts AC, Leufkens HG - Klinisch onderzoekers en farmaceutische industrie. Troglitazon en mibefradil in opspraak *Ned Tijd Geneesk* 143, 34, 1727-1729.

For further information on GRAS's activities, go to:
GROUPE DE RECHERCHE ET D'ACTION POUR LA SANTE
154, rue de Courcelles, B-6044 ROUX
<http://www.ulb.ac.be/esp/gras>

THE INFORMED PRESCRIBER AND JAPAN INSTITUTE OF PHARMACOVIGILANCE

Report of the seminar in October 1999.

The Informed Prescriber (TIP) and the Japan Institute of Pharmacovigilance for Evidence-based Healthcare (JIP) held their second biennial seminar on 2-3 October 1999 at the University of Osaka Medical School. The seminar, Watching Drugs and Watching Medical Practices, was co-sponsored by the Japanese Informal Network for the Cochrane Collaboration (JAN-COC).

The purpose of the seminar, was to promote a better understanding of, and implementation of evidence-based medicine, health care and drug information.

Many individuals had input into the seminar by chairing sessions, presenting papers and contributing valuable comment.

In addition to the plenary sessions, there were workshops on EBM and the Cochrane Collaboration, including short sessions on:

EBM for beginners using the CASP CD-ROM

Retrieving information from the Internet and Cochrane Library; systematic reviews of Cochrane Collaboration

EBM for daily practice: a typical EBM training program

The essence of the major presentations is summarised below.

Rational Use of Rational Drugs

Dr. Hirokumi Beppu

Japan has experienced many drug-related catastrophes not seen in other countries. Unlike many other countries which introduced tighter controls after the thalidomide tragedy, Japan introduced few measures to avert further drug-related disasters. However, increasing medical expenditure, which is now one of the highest priorities in health care, is driving the rationalisation of medical practice.

In Japan, drug prices are much higher than in Western countries and wasteful and unsafe medical practices are widespread. A major factor for this is the imbursement ►►

► system which discourages the prescription of inexpensive drugs that are used as standard treatment in other countries and encourages the prescription of expensive new drugs which may be of uncertain value.

Rational use of drugs is not just 'the correct use of drugs' but rather 'the correct use of the right drugs'. Having experienced many drug disasters, we decided to study the efficacy and safety of new drugs and discovered an inverse correlation between the real quality of drugs and their prices, ie many drugs used routinely in Japan are of doubtful quality. We felt it was essential to start monitoring local drugs and medical practice.

Evidence-Based and Meaningful Healthcare

Dr. Rokuro Hama

There is now a global movement to evaluate and synthesise the scientific evidence for efficacy and safety of drugs. The Cochrane Collaboration is a huge project that aims to help people make well informed decisions about health care by preparing, maintaining and ensuring the accessibility of systematic reviews of the effects of health care interventions.

Here in Japan in 1968 Dr. Beppu established a drug bulletin, The Informed Prescriber (TIP), which is a member of ISDB. Ever since then TIP has been providing evidence-based drug information to promote the rational use of drugs in daily medical practice.

However, in producing articles for TIP, we became aware that many drugs sold in Japan are not approved for use in other countries. So, we decided that all such drugs needed to be systematically assessed and to undertake this work a new research institute was required. Thus in April 1997, the Japan Institute of Pharmacovigilance for Evidence-based Healthcare (JIP) was established. This institute is directed by Dr Rokuro Hama and it works in close cooperation with TIP.

Over the past two-and-a-half years, we have achieved much; we held our first seminar on pharmacovigilance and evidence-based medicine/evidence-based healthcare which over 500 people attended; we have evaluated many drugs and we have translated, edited and published two of the evidence-based Australian Therapeutic Guidelines (Antibiotic and Gastrointestinal).

The information we produce is not only for health professionals but also for consumers, to assist them in gauging the quality of drugs for themselves.

This seminar will focus on:

(1) the evidence for the rational use of antibiotics and how to implement this evidence in medical practice by learning from the Australian experience;

(2) how we use foreign evidence in Japanese practice, especially in managing persons (not patients) with hyperlipidaemia and peptic ulcer patients;

(3) the removal of the requirement for published evidence of efficacy and safety in the approval of new medicinal products.

Antibiotic Use and Hospital-Acquired Infection

Ms. Emiko Tomiie, author of 'Hospital-Acquired Infection'

My husband died in October 1987 of MRSA infection, complicated with multi-organ failure after oesophageal resection surgery at Tokyo University Hospital. He was 52 years old. At that time hospital-acquired infection was not widely accepted, even among the medical profession, and prophylactic measures were not in place.

With the development of antibiotics, it was the general expectation that infections would no longer be life-threatening. No-one foresaw the emergence of resistant organisms and the dangers they pose.

Even though it makes common sense for infection to be continually controlled in hospitals, it is still not common place. Basic infection control measures such as hand washing, disinfection and rational use of antibiotics are not routine.

There is a wide discrepancy between society's perception of risk associated with hospital treatment and recognition of the problem by medical and other health professionals.

Memorial Lecture: Lessons from Australia Focussing on Antibiotic Guidelines

Mary Hemming, Chief Executive Officer, Therapeutic Guidelines Ltd.

In Australia in the late 1970s, in response to concern about the rising incidence of antibiotic-resistant bacteria, the first edition of Antibiotic Guidelines was written by a group of experts and published.

The availability of the guidelines as an assessment tool stimulated audit activity. Between 1978 and 1982, surveys of antibiotic prescribing were undertaken at The Royal Melbourne Hospital. Appropriate and inappropriate use (eg, drug not required, wrong

choice, incorrect administration and inadequate cover) was assessed according to the Guidelines and antibiotic usage was surveyed before and after 3 separate traditional interventions.

These early audits showed that even though Guidelines have some impact on improving the use of drugs, some inappropriate prescribing persisted.

To address the problem of persisting inappropriate prescribing, it was decided to employ the techniques used in commercial advertising.

In 1983, a study in a single hospital was undertaken to measure the effectiveness of these techniques. To allow measurement of the effects, two aims were selected. The first was to replace IV amoxycillin with IV benzylpenicillin for the treatment of primary pneumonia. Following the intervention, the use of IV amoxycillin fell from 50 percent to 8 percent, and benzylpenicillin increased to 85 percent. The second aim was to encourage 8-hourly prescribing of oral amoxycillin rather than 6-hourly prescribing. Following the intervention, 6-hourly prescribing fell from 37 percent to 10 percent.

To obtain stronger evidence of the effects of commercial advertising, a controlled study of crossover design was undertaken in 1985-86. In this study, the topic chosen was antibiotic prophylaxis at the time of surgery. Specifically, the study focussed on the timing of administration of the antibiotic and the duration of therapy. The interventions in this study resulted in substantial savings which were mainly the result of improvements in the duration of prophylaxis but the choice of antibiotic agents used were also a factor. The savings, if they were extrapolated to all the hospitals for a full year, more than outweighed the costs of the campaign.

The use of commercial advertising in community practice was also studied, the target being the use of penicillin V or erythromycin, rather than amoxycillin, for the treatment of tonsillitis. The results of this study showed that appropriate prescribing in the intervention group increased from 60.5 percent to 87.7 percent and from 52.9 percent to 71.1 percent in the control group.

This series of studies showed the effectiveness of the interventions utilising commercial methods or educational antibiotic advertising and audit and feedback.

Guidelines are essential to encourage good prescribing, but mere publication of

Guidelines is not enough in itself to change prescribing. Prescribers need to be encouraged to implement the recommendations.

In Australia, the Therapeutic Guidelines have proven their worth as an element of quality assurance cycle. In fact they have become an essential part of the medical culture in Australia. When people in Australia talk about prescribing and want to know what is appropriate, the reply is invariably 'What does it say in Therapeutic Guidelines?' I do hope this becomes the case in Japan too.

Controlling Antibiotic Use and Infection Control Activities in Hospital

Dr. Takasi Fijimoto, Department of Internal Medicine, Sakai Municipal Hospital

Significantly more antibiotics are used in Japan than in western countries: almost 3 times more than in the USA, over 3 times more than in Germany and almost 10 times more than in the UK and France. It is most likely that the prescribing of individual physicians is being influenced by the medical economic system rather than the real need for antibiotic therapy.

Gram stain is a convenient and useful technique to assist in the diagnosis of infection and selection of an appropriate antibiotic. It should fulfil the same role as that of an ECG in the diagnosis of a cardiac arrhythmia and the selection of an anti-arrhythmic drug. Unfortunately, Gram stains are rarely performed before antibiotics are prescribed, even when a specimen is easily obtainable.

With the emergence of antibiotic resistant bacteria it is essential that certain antibiotics be carefully monitored and severely restricted even though this encroaches on prescribers' rights in prescribing drugs.

Infection Control Teams are well placed to play an important role in the monitoring and control of antibiotics.

Influenza Vaccination

Ms. Sigeko Amano, Dr Isamu Takamatsu

There are no randomised controlled trials (RCT) to support the efficacy and safety of influenza vaccine in Japan. The only studies that support the use of influenza vaccine in Japan are non-RCTs in which one group who requested and received vaccine were compared with another that neither requested nor received vaccine.

On the other hand, there have been important large scale studies in Japan which clearly showed that influenza vaccine was inef-

fective. In 1984 and in 1985, no significant difference was observed in the incidence of influenza (fever and two or more days absence from school) between 2 cities (43.7% incidence: n=45,327) where 72 percent of school children were vaccinated and one neighbouring city (42.8% incidence: n=25,122) where no children were vaccinated. In this city physicians ceased influenza vaccination after a severe case of vaccine-induced encephalopathy.

A systematic review of the world literature by the TIP/JIP influenza vaccination team found that only 9 RCTs have been conducted. Of these 9 studies, only 3 showed a significant difference in the incidence of influenza when it was diagnosed clinically, but even these 3 studies have faults. In one, where the incidence of influenza was found to be 58 percent in the placebo group, patients with the common cold may have been included in the subjects.

Some studies showed a significant difference in incidence when influenza was diagnosed by antibody however this method of diagnosis is theoretically incorrect in vaccinated persons.

Another study showed a significant difference using one clinical endpoint, but no significant difference using another clinical endpoint. In this study, 6 of 927 patients in the vaccine group died, while 3 of 911 control patients died. This was not significantly different but the relationship is not fully denied.

In the third study, even though drift of the virus was observed (ie the type of the vaccine and that of the virus which prevailed in that season were different) the incidence of influenza was lower in the vaccine group than in the placebo group. Moreover in this paper, another study was reported, in which no vaccine was included for influenza B, but the incidence of influenza B was significantly lower in the vaccine group than the placebo group. Blinding may not have been complete in this study.

Endpoint and Fundamental Terms for EBM

Dr. Hirokuni Beppu

Because of the paucity of Japanese evidence it is essential that the implementation of foreign evidence into Japanese practice be considered. Endpoint, intervention, event rate in the intervention group and the control group (non-intervention group), and the

terms relative risk reduction (RRR), absolute risk reduction (ARR), number needed to treat (NNT) and number needed to harm (NNH) were discussed.

Endpoint in Statistical Principles

Dr Motokazu Yanagi

In November 1998, the MHW: Koseisho introduced statistical principles for clinical trials, one principle being that only one primary clinically relevant endpoint should be used. Global assessment variables such as the global improvement rating (GIR, or Zenpan-kaizendo) should not be used unless relevance of the scale and the validity and reliability of the scale is confirmed.

Cholesterol-Lowering

Dr Rokuro Hama

A high cholesterol level is a very important risk factor for ischaemic heart disease, but it is inversely correlated with almost all other diseases including cancer, diseases of the gastrointestinal tract and liver, respiratory diseases, accident and others.

As more than 40 percent of people in western countries die from ischaemic heart disease, the risk of mortality from all causes is U-shaped rather than J-shaped; the risk of mortality from all causes is high with a very low cholesterol level as well as with a very high cholesterol level.

As only 6 to 8 percent of Japanese people die from ischaemic heart disease, the overall risk of mortality from all causes is rather low in Japanese people with a cholesterol level greater than 240 mg/dl. Thus the risk of mortality from all causes and cholesterol level is inversely correlated. So cholesterol lowering may be meaningless for those Japanese people with a cholesterol level greater than 240 mg/dl without ischaemic heart disease.

When considering the endpoint of cholesterol lowering, the difference in the mortality pattern between Japan and western countries should be considered. This difference may also be true in developing countries.

Cholesterol-Lowering for Japanese: NNT with Cholesterol-Lowering Agents to Prevent Ischaemic Heart Attack and/or Death

Dr. Manabu Yoshimura, Dr. Atsushi Hashimoto

Intervention studies using statins and the incidence of ischaemic diseases in ►►

► Japanese people was systematically reviewed. The effectiveness of drugs that lower cholesterol level was estimated, expressed as NNT and the cost of preventing one person from ischaemic heart attack.

The incidence of ischaemic heart events in Japanese people with a cholesterol level of 240 mg/dl or more was found to be 1.98 per 1000 person-year for middle aged men, and 0.48 per 1000 person-year for middle aged women.

Assuming that pravastatin decreased the event rate for Japanese people by 31 percent as shown in the WOS-COPS study, the NNT to prevent ischaemic heart disease of Japanese was estimated as 376 per 5 years for men, and 1550 per 5 years for women.

The relapse rate of myocardial infarction in Japanese people was shown to be 24 per 1000 person-year. If the relapse rate can be decreased by 34 percent as shown in the 4S study, NNT was estimated as 22.7 per 5.4 years.

To prevent one person without any ischaemic diseases from myocardial infarction it may cost ¥130m (USD1.2m) for men and ¥530m (USD5m) for women.

Although prevention of heart diseases is important, given the lower incidence of ischaemic heart disease in Japanese people and the efficacy, safety and cost of cholesterol-lowering agents, these agents should only be administered to people with a very high risk of heart attack.

Cholesterol-Lowering for Japanese: NNT/NNH with Cholesterol-Lowering Treatment to Prevent Death in Japanese People

Dr Rokuro Hama

Because only 6 to 8 percent of Japanese die from ischaemic heart diseases and the risk of mortality from all causes is inversely related to total serum cholesterol level, it can be predicted that overall harm will result by lowering cholesterol levels in Japanese people without ischaemic heart disease.

The NNT for prevention of ischaemic heart attack by lowering cholesterol levels of 240 mg/dl or greater to below 200 mg/dl, was estimated to be 230 to 330 per 5 years for men and 1400 to 1900 per 5 years for women.

To prevent myocardial infarction in one person without any ischaemic disease the cost may be ¥450m (USD4.3m) for men and ¥2600m or (USD24.8m) for women.

NNH of death was estimated as 97 per 5

years for men and 386 per 5 years for women.

One man during using ¥170m (USD1.6m) and one woman during using ¥420m (USD4m) may die. So excess death from lowering cholesterol by ¥300b (USD2.9b) of statins and other cholesterol lowering agents may be estimated at least as 1400 persons per year.

Brain Stimulants in Japan

Dr. Kentaro Hashimoto, Dr. Tadahito Umeda

Over the past ten years, Japan has spent more than one trillion yen (more than USD10b) on so-called 'brain stimulants'. This is in spite of a caution from TIP ten years ago that there was insufficient evidence for their efficacy. This warning was issued after the banning of hopatenate, an early 'brain stimulant' that was used as the active control in most of the studies on which the approval of 'brain stimulants' were based.

The advice given by TIP was that there was insufficient evidence for the efficacy of these agents because the endpoint (global improvement rating or Zenpan-Kaizendo) was subjective and had not been shown to be relevant or reproducible. Four major agents in this class, including idebenon, were withdrawn from the market in April 1998 on the basis that recent clinical trials had failed to demonstrate their efficacy. By June 1999, almost half of the agents of this class had been withdrawn from the market for similar reasons.

Although aniracetam is no different to the other agents that have been withdrawn from the market, it is still sold because it was approved on the basis of clinical trials conducted after the introduction of the guidelines introduced by MHW for assessing new agents that are claimed to improve brain circulation and/or metabolism.

Anti-Ulcer Drugs

Ms. Hiroko Mita, Dr. Noritoshi Tanida

The treatment of peptic ulcer has improved significantly since the introduction of H₂-receptor antagonists in the 1980s and proton pump inhibitors in the 1990s.

The top selling anti-peptic ulcer drug is famotidine (¥73b) followed by some so-called 'mucous membrane protecting agents'. Expenditure on these agents is ¥31b and ¥30b. All of these agents except sucralfate are local Japanese drugs.

The evaluation of these agents using published data required by law was presented.

Towards a Japanese Golden-Pill and Devil-Pill Prize • Dr. Kiichiro Tsutani presented an extract of the video of a Golden Pill Prize ceremony of *La revue Prescrire*.

Dr. Hirokuni Beppu and Dr. Rokuro Hama presented some ideas for discussion on how and why the Japanese Golden Pill Prize could be determined.

It was suggested that criteria for drugs nominated for the Golden Pill Award could be drugs:

for which there is substantial evidence of efficacy, and

which are well-established and used world-wide, and

which have not yet been accepted into Japanese practice because they have not been approved for use in Japan and/or there are economic disincentives for them to be prescribed.

Examples of drugs that would fulfil these criteria are low-dose aspirin for secondary prevention of myocardial infarction, oral sustained release morphine for cancer pain control and sucralfate for stress ulcer prophylaxis.

We would like to undertake some intervention studies to promote the use of these Golden Pills, rather than less useful pills.

Disclosure of Evidence Used in the Drug Approval Process

Dr. Hirokuni Beppu, Mr. Mitsuishi

Abolition of requirement for publication of papers to support the efficacy and safety of approved drugs

Closing Remarks • Many things need to be done to improve medical practice. Data needs to be gathered on medicinal products, medical practice and regulatory drug affairs so that they can be reviewed and systematically assessed, not only for medical and other health professionals, but also for medicinal consumers.

We guarantee that TIP and JIP will continue to produce and provide such information for these people.

[This report was written by Kokuro Hama, and edited by Mary Hemming]

JAPANESE CONSUMERS FINANCE INFORMATION FOR PROFESSIONALS

This paper was first published in la revue Prescrire. Information was provided by Hirokuni Beppu, Chief Editor of Tadashi Chiryō to Kusuri no Jōhō, which means literally "Information on Medicines and Rational Treatments". Tadashi Chiryō to Kusuri no Jōhō is a member of ISDB since its foundation

Several cases of retrobulbar neuritis were observed in Japan in the 1960's. Clioquinol, sold as an "anti-diarrhoeal", was found to be the cause, and an association of victims was created (1). The victims' representatives donated part of the damages paid to a non-profit organisation of pharmacists and physicians. In 1986, the organisation launched a drug bulletin, independent of the pharmaceutical industry and the Japanese government. For more than 13 years, *Tadashi Chiryō to Kusuri no Jōhō* (known outside Japan as *The Informed Prescriber*) has been informing its subscribers, Japanese physicians, and pharmacists, focusing on the adverse effects of drugs (a).

More recently, the Japanese organisation

of victims of HIV contaminated blood also gave financial support to the bulletin. Since the contaminated blood case, *Tadashi Chiryō to Kusuri no Jōhō* and consumers groups have lobbied to get a bill passed requiring more transparency on governmental decisions related to medicines.

The editors of *Tadashi Chiryō to Kusuri no Jōhō* are convinced that in order to draw the attention of physicians and pharmacists to a more rational use of medicines, the pressure must come from the consumers who must be made aware of the problem. The provision of funds by Japanese consumers groups shows that they are aware of the importance of keeping health professionals adequately informed.

One day, the idea might well prevail in all countries.

a- Except for the funds provided as mentioned by consumers organisation, the 12-page monthly publication in Japanese is exclusively financed by its subscriptions. Some articles are translations of papers published in other ISDB bulletins.

1- "Halogenated quinolines". In : Dukes MNG "Side Effects of Drugs" 13th ed. Elsevier, Amsterdam 1996 : 1078-1079.

TRAINING COURSE FOR EDITORS AT THE DTB

Drug and Therapeutics Bulletin will run a training course for bulletin editors at its offices in central London on 2-6 October. The course will consist of a series of brief talks and practical exercises. These will provide some background to our work, for example the history of *DTB* and a description of organisations that make up the environment in which *DTB* is published, such as the national health service, medicines regulatory authorities, and the pharmaceutical industry. However, most of the programme will be about how to produce articles and will

cover: the responsibilities of members of the team; deciding on the topics of articles; choosing and commissioning external authors; the consultation process; editing; verification; sources of information; and different types of evidence. Other subjects that will be covered briefly include readership surveys; relating to the media and to government; financial support and independence; the electronic format of *DTB*; and Treatment Notes (a bulletin for patients).

The course will be held during a 'press week', when the final discussions and checks take place before sending an issue

STATEMENT ON TRANSPARENCY ACCOUNTABILITY IN DRUG REGULATION

In September 1996 Health Action International and the Dag Hammarskjöld Foundation jointly convened an International Working Group to seek ways of promoting openness and accountability in drug regulation, both in developed and developing countries. The Working Group that included several ISDB members met in Uppsala, Sweden, and published a joint Statement (a). The Statement includes a General principle on Freedom of Drug Information : *'In principle information available within regulatory agencies should be freely available to any party requesting it(...). There must also be a right of appeal to an independent higher authority if the regulatory authorities refuse to disclose. The Working group further noted that:*

-Availability of information must extend not only to data reaching the agency from the outside, but also to its own deliberations, conclusions and actions.

-Data should where possible be released with some indications as to what is fact and what is hypothesis, but the release of the basic facts must not be restricted or delayed in order to add such commentary.

-The provision of information should not only be passive; agencies should actively provide and publish information in the public interest wherever possible.

a- Please contact HAI-Europe for a free copy of the Statement, which is available in Portuguese, Spanish, French and English. See also presentation of the Statement in Newsletter January 1997 page 2.

to the printer; we believe holding the course at this time will give participants a good insight into the way *DTB* works.

There are places available on the course for up to 6 people. Those attending, who must have a good working knowledge of English, will need to arrange and fund their own travel and accommodation. There will be no fee for the course. Anyone interested in attending the course should contact Andrea Tarr (at Drug and Therapeutics Bulletin, 2 Marylebone Road, London, NW1 4DF, UK; e-mail: andrea.tarr@which.co.uk; fax: + 44 207 770 7665.

DEAR FRIEND

As members of the ISDB committee, we feel that it is important for us to be familiar with ISDB member bulletins. To enable us to get to know all members, we would like you to send one issue only of your bulletin to both Margaret Ewen and Andrea Tarr. Our addresses appear at the bottom of this letter.

If you already send your bulletin to Christophe Kopp in Paris, then please continue to do this, so that Christophe can report members' activities in the ISDB Newsletter. If you do not already send a copy of each issue to Christophe, we ask that you begin to do this as soon as possible.

Thank you for your co-operation.

We look forward to receiving your bulletin.

With best wishes

Margaret Ewen

Christophe Kopp

Andrea Tarr

Please send one recent issue only of your bulletin to:

Margaret Ewen
Medsafe
PO Box 5013
Wellington
New Zealand
and

Andrea Tarr
Drug and Therapeutics Bulletin
2 Marylebone Road
London NW1 4DF
UK

Please send one copy of each issue of your bulletin to:

Christophe Kopp
La revue Prescrire
BP 459
75527 Paris
Cedex 11
France

*Thank you to all members who
have paid the membership fee
this year*

ISDB ACCOUNTS FOR 1999

Income And Expenditure, January–December 1999

Income	£sterling
Membership fees & donations	9110
WHO grant (manual)	1316
Reimbursement of travel expenses by Cito!	297
Total income	10723
Expenditure	
Co-ordinators' fee (Jan–Oct)	2767
Administration	1600
Telephone & photocopying	423
Grant for maintaining web site	500
Other expenses*	333
Coordination work on ISDB/WHO manual	1283
Bank charges	98
Exchange losses	484
Total expenditure	7488
Balance for the year	3235

*other expenses: travel expenses of ISDB advisor; fee for attending INASP seminar on fundraising.

ISDB BUDGET FOR 2000

This budget has been prepared by the executive committee and is based on activities planned so far. Activities that are expected later this year, but for which the costs are not yet known, are the production and circulation of the ISDB manual for bulletins.

ISDB DRAFT BUDGET 2000 Estimated Income during 2000

Membership fees	£9000
Total estimated income	£9000
Estimated Expenditure	
Administration	£1100
Bank charges	£100
Web site development	£2000
Coordinator feasibility study	£1200
Printing and distributing newsletter	£1500
Assistance with travel expenses for one executive committee meeting	£950
Total estimated expenditure	£6850

Share your news

Newsletters are planned well in advance, with four issues a year scheduled.

We warmly invite you think about contributions, suggestions and comments. For more information please contact Christophe Kopp:

E-mail: christophe.kopp@wanadoo.fr - Phone: +33 1 47 70 86 06 - Fax: +33 1 47 70 52 04

WELCOME TO NEW FULL MEMBERS

Drug Bulletin from Eritrea
1500 copies per issue, 4 issues a year
Distributed free
Date of foundation: 1995
Language: English
Geographical spread: national
Source of funding: Ministry of Health, Department of Pharmaceutical services, Drug Information service
Contact: Embaye Andom
P O box 212
Asmara, Eritrea
Tel: 291 1 20297
Fax: 291 1 122899
E-mail: asgm@eri.healthnet.org

Boletin AIS-COIME from Nicaragua
9000 copies per issue, 4 issues a year
Date of foundation: 1992
Language: Spanish
Distributed free
Geographical spread: national
Source of funding: PAHO, NGOs (MEMISA, Medico International..),
Contacts: Benoit Marchand, Carlos Berrios
AIS-Nicaragua
Apto 184
Matagalpa, Nicaragua
Tel: 505 6124462
Fax: 505 6122458
E-mail: aisnic@ibw.com.ni

DRUG REGULATORY PRACTICES - THE WATCHDOG

SWEDEN EVOLUTION OF DRUG REGULATORY PRACTICES

A not so common symposium, organised by the Swedish Medical Product Agency

Having a fresh look at key issues on drug assessment is a welcome initiative, even if some people are embarrassed when it's directly related to consumers. The Swedish Medical Product Agency (MPA)(a) took the opportunity of the departure of its Director General, Kjell Strandberg, to organise a symposium on the evolution of drug regulatory practices in November 1999. Around 150 people attended the meeting, mainly drug regulators from many European countries and the United States, members of most big drug companies and academics.

MPA's objective was to open a public debate on drug assessment without the participation of health professionals and consumers, but discussing fundamental questions about the needs of patients and consumers.

Among the topics there was:

- How successful are we in selecting the right dose?
- Who decides what is clinically relevant?
- Fast track approval: is it a desired procedure?
- Are we doing the right thing to achieve reliable clinical data?
- Weighing risks against benefits: can we do better?
- Will the current drug approval procedure in Europe work in the next millennium?
- How can regulatory agencies better meet expectations of health care systems?
- And particularly interesting for ISDB: Can independent information activities promote the rational use of drugs? Among other items, access to

all data (published and unpublished) was dealt with, together with the role of independent opinions. Danielle Bardelay from *la revue Prescrire* was the contributor for this topic. ISDB's view was widely expressed, including in hot discussions outside sessions!

In the context of industry merging, regulatory harmonisation and intense

direct-to-consumer advertising, we are happy that some agencies, like the Swedish one, keep their eyes open. With the help of independent sources of information these agencies could have an invaluable role in opposing the negative effects of some other agencies that dismiss their public health mission.

[This note was written by Danielle Bardelay from la revue Prescrire]

a- The MPA publishes Information from Läkemedelsverket, a full member ISDB bulletin for several years. For more details go to the MPA's web site (English version): http://www3.mpa.se/ie_engindex.html

USA FREEDOM OF INFORMATION ACT (FOIA)

Extract from a communication given by Amanda Frost at the Informed Prescriber Seminar in 2-3 October, Tokyo (Japan)

I will discuss the Federal Freedom of Information Act, or FOIA as it is called by those who use it, and the lessons learned in the United States after 33 years of experience with the law. I will focus on how FOIA has enabled the public to gain information about the safety and effectiveness of drugs and medical devices marketed in the United States.

I am an attorney for Public Citizen Litigation Group, a ten-lawyer public interest law firm co-founded by Ralph Nader and Alan Morrison in 1972. The Litigation Group is an arm of Public Citizen, a non-profit consumer advocacy organization with approximately 150,000 members. From its founding, Public Citizen Litigation Group has focused a significant portion of its efforts on fighting government secrecy.

I also serve as director of the Freedom of Information Act Clearinghouse, a project begun by Ralph Nader and housed at the Litigation Group offices. Since 1972, the

Clearinghouse has provided technical and legal assistance to individuals, public interest groups, and members of the media who seek access to information held by government agencies. Over the last 27 years, Public Citizen Litigation Group and the Freedom of Information Act Clearinghouse have sought to enhance public access to government-held information under the FOIA and other open government laws, through litigation, the dissemination of information designed to educate and assist the public in obtaining information, and congressional and administrative advocacy.

Since the adoption of FOIA in 1966, millions of Americans — including scholars, journalists, and private citizens — have made use of the law to monitor the government's activities and to hold the government accountable for its actions. By giving the public an enforceable right of access to government information, FOIA has enabled American citizens to be informed of the government's actions and to participate more effectively in the public debate that is vital to a strong and vibrant democracy. No nation that shields the workings of its government from the governed can rightly call itself a democracy. ►►

FOIA and the FDA

FOIA has been particularly instrumental in helping the public obtain information about unsafe and ineffective drugs. Thanks to FOIA, doctors, patients, journalists, and watchdog organizations that wish to learn more about a drug that has been approved for market in the United States have numerous sources of information about that drug. Public Citizen Health Research Group, which is an arm of Public Citizen devoted to monitoring the safety of drugs and medical devices, has used FOIA with great frequency and success to obtain information it needs.

The first place to look for information on an approved drug is the Food and Drug Administration's (FDA) web site. In 1996, Congress amended FOIA to provide for greater access to government information via the internet. The amendments, which are known as the Electronic FOIA Amendments, or referred to as E-FOIA for short, require that agencies post on their web site all records that have been requested under FOIA in the past, and that have been, or are likely to be, subject to additional FOIA requests. As a result, the most popular and frequently requested records will be available to the public without the need to submit a FOIA request. For example, because members of the public frequently request information about popular drugs such as Viagra and Prozac, the FDA posts the drug approval packages for those drugs on its web site, where they are available to anyone with access to the internet.

Also beneficial is the provision in the Electronic FOIA Amendments that requires agencies to post indexes on their web sites that identify and describe the records possessed by the agency. FOIA requesters can use these indexes to determine which of the records in the agency's possession are likely to contain the answers to their questions. The indexes streamline the process of requesting documents: They allow members of the public to target their requests for documents containing the information they seek, and reduce the time agencies waste searching for and copying unresponsive records.

Unfortunately, not all agencies have complied with the Electronic FOIA Amendments as willingly as FDA. Public Citizen has filed a lawsuit against seven government agencies — among them the Departments of

Justice, State, and Education — charging them with violating the indexing requirement in E-FOIA. (Public Citizen v. Lew, No. 97-2891 (D.D.C. 1997)

Although FDA's web site is a useful source of information about drugs approved for market, it is incomplete. Significant amounts of information in New Drug Applications and in FDA reviews of new drugs are either redacted from the material on FDA's web site, or are not posted on the web site at all. For example although the FDA posted the graphs concerning testing of sildenafil (Viagra) on its web site, it has redacted the results of the clinical tests on the drug. Public Citizen Health Research Group is concerned that Viagra may cause adverse reactions in some users, and it is seeking the results of these tests under FOIA.

If information is not on the FDA's web site, it is necessary to submit a FOIA request to the agency. The FOIA request must specifically identify the material sought. The FDA then has 20 business days to respond to the request. If the FDA fails to respond, the requester can file suit. If, instead, the FDA denies the request, the requester must appeal the denial, and wait another 20 business days, before he or she can file suit. This process ensures that the agency has had an opportunity to consider whether to grant or deny the request before the courts become involved.

If the FDA denies a request for information about a drug — for example, the information about Viagra that was redacted — the usual ground is that the information qualifies for the fourth Exemption to FOIA, which bars public access to "trade secrets and confidential commercial information." "Trade secret" is narrowly defined as "a secret, commercially valuable plan, formula, process, or device" that is used to make a trade commodity and that is "the product of either innovation or substantial effort." (Public Citizen Health Research Group v. FDA, 704 F.2d 1280, 1288 (D.C. Cir. 1983)) "Confidential commercial information" is defined as information that, if disclosed "is likely to cause substantial competitive harm" to the submitter of the information. (National Parks & Conservation Ass'n v. Morton, 498 F.2d 765 (D.C. Cir. 1974)). In determining whether any of the requested information qualifies for Exemption 4, the FDA will ask the drug sponsor if the release of information that the sponsor submitted to

the FDA in its New Drug Application would cause it substantial competitive harm. Not surprisingly, drug sponsors usually argue that a large amount of information in the New Drug Application constitutes "confidential commercial information" that cannot be disclosed. If the FOIA requester files a lawsuit against the FDA in an attempt to obtain the information, the drug company will almost always intervene to argue against disclosure. Indeed, if the drug company does not intervene and litigate the case on its own behalf, the FDA will deem the Exemption 4 claim waived by the drug sponsor, and will disclose the requested information.

Although it is clear that "trade secret" covers no more than a drug's formula, there is still much disagreement over what constitutes "confidential commercial information." Drug companies and the FDA claim that a great deal of information in New Drug Applications, including safety and efficacy data, qualifies as "confidential commercial information." Public Citizen strongly disagrees, and has litigated a number of cases arguing that data relating to a drug's safety and efficacy does not qualify for withholding under Exemption 4.

An example is a case decided a few years ago, in which Public Citizen sought the clinical protocols used to test the drug metformin, which the FDA and Bristol-Myers Squibb (the drug's manufacturer) both claimed were nondisclosable as confidential commercial information. They argued that, if disclosed, the protocols could be used by Bristol-Myers Squibb's competitors to develop their own drugs. Public Citizen disputed that assertion, pointing out that the protocols were not at all unique or unusual, and thus would not benefit a competitor, and the court eventually agreed with us.

FOIA creates a presumption in favor of disclosure. Thus, the burden is on the FDA and the drug manufacturer to justify withholding information under an exemption to FOIA. The FDA and the drug sponsor cannot rely on generalized and conclusory allegations of competitive harm; they must be specific when explaining why they think disclosure of the information will put them at a competitive disadvantage. The FDA and drug sponsors usually provide affidavits from employees who give further explanation for withholdings. In the vast majority of these cases, the agency or drug sponsor must prepare a Vaughn index, which provides a

summary of the information withheld and the government's rationale for nondisclosure

Although FOIA itself does not require each agency or interested party to prepare such an index, agencies have been required to produce such indexes ever since 1974, when Public Citizen argued for, and won the right to, such an index, in the case Vaughn v. Rosen. Without these indexes describing the information withheld and the reasons for withholding, it would be very difficult for litigants to contest an agency's reliance on a FOIA exemption, or judges to determine if withholdings were justified.

FOIA requesters such as Public Citizen Health Research group then have an opportunity to contest the drug manufacturers' claim that it will suffer harm from disclosure

Courts often have difficulty deciding Exemption 4 cases, because they do not have the scientific background to determine whether disclosure would harm the competitive position of the drug's sponsor. Some judges rely on independent experts to help them make the determination. In such cases, the judge will ask the FOIA requester and the drug manufacturer to choose an expert that is acceptable to both sides, and then have the expert prepare a report for the judge explaining why disclosure is, or is not, likely to cause the drug sponsor substantial competitive harm. Public Citizen has been involved in one such case, which I briefly described above, where the drug company Bristol-Myers Squibb claimed that it would suffer harm from release of a clinical protocol used in testing the drug metformin. The expert approved by both Public Citizen and Bristol-Myers Squibb concluded that release of the information would not harm the competitive position of Bristol-Myers Squibb. As a result, the judge ordered that the information be disclosed.

One of the major benefits of FOIA is that it requires agencies to release all information that does not qualify for an exemption. Therefore, even if some information in a New Drug Application qualifies for an exemption from FOIA, the rest must be disclosed. As I have already explained, the agency cannot simply assert an exemption to avoid disclosing many pages of information. Instead, it must submit a Vaughn index that explains each deletion. Often, agencies make the mistake of redacting non-exempt information that is in the same document as exempt information. If a judge feels that an agency

has failed to segregate and disclose non-exempt information, the judge will order the agency review the documents and release the improperly withheld information. These segregability determinations are a vital aspect of FOIA, since they allow a great deal of useful information to be released even when it is intertwined with exempt information.

Access to information before drug approval

Public Citizen Health Research Group seek access to information about drugs before they are approved, so that they can lobby against approval if they think that a particular drug is unsafe or ineffective. The Health Research Group is also interested in obtaining information about the safety of drugs that are in clinical trials to ensure that FDA is protecting the human trial participants on whom the drug is being tested.

Obtaining information about drugs that have not yet been approved by the FDA is difficult, even under the broad, pro-access provisions of FOIA, because the FDA has promulgated regulations denying public access to information in New Drug Applications prior to a drug's approval. Indeed, FDA regulations requires that the very fact that a New Drug Application has been filed be kept a secret. However, the FDA's regulations conflict with FOIA, which mandates disclosure unless information qualifies for one of FOIA's nine narrow exemptions. In theory, agency regulations are trumped by a conflicting statute, so FDA's regulations denying access must give way to FOIA. Nonetheless, it is difficult to obtain information about a yet-to-be-approved drug from the FDA when its official policy is to keep all the information about that drug secret.

Public Citizen has recently made great strides in gaining access to information about drugs pending FDA approval. In January 1999, Public Citizen brought suit against the FDA under the Federal Advisory Committee Act, or FACA as it is called for short. Under FACA, FDA holds advisory committee meetings, in which a panel of independent medical experts evaluate the safety and efficacy of a proposed new drug, and then recommend whether or not the drug should be approved. These meetings are open to the public, and the public is given an opportuni-

ty to participate in the discussion. Members of advisory committees are provided selections from the New Drug Application submitted by the sponsor and from the FDA's evaluation and review of the drug — information which assists the panel in discussing the safety and efficacy of the drug and in making their determination whether to recommend the drug be approved for market. Although FACA requires that materials provided to advisory committee members also be given to the public, the FDA's practice had been to deny public access to advisory committee materials. After we filed suit, the FDA agreed to provide to the public the materials given to advisory committee members at or before the meeting. Although this agreement will not go into effect until January 2000, we expect that the newly available information will prove to be enormously beneficial to all individuals who wish to participate in advisory committee meetings.

Improving Government performance and holding the Government Accountable

FOIA is valuable not just as a tool for gaining access to information, but also as a means of shedding light on the activities of the government. Greater openness enhances public understanding of the Government's actions and also makes it possible for the government to respond to criticism and justify those actions. It makes free exchanges of scientific information possible and encourages discoveries that foster economic growth. In addition, by allowing for a fuller understanding of the past, it provides opportunities to learn lessons from what has gone before — making it easier to resolve issues concerning the Government's past actions and helping prepare for the future. Most importantly, FOIA serves to hold the government accountable to the public that it serves.

In the United States, administrative agencies oversee an ever-increasing number of laws, and they promulgate regulations that effect every area of public life. Unlike Congress and the President, agency officials are not elected by the public. As a result, agencies can sometimes lose sight of the public interest, particularly when the entities they regulate have gained influence over agency policymakers. FOIA serves ►►

► the important purpose of ensuring that agencies remain accountable to the public

Public Citizen Health Research Group has often used FOIA as a means of monitoring the FDA's activities. For instance, in 1993, the Health Research Group became alarmed with FDA's monitoring of pre-clinical and clinical studies after a number of individuals who took the drug fliafluridine as part of a clinical trial developed irreversible liver damage, resulting in five deaths. This tragedy inspired Public Citizen Health Research Group to review the FDA's methods of ensuring the safety of drug trial participants. The Health Research Group discovered that a drug need only be tested on animals for 2 weeks before the FDA will give its approval to have the drug tested on human volunteers. Public Citizen then submitted a FOIA request asking for all safety and efficacy information concerning drugs that were tested on humans but were later abandoned for health and safety concerns. Using the information gained from this FOIA request, Public Citizen has successfully lobbied for greater FDA oversight of clinical testing.

FOIA's weaknesses

At the same time that FOIA has been an overall success in expanding public access to government information, the Act has certain weaknesses. First and foremost is the problem of delays. Under FOIA, agencies are required to respond to requests within 20 business days. Unfortunately, these limits are more often honored in the breach. However, the E-FOIA amendments provide that, if the requester shows a compelling need for the information, such as to protect human life, the agency should expedite the disclosure process.

A second problem area — and one not addressed by Congress in the 1996 amendments — is that agencies have used broad or vague terms in an exemption to expand secrecy beyond the purpose the exemption is meant to serve. Unfortunately, at times, the courts have upheld the government's broad interpretations and withholding decisions. For example, a significant loss for our office and for those who support broad access to government information was the Critical Mass Energy Project v. NRC decision in 1992. In Critical Mass, we sought access to analytical safety reports about nuclear power

plants submitted to the Nuclear Regulatory Commission (NRC) by a non-profit organization created by the nuclear industry after the accident at Three Mile Island. Although the reports were circulated widely within the industry, they were not available to the public, and the industry argued that the reports constituted "confidential commercial information" that qualified for Exemption 4 of FOIA.

In Critical Mass, the court distinguished between information that is voluntarily submitted to the government and information that must be submitted to the government either because of regulatory requirements or as a condition for a government benefit. If submission of information is mandatory, that information will be disclosed to the public unless the disclosure would cause substantial competitive harm to the company. However, Critical Mass allows the government to withhold information that was voluntarily submitted so long as the submitter can show that it does not customarily release the information to the public. In practice, this allows a company that submits information voluntarily to prevent any of its information from being disclosed to the public. After all, a company is not likely to customarily release information that reflects badly on its products or that is embarrassing, even if the release would not cause it competitive harm.

Or organization often uses the FOIA to seek safety and effectiveness data submitted to the FDA for drugs and medical devices. This data is required to be submitted under our country's extensive regulatory reporting scheme, and so falls outside of the Critical Mass decision and may be released unless the company shows substantial competitive harm. Thus, the harmful impacts of Critical Mass on public access are somewhat minimized by virtue of the significant reporting requirements established by Congress and by the regulations of our nation's health and safety agencies. The Critical Mass standard would be much more dangerous in a society with a less-developed regulatory structure.

Another problem with FOIA has been the tendency by agencies to drag their feet and avoid complying with FOIA's mandate. The FDA has not always made it as easy as it should be to gain information about drugs and medical devices. For one, when it comes to FOIA, the FDA tends to follow the lead of the companies it regulates. If a company that submitted a new drug application

or a medical device application believes the information qualifies for FOIA Exemption 4, the FDA will almost always support the drug sponsors position by submitting briefs arguing that the information should be withheld, even though the company itself has intervened and is defending against disclosure as well. FOIA certainly does not require FDA to take the drug companies' side in these disputes, and the FDA is free to take at least a neutral stance and simply let the drug company litigate the case against disclosure. Although judges are not supposed to defer to the FDA in FOIA cases, the agency's participation often influences the judge to find that the information is nondisclosable. This is particularly true in Exemption 4 cases, when judges sometimes feel that they do not have the necessary familiarity with the drug testing and approval process to determine whether disclosure is likely to cause substantial competitive harm. As previously discussed, some judges are beginning to rely on the advice of independent experts to help make the Exemption 4 determination. Public Citizen Health Research Group supports this practice, since it serves to ensure that the public gets the information it needs without jeopardizing the financial health of drug manufacturers.

Conclusion

The Freedom of Information Act has revolutionized public access to information in the United States. At the same time, however, more must be done in our country to improve the FOIA process, make government records more accessible to the public, and to reduce government secrecy.

THE PRO-PLACEBO-CONTROLLED TRIAL IDEOLOGY

The Public Citizen health Research Group, ISDB member through its bulletin 'Worst Pills Best Pills, reacted strongly to a tendency among the leading drug regulatory agencies to favour placebo-controlled trial instead of active-controlled trials. La revue Prescrire expressed similar concerns in an editorial, taking the case of entacapone

We present an extract of Public Citizen's comments dated December 23, 1999, the full version is available on: <http://www.citizen.org/hrg/PUBLICATIONS/1503.htm>.

The Draft Guidance on Choice of Control Group in Clinical Trials, prepared as part of the International Conference on Harmonisation (ICH), is a clear attempt by the Food and Drug Administration (FDA) to spread its pro-placebo-controlled trial ideology globally. This proselytizing intent was made clear at an FDA meeting on the use of placebos in clinical trials in which we participated in April of this year. Dr. Robert Temple, Director of the FDA's Office of Medical Policy, stated at the meeting, "And people do active control trials in Europe all the time. Europe is finally getting the idea that they need to add a placebo group to make them informative." This sometimes unethical ideology has been laid out in a series of publications by an FDA employee and would take on added force if this poorly thought-out Guidance were finalized and adopted by other ICH countries.

The zeal to expand the use of placebos in clinical trials has resulted in a document that is so unbalanced that its credibility is undermined. The structure of the document reflects that bias:

* An entire section (section 1.5) is devoted to attacking active-controlled trials; there is nothing similar for any of the other study designs, even clearly weaker designs such as historical controls.

* This section attacking active-controlled trials actually precedes the detailed descriptions of the types of controls, so the reader is poisoned against active-controlled trials before he or she even learns fully about them.

* The purported weaknesses of active-controlled trials are mentioned repeatedly, leading to an extremely redundant and tedious document.

* Ethical considerations are treated as subordinate to supposed data collection needs; ethics does not even appear in the critical Table 1, which describes the attributes of the different trial designs. The question confronting researchers is not and should not be: "How do I get the most easily interpreted data?" It is: "Given the available study designs, which one will provide the most useful data while maximizing the protection of patients?" When ethical concerns are quite literally out of the picture, researchers will be led to the first question instead. The Draft Guidance is a transparent attempt to legitimize evasions of the clear requirements of the Declaration of Helsinki, which requires that, "In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists."

In addition to its attempts to water down the existing ethical codes, the document places undue emphasis on the supposed needs of regulators and pharmaceutical companies (who together make up the ICH) and places these above the needs of patients or physicians. Most patients and physicians have little need for information addressing whether a new drug for a disease for which there already is an effective therapy is better than nothing; they would like to know whether the new drug is better than the existing drug. But the proposed Guidance would drive clinical trials in the opposite direction. While this may make things easier for regulatory bodies, which can approve drugs simply on the basis of superiority to placebo, and to the pharmaceutical industry, which can more easily prove a new drug superior to placebo than approximately equivalent to a known effective treatment, patients will often not receive optimal medical treatment during the trial.

The remainder of our comments address

particularly problematic aspects of the Draft Guidance.

Peter Lurie, MD, MPH

Deputy Director

Public Citizen's Health Research group

Curt Furberg, MD, PhD

Professor

Wake Forest University School of Medicine

The lowest common denominator

Entacapone was approved in 1999 for use in Parkinson's disease by the European medicines agency on the basis of placebo-controlled trials only. *La revue Prescrire* n°197 and *Prescrire International* n°44 reserved its judgement on the value of the drug, pending comparative data. The editorial below put the finger on the problem.

Our systematic scrutiny of clinical files on new drug products released onto the French market over the last decade reveals an alarming deterioration. New products are increasingly authorised on the basis of placebo-controlled trials alone; i.e. without comparative trials versus reference. Entacapone is a good example (see *Prescrire International* n°44).

It is as if medicines agencies now only demand proof of minimal efficacy and no major adverse effects, leaving commercial competition to decide which drug is actually adopted by prescribers. If so, these agencies are neglecting a major element in their public health remit.

Under current French legislation new drugs cannot be authorised unless their benefit is sufficiently 'justified'. Theoretically, this means that efficacy must be at least equivalent to that of existing products in the relevant indication. Or that lesser efficacy is offset by fewer or less severe adverse effects (difficult to show until the drug has been in widespread use for some time); or that compliance is improved; or that the new drug is a clear second-line alternative for patients in whom the reference drug fails or cannot be used. Indeed reference treatments, sometimes non drug therapies, are available for most conditions.

Understandably placebo-controlled trials are far less costly than trials versus reference treatments: a statistically significant difference will emerge in a smaller study population. But it might be considered unethical to give some study patients a placebo when a reference treatment is available. In addition, how ►►

► can a prescriber know which of several drugs will be safest and most effective for a given patient if no comparative data are available.

Why do medicines agencies, particularly those in Europe, grant marketing authorisation for drugs that have not been compared with reference treatments? Who were these agencies created to serve: the public, or profiteering drug companies?

INRUD NEWS NOW AVAILABLE ON THE INTERNET

The International Network for Rational Use of Drugs (INRUD) is pleased to announce that INRUD News is now available on the Web. INRUD News is published twice a year, and over 3,000 copies are distributed free worldwide. Contents include updates on INRUD global activities, country and support group reports, reports on meetings and workshops, research briefs, samples of E-Drug communications, and references to articles on rational drug use. You can subscribe to INRUD News and read current and past issues by clicking on the newsletter icon at the following Web site address: <http://www.msh.org/inrud>.

INRUD News is produced with support from the Danish International Development Agency (DANIDA). We thank the Communications and Public Information office, the Drug Management Program, and the Information Technology office at Management Sciences for Health for the development and maintenance of the Web site. We welcome comments, suggestions, and particularly summaries of rational drug use intervention research and projects.

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CONFLICTS OF INTEREST

Relations between health professionals and drug companies or manufacturers of medical devices can be hazardous. An international debate has developed in recent years in an attempt to limit or, at the very least, elicit conflicts of interest. Here we reprint an article taken from la Revue Prescrire March 2000.

Your comments are welcome for publication in this section. We would like to publish any document on this issue regarding your bulletin's policy.

We can all find ourselves torn between divergent interests, and thus have to deal with what is known as a "conflict of interest". In the biomedical field, the notion of conflict of interest usually refers to links (especially financial links) that authors of scientific articles and experts in scientific commissions have with the health industry in general and drug companies in particular.

The notion of conflict of interest became a major issue in the 1980s (1). Many books and articles in international biomedical journals refer to a definition published in 1993: "A set of conditions meaning that a professional judgment on a principal interest may be inappropriately influenced by a second interest" (2).

Over the years, increasing numbers of studies have shown that authors' conclusions can be influenced by their links with manufacturers (3,4). More and more editorials have been published demanding that conflicts of interest be restricted or at least divulged (5-7).

Publication of conflicts of interest has become a widespread practice, at least in international journals. These journals follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals that now serve as the basis for journals' instructions to authors (8).

According to these requirements, researchers should avoid finding themselves in a position where they cannot alone decide whether or not to publish their results (i.e. they need to obtain approval from the study sponsor). When they submit a manuscript to a journal, authors should divulge their conflicts of interest and any financial support

they received in relation to that manuscript and the work it reports. Members of journals involved in the selection of published articles, i.e. editors and reviewers, should also divulge their own conflicts of interest and refrain from making decisions that may be influenced by such conflicts. Each article and letter published in journals should include a description of all financial support and any conflict of interest of which the journal editor considers readers should be aware (9).

The rule that conflicts of interest should be divulged does not solve all problems. It has been shown for example that, even in large international biomedical journals, articles have been published without all the authors being named; their conflicts of interest are, by definition, unknown. They are generally authors linked to industry ("ghost authors", often paid by industry) (10).

The interpretation of the Uniform Requirements varies according to the journal. The *Lancet* considers, for example, that readers do not systematically have to be informed of conflicts of interest but that the editors are free to publish them according to whether they are considered to be important or not (11).

The *Lancet's* position is a good example of the debate in the biomedical field over conflicts of interest and how to handle them. The main question is the interpretation of a conflict of interest. Is the opinion of an author with a conflict of interest necessarily biased? Can a research clinician avoid dealing with the industry? Are financial links the only important ties? Indeed, what of academic bonds (career advancement, prestige), politics, friendship, which can have the same consequences as financial links but are more difficult to unearth (12,13)? Many commentators consider that conflicts of interest are common, normal and difficult to interpret.

This debate has led to proposed changes in terminology: it has been suggested that the classical term "conflict of interest" be replaced by "dual commitment" (11). The *British Medical Journal* has opted for the expression "competing interest". When no conflict of interest is declared, it is suggested that the author should write "none stated" rather than "none". It is then up to the reader to guess the

possible implications of such a statement.

Members of the French medicines agency and the national health accreditation and assessment agency are now obliged to divulge their conflicts of interest. The medicines agency has published conflicts of interest in its yearly report since 1995 (14-16). In its 1998 report on the French social security system, the *Cour des Comptes* (audit body) stated that the number of conflicts of interest among members of the drug licensing commission raised questions about their independence and neutrality, especially as they were allowed to be present during the examination of drugs from firms with which they had a conflict of interest (17).

Since February 1999, the US Food and Drug Administration (FDA) has demanded that drug companies submitting market authorisation files specify whether the investigators in the trials quoted have any financial interests in the company concerned. The financial links targeted include shares, patents, and money (exceeding \$25 000) in the form of research credits, gifts, equipment or fees (18). This also applies to the investigator's spouse and children (19).

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PRESCRIRE'S POSITION

All health care systems are based on a "balance of forces" between four groups with partly differing and potentially conflicting interests, namely patients, health professionals, regulatory authorities and health care providers, and manufacturers (see column page 1). It is healthy that each group should state its viewpoint or interests openly and independently. Information can only be interpreted correctly when the source is known. The existence of a conflict of interest can scramble the message.

As a rule, situations giving rise to conflicts of interest should be avoided. The situation at the French medicines agency, where many experts have links with manufacturers, is unsatisfactory. It is unacceptable that experts with links to a drug company should participate in decisions concerning the products of that company (or those of a direct competitor).

As regards links between research clinicians and manufacturers, the financial dependence of the former on the latter is a source for concern. It means that many lines of research are not followed, simply because manufacturers see so financial interest. This is often deplored by research clinicians, who criticise the lack of public funds available.

When researchers work with manufacturers, they should only accept contracts that leave their hands untied (no permission required to publish the results, no promotional activities in return for publication, etc.).

Many people who find themselves with conflicts of interest consider they are "making the best of the situation" and would be insulted if one challenged their intellectual independence. However, this question cannot be solved only by trusting the good faith of the persons concerned. In the name of probity they should not hide links creating conflicts of interest.

The FDA's stance is welcome and should

be adopted by all drug agencies. Yet even the FDA's position is incomplete. Possession of patents or shares by investigators, for example, clearly poses a problem, because it can undermine confidence in their scientific judgment.

The medical-pharmaceutical community is not taking the clarification of links between investigators and the industry seriously enough. The financial world is less naive. In the stock markets, when investigators use information known only to them to make a quick profit (share purchase or sale based on unpublished results of a clinical trial, for example), they are committing illegal "insider trading" (1).

The conflict of interest concept is useful when examining situations involving health professionals. Doctors and pharmacists, in particular, are confronted daily with the need to strike a balance between their own interests and those of their patients/clients. Interpreting this balance in terms of conflicts of interest can be enlightening.

As regards clinical trials, patients need to be legally protected, especially from conflicting interest among doctors acting as investigators.

Health professionals with financial links to the industrial sector are sometimes approached by *Prescrire*. This is especially the case during the manuscript review process, when the aim is to obtain criticisms and arguments from the broadest possible range of health professionals. These persons are asked for their opinion but have no decision-making role, none of the members of the editorial board have any financial links with manufacturers: they would be ineligible if this were the case.

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BENEFIT AND RISK HAVE DIFFERENT DIMENSIONS

Andrew Herxheimer, former Chairman of ISDB and now adviser, posted a summary of the following message to members of the World Association of Medical Editors

Many papers aim to assess the value of an intervention. That involves estimating its positive and its negative outcomes, which we can call benefits and harms. Each of these embraces two concepts that need to be clearly distinguished: probability and magnitude. We want to know both. Unfortunately the terms that are often used, like 'risk-benefit assessment', 'risk-benefit ratio', 'benefit/risk evaluation', tend to muddle these quite separate aspects. It is often politically convenient to muddle them - e.g. the risks of nuclear power have been traditionally described as minuscule. This may accurately reflect the probability of a nuclear reactor going out of control, but fails completely to reflect the magnitude of the harm that might result if something did go wrong. Time is also important: someone might accept an operation with a long-term risk for an immediate benefit, and refuse the operation if the same risk were immediate. Economists seem to consider this dimension more regularly than do doctors.

'Risk' is a word that refers to the probability of an adverse event, but we don't have a word for 'probability of benefit'. We will be clearer if we stop using expressions like 'risk-benefit' or 'benefit/risk', and instead use 'benefit/ harm' (and contrast the likelihood or chance of benefit with the risk of harm). The idea of a ratio is especially wrong, because very often, the benefit and the risk are not of the same nature, and no one can really "weight" them. One can ask populations about how many days, weeks or years of their life they would exchange to get rid of this or that handicap, but such comparisons are very fragile, and such enquiries quite rare. So we are left with comparing a benefit that is making love with no fear of getting pregnant (tomorrow) with a risk that is venous thrombosis or myocardial infarc-

tion (15 to 25 years in the future). Doctors should not take such decisions unless the case is very clear: it is the population or the individual patient who should decide for itself or for him (her) self.

The idea of risk-benefit ratios can only be useful in comparing different options with the same global (qualitative) kind of benefits and burden of risk. Even then it is better to separate explicitly the dimensions of magnitude and probability. For these reasons I appeal to members of WAME to banish all expressions that link benefit and risk from their journals.

Controlled trials are much better at assessing benefits than at estimating harms because they are designed to measure specified benefits, while harmful effects are mostly unexpected and noted only incidentally and unsystematically. This asymmetry is inherent in reports of trials and in systematic reviews of trials, and leads to a bias that has been insufficiently recognised.

We need to consider it explicitly, and to do our best to minimise it, as with other biases. That is another task for medical editors.

I would be glad to have your opinions on this problem.

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The World Association of Medical Editors (WAME, pronounced "whammy!") is a voluntary association of editors from many countries who seek to foster international cooperation among editors of peer-reviewed medical journals. Membership is free and open to all editors of such journals.

Medical journal editors have an important responsibility to ensure that reports of medical research provide valid information in a form that is readily accessible by the researchers, medical practitioners and others who need it. WAME exists to help medical edi-

tors fulfil this responsibility by providing educational resources and a forum for discussion of issues in research publication. In particular, WAME aims to help editors in developing countries and editors of small journals, who often face special obstacles such as lack of formal training in editing, limited finance, and limited access to publication expertise.

WAME relies mainly on the Internet to disseminate information and broaden communication between members. Its web address is www.wame.org.

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If you have not yet paid your membership fee for 2000, please pay as soon as possible. ISDB's activities depend on your contribution.

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The ISDB Newsletter is sent free of charge to ISDB members and corresponding members.