

Column

Campaigning for access to data

When comparing benefits and harm of drugs available for the same indications, drug bulletins help health professionals and the public to make evidence-based choices. ISDB decided at the Melbourne GA that it should help bulletins access data needed for such comparisons (see December Newsletter on page 2).

For obvious commercial reasons, pharmaceuticals companies won't make negative studies or pharmacovigilance reports publicly available if they are not obliged to.

It should be the role of public authorities or regulatory authorities (when they exist) to organize access to such data, but many of them, all over the world, keep data secret, probably to please pharmaceutical companies i.e. their main fee providers.

Drug bulletins need legislative tools to obtain information collected by "non cooperative" authorities.

The law should of course put patients interest first, before commercial interests. Commercial interests are strongly defended by pharma lobbyists when such where such laws are revised

or in the making. ISDB bulletins should therefore "counterattack": participate in the drafting process, make amendments, and then see to it that the laws are implemented, especially public health-oriented provisions.

ISDB actions can take various guises:

- Internationally, an ISDB survey on transparency is being prepared, with creation of a transparency indicator that will expose access problems and achievements among countries;
- Regionally such as in the EU, individual bulletins or coordinated groups of bulletins can lobby their collective institutions (see "Ask your regulator" on page 10);
- Nationally, member bulletins can call for help and support from ISDB when a pharma law is drafted (see "An example of ISDB collaboration" on page 12).

Laws are not dull pieces of paper, but effective tools that have tremendous impact on day-to-day work of drug bulletins.

Transparency campaigning is a long-term battle. Let's be persistent and join forces: campaigning for more transparency means more access to data!

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Warning!
The pages 2 to 4 (minutes of the Committee) are in the full newsletter only (area of the website restricted to members).

ABOUT THE NEWSLETTER

**Improvement:
Web links and illustrations**

You can directly click on links to reach your destination on the web, which should make the ISDB Newsletter more user friendly.

You will also find more illustrations from several bulletins. They are not used as text illustration, but to show the variety of design among ISDB bulletins and to make the Newsletter more lively.

**What's the ISDB
Newsletter for ?**

ISDB Newsletters must be a stimulating media; a way to boost collaboration among members.

A stimulating media. The ISDB network is disseminated around the world, ISDB Newsletter should be a link between us, where we expose and share our actions, or the problems we face (see Conflict of interests page 15 an example of worldwide tendency in health care). Sharing our good editorial practices, our good sources is also the role of Newsletters.

According to Constitution Rule III: "An official publication (Newsletter) of ISDB, issued at least 3 times a year, and a Website are the responsibility of the Committee of the Society. The Committee will serve as editorial board of both. The Newsletter will report events important for the Society, news from the various member bulletins, interesting articles, activities of ISDB, reports of the Committee. Both the Newsletter and the Website will serve as a way of communication between the members and the Committee as well as a way of transmitting important events which happened in and outside ISDB". And in Article 5.4 about decision making by the Committee: "The minutes shall be recorded and published in the Newsletter".

From now on full ISDB Newsletters are restricted to members. So far ISDB newsletters have been freely accessible, which means sensitive information such as finance data or campaigning activities cannot be kept secret or must be deleted before posting on

website.

If we want a Newsletter that provides meet on the bone, political debates on transparency issues, uncensored exchanges of opinions on ISDB strategy towards drug companies or regulators, we need to restrict full Newsletters to membership only. That is why, full ISDB Newsletters are from now on in "members only" section.

The Newsletters without the minutes and other sensitive information such as campaigning activities can be found in What's New section of ISDB website.

Some bulletins are missing in ISDB library

**Please, Don't forget to
send each issue of your Bulletin to
the ISDB library!**

**(either by post or by email if you make
an electronic edition)**

**The library is located at the ISDB
Secretariat:**

Post address:
**la revue Prescrire
DOCUMENTATION
83 boulevard Voltaire
75558 PARIS CEDEX 11
France**

Email addresses:
**docuserv@easynet.fr
with copy to
christophe.kopp@wanadoo.fr**

Thanks !

MEMBERSHIP FEES 2006

Call for subscription

Dear members,

Your membership fee for 2006 is due. The account is based with the new treasurer in a Euro country. The Committee has decided to convert the fees from British Pounds into Euro to prevent double currency conversions.

There are three categories of membership to ensure that there is no financial barrier to membership of the society.

We suggest contributions depending on the member's overall budget. This is not definitive but serves as a guide only. Financial constraints are not a bar to membership of ISDB.

Members who cannot afford to pay even the lowest rate of 45 Euro can apply for exemption.

- 45** Euros Developing countries
- 225** Euros Bulletins with budget of under 20,000 Euros
- 900** Euros Bulletins with budget of 20,000 Euros and more

Payments should be directed to:

Int. Society of Drug Bulletins
Bank: Sparkasse Bielefeld, Germany
Account No.: 124 156
IBAN: DE43 4805 0161 0000 1241 56
SWIFT-BIC: SPBIDE3BXXX

If you have any questions related to your membership fee or want to apply for an exemption please contact me.

Jörg Schaaber
ISDB treasurer
pharma-brief@bukopharma.de

**Precision and correction
December 2005 Newsletter**

Details about Boletín Fármacos in December Newsletter were somewhat inaccurate. Martín Cañas is pharmacology advisor and associate editor, the chiefs editors being Núria Homedes and Antonio Ugalde. The aim of this electronic bulletin is to promote the appropriate use of medicines in Spanish speaking countries, not only Argentina. And the initiative came from the USA.

<http://www.boletinfarmacos.org/>

MEMBERSHIP APPLICATIONS

-The Committee failed to reach the requested majority to grant full membership to Drug Information Bulletin from Nepal, who therefore remains associate member. The Committee proposed its help to improve the quality of the bulletin so that it can distinguish what is established from what is not. An effective way could be a training in a well established bulletin in an English speaking country.

-Medex from Moldova, also an associate member for many years, has applied for full membership. The Committee is examining the application.

ISDB SURVEY

Evaluation of medical devices

Results of a survey among ISDB members

The number of medical devices is growing and sometimes the boundaries between drug and medical device is not that clear cut (e.g. drug-coated devices). Regulation (a) and evaluation are generally much less stringent than for drugs, and this places patients at a higher risk of serious adverse effects, which are only discovered once a product has already been on the market for some time.

Although medical devices are mainly used in the hospital setting, community healthcare professionals may also encounter such patients and must therefore be informed. Some countries such as the UK, ensure that safety warnings about medical devices are not restricted to hospital physicians (1). For instance in 2001 GPs were sent warnings on failure of zirconia ceramic femoral heads and diathermy devices (2).

So there may be room for ISDB members to provide independent information on medical devices. ISDB members were asked through the ISDB electronic forum whether they evaluate medical devices regularly or occasionally, or report on safety problems with medical devices; see

<http://it.groups.yahoo.com/group/isdbweb/> dated January 30 and beyond for details.

Results. A majority of Bulletins do not publish regularly on medical devices, but many express concerns about medical devices and publish papers occasionally, mainly on safety issues: *Informazioni sui farmaci, arznei-telegramm, la revue Prescrire, Kusuri-no-check, Pharma-kritik, Australian Prescriber, Drug and Therapeutics Bulletin, Public Citizen's Health Research Group, Arzneimittelbrief, Pharma Israel Drug Bulletin, La Lettre du CEDIM.*

Many thanks to those of you who responded to the survey: Rose de Groot, Walter Thimme, Sidney Wolfe, Andrea Tarr, John Dowden, Ciprian Jauca, Rokuro Hama, Hirokuni Beppu, Jules Desmeules, Blanka Pospisilova, Dick Bijl, Etzel Gysling, Danielle Bardelay, Wolfgang Becker-Brüser, Daniela Zanfi, Anita Conforti, Carlos Fuentes, Nuria Homedes, Philip Sax, Clotaire Nanga, Lennart Philipson.

Follow-up. We'll continue the survey with a another question about the principal sources of information on medical devices.

a- *In December 2005 the EU Commission launched a revision to the medical device Directive. Following public consultation the draft Directive was forwarded to the European Parliament and Council for co-decision; see http://europa.eu.int/comm/enterprise/medical_devices/revision_mdd_en.htm Note that an ICH-like organization, the Global Harmonization Task Force (GHTF), has been set up since 1992 "in an effort to respond to the growing need for international harmonization in the regulation of medical devices". "The Global Harmonization Task Force (GHTF) is a voluntary group of representatives from national medical device regulatory authorities and the regulated industry. Since its inception, the GHTF has been comprised of representatives from five founding members grouped into three geographical areas: Europe, Asia-Pacific and North America, each of which actively regulates medical devices using their own unique regulatory framework." See <http://www.ghtf.org/index.html>*

1- Prescrire Editorial Staff "Medical devices surveillance: be on the look out" *Prescrire International* 2002; 11 (58): 51.

2- see

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=365

Colophon

Editor: Christophe Kopp
Coordinator and lay-out:
Florence Vandeveld

The following people contributed to this newsletter:

Maria Font, Jörg Schaaber,
Wolfgang Becker-Brüser, Ayyaz Kiani, Vija Berlande, Barbara Mintzes, Danielle Bardelay, Joan Ramon Laporte, Rokuro Hama, Blanka Pospisilova, Benoit Marchand.

News of the Network for Consumer Protection

Here are some news of The Network for Consumer Protection in Pakistan.

Call for help: following-up. Following the earthquake, the Network for Consumer Protection in Pakistan tried to help the population, together with other NGOs (we relayed his call for help in December 2005 Newsletter). Ayyaz thanked all contributors: "We have received nearly 3,000,000 (124% of target) in less than a month. We are highly grateful to all the contributors. We are now leaving for village Burka, Bagh. Our team will spend six days (18-23 December) there in meeting families and distributing the collected money. (...) We thank all our friends again who have supported our initiative in such an enthusiastic manner. It's really heartwarming."

The situation is still very worrying due to a very cold winter. You can still donate. Please remit the funds to ABN AMRO Bank Newyork (Swift Address ABNAUS33) for account of ABN AMRO Bank Karachi (Swift Address ABNAPKKA) for further credit to account # 311442005 of TheNetwork for Consumer Protection in Pakistan with ABN AMRO Bank Islamabad (Swift Address BNAPKKAISB).

A new executive coordinator. Ali Qadir is leaving the post of executive coordinator and is replaced by Ayyaz Kiani since the 21. of November. Ayyaz has been working with TheNetwork since its inception, in 1992, and brings to the position tre-

mendous experience in working on advocacy for rational use of pharmaceuticals, as well as for consumers right in Pakistan.

Change of the bulletin name. "Watch on medicines" replaces "the Network's Drug bulletin" edited by TheNetwork's for Consumer Protection Pakistan <http://www.thenetwork.org.pk/>

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CITO! and pharmacovigilance

On 4 November 2005 the 1st conference on pharmacovigilance was held in Latvia on "The Role of Health Care Specialists in Studying Adverse Drug Reactions". This conference is the last event within the Phare (a) project "Medicinal Products Market Surveillance and Pharmacovigilance" (involving Latvian, Dutch and German specialists) supported by the European Union. The project started with lectures on "Adverse Drug Reactions and a Proper Clinical Evaluation" at the Clinical Hospital "Gaiļezers". The objective of this collaboration project was to promote a pharmacovigilance system in Latvia by emphasising doctor's paramount role in detecting and reporting adverse reactions. Within the framework of the project a pilot study on detecting and reporting adverse reactions was conducted in the months of June to September at the Clinical Hospital Gaiļezers ("Character and Frequency of Suspected Adverse Drug Reactions in the Riga municipal Clinical Hospital Gaiļezers").

Quotes from the conclusions of the conference:

-Education has a principal role. That is why it is necessary to include pharmacovigi-

lance in the professional pre-diploma and post-diploma training. -In order to secure and maintain freedom and independence in science and medicine it is essential to determine conflicts of interest of experts evaluating drugs. A speaker referred to the creation of artificial diseases. For example, changes within the hormonal system due to a physiological aging or osteoporosis are not considered natural processes any more but are declared

diseases with a necessity for a respective therapy. It was emphasised that before prescribing drugs, a doctor should consider other ways for health improvement. Women in menopause often unreasonably use hormone replacement therapy, which may lead to breast cancer, cerebral thrombosis, or cardiac infarction. It is always essential to evaluate if the risk associated with drug use does not outweigh the benefit.



Benefits & Harm of medicine: inseparably bound with each other

Kusuri-no-Check

- ▶ -Cooperation between doctors and pharmacists is crucial.
- Medicinal products are put on the market even though they are insufficiently investigated. That is why each adverse reaction report has a significant role in post-authorisation studies.
- Information on drug safety would improve if all GPs had computers and they could use Internet.

The culmination of the conference was the presentation of "Introduction into Pharmacovigilance" (a book on adverse reactions). This is the first edition in Latvian aggregating information on drug safety.

Let's hope that "Introduction into Pharmacovigilance" will be a good guide in drug safety issues for all doctors and healthcare professionals, as well as medicine and pharmacy students in Latvia.

Vija Berlande
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a- The Phare programme is one of the three pre-accession instruments financed by the European Union to assist the applicant countries of Central and Eastern Europe in their preparations for joining the European Union.

CONFERENCE

Disease-mongering

A conference on disease-mongering will be held from 11th to 13th April 2006 in Newcastle, Australia. Two ISDB members, Barbara Mintzes and Joe Collier, are scheduled to speak. Barbara Mintzes's abstract for the Conference is reprinted below.

@→ For more details about the Conference, go to www.diseasemongering.org.

Disease-Mongering in Drug Promotion: Do Governments Have a Regulatory Role?

This presentation examines activities financed by drug companies to promote product sales by expanding disease definitions and the pool of potentially treatable patients, when no benefit is likely in terms of reduced morbidity. New diseases may be 'created' or existing conditions redefined. In many countries, including those with laws prohibiting direct-to-consumer advertising (DTCA) of prescription drugs, unbranded 'disease-awareness' advertising by pharmaceutical manufacturers has become increasingly common. A claimed benefit is that the public becomes more aware of untreated health problems and seeks effective care at an earlier stage, leading to better health. For this to happen, the campaigns must address important health concerns, focus on patients likely to benefit from diagnosis and treatment, and steer them towards appropriate care. These conditions are rarely if ever met.

For example, a Novartis campaign for onychomycosis (toe-nail fungus) stimulated extra physician consultations and antifungal sales, diverting resources from more serious health concerns to this essentially cosmetic condition. A Pfizer campaign used fear of fatal heart attacks to steer viewers to cholesterol testing and ideally to treatment with its product, Lipitor (atorvastatin). The

impressions conveyed about the role of cholesterol in heart disease and the ability of statins to prevent cardiac death in people without previous heart disease was inaccurate. Many U.S. direct-to-consumer advertisements fail to distinguish adequately between milder symptoms that do not require drug treatment, and more serious health concerns. Antidepressant advertisements universally fail to distinguish between distress caused by difficult life situations and psychiatric illness.

Disease-mongering by definition create erroneous impressions of the condition a product aims to treat and the merit and safety of treatment, and frequently provokes undue anxiety or exaggerates prevalence rates. In theory, these activities are covered by national laws governing drug promotion that forbid misleading or deceptive advertising. However, enforcement is piecemeal and largely ineffective. There are some regulatory precedents. For example, the U.S. Food and Drug Administration frequently cites public health concerns in its letters to companies about promotional violations. These included disease-oriented concerns in 15 of 21 letters of violation about direct-to-consumer advertisements in 2004 and 2005.

In most countries, a more robust regulatory response to misleading promotional messages about diseases and health risks is possible without a change to law. Better definition is also needed of the indications drugs are approved to treat, to ensure consistency with assessed outcomes in pre-

market trials. Evidence of benefit should be based on clinical outcomes, and greater caution is needed in introducing new diagnoses. A key question is whether the political will exists to better enforce existing regulations governing drug promotion or to introduce new solutions.

Barbara Mintzes
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One young and spirited statistician

Kusuri-no-Check

BULLETINS ROUNDUP

This section briefly points out articles of interest that were recently published in ISDB member Bulletins. Their choice is the result of random browsing. Please tell us about your actions or papers of interests that we might not detect due to language barrier. For each article we specify if it's available free or not on the internet. If not, ask the relevant ISDB member for it.

► **Dialogo sui farmaci**

<http://www.dialogosuifarmaci.it/default.asp>

The Bulletin includes a section dedicated to patients and the public, with articles on common conditions.

Dialogo sui farmaci, as many other Bulletins, features a section on 'distance learning' for healthcare professionals. This service is offered free of charge.

Available free

Language: Italian

► **Worst Pills Best Pills**

<http://www.worstpills.org/>
In January 2006 Vol 12. N°1 issue:

Erectile Dysfunction Drugs Can Cause Visual Loss: Public Citizen Petitions FDA for Black Box Warnings on the Erectile Dysfunction Drugs.

Available on subscription only

► **La Lettre du CEDIM**

An editorial of the December 2005 issue of La Lettre du CEDIM calls on public authorities to better inform healthcare professionals about medicines withdrawn from the market, and about the reasons for withdrawal. It also advocates establishing a pharmacovigilance system in Burkina Faso. "Like other African countries, Burkina Faso has no organized pharmacovigilance system (...) The aim would be to protect the population thanks to our own system. Let's not wait for others to do the job, we have problems that are peculiar to our country".

Available on request

Language: French

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► **Boletín Terapéutico Andaluz**

http://www.easp.es/web/cadime/cadime_bta.asp?idCab=303&idSub=378&idSec=303

A review on the use of performance enhancing substances and related health problems can be found in Vol 21 n°4, year 2005.

Available free on internet

Language: Spanish

► **The Therapeutics Initiative**

<http://ti.ubc.ca/pages/letter52.htm>

Worth reading: this Therapeutics Letter on Antidepressant Medications in Children and Adolescents

Quotes: "The prescription of an antidepressant to a child or adolescent is like an open trial with up to 80% of patients expected to improve. When improvement occurs, it is most likely due to a placebo group response, which includes spontaneous remission, response to supportive care, and other components. Because of the unfavorable harm to benefit balance for antidepressants in this age group, first-line therapy is multiple supportive interventions: sleep hygiene, exercise, regular dietary patterns, consistent parenting, and practical problem-solving regarding schooling and life stressors. For those who do not respond, individual or group cognitive behavioral therapy or interpersonal psychotherapy should be arranged, if possible. Medications are reserved for add-on therapy when the first two approaches are not working. When an antidepressant is prescribed, the patient must be monitored for signs of deterior-

ation: behavioral and psychiatric changes, including increases in suicidal thinking, as emphasized by the new Health Canada labeling.

► **Centro Vasco de Información de Medicamentos CEVIME-MIEZ**

http://www.osanet.euskadi.net/r85-6733/es/contenidos/informacion/critica_publicidad/es_9911/critica_publicidad_c.html

One among many ISDB members who critically appraise drug advertising material: "Crítica a la publicidad del material promocional de medicamentos"

Available free

Language: Spanish

► **Pharmaca**

In its 43; 4 2005 issue, an editorial in English can be found: "Prescribing of pharmaceuticals in countries with limited resources".

Quotes: "In international organizations and meetings, 'experts from rich countries 'teach people from poor countries what to do. They have a lot of data, nice photos and slides, which often are not transferable to the more or less completely different situations and conditions. Very often, the message is not understood and not accepted. (...) Characteristics of less developed (in transition) countries include less funds for health and pharmaceuticals, higher percentage for pharmaceuticals in the health bill, often higher prices than in developed countries, sometimes biased decisions (personal interests),

inadequate information on prescribing (main source = manufacturers), less rational prescribing with wide prescribing of non-essential agents, unjustified enthusiasm for those recently approved, fierce competition of generic and me-too agents almost unknown.

Language: Croatian, with abstracts in English

Available on request

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► **Kusuri-no-Check and The Informed Prescriber**

On TGN1412 Tragedy
<http://www.npojip.org/english/no65.html>

<http://www.npojip.org/english/tip21.html>

Web Kusuri-no-Check No65 and March 2006 issue of TIP reported a tragedy caused by TGN1412 which happened in London, UK on 13 March 2006. TGN1412 is a superagonistic humanized anti-CD28 monoclonal antibody. TeGenero and PAREXEL say that the dose administered was one five hundredth of that produced no harm in animal and MHRA approved the trial. However, lymph nodes and spleens of healthy rats administered superagonistic anti-rat CD28 antibody (JJ316) swollen severely [1].

Relevant Clinical trial methods for new biological agents are needed!

Web Kusuri-no-Check International (English version) is also available.

[1] Tacke M et al. Eur J Immunol (1997), 27(1): 239-47.

Ongoing campaigns

Canada

Support editorial freedom at CMAJ

The Canadian Medical Association (CMA) fired Dr. John Hoey, the CMAJ Editor, and Anne Marie Todkill, Senior Deputy Editor, of the CMAJ, following a dispute over edito-

rial freedom (see CMAJ January 3 2006 editorial at

<http://www.cmaj.ca/cgi/content/full/174/1/9>).

This firings relate to the CMA's violation of the principle of editorial autonomy that guarantees both scientific integrity and freedom of expression.

The ISDB executive Committee sent a letter to the CMA board (see below).

A petition to reinstate Dr. Hoey and

Ms. Todkill to their previous editorial positions, and to exhort CMA to protect the editorial freedom and independence of the CMAJ is available at <http://www.chaps.ucalgary.ca/cmaj.htm>.

Support editorial freedom by signing it!



Dr Louise MC Cloutier
President of the Management Board
Canadian Medical Association

Verona, March 24, 2006

Dear Ms Cloutier,

The International Society of Drug Bulletins (ISDB) has been promoting independent and impartial information on medicines since nearly 20 years. The Society has more than 50 full members in 33 countries around the globe.

ISDB is deeply concerned about the dispute between the CMA and the CMAJ editorial board. Especially after the attempts to consolidate the Journal's editorial freedom over the years (see editorial of the 3 January 2006 CMAJ issue), we are irritated by the subsequent dismissal of the CMAJ editorial board.

CMA should restore its reputation:

- by reinstating John Hoey and Anne-Marie Todkill,
- by signing the commitment proposed by the CMAJ editorial board:

"The CMA will protect the editorial freedom and independence of the CMAJ and is committed to continually striving to maintain CMAJ's excellence in the science and art of medicine and its mission to uphold the ideals of the medical profession and to promote the health and wellbeing of the public."

Thanks to the efforts of the current editorial staff, CMAJ is now an internationally recognized source of scientific information, and is highly respected by ISDB members. The CMAJ will lose this excellent reputation unless the international scientific community is convinced that the editorial policy is entirely free, even from special interests within CMA itself.

We therefore politely but firmly ask you to reinstate John Hoey and Anne-Marie Todkill, and subsequently guarantee the editorial freedom of the CMAJ.

Sincerely yours,

Maria Font
ISDB Chair
Editor in chief at
Dialogo sui Farmaci
(Italy)

Christophe Kopp
ISDB General Secretary
Editor in chief at
Prescrire International
(France)

Jörg Schaaber
ISDB Treasurer
Editor in chief at
Pharma-Brief
(Germany)

Ask your regulator!



Data that should publicly be available: Quotes of legislative articles of interest

In Europe, a new legislative framework on “medicinal products for human use” was adopted in 2004: Directive 2004/27/EC, applicable after transposition into national legislation (1), and Regulation 726/2004 (2), directly applicable at centralised European level.

Some ISDB members, together with other groups within the Medicines in Europe Forum, campaigned to put patients’ interests first in the two drafts, before commercial interests strongly defended by pharmaceutical companies (3). They managed to impose transparency provisions in the EU legislation.

European ISDB members can check if the Directive that is transposed in their countries is in accordance with Directive 2004/27/EC (see box “Warning” and text on new medicines law page 13);

Other ISDB members can compare their legislation and level of access to data with European legislation: if weaker, why not use this article to ask regulators for more data?

D means Directive
R means Regulation

1. Transparency of EU regulatory agencies: new obligations

- **National agencies: public access to agendas and reports**

“the Member States shall ensure that the competent authority makes publicly accessible its rules of procedure and those of its committees, agendas for its meetings and records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions.” (D 126-b)

- **European agency: public access to all documents motivating centralised decisions**

“The Agency shall set up a register pursuant to Article 2(4) of Regulation (EC) No 1049/2001 [regarding public access to European Parliament, Council and Com-

mission documents] to make available all documents that are publicly accessible pursuant to this Regulation.” (R 73)

More transparency about EMEA: “The internal rules and procedures of the Agency, its committees and its working groups shall be made available to the public at the Agency and on the Internet.” (R 80)

- **Companies: Respect of Regulation on marketing authorisation: name and shame**

“The Commission shall publish the names of the marketing authorisation holders involved and the amounts of and reasons for the financial penalties imposed.” (R 84)

2. Independence of agencies: small progress

- **Declaration of conflicts of interest**

“1. The membership of the committees referred to in Article 56(1) shall be made public. (...)

2. Members of the Management Board, members of the committees, rapporteurs and experts shall not have financial or other interests in the pharmaceutical industry which could affect their impartiality. They (...) shall make an annual declaration of their financial interests. All indirect interests which could relate to this industry shall be entered in a register held by the Agency which is accessible to the public (...). Members of the Management Board, members of the committees, rapporteurs and experts who participate in meetings or working groups of the Agency shall declare, at each meeting, any specific interests which could be considered to be prejudicial to their independence with respect to the items on the agenda. These declarations shall be made available to the public.” (R 63)

- **Mandatory databases**

“the Agency, acting particularly through its committees, shall undertake the following tasks: (...) (d) ensuring the dissemination of information on adverse reactions to medicinal products authorised in the Community, by means of a database perma-

nently accessible to all Member States; health-care professionals, marketing authorisation holders and the public shall have appropriate levels of access to these databases, with personal data protection being guaranteed; (...)

(1) creating a database on medicinal products, to be accessible to the general public, and ensuring that it is updated, and managed independently of pharmaceutical companies [leaflets, etc.]” (R 57)

3. Marketing authorisations: more information publicly available

- **Information on company withdrawals of applications and on Agency refusals.**

“If an applicant withdraws an application for a marketing authorisation submitted to the Agency before an opinion has been given on the application, the applicant shall communicate its reasons for doing so to the Agency. The Agency shall make this information publicly accessible and shall publish the assessment report, if available, after deletion of all information of a commercially confidential nature.” (R 11)

“Information about all refusals and the reasons for them shall be made publicly accessible.” (R 12-3)

- **Public access to conditions attached to a ‘conditional marketing authorisation’.**

“In exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to meet certain conditions, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. (...) The list of these conditions shall be made publicly accessible without delay, together with deadlines and dates of fulfilment.” (D 22)

Ongoing campaigns

“Following consultation with the applicant, an authorisation may be granted subject to certain specific obligations, to be reviewed annually by the Agency. The list of these obligations shall be made publicly accessible.” (R 14-7)

4. Packaging and leaflets: better information for patients

• **Generic name more visible and in Braille for blind people**. “where the product contains up to three active substances, the international non-proprietary name (INN) shall be included» (D 54-a) «The name of the medicinal product (...) must also be expressed in Braille format on the packaging.” (D 56-a)

• **Product Information Leaflet tested by patients**. “The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.» (D 59-3) «The results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority.” (D 61-1)

5. Pharmacovigilance: still too much secrecy

In the two texts, reporting of adverse effects by patients and the public is not considered: reporting is still reserved to health professionals. There is still too much secrecy: the pharmaceuticals companies have to regularly send their reports on adverse effects to agencies (“periodic safety update report”) (D 104-6, R 24-3), but there is no binding provision for making them publicly available.

• **Communication policy: EMEA opinions on pharmacovigilance data (if they exist) but no direct access to data**. “The Agency (...) shall receive all relevant information concerning suspected adverse reactions to medicinal products for human use (...). Where appropriate, the Committee for Medicinal Products for Human Use shall, in accordance with Article 5 of this Regulation, draw up opinions on the measures necessary. These opinions shall be made publicly accessible.” (R 22)

• **Public access without delay to the mandatory database**. “Member States shall ensure that suitable information collected within this system is communicated to the other Member States and the Agency. The information shall be recorded in the database referred to Article 57-1-1 of Regulation 726/2004 (see point 2.) and shall be permanently accessible to

all Member States and without delay to the public.” (R 22)

• **A minor improvement: public funding of pharmacovigilance activities**. “The management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the competent authorities in order to guarantee their independence.” (D 102-a) “Activities relating to pharmacovigilance, to the operation of communications networks and to market surveillance shall receive adequate public funding commensurate with the tasks conferred.” (R 67-4)

In short.

The Medicines in Europe Forum campaign lead to improved access to data from EU agencies. Drug regulatory agencies must follow their new obligations. The law give agencies the needed authority to relay information, even if it runs counter pharmaceutical interests (i.e. on pharmacovigilance). Drug bulletins and the public must therefore check whether all good provisions are implemented. Despite these campaigning efforts, the pharmacovigilance field remains too opaque. One more reason for ISDB bulletins to be vigilant and check that the Directive is properly transposed into national law. It is the only way to avoid losing of the transparency advances during the transposition process in national legislation.

1- “Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use” Official Journal of the European Union of the 30th of April 2004: L 136/34 – L 136/57 (24 pages).

For convenient reading, you can use the consolidated Directive (informal codification of the Directive 2001/83/EC) : “Directive 2001/83/EC (...) as amended by Directive 2002/98/EC; Directive 2004/24/EC; Directive 2004/27/EC”

(<http://pharmacos.eudra.org/F2/review/index.htm>).

2- “Regulation (EC) N° 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency” Official Journal of the European Union of the 30th of April 2004: L 136/1- L 136/33 (33 pages). (<http://pharmacos.eudra.org/F2/review/index.htm>)

3- Prescrire Editorial Staff “Reorienting the course of medicines policy: actions are bearing fruit” Prescrire International 2003 ; 12 (67) : 192-194.

4- Prescrire Rédaction Medicines in Europe Forum: the most important changes in the new legislation” Website:

<http://www.prescrire.org/aLaUne/dossierEuropeSynthese2En.php>

Warning:

EU Directive risks being poorly transposed in France

La revue Prescrire is monitoring transposition of Directive 2004/27/EC into national law.

And the French draft is not in accordance with the Directive (1):

- Transposition is late (except for items in the interest of pharmaceutical companies (1)) ; it must have been done by November 2005;

- The draft ignores transparency obligations mentioned above, as well as improvements in product information leaflets and packaging;

- The draft introduces provisions that were not in EU Directive, namely the possibility for drug companies to organize ‘assistance programs for improving treatment compliance’ ;

- The government has chosen to bypass debate in Parliament, so as to accelerate the process.

Prescrire, together with Medicines in Europe Forum, is campaigning against the draft and pushing for full implementation of public health provisions they managed to introduced in Directive 2004/27/EC.

Be vigilant in your countries, and let know other ISDB bulletins if you notice the same problems.

1- Prescrire Rédaction “Transposition de la Directive 2004/27/CE sur le médicament : la France en retard” Rev Prescrire 2005 ; 25 (267) : 817-818.

2- Prescrire Rédaction “Alerte citoyenne” Rev Prescrire 2006; 26 (271): 241.

New medicines law in Spain

An example of ISDB collaboration

A new medicines law is underway in Spain. Maria Font was invited by Joan Ramon Laporte to go to Spain and make an intervention aimed at improving the Spanish draft law.

Quotes from Maria Font's speech:

“My presentation will regard some aspects of the law related to information and drug assessment, aspects where the International Society of Drug Bulletins (ISDB), which I represent as Chair, can bring its experience.

The ISDB comprises 70 drug information bulletins in more than 40 countries around the world. They are independent, both intellectually and financially, from pharmaceutical companies. In Spain 6 bulletins belonging to this society regularly assess new drugs and inform healthcare professionals.

The draft law has many positive aspects: for instance the guarantee of independence and high quality training and information for rational use of drugs, considered in Chapter VI; the guarantee of healthcare professionals' independence from drug companies; the separation between drug approval and reimbursement; the possibility to prescribe using INNs.

Several aspects could still be improved.

Drug reimbursement. International health data reports that Spain is one of the industrialized countries that spend more on drugs with respect to overall health expenditures, with new drugs representing a major market share. The law contains some elements of effective rationalisation of the pharmaceutical expenditure, however the proposed procedure contains ambiguities. In the financing procedure (article 88), 6 criteria for including a new drug in the reimbursement list by the Spanish National Service are described. They are defined as objective criteria. However, one of them - the degree of innovation of a drug - is far from being a straightforward criteria. Innovation can have

different meanings: the commercial concept which refers to any new marketed drug; the technological meaning which refers to every industrial innovation, such as biotechnology or the development of new drug delivery systems. The ISDB considers innovation must be better defined in terms of real therapeutic advance. A drug or an indication is a therapeutic advance if it offers patients an increased benefit in terms of efficacy, safety or convenience with respect to the therapeutic options already available. This definition is quite similar to the concept of therapeutic and social utility already considered in the criteria for reimbursement. If the term innovation is not defined more clearly, it is of little practical use.

The process of selecting medicines for financing is not a simple on/off mechanism. The selection of a new drug for reimbursement needs further limitations, for instance the exclusion of some of the labelled indications of the drug or exclusion of some types of patients, thereby limiting full access to the drug. Even if the law considers the possibility of limiting conditions of prescription, dispensing or financing of a drug, or total or partial exclusion of some drugs, the procedures and the competent committee are not clearly defined. Nor is it clear whether the Agency reports will be binding on the inter-ministerial pricing committee. The majority of new drugs need some reimbursement limitations but this process should have consistency, continuity and representativity.

Transparency: confidentiality and access to information. Article 15 states that: “The content of the proceedings leading to authorization of a new drug will be confidential”. The limitation of access to information on new drugs is a big obstacle for the assessment of drugs by independent bulletins or others

wanting to objectively assess a drug, leaving the drug companies with a monopoly on key information. Current information available for drugs registered through the national or mutual recognition procedures is very limited, therefore this confidentiality clause will be a strong limitation to independent evaluation.

The new European directive 2004/27/EC introduces new obligations for transparency: “(...) The Member States shall ensure that the competent authority makes publicly accessible its rules of procedure and those of its committees, agendas for its meetings and records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions”.

As ISDB, we also ask that the clinical trials be submitted with the drug application: all trials, whether completed or not, together with their protocols. We believe this will ensure better availability of information to the public (who participates in clinical trials) and healthcare professionals, without damaging the interest of drug companies.”

Maria Font
maria.font@ulss20.verona.it

Mental health screening



We are witnessing a wide ranging campaign in favour of mental health screening worldwide.

Source : Alliance for Human Research Protection (AHRP)

<http://www.ahrp.org/ahrpspeaks/TeenScreen/index.php>

Vera Sharav presented the US "National Plan for Universal Mental Health Screening: A Pharma Friendly Remedy for Societal Problems" at the American Public Health Association on December 12, 2005. Her complete powerpoint presentation can be downloaded.

Quotes: "I'll begin with the President's New Freedom Commission on Mental Health recommendation to screen the US population for mental illness - 52 million children first. In no other democratic country has the government adopted a policy to screen the population for presumed, undetected, mental illness. The rationale behind this mind-boggling Orwellian nightmare is not improving mental health, but rather increasing life-long consumers of psychoactive drugs and to control behavior. Two NFC recommendations are designed to do just that. TeenScreen is promoted as a suicide prevention model when it in fact, increases the number of children labelled suicidal and depressed. And TMAP (the Texas Medication Algorithm Project) whose prescribing guidelines are promoted as "evidence-based" medicine - is nothing but a market expansion scheme.

The unprecedented increase in children being diagnosed with psychiatric conditions and prescribed drugs can be traced to TMAP and the collaborative efforts of the drug industry, organized psychiatry, and government. A series of federally sponsored mental health initiatives promoted the unsubstantiated idea that children's mental health was in crisis, and early intervention is essential. In fact, as Dr. Julie Zito and Dr. Gretchen Levere documented, the crisis is the irresponsible

over prescribing of drugs for children. Indeed, a 2002 survey of young child /adolescent psychiatrists found: 91% of the time - 9 out of 10 children - were Rx psychoactive drugs when referred to a professional - only 9% received psychotherapy."

Vera Sharav

In the USA "The Texas Medication Algorithm Project (TMAP) is a controversial corporate-sponsored set of psychiatric management guidelines designed to enable doctors to systematically screen and treat patients for diagnosed mental disorders within Texas' publicly-funded mental health care system. TMAP was initiated in the fall of 1997 to provide more uniform early intervention screening and treatment for Texas children. The pharmaceutical companies who funded the development of TMAP include Janssen Pharmaceutica, Johnson & Johnson, Eli Lilly, AstraZeneca, Pfizer, Novartis, Janssen-Ortho-McNeil, GlaxoSmithKline, Abbott Laboratories, Bristol Myers Squibb, Wyeth-Ayerst and Forrest Laboratories." [source: Wikipedia].

For more details on what's happening in the US, you can download a report from Alliance for Human Research Protection (AHRP) on the "National Plan for Universal Mental Health Screening: A Pharma Friendly Remedy for Societal Problems". <http://www.ahrp.org/ahrpspeaks/TeenScreen/index.php>

In January 2005 was held a joint WHO-EU meeting: "WHO European Ministerial Conference on Mental Health: Facing the Challenges, Building Solutions" where "52 WHO Member States adopt Mental Health Declaration and Action Plan for Europe". http://www.euro.who.int/mentalhealth2005/press/20050114_1

In October 2005 the European Union launched an "EU-wide consultation process on mental health". http://europa.eu.int/comm/health/ph_determinants/life_style/

[mental_health_en.htm](#)

In France a panel of experts under the auspice of the publicly-funded research body INSERM has published a paper on 'conduct disorder' in children and adolescents (DSM-IV category). This controversial document recommends among other things that conduct disorder and risk factors be identified in early childhood (as early as 36 months or even during pregnancy), and possibly treated with psychotropic agents later on.

http://ist.inserm.fr/basisrapports/trouble_conduites/trouble_conduites_synthese.pdf

Also the French government wants to set up a national programme for preventing child behaviour disorders and juvenile delinquency. As of March 8 more than 100 000 people in France have signed a petition against INSERM recommendations and this government initiative.

<http://www.pasde0deconduite.ras.eu.org/>

Please tell us about similar repercussions of this mental health screening offensive in your country!

Contact : christophe.kopp@wanadoo.fr

ISDB commented on an EU Commission Guideline

After strongly campaigning to improve European Directive 2004/27/EC, the notion of “added therapeutic value” finally appeared in official texts (see box one), and by this way the need for comparison can be recognised.

Within this framework, an European guideline was elaborated in order to define more precisely the a “therapeutic added value” (1). ISDB defined it in the Declaration of Paris in 2001 (http://66.71.191.169/isdbweb/pag/therapeutic_dec.php).

ISDB contributed to an EU public consultation on a draft ‘Guideline on the elements required to support the significant clinical benefit in comparison to existing therapies of a new therapeutic indication in order to benefit from an extended (11-years) marketing protection’ ISDB welcome this guideline. Indeed, the definition of ‘significant clinical benefit’ is in line with the ISDB Declaration on therapeutic advance in the use of medicines.

The draft guideline is available at: http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/12-05/Guideline%20on%2014_11_%20for%20public%20consultation.pdf

“Added therapeutic value” was introduced in European legislation

« At the request of the Commission, the Agency shall, in respect of authorised medicinal products, collect any available information on methods that Member States' competent authorities use to determine the added therapeutic value that any new medicinal product provides. » (Article 60 of Regulation EC n°2004/726).

The notion of “significant clinical benefit in comparison with existing therapies” was introduced as a condition for pharmaceuticals companies to prolong the protection of their commercial and industrial property: “The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if (...) the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.” (Article 10 of Directive 2004/27/EC).

Medicines in Europe Forum got the credit for this important legislative tool. It applies for new indications of drugs already approved, but is clearly a precedent.

Next step could be the need to demonstrate “added therapeutic value” before the first marketing authorisation...

Public health risks

Definition: "any risk relating to the quality, safety or efficacy of the medicinal product as regards to patients' health or public health"



AIS COIME

EU GUIDELINES

Take position on EU guidelines!

The risk to public health posed by insufficiently evaluated drugs has to be considered

The marketing authorisation for drugs on sale in European countries may have been issued by the European Medicines Agency, a national regulatory agency, or through the mutual recognition procedure ▶▶

VOCABULARY

Partner fish

A ‘partner fish’ is a very common species of healthcare professionals, patient groups, drug regulatory agencies, or international organizations (EU Commission, WHO), who engage in close partnership with pharmaceutical companies, like pilot fish with sharks.

Partner fishing: participating willy-nilly in marketing strategies of pharmaceutical companies.

More information on partner fish go to public-private partnership, conflict of interest; see also corruption.



Christophe Kopp

► that accepts an authorisation issued by another member state. European legislation permits a Member State to refuse to recognise a marketing authorisation issued by another Member State only in the event of a potentially “serious risk to public health”. However, the Commission is careful to ensure that this clause does not hinder the “free movement of goods”, and has published draft “guidelines” defining this serious risk to public health (1). The European Commission has adopted a list of exclusion to the definition of public health risks. According to this exclusion list explaining what is NOT a “public health risk”, inadequate and insufficiently evaluated drugs are not a “source of risk” for patients.

This interpretation of risk wilfully ignores all the current major drug evaluation shortcomings. In practice, for the European Commission, a drug must be accepted without protest by a member state even if it has been evaluated solely against a placebo, in adults with no particular risk factor, or its performance compared with other already available drugs in the same class has not been measured and its optimum dose is not known.

The guidelines are dangerous because they accept that patients are exposed to harm of a new medicine, even if it does not provide any added therapeutic value. (→ see the way arzneitelegramm make its reader aware of this risk in section “Editorial methods” page 18). National health authorities should be more stringent and oppose mutual recognition if necessary, in the best interests of patients.

For more details, go to

<http://www.prescrire.org/bin/cqp/index.php?id=26037> (in French).

1- European Commission – Enterprise and industry Directorate general – Consumer goods – Pharmaceuticals “Proposal for a guideline on the definition of a potential serious risk to public health” February 2005 : 5 pages.

http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/02_05/guideline_risk_human_02_05.pdf

EMA, together with WHO, gives opinions on medicines for use outside the EU

In a press release (Ref. EMEA/382477/2005) dated 17 November 2005 EMA announced: “The European Medicines Agency today gave, for the first time, a scientific opinion in the context of cooperation with the World Health Organization (WHO) for medicinal products intended exclusively for markets outside of the European Union.

The revised EU pharmaceutical legislation has introduced a new provision, which allows the Agency’s Committee for Medicinal Products for Human Use (CHMP) to give opinions, in cooperation with the WHO, on products that are intended for use outside of the EU. Previously, the CHMP could only review products intended for the EU market.

Medicines eligible for this new procedure are used to prevent or treat diseases of major public interest. This includes vaccines used in the WHO Expanded Programme on Immunization or for protection against a public health priority disease, as well as medicines for WHO target diseases such as HIV/AIDS, malaria, or tuberculosis”.

(@→ <http://www.emea.eu.int/>)

EMA approval decisions will concern a greater number of patients. This is all the more reason to demand that the new EU transparency obligations be implemented rapidly and comprehensively.



Prescrire

Conflicts of interests

PHARMA COMPAGNIES

Scientific Fraud & Corruption on Both sides of Atlantic: Merck/Proctor & Gamble

(Source: Alliance for Human Research Protection)

Two major cases of medical research fraud on each side of the Atlantic involve evidence of fraud and data tampering by pharmaceutical company giants. Both cases provide insight into the way in which academics are used by pharmaceutical companies that are desperate to obtain a stamp of respectability to their drug research.

Press release (dated 11 december 2005) available on AHRQ website:

<http://www.ahrp.org/infomail/05/12/11.php>

Widespread Drug Marketing Violations occurred at American Psychiatric Association Convention

(Source: Public Citizen)

“WASHINGTON, D.C. – More than half the drug makers that participated in the 2002 American Psychiatric Association (APA) convention violated drug marketing rules set up by the association or the Food and Drug Administration (FDA), Public Citizen writes in a study in the current issue of The Journal of Public Health Policy. (...)The most common APA violations were providing gifts valued at more than \$10, booths with “glaring lights,” promotional activity outside of the booth and giving away toys or stuffed animals. The companies distributed a range of items including CDs, personalized luggage tags, palm, pilot cases, bags, travel guides, mugs in velvet bags and phone cards. Other giveaways were invitations to meals, entertainment and art-related events. (...) Some companies were in violation of the FDA off-label marketing rules, either mentioning products for uses not approved by the FDA or discussing drug use at doses higher than what is recommended. Mallinckrodt violated both FDA and APA guidelines.”

For more info, see public citizen press release dated Dec. 15, 2005

<http://www.citizen.org/pressroom/release.cfm?ID=2101>

Corruption and Health

The ‘Global Corruption Report 2006’ focused on corruption in the health sector. The report can be downloaded from Transparency International website.

<http://www.transparency.org>

Here are presented some quotes from Transparency International website.

Market distortions and counterfeit drugs.

Aggressive marketing techniques buy physicians’ support for specific drugs, leading to a high rate of prescriptions that are not always based on patient need. With individual “blockbuster” drugs pulling in tens of billions of dollars each year for pharmaceutical companies, ballooning marketing and lobbying budgets have outpaced the research and development outlays necessary to create new and critical medicines that could save lives in low-income countries.

Corruption underpins a lucrative counterfeit drugs trade. Payoffs at every step of the chain smooth the flow of counterfeit drugs from their source to the unwitting consumer. With pharmaceuticals often the largest household health expenditure in developing countries – estimated at 50-90 per cent of total individual out-of-pocket health expenses – corruption in the pharmaceutical industry has a direct and painful impact on people struggling for survival.

Transparency International recommendations to improve physicians behaviour.

The best hope for improving physician behaviour is a combination of the following:

- reasonable and well-publicised standards on how to avoid conflicts of interest between physicians and the pharmaceutical industry, including strict prohibitions on marketing by physicians of drugs or devices in which they have a financial interest, and on participation in company-sponsored speakers’ bureaus;
- continuing education about the standards and their foundations, beginning in medical school and continuing at all other levels;
- peer pressure from colleagues and medical associations, including a requirement that clinical practice guideline committees and advisory panels contain a minority of individuals with financial conflicts of interest and that positions of journal editors, officers of major professional organisations and leaders of medical centres and

academic institutions be preserved only for individuals without conflicts;

- stricter government regulation of industry involvement in medical research and practice;
- full disclosure of relevant financial conflicts on an easily searchable web site;
- disciplinary action for egregious breaches of such standards.”

HEALTH PROFESSIONALS

Institute of Medicine as a profession

(Source: Transparency International)

Worth a visit: the US Institute on Medicine as a Profession (IMAP) ‘Managing Conflicts of Interest’ pages, where can also be found a link to ‘Medical Professionalism in the New Millennium: A Physician Charter’.

http://www.imapny.org/activities/activities_show.htm?doc_id=305828

Extracts:

Managing Conflicts of Interest of health professionals. “Physicians and medical organizations have many opportunities to compromise their professional responsibilities by pursuing private gain or personal advantage. Such compromises are especially threatening in the pursuit of personal or organizational interactions with for-profit industries, including pharmaceutical firms, medical equipment manufacturers, and insurance companies.

As stated in the Charter on Medical Professionalism, “physicians have an obligation to recognize, disclose to the general public, and deal with conflicts of interest that arise in the course of their professional duties and activities.”



Watch on medicines

No thanks: hospitals too.

“Citing “A Serious Threat” to Medical Professionalism, National Health Leaders Urge Teaching Hospitals to “Put Patients First” By Abolishing Gifts, Payments that Unduly Influence Physicians”.

http://www.imapny.org/news/news_show.htm?doc_id=343194

FOLLOW-UP

Australian T-score: la revue Prescrire follows suit

La revue Prescrire created a new transparency score, and thanked *Australian Prescriber* for showing the lead (see T-score in December 2005 Newsletter). Prescrire adapted the idea, and hope to be able to confirm John Tiller's impressions: "it seems that companies are more willing to

assist in the provision of information (and get the credit for that with a positive T score) than to ignore or decline our requests. This change in response is just an impression at this stage but we will get a better idea over time."



John Tiller and John Dowden
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
Melbourne, AUSTRALIA

Dear John & John,

We have tried to emulate your T score in la revue Prescrire in order to expose pharma companies' readiness to respond to our request for information on their products.

Our rating is similar to yours even though its insists on unpublished data and packaging information (see bellow).

We presented our rating during our Pill Awards Ceremony in January this year.

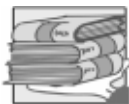
We wish you all the best with your T score, and hope ours will improve access to key data.

Thanks for showing the lead!

With our best wishes,

Christophe Kopp
For Prescrire team

1-manufacturer provided detailed information, including unpublished data and packaging items



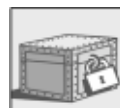
2-manufacturer provided information limited to administrative and published data



3-manufacturer provided minimal information, mainly administrative data



4-manufacturer provided no information



CREATIVE PICTOGRAMME

arznei- telegramm's black triangle ▼

arznei-telegramm uses a simple way to make readers aware of uncertainties due to insufficient evaluation of drugs. It uses the well known sign "▼" before the international non proprietary name if the drug has been authorised less than 5 years previously. The meaning is: "Be careful: less than 5 years authorised, little experience".

How meaningful are studies that are stopped early?

Reprint from *arznei-telegramm* Redaktion "Wie aussagekräftig sind vorzeitig abgebrochene Studien" 2005; 36 (12): 107-108.

Randomised clinical studies that are stopped prematurely because a benefit of the tested intervention is recognised generally attract special attention and not infrequently affect treatment standards. The most recent example is the situation with trastuzumab (HERCEPTIN) in the adjuvant treatment of breast cancer (a-t 2005; 36: 96-8). However, the authors of a systematic review are now calling for the results of such studies to be viewed with scepticism (1). They assessed studies stopped early due to apparent benefits for their frequency, the extent and plausibility of the treatment effect as well as the quality of the published information. They found 143 discontinued studies between 1975 and 2004, over half in the fields of cardiology, cancer and HIV/AIDS. One in two came from the *New England Journal of Medicine* (55) or *The Lancet* (27). In the period studied, the proportion that such reports account for out of all the randomised studies listed on Medline increased ten-fold from 0.01% to 0.1%. The **quality of the publications** in terms of information relevant to the early discontinuation (e.g. planned sample size or the interim analysis after which the study was ended) also falls short: only eight studies (6%) reported criteria of importance for assessment. At the time the study was stopped, an average 63% of planned participants had been recruited, the median follow-up observation time was 13 months, and the analysis was based on a median of 66 events (1).

Studies stopped prematurely for apparent benefit frequently show a **strikingly large treatment effect** (ratio of rates of events in the intervention group to those in the control group). In order to be able to justify the stoppage and exclude any chance effects as reliably as possible despite multiple analyses, stringent criteria are set by choosing a very low p-value, for example $p < 0.001$. Particularly in studies with few events, the risk reduction must be 50% or more in order to achieve a p-value of this kind (2). In view of the 25% to 30% therapeutic effect usually achieved, such a result often does not seem plausible. Furthermore,

there is always the danger that – despite every precaution – it is a random high. Since the likelihood of early termination increases with – even purely chance – fluctuations or even a large effect, the risk of random effects being involved increases with studies stopped early for benefit (3).

Interim analyses can therefore be misleading despite highly significant results. This is made clear by studies that were continued and at the end show only weakly positive or even negative results:

n In the *CHARM** study, which consisted of three separate trials and investigated the benefit of the angiotensin-II-blocker candesartan (ATACAND, BLOPRESS) in heart failure (a-t 2003; 34: 81-2), all-cause mortality in all the participants was calculated every six months. At the fourth interim analysis, when patient recruitment was nearly complete, the boundary set by the predetermined threshold value of $p < 0.001$, from which early termination was to be considered, had been crossed (260 vs. 339 deaths, hazard ratio [HR] 0.76; 95% confidence range [CI] 0.64-0.87; $p = 0.0006$). Nevertheless, the study was continued because, amongst other reasons, the results in two of the three separate trials did not even reach the usual significance level of $p = 0.05$ and the follow-up period was short. Furthermore, the members of the independent data-monitoring committee were aware that the treatment effects of trials stopped early are often greatly exaggerated and that a "regression to the truth" is possible with continued observation. In subsequent analyses, the benefit for candesartan became less and less. In the final analysis two years later, no significant difference in all-cause mortality could be found any more (886 vs. 945 deaths; HR 0.91; 95% CI 0.83-1.00; $p = 0.055$) (4).

▪ In the *OPTIMIST** study in patients with severe sepsis, the second interim analysis for tifacogin also showed enhanced survival versus the placebo (29.1% vs. 38.9%; $p = 0.006$). At the end of the study, the mortality rate was numerically higher on tifacogin (34.2% vs. 33.9%) (5).

▪ The *twelfth Medical Research Council acute myeloid leukaemia trial* showed a fifth cycle of chemotherapy to offer no survival advantage over a four-cycle regimen (HR 1.09; 95% CI 0.87-1.37; $p = 0.4$). Two interim analyses had previously shown highly significant effects in favour of the additional cycle (HR 0.47; $p = 0.003$ and HR 0.53; $p = 0.002$). The reporting authors, the head of the data-monitoring committee and the study statisticians warned against deciding to stop a study early solely on the basis of rigid threshold values, without considering the context. They pointed out that chance effects do occur and happen "more frequently than many clinicians realize" (6).

Besides fundamental reservations about the results of trials stopped early, the choice of a **decisive endpoint for discontinuation** also plays an important role. In cancer, for example, treatment interventions are supposed to prolong life and/or improve quality of life. However, in adjuvant treatment situations as well as in the trials of trastuzumab or aromatase inhibitors in breast cancer, the decision to stop the trial early is usually based on a benefit in terms of disease-free survival (7). Conversely, an effect on all-cause mortality is not sufficiently proven and in some circumstances cannot be explained. The crucial safety factors also remain open, including because the side effect rate is too low to allow sufficiently reliable statements due to the short follow-up period. Similar reservations apply to the endpoint of "progression-free survival" in advanced cancer (1,7). Where there are combined endpoints, it matters that the benefit does not rest solely on the event of less importance to patients (e.g. a fall in the angina pectoris rate with a combined endpoint of death, cardiac infarction or angina) (1).

In most cases, ethical reasons are cited as a justification for early stoppage: since the "benefit" of the intervention has been proven, it can no longer be withheld from the control group. However, the interests of patients in randomised trials have to be safeguarded while also protecting society (and, of course, the participants) from "overzealous premature claims" of apparent treatment successes (2).



► What are the implications of this for trastuzumab in adjuvant breast cancer treatment? "The best that can be said about Herceptin's efficacy and safety for the treatment of early breast cancer is that the available evidence is insufficient to make reliable judgments.", commented The Lancet, and noted that the manufacturers, Roche, do not yet have sufficient data to submit to the licensing authorities (8).

▪ **Controlled clinical trials are increasingly being stopped early due to highly significant positive interim results.**

▪ There is a danger that the – often strikingly large - treatment effect is a random high that will become smaller if the study is continued.

▪ **Where prematurely stoppage of a trial is being considered, a statistical "threshold value" should therefore be considered as only one aspect among others.**

▪ **The availability of sufficient data on which to assess patient-relevant end-points such as overall survival or safety is more crucial.**

(R = randomised study, M = meta-analysis)

M 1 MONTORI, V.M. et al.: JAMA 2005; 294: 2203-9

2 POCOCK, S.J.: JAMA 2005; 294: 2228-30

3 SCHULZ, K.F., GRIMES, D.A.: Lancet 2005; 365: 1657-61

4 POCOCK, S.: Am. Heart J. 2005; 149: 939-43

R 5 ABRAHAM, E. et al.: JAMA 2003; 290: 238-47

6 WHEATLEY, K, CLAYTON, D.: Contr. Clin. Trials 2003; 24: 66-70

7 CANNISTRA, S.A.: J. Clin. Oncol. 2004; 22: 1542-5

8 The Lancet: Lancet 2005; 366: 1673

* CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; OPTIMIST = Optimized phase 3 tifacogin in multicenter international sepsis trial

Many thanks to arznei-telegramm for translating the paper for this Newsletter.

How to do a press release

Writing a press release is by no mean easy. It must be short and memorable. Some simple rules can make it easier.

What is the message?

Two main messages is the maximum, one is better (rather do a second press release on one of the topics a bit later)

What do you want? Be clear what you want to achieve. It is often not enough to expose bad things. People want to hear what to do about it. Say who is asked to act (government, doctors, a company)

Make **news**. Give your message something "new". You may be the first to report to the public. You can also use a certain date (like the World AIDS-day). Nothing is older than yesterdays news.

Be brief.

One page should be enough (rather add a background document if needed). Say the key things at the beginning. Use at least 12 pt size and enough space between the lines.

Use lay language.

Journalists are no medical experts.

Write to print.

Write the text so that it could be printed without much editing. This makes life easier for journalists and prevents (to a certain extent) misrepresentation of your message. Don't say "we" but 'a ISDB spokesperson' or 'Dr. Y from the drug bulletin Z said:' "Drug X does serious harm to patients and should be removed from the market immediately"

Be accessible.

Journalists may have questions. Give a phone number /e-mail where you can be reached on your press release. Be available for them on the phone after sending the press release out.

Don't forget.

Don't forget to write a date on the press release; to add your address, e-mail and phone.

It may be good to give a 2-3 sentence portrait of your bulletin on the bottom of the page in smaller print (especially when you start making press releases and are not well known to the journalists)

Ask others.

Some bulletins are experienced in writing press releases. Ask them for help. E.g. you could send them your release as draft asking for comment. A friendly journalist may be of help too. Even asking anybody not directly involved in the topic to read the release in advance may be a big help. This may be a relative or your secretary.

Jörg Schaaber
Pharma-Brief

Media Doctor

► <http://www.mediadoctor.ca/>

Media Doctor Canada was launched in September 2005. A US Media Doctor is in the pipeline. The original Media Doctor (www.mediadoctor.org.au), established in Newcastle, Australia is the model upon which Media Doctor Canada is based. The Media Doctor Canada team includes, among other people, Alan Casseles, Joel Lexchin, and Barbara Mintzes.

Extracts from 'what media doctor is', taken from the website.

"The goal of Media Doctor Canada is to improve Canadian media coverage of new medical drugs and treatments. The Media Doctor Canada team reviews current news stories about medical drugs and treatments, and assesses the stories' quality using a standardised rating scale. Using a five star system, we evaluate stories based on how well they do, providing the important information you need to make an informed decision about the drug or treatment being reported on.

Specific Objectives.

- Ensure that, when possible, all important information associated with new treatments are reported, including benefits, harms, costs, adverse effects, availability, and conflict of interest.
- Establish the interest and usefulness in providing alerts to GPs on media coverage of new treatments.
- Establish a website called Media Doctor to provide feedback to journalists about the quality of their news stories.
- Evaluate the impact of Media Doctor on the quality of reports on new medical treatments in the lay press using time series analysis of serial scores achieved by individual media outlets.
- To investigate the international potential for such a process, especially in developing countries.

A secondary aim is for Media Doctor to act as a GP service in providing email alerts to relevant, current media articles that patients may approach them about. We believe the impact on the media

would be far greater when applied in developing countries.

The main outcome will be an objective evaluation of the quality of current health reporting in the lay press and a mechanism by which to inform journalists and media organisations on the quality of their stories with the view to improvement.

With increasing pressure on healthcare funding, it is important that the lay press adopts a neutral position on the value of new expensive medical treatments, and is able to provide accurate and unbiased information to the public. It is hoped this site will have a positive influence on journalists, their editors and executive producers, and that it may change the internal culture of the media organisation.

A major and sustained improvement in reporting standards will probably require changes to the culture of media companies, improved education of young journalists, and a change in the behaviour of drug companies and researchers. What we have outlined here is a 'minimal' intervention, but if it works it will be sustainable and cost-effective and could be used to educate the industry, health professionals and the public.

Developing Media Doctor will assess the impact of the system on the western media. However we feel this impact could be even greater if applied in developing countries. Increasingly news in developing countries is available online, making it easier to retrieve medical news stories. The Media Doctor team is interested in working with partners to extend the appraisal of medical news stories to other countries."

Entertainment A funny song!

"The Drugs I Need" can be listened on Consumers Union website, a US based non-profit organization.

www.PrescriptionforChange.org



Two HAI-WHO reports on drug promotion

HAI, together with the World Health Organisation (WHO), has produced a database of how prescribers and others are influenced by drug promotion and is involved in the production of a manual on educational initiatives to teach medical and pharmacy students skills in appraising promotional approaches by drugs companies.

For more information, reviews of materials in the WHO/HAI database on drug promotion @→ <http://www.drugpromo.info/>.

Here are already the links to two reports on drug promotion that may interest you.

"Educational initiatives for medical and pharmacy students about drug promotion: an international cross-sectional survey" WHO/PSM/PAR/2005.2, 61 pages ; edited by Barbara Mintzes (Therapeutics initiatives).

http://www.who.int/medicines/areas/rational_use/haipromosurvey.pdf

"Drug promotion : what we know, what we have yet to learn, Reviews of materials in the WHO/HAI database on drug promotion" WHO/EDM/PAR/2004.3, 2004, 102 pages ; edited by Pauline Norris, Andrew Herxheimer, Joel Lexchin et Peter Mansfield.

http://www.who.int/medicines/areas/rational_use/drugPromodhai.pdf