



Vol. 15, N°2, June 2001

NEWSLETTER

WELCOME TO TWO NEW FULL MEMBERS

BUTLLETÍ D'INFORMACIÓ FARMACOTERAPÈUTICA from Spain has been granted full membership.

The bulletin is financed by the *Sanitari Consorci de Barcelona*.

4 issues per year, 3000 per issue

Distributed free of charge

Commenced publishing: September 1991

Language: Catalan

Geographical spread: Catalonia

Website: <http://www.csbcn.org/public/bif>

Contact person: Corinne Zara

e-mail: czara@rsbcn.scs.es

address: Editorial office, Consorci Sanitari de Barcelona, Calabria, 169 08015 Barcelona, Spain

ARZNEI-TELEGRAMM from Germany has been granted full membership

The bulletin is financed by subscribers only

12 issues per year, 30 000 per issue

Distributed on subscription only

Commenced publishing: 1970

Language: German

Geographical spread: Germany, German speaking EU countries (35 countries worldwide)

Website: <http://www.arznei-telegramm.de>

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COLUMN

Funding of ISDB bulletins on the Internet

Transparency begins at home pages

Regularly browsing through ISDB bulletins on the Internet, one can find that not all web sites clearly specify how the sites are financially maintained. Some bulletin sites are part (Russian doll-like) of huge sites belonging to academic societies or other organisations, themselves sometimes funded by the pharmaceutical industry. It is therefore particularly hard to check for financial independence on these bulletin sites. This is especially worrying when it comes to members of a society claiming financial independence of drug companies as a prominent characteristic.

We all know independence from industry is not a fashionable gimmick: producing comparative information of good quality is a real challenge. Although independence is more than a slogan, it could also be a slogan prominently on display, and it should comprise the source of funding for the websites.

We will debate the ISDB Constitution at the next General Assembly in 2002 (see page 2), including the membership status of electronic-only bulletins. Let's add the issue of web site independence to the agenda.

Christophe Kopp
ISDB chairman

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DEBATE ABOUT THE ISDB CONSTITUTION

Should we update or amend some of our Articles and Rules?

Background

In May 1985, a group of people involved in developing independent drug information met in Madrid. The decision to establish an international society of independent drug bulletins was made by an interim committee that met in London (October 1985) and in Paris (March 1986). The interim committee comprised Gilles Bardelay (la revue Prescrire), Danielle Bardelay (la revue Prescrire), Hirokuni Beppu (The Informed Prescriber), Albano del Favero (Informazioni sui Farmaci), Etzel Gysling (Pharma-Kritik), Andrew Herxheimer (Drug and Therapeutics Bulletin), Karl Kimbel (Arzneiverordnung in der Praxis), David Lee (Medicamentos y Terapeutica).

A general assembly was then held in Stockholm (August 1986) at which time the International Society of Drug Bulletins was officially established. The Constitution was registered on 31 March 1987 in London (Bates, Wells & Braithwaite Solicitors) by Andrew Herxheimer, the first chairman.

A few months before the last General Assembly in 1999 in Amsterdam, there was some discussion amongst members about whether the Constitution and Rules of the ISDB should be updated. At the Amsterdam General Assembly there was not a consensus on the amendments that were put forward, so it was agreed that the Committee should organise a debate on the issues. It was subsequently agreed that this debate should occur over the following three years so that informed decisions could be taken to the next General Assembly in September 2002.

Method

Though the Constitution is both the policy statement of our society and the definition of its essential characteristics, you may not be very familiar with it (see electronic edition on our provisional website <<http://prn.usm.my/isdb/articles.html>>). The Constitu-

tion comprises 11 Articles and a set of Rules. The Articles deal with the core elements of the society: Purpose, Definitions, Secretariat, Official languages, Member status, Committee, General meetings, Dissolution, Subscription, Resources and Rules.

The **Article 11 - Rules** stipulates that: "A set of Rules governing the implementation of the Articles hereof may from time to time be voted by members at the OGM on a motion put before it by the Committee.

The said rules shall be appended hereto and shall apply to members in the same manner as the Articles hereof."

There are two Rules at the moment: one regarding subscription as a supplement to Article 9, and one regarding Member status and application files as a supplement to Article 5.

Whether the Constitution and/or Rules need to be updated or amended will therefore be decided at the next General Assembly in September 2002. Note that **Article 7.3 g** of the Constitution stipulates that: "Resolutions to change the Articles or Rules of the Society and to dissolve the Society shall require at least a three-quarters majority vote of a General Meeting and shall be taken by secret ballot."

We should be well aware that amending the Articles of the Constitution could be a major political decision. On the contrary, amending the Rules (aimed at implementing Articles), or adding new ones, may have much less impact on the substance of the Society. Indeed, the fact that a three-quarters majority vote is required to amend both the Articles and the Rules is probably an anomaly. Similarly we should distinguish between minor (and obvious) changes (such as level of subscription fees, 125 Swiss Francs, in Rule I, location of the Secretariat in Paris in Article 3), and major controversial changes (such as membership criteria, definition of a drug bulletin).

Why is the Constitution being debated now? Since the creation of our Society several new situations and issues have emerged that were not considered, or applicable, when the Society was founded. Examples

are: bulletins for consumers, electronic-format bulletins, status of bulletins supported by medicines agencies, status of bulletins publishing research papers, status of bulletins temporarily unable to publish.

In a further article I will present different proposals for amendments put forward by some members. In the meantime you are invited to examine the Constitution and consider if, and what kind of, amendments are needed.

Proposals and counter-proposals will be published in the Newsletter. At the General Assembly we will organise a comprehensive discussion on the subject, with all proponents presenting their position. Then we will proceed to vote.

The debate on the Constitution could be an excellent opportunity to test and reaffirm our identity.

Christophe Kopp
ISDB chairman

ISDB Income and Expenditure for the year ending 31.12.00

Income

Membership fees9,311
Interest received89

Total income£ 9,400

Expenditure

Administration*643
Travel & hotel expenses
(Committee meeting, London).....687
Bank charges143
Consultancy fee (coordinator
feasibility study).....208

Total Expenditure£ 1,681

* the cost of preparing, and distributing the newsletter was covered by Prescrire (France), and the cost associated with collecting membership fees was covered by DTB (UK). Cost covered by Prescrire will be charged to ISDB in 2001.

Funds available at the start of 2001 (includes surplus from 2000)£ 15,152

UPCOMING MEETING

ISDB meeting on what is and what is not an advance in drug therapy

Paris, November 15-16 2001

A working group of ISDB and non-ISDB people will gather in Paris on November 15-16 to put the finishing touches to a Declaration defining what is an advance in drug therapy.

All ISDB members will be involved in the review process of the Declaration.

Background

'Innovation' is the key concept for regulators and industry, who create the impression that an irresistible and faster growing flow of

innovative products should be made available to patients, as rapidly as possible. Yet for ISDB bulletins and the patients, the picture is quite different. A number of ISDB bulletins critically appraise the evidence on all new products released onto the market, and tell doctors, pharmacists, and sometimes consumers, if, and to what extent, these new products add to the clinical possibilities offered by available medicines. Experience has consistently shown over the years that only a small minority of new products released onto the market offers a comparative advantage to patients. The objective of the Declaration is to define what is a 'comparative advantage in therapeutics'.

The Declaration could help demystify the term 'innovation' by qualifying it properly from the patient's viewpoint. It will break 'innovation' into three concepts: *newly marketed items* (any new product or indication), *industrial innovation* proper (technical), and *therapeutic advance for the patient* (clinical benefit). Industry's strategy aims at blurring the definition of the three concepts, either through advertising techniques targeting professionals and consumers, or by imposing its agenda on regulators.

For those of you who are interested in this meeting, please do contact me.

Christophe Kopp
(christophe.kopp@wanadoo.fr)

GOOD / POOR SOURCES

POOR SOURCE

The World Health Organisation to revise the hypertension guidelines

The 1999 hypertension Guidelines must be discarded. Drug companies that still use part of it to promote their antihypertensives should be denounced. Above all the World Health Organisation should withdraw these Guidelines from its web pages (still there in March 2001).

In the June and December 1999 we reported on the biased recommendations made by the guidelines on hypertension published by the World Health Organisation and the International Society of Hypertension. In October 2000 Andrea Tarr and Christophe Kopp published an electronic letter on the subject in the BMJ (see <http://bmj.com/cgi/eletters/320/7246/1362#EL1>).

In 1999 the World Health Organisation promised to revise the hypertension guidelines, as usual in collaboration with the International Society of Hypertension. The Non-communicable diseases Department at WHO euphemistically states on its website that:

"Because of emerging evidence and in order to take into consideration the new principles for guideline development adopted recently by WHO, the hypertension guidelines are currently being reviewed. Special emphasis will be made on public health implications and the evidence-base of recommendations."

According to Joel Lexchin (joel.lexchin@utoronto.ca) who has been asked to sit on one of the three committees, the new Guidelines should be completed by the end of 2001.

Note that in Europe and elsewhere this 1999 Guidelines is still in use. And according to Peter Mansfield (peter.mansfield@flinders.edu.au) from MaLAM (Medical Lobby for Appropriate Marketing): *"Sadly the WHO/ISH hypertension guidelines still influence doctors in Australia. The main promotion of the guidelines has been by drug companies but in 1999 the Heart Foundation of Australia sent to all GPs "Australian" guidelines which are based on WHO/ISH and are very similar."*

Note that so far the World Health Organisation has failed to clarify its relations with

the private sector. In its report of the Executive Board A54/2, dated 30 March 2001, available on the WHA documentation pages (http://www.who.int/waha-1998/EB_WHA/english/ANG_docWHA54bis.htm), we can read that: *"The guidelines on working with the private sector to achieve health outcomes were seen as helping to ensure transparency and avoid potential conflicts. However, members considered that the guidelines needed refinement and they asked the Organization to continue to examine the matter, taking into account the comments expressed at the meeting, as well as additional views that should be obtained by a process of further consultation with Board members. They requested the Director-General to report back to the Board at its 109th session in January 2002"*.

For background information on needed 'refinements' see *Global Compact with Corporations: "Civil Society" responds*, available on Health Action International website (<http://www.globalpolicy.org/reform/2001/0308fel.htm>).

GOOD SOURCES

The Medical Letter

The Medical Letter on Drugs and Therapeutics has started a new section dealing with direct-to-consumer advertising of prescription drugs in the US.

Visit their corresponding website pages where you can download free PDF papers: http://commerce6.ba.best.com/~medlet/html_files/direct_consumer.htm

The Medical Letter is the ancestor of independent drug bulletins. It started

publication in 1959 and is available on subscription only. It now has a circulation of more than 120,000 including practising physicians in every medical specialty, medical educators, interns, residents and medical students.

La Lettre du GRAS

We recommend French speaking people to regularly visit *La Lettre du GRAS* website (<http://www.ulb.ac.be/esp/gras/index.html>). In its March issue

you can find a paper on ethical problems raised by unpublished studies and irrational prescribing of antibiotics.

For more details about *la Lettre du GRAS* see also ISDB Newsletter May 2000, pages 2-3.

Prescriber Update

We recommend the pharmacovigilance reports of the New Zealand medicines agency, an ISDB member through its bulletin *Prescriber Update*.

Website addresses: (<http://www.medsafe.govt.nz/profs/adverse/pharmaco.htm>) and (<http://www.medsafe.govt.nz/profs/PUarticles.htm>)

EDITORIAL METHODS

UNPUBLISHED DATA AND THE HELSINKI DECLARATION

A debate is endemic among ISDB bulletins about whether critical appraisal of newly approved drugs should rely only on published data, or should also include unpublished material. Some editors think that unpublished data, being not peer-reviewed by definition, should be excluded. Others believe unpublished data should be identified to minimise publication bias. When asked whether they use unpublished literature, a group of 36 ISDB bulletins gave the following answer: a minority of responders do use unpublished literature as much as possible, the majority does not, and some responders use it rarely.

Those bulletins searching unpublished clinical trials have to request them from pharmaceutical companies, or from regulatory authorities who are supposed to have in stock published and unpublished studies.

The October 2000 version of the Declaration of Helsinki has been adopted at the 52nd General Assembly of the World Med-

ical Association (http://www.wma.net/e/policy/17-c_e.html). It provides an interesting lever for bulletins searching unpublished data.

In its 16th provision it stipulates that: "...The design of all studies should be publicly available." And in its 27th provision it says: "Negative as well as positive results should be published or otherwise publicly available."

COMMENTS

• William Bredal (*Nytt om legemidler*, Norway) believes some international effort should be made to register all clinical trials and their results in a centrally accessible database.

• Larry D. Sasich (*Public Citizen's Health Research Group-Worst Pills Best Pills*, USA) posting about FDA evaluation of telithromycin on E-DRUG is of direct relevance here: "As a result of a lawsuit Public Citizen filed against the FDA in early 1999, the reviews done by agency scientists of data

submitted by manufacturers in support of the approval of new drugs that go before advisory committees are now available on the Internet 24 hours prior to meetings. Before the settlement of our lawsuit, FDA reviews were not disclosable to the public until after a drug was approved. (...) Unfortunately, the management of drug information, including which information will be published and where, is now but one step in a corporate marketing strategy. We believe that it is no longer possible to conduct independent appraisals of the therapeutic value of new drugs by relying solely on published clinical trials. Research submitted to the FDA that shines a less than favorable light on a new drug is, at times, not published or its publication can be delayed. We urge those who conduct systematic reviews of new drugs to include these FDA reviews in their work for completeness.

• Maria Font (*Dialogo sui Farmaci*, Italy) asks whether the Helsinki Declaration is legally binding, and whether we can request unpublished studies from companies sheltering behind confidentiality.

Editor: To the first question, the answer is no, to the second, yes! For more details on 'confidentiality' and 'secrecy', see the *Uppsala Declaration on Transparency and Accountability in Drug Regulation*, avail-

able from Lisa Hayes, HAI-Europe (lisa@hai.antenna.nl).

- Silvio Garattini (member of the *Committee for Proprietary Medicinal Products* at the European Medicines Evaluation Agency) believes the new provision of Helsinki Declaration is certainly an improvement from the point of view of principles. However to implement the principle there should be a European register where the information about negative and positive clinical trials are collected and made publicly available.

- Ksenija Makar-Ausperger and Bozidar Vrhovac (*Pharmaca*, Croatia) believe the idea is good but not realistic. They ask how manufacturers can be forced to provide negative trials.

- Danielle Bardelay (*la revue Prescrire*, France) says that according to a French law (article L.1123-8) and probably to laws of other countries, investigators and sponsors must register clinical trials to the national medicines agency. They must also inform regulators of any unexpected trial interruption. Registers of clinical trials therefore exist in this country, and they should be accessible to professionals and the public. Though France has no equivalent of the US Freedom of Information Act, Article XV of the French *Déclaration des droits de l'homme et du citoyen* stipulates that any civil servant is accountable to the public as regards his/her administration. Moreover, a French law (79-587, July 1979, art.8) stipulates that information of the public is warranted for anonymous administrative documents. Clinical trial registers fall within this category of public documents. She reminds us of the *Eric Declaration* on communication in pharmacovigilance published in 1997 (see ISDB Newsletter December 1999), which specifies that: "All the evidence needed to assess and understand risks and benefits must be openly available. Constraints, on communication parties, which hinder their ability to meet this goal must be recognised and overcome". And the *Uppsala Declaration*, already mentioned, specifies that: "Copies of the pharmacological, toxicological and clinical reports submitted to obtain the initial or modified registration of a drug and those added to the file subsequently" should be available, which is not the case at the moment in France.

- Gilles Bardelay (*la revue Prescrire*)

thinks that if drug bulletins are to carry out systematic review on new treatments, they have to consider all data, good and poor, published or not, before sorting out the evidence. The *Prescrire* staff use all documents available to prepare papers in the New Product section. He stresses the invaluable input of FDA documents. He also thinks this revised Helsinki Declaration is a welcome tool for ISDB members willing to fight secrecy still prevailing in medicines agencies. Drug companies not complying with these provisions can now be morally pressured in our bulletins as violating the Helsinki Declaration.

- Alberto Figeras (*Institut Català de Farmacologia-Bulleti Groc*, Spain) totally agrees with 16th and 27th provisions, but asks: Where? How to do? He suggests that designs and results of all studies might be publicly available via the Internet from a big database hosted by an international and allegedly independent society/group such as the World Medical Association. The cost for updating this database as well as developing useful search engines could be financed by a small fee that all investigators should pay to get their study design introduced in the database. And no editor should accept to publish a paper showing results of a study whose design had not been introduced in that database. And Ethical Committees should search the database before approving a study in their hospital/centre.

- Rokuro Hama (*Non-Profit Organization Japan Institute of Pharmacovigilance for Evidence-Based Healthcare* and its bulletin for consumers, Japan) also underlines the need for unpublished studies, including randomised and non-randomised trials, as well as unpublished animal toxicity studies. He repeatedly tried to get the study designs of mega-trials sponsored industry in Japan: company members and investigators refused to provide information. Very unfair he says!

- Philip Sax (*Pharma*, Israel) says: "Until now we only handle published data, although we have quoted from another bulletin (e.g. *Prescrire*) when they have managed to get unpublished data which we feel is critical or adds further light. I don't even try to get the local regulatory authorities here to give us material as they are sure to refuse in the name of confidentiality. This "policy" of ours may change if there was effective 'leverage' that could be applied (e.g. WHO

declarations). Then, we may need to build up expertise and confidence in handling such (non peer-reviewed) data before actually using it. The other point is that until we see and use this sort of data ourselves on a regular basis, I'm not sure to what degree it really would add to the quality of the Bulletin. Some questions - couldn't data being submitted to health authorities also have a bias/spin on it, even if it isn't a publication bias? Do companies always submit all negative or neutral study results to the regulation authorities?

- Björn Beermann from *Information from Lakemedelsverket* (Swedish Medical Product Agency) completely agree with the majority of the respondents. An open data base is absolutely necessary. Ethics committees should not approve clinical studies unless it is clearly stated in the protocol that the Helsinki declaration will be followed in all aspects. It is not possible to give independent drug information unless you include unpublished studies in the evaluation. This is valid especially for recently approved drugs. It is very easy demonstrate, just check how many clinical studies are available via PUBMED at the date of approval of a drug. In many cases none.

[Many thanks to those of you who contributed to this piece. A debate will be organised on the use of unpublished literature at the next General Assembly in September 2002.]

WARNING!

Note that the ISDB E-mail account has been closed. A new address will be reinstated once the new website is upgraded.

THE REGULATORY WATCHDOG

QUOTE UNQUOTE

• 'He thought he saw an Argument That proved he was the Pope. He looked again, and found it was A Bar of Mottled Soap...'

Lewis Carroll

• 'The latest corporate buzzwords of 'innovation' and 'creativity' can be credited to the influence of the European Roundtable of Industrialists (ERT). In November 1998, the ERT's Working Group on Competitiveness, chaired by Solvay's Baron Daniel Janssen, produced a report entitled Job Creation and Competitiveness through Innovation, where the business terms can be said to have been first coined. The report describes a global economy in turmoil with an, "irresistible flow of newer, better or cheaper goods and services that is constantly making older products uneconomic or obsolete - along with the jobs attached to them." In order to 'compete', the report argues, the European Union needs to do everything it can to foster corporate 'innovation' in order to unlock the 'creative' potential of European industry. Since then, other corporate actors, and now the EU

leadership, have adopted the ERT's positive-sounding language. But at the heart of these terms, are the key concepts espoused by the ERT for years now: rapid deregulation, unbridled free markets, and institutional reforms which boost European corporations' 'competitiveness on the international stage'.

Corporate Europe Observer issue 7 (<http://www.xs4all.nl/~ceo/observer7/ebs.html>)

• 'Research is being driven by lawyers, financial experts, salesmen and market strategists who are unable to develop new ideas'.

Jürgen Drews (former research director at Roche)

In Quest of Tomorrow's Medicine. New York: Springer-verlag, 1999

• 'Top managers of the industry have rarely believed their own external propaganda concerning success of their internal research'.

David F Horrobin

Innovation in the pharmaceutical industry
J R Soc Med 2000; 93: 341-345

• 'India said an example of a real global partnership would be if pharmaceutical companies were to develop cures for diseases that mainly affect poor citizens in the developing world, even though there would be less profit for them'

Global Partnerships initiative (Go-Between 2001: n°84 page 13, United Nations Non-Governmental Liaison Service
www.unsystem.org/ngls)

• 'Drug companies now spend more on branding and marketing than on research and development'.

Financial Times October 24, 2000

• 'Glaxo-SmithKline...boasts that it spends \$400,000 an hour on research and development. But it invests nearly twice as much in sales and marketing. It employs 10,000 scientists, and 40,000 salesmen'.

Financial Times March 20, 2001

• 'To meet its constitutional commitment, EMEA should be required to identify any qualifying advantage of a new product over existing ones, including cost'.

Garattini S and Bertele V Policing the European pharmaceutical market's priorities Eur J Clin Pharmacol 2000; 56: 441-443

DIFFERENT REGULATORY STATUS OF MEDICAL PRODUCTS

Medicines agencies differ in quality and degree of transparency

Glucosamine is regulated as a dietary supplement in the USA, as a drug in Italy; it is differently regulated in other countries. Following publication in *The Lancet* of a paper in favour of glucosamine in the treatment of osteoarthritis, the March *Worst Pills Best Pills* issue shows these different regulatory statuses have dramatic impacts on the quality of the preparations. It also shows

the US Freedom of Information Act makes the FDA more transparent than many European medicines agencies as regards access to evaluation data.

(...) The results of this study (Editor's note: a Belgian study appearing in the January 27, 2001 issue of *The Lancet*) cannot be translated to the numerous unregulated glucosamine products sold in health food stores and pharmacies in this country. Because glucosamine can be sold as a dietary supplement under the Dietary Supplement Health and Education Act of 1994,

manufacturers of glucosamine products and other dietary supplements are not required to follow pharmaceutical-type Good Manufacturing Practice (GMP) guidelines. Such GMPs ensure that what is listed on the label is in fact in the bottle and, among other things, tablets and capsules consistently disintegrate and dissolve rather than passing straight through the body without being absorbed. The Council for Responsible Nutrition, a trade group representing largely unregulated dietary and herbal supplement producers in the U.S., is having a field day trying to piggyback results for Xicil, which is regulated as a drug in Italy, to the products sold by their members that are not required to adhere to pharmaceutical type GMP guidelines. Although the Council maintains that its members follow GMPs, they fail to mention that the GMPs that they

follow are food GMPs that only require supplements to be produced in relatively clean facilities, not the more stringent pharmaceutical GMPs.

We have several caveats concerning the interpretation of the Belgian study. First, even though the glucosamine that was used in Xicil is regulated as a drug in Italy and some other European countries, not all drug regulatory authorities are equivalent to the FDA. In many European countries, Germany for example, the manufacturer and content of natural products is regulated but these products have never been reviewed for effectiveness. Since Europe has no Freedom of Information Act, the public has no way of knowing what the basis was for allowing glucosamine to be sold for osteoarthritis. There may be none.

Second, the boundaries between science and promotion have been blurred. It is no longer possible to accept at face value the veracity of data from published clinical trials — even those appearing in the most prestigious medical journals such as *The Lancet*. What is required is a rigorous review process that is open to the public, something that is lacking even in this country (...).

The National Institutes of Health is sponsoring a large study of glucosamine and chondroitin in the treatment of arthritis. This study will not be completed until March 2005. We strongly support this type of drug development research.

[Relevant extracts reprinted from "The Italian Drug Glucosamine (XICIL) In the Treatment Of Osteoarthritis", *Worst Pills Best Pills* March 2001, page 20-21]

THE DECLARATION OF HELSINKI AND THE PLACEBO-CONTROLLED IDEOLOGY

In the E-Drug posting below, Peter Lurie from *Public Citizen's Health Research Group* shows us how to draw on the Declaration of Helsinki. Well done *Public Citizen*!

E-drug: Surfaxin trial

About 6 weeks ago we wrote to you about a proposed study by Discovery Labs of a surfactant for the treatment of Respiratory Distress Syndrome in neonates. While the company planned a study comparing their drug to one of the four FDA-approved surfactants in Europe, they also planned a placebo-controlled trial in Latin America. We wrote to Health and Human Services Secretary Tommy Thompson asking that the trial be redesigned so that all patients received active treatment. Today we learned that the company will be going forward with an active-controlled trial instead (no placebo). Beyond the importance of assuring active treatment for all infants in this particular study, the decision should be a message

that one cannot conduct studies abroad that one would not conduct in the country of the sponsoring company. The study is now consistent with the latest version of the Declaration of Helsinki, which requires that "*The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.*"

Public Citizen's original letter on this can be found at <http://www.citizen.org/hrg/PUBLICATIONS/1558.htm>. Our press release announcing the redesign of the study can be found at <http://www.citizen.org/hrg/PUBLICATIONS/1564.htm>

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[See 'Surfactant trial in Latin American infants criticised' in *BMJ*, 10 March 2001]

NEWS OF BULLETIN

HEALTH ACTION INTERNATIONAL

THE WORLD HEALTH ORGANISATION AND ONE OF ITS CURRENT PARTNERSHIPS...OH SORRY, INTERACTIONS!

We reprint below a paper by Anita Hardon published in *HAI-Lights*-March 2001 (vol 6, No 1). This is a timely report on the drawbacks of public/private business that the World Health Organisation encourage.

The paper deals with the Global Alliance for Vaccines and Immunization (GAVI). From the report it is hard not to

conclude that the main problem originates in the strong partners of the Alliance, the Bill Gates foundation and pharma companies, who meddle in the allocation of resources and the type of vaccines to be offered.

Even transparency of decision-making will not prevent Bill Gates from quietly blue-washing his image, or pharma companies from setting their profit-driven ►►

► agenda under cover of humanitarian motives.

The only solution would be for experts independent of vaccine manufacturers, together with national health authorities, to decide on immunisation priority and allocation of resource. This is the only way to respect dignity of targeted people and equity in vaccine coverage.

Immunisation for All?

A critical look at the first GAVI partners meeting by Anita Hardon [i]

"Concerns about rational drug use, accountability and sustainability have led HAI Europe members to scrutinise the growing number of public/private interactions involving pharmaceuticals and health care services. One of the largest and most publicised of these is the Global Alliance for Vaccines and Immunization, better known as GAVI. This new alliance was launched in early 2000. It was initially backed by a US\$750 million donation from computer magnate, Bill Gates. Since then, it has received significantly smaller grants from a number of governments. In its short history, the Alliance's structure and funding base have already altered the way in which vaccination policy is developed and implemented. The financial resources at its disposal have made it perhaps the most important actor in the vaccination field today.

In our lead story, HAI member Anita Hardon analyses the impact that GAVI has already had on vaccine policy and reports on the first GAVI partners meeting held in The Netherlands late last year."

The road to GAVI

The global effort to immunise the world's children is a remarkable success story. Building on the gains of the global smallpox eradication programme, the World Health Organization (WHO) launched the Expanded Programme on Immunisation (EPI) in 1974. At the time less than 5% of the world's children were immunised against the six main target diseases, diphtheria, tetanus, whooping cough, polio, measles and tuberculosis, though vaccines for them were inexpensive. The EPI effort was accelerated when the Universal Childhood Immunisation (UCI) campaign was adopted. At the 1990 World Summit for Children, the United Nations Children's Fund (UNICEF) declared that the

UCI target of 80% had been achieved.[ii] When this success was announced in 1990, the main actors initially planned to continue the effort to reach the 10-20% of the population still lacking vaccine coverage. As the then assistant Director-General of WHO stated:

"Vaccination coverage does not only need to be sustained, ... it needs to be increased. The reason for setting a goal of 90% coverage by the year 2000 is that this requires extending vaccination to the currently unreachd. These are the poorest of the poor, and those to whom vaccination especially benefits, as they are at special risk from disability and death from vaccine preventable diseases. [iii]"

Instead, the thirty year effort to immunise children and adults began to break apart in the 1990s. The change happened for a number of reasons including war, new diseases (such as HIV/AIDS), donor fatigue and a change of leadership at WHO. (Dr Hiroshi Nakajima of Japan became the organisation's new Director General, replacing Dr. Halfdan Mahler, a staunch advocate of "Health for All" [iv]) These changes influenced international agencies involved in immunisation programmes and caused them to decrease their emphasis on reaching out to under-served populations. In the 1990s, agencies followed more selective approaches, including the eradication of polio and the development and introduction of new and improved vaccines.

The results of immunisation efforts in the 1990s were dismal. Immunisation coverage deteriorated in most of the world's poorest countries. By 2000, global coverage for the six traditional vaccines had dropped to 75%[v]. More disturbing still, UNICEF identified 19 countries, mainly in Africa, where diphtheria, tetanus and polio (DTP3) coverage dropped below 50%. In another 22 countries, fewer than 75% of children receive DTP3 immunisation. Some countries were hit even more severely: Nigeria's overall coverage went from 80% in 1990 to 27% in 1998; the Democratic Republic of Congo's immunisation rate dropped from 46% to 25% for the same period, while Togo went from 100% coverage to little more than half of that (54%)[vi]. The result is an estimated 3 million unnecessary vaccine preventable deaths per year[vii].

How GAVI works

This deterioration of immunisation ser-

vices is now being addressed by a multi-million dollar Global Fund for Children's Vaccines launched by the Global Alliance for Vaccines and Immunization (GAVI), a public-private venture formally launched at the World Economic Forum in Davos in January 2000. GAVI's strategy involves improving access to sustainable immunisation services, expanding the use of all cost-effective vaccines, accelerating the introduction of new vaccines, speeding up efforts to create new vaccines and making immunisation a central part of assessing international development efforts[viii]. Its founding partners include the WHO, UNICEF, the World Bank, The Bill and Melinda Gates Children's Vaccine Program, the Rockefeller Foundation, the International Federation of Pharmaceutical Manufacturers' Associations (IFPMA) and some national governments.

The Global Fund and GAVI were created when the Bill and Melinda Gates Foundation made a US\$750 million donation to reach a "simple" goal: "to fulfill the right of every child to be protected against vaccine-preventable diseases of public health concern"[ix]. Since this initial donation, the Fund has received commitments from the governments of the US (\$US50 million), Norway (US\$125 million), the United Kingdom (\$US5 million) and The Netherlands (US\$100 million). This massive monetary support to the Fund has revitalised global immunisation efforts.

GAVI documents state that the Global Fund's Board decides on the allocation of resources to projects and programmes that GAVI has recommended. The Fund is not obliged to follow GAVI's recommendations. Responding to queries on the composition of the Global Fund's Board, a communication officer for the Bill and Melinda Gates Vaccines Programme explained that, at present, it had renewable and rotating members.

A first assessment of GAVI

The Global Fund's operations and the GAVI were discussed at the first biannual meeting of GAVI partners held in Noordwijk, The Netherlands from 20-21st November 2000. At the meeting, members of GAVI's Board and its task forces presented summaries of the progress made during the past year. Through an independent review process, GAVI's Board has recommended to the Global Fund that 23 countries receive

support to strengthen their national immunisation plans. Thirteen countries were selected in September. An additional ten were chosen during the Board meeting preceding the GAVI partners meeting

Details of the first round of approvals reveal that a total of US\$150 million in vaccines and funding [x] is to be given to the 13 countries already involved over a period of five years[xi]. Details on the first disbursements (2000/2001) reveal that approximately 10% of these funds are earmarked to strengthen immunisation services, while 90% will go towards introducing new vaccines, mainly hepatitis B[xii]. GAVI policy encourages the use of the newly developed DTP-hepatitis B vaccine, especially in countries with a weak immunisation programme. The emphasis on the introduction of new and under-used vaccines in GAVI reflects a more general shift away from equity towards technological innovation and disease eradication in global health programmes. This appears to indicate a fundamental move in vaccine policy from the values of the Post Alma-Ata (Primary Health Care era). The dominant themes in international health at that time included community participation, the right to health, and equitable distribution of health resources. Now in the opening days of the new millennium, international health policy makers involved in immunisation programmes seem to view developing countries no longer primarily as recipients of internationally procured essential vaccines, but rather, as markets for new ones.

By spending such a large amount of its resources on new vaccines, GAVI and the Global Fund run the risk of compounding health inequities in the poorest countries which they have prioritised for support. In nine of the countries selected for support in the first round, immunisation coverage remains below 75%. However, under new arrangements, the remaining 25% or more are likely to remain "unserved". By introducing a hepatitis B vaccination in these countries, children who are already being immunised with the traditional EPI vaccines will be protected against yet another disease. The under-reached children are most likely to be those living in the worst poverty. Another concern, acknowledged at the Noordwijk meeting by a spokesperson from the Vaccines Supply Division of UNICEF, is that the rapid increase in demand for the hepatitis B-DTP combination vaccine cannot be met.

GAVI's appeal for industry

The emphasis on the introduction of new vaccines makes GAVI an alliance in which industry is willing to participate. The GAVI Board's seats include two for industry - one for an Organization of Economic Cooperation and Development (OECD) industry representative and one for an industry representative from a developing country. Jean Stephenne, president of SmithKline Biologicals (a company producing the combination DTP-hepatitis B combination which is now in great demand) outlined in one of the meeting's keynote speeches the conditions for industry participation in the Alliance. This included a guarantee for "reasonable prices", support for a credible and sustainable market, respect for international property rights, a tiered pricing system including safeguards against re-export of products back from developing countries to high-priced markets, and a prohibition on compulsory licensing[xiii]. In plenary discussions and breakout sessions in Noordwijk, industry representatives involved in vaccine development stressed the need to rely on research-based companies to develop the needed new vaccines, and said that they opposed technology transfer proposals. They stressed that vaccine development is too complex for public research institutes and local producers in developing countries. "Push and pull" mechanisms to accelerate vaccine development were proposed, involving public sector subsidies to companies to conduct clinical trials and set up manufacturing plants.

The GAVI partners appeared unconcerned about some possible conflict of interest between the large research-based companies' interest in markets for new products and the public health objective of preventing childhood mortality in developing countries. In what is proposed as the "win-win-win" paradigm, there is little room for critical questions.

Asking critical questions

The problem with the new ideology governing public/private interactions is the firm conviction that everyone benefits and no one loses. In the programmes approved by GAVI, developing country governments will join hands with multilateral and bilateral agencies to increase the number of children reached by the services who receive new, expensive and under-used vaccines. Those children not reached by current immunisation pro-

grammes will probably lose out again. As inequity in access to vaccines increases, they remain the losers.

While many developing countries have seemed eager to benefit from the Alliance's support, some lone voices of dissent could be found in Noordwijk. "We know what needs to be done," said Dr. Muga, a representative of the Kenyan Ministry of Health, during the meeting's open forum. "GAVI partners don't take the time to find out why we don't do what we should be doing." He stressed the need to support local systems and enable people at country level to perform.

GAVI's effects on the UN

Have public/private interactions, such as GAVI, weakened or strengthened the role of UN agencies including the WHO and UNICEF? This question must be asked remembering that they achieved near universal immunisation coverage by 1990. Other important questions arise from the fact that, in GAVI, UN agencies are partners, and no longer the leaders. WHO's Director General has been appointed the Board's chair for its first two years and she will be followed by Carol Bellamy, UNICEF's Executive Director for another two years. But it is unclear who will lead the initiative after that. GAVI's structure also includes no clear mechanisms for accountability nor is there transparency in its decision-making. Decisions are made by the board which is dominated by donors and Northern representatives (including the Gates Foundation and representatives from the industrialised country governments which have contributed to the Global Fund).

In Noordwijk, the GAVI Board first met with other partners and made a number of key decisions including which diseases would be the focus of the vaccine research and development programme. The first GAVI partners meeting felt somewhat like a public relations event: partners were told what was happening, but given little opportunity to contribute to strategy development and decision-making. By contrast, in the UN system, there are some mechanisms for accountability, e.g. during General Assemblies. And importantly, in the UN structure, developing countries rather than donor countries and agencies, hold the majority vote.

Further concerns involve the lack of sustainability. From 1990, in the era of donor fatigue, developing country governments ►►

► started to develop mechanisms to become more independent in vaccine needs. They were supported in this by the UNICEF Vaccine Independence Initiative. Under GAVI, donor dependence for the procurement of vaccines is being reinforced. What will happen in five years' time when the Gates Foundation donation has been spent? Will the necessary global, political will still exist to support immunisation programmes in the poorest countries? Or will these countries be left to find resources for the expanded, and more expensive, immunisation programmes that GAVI brings? As William Muraskin, a writer who has studied the politics of public health commented on the Gates initiative: "They are as bright as hell, and I'm very impressed with the Gates people, but it doesn't answer the question of sustainability." He continued, "Bandwagons can stop as well as go." [xiv]

It is difficult to criticise a vaccine initiative. No one is against increased immunisation coverage. That isn't the real issue. Rather, what needs to be examined and discussed openly is the question of who is going to direct these important efforts and make sure that they reach the people who most need them. Who will ensure that public health needs are addressed before the private sector agenda or that of the research-based industry? Can private foundations, providing the overwhelming majority of funds for such efforts, be held accountable in the way that governments or UN agencies can? And is it really their role to provide the financial support to vaccinate the world's children? What responsibility do national governments have to continue their commitment to reach this crucial goal? As Jeffrey Sachs, an international economist at Harvard University and chair of the WHO's Commission on Macroeconomics and Health has said, "It's not a year or two of help that we need, but it's 20 years of help. What Gates has done is fantastic. But Gates by himself can't carry the world on this." [xv]

1- Anita Hardon is an Associate Professor at the University of Amsterdam, where she directs the Medical Anthropology Unit. She led the transnational team "Global Immunization Policy and Technology Development" of the Social Science and Immunization project (1994-1998), and has also conducted policy-oriented research in other fields of international health, including extensive field research on the use and distribution of medicines in diverse health systems, and studies on gender and reproductive health. She chairs the HAI Europe Foundation Board.

2- The achievement is a global estimate: in many countries coverage rates had not yet reached 80%; and within countries there were also still disparities in immunisation coverage.

3- Henderson, 1994, P. 9 .

4- The Health for All concept started in 1977 when the World Health Assembly determined that the main social target for governments and WHO should be "the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life", otherwise known as "Health for all by the year 2000" (resolution WHA30.43) taken from Implementation of the Global Strategy for Health for All by the year 2000, Eighth report on the world health situation, Vol. 1, WHO, Geneva.

5- The State of the World's Children 2001, UNICEF. <http://www.unicef.org/sowc01/tables/table3.htm> (back...)

6- Donnelly, J. Immunizations plummet in poorest nations wars, funding cuts blamed for decline, The Boston Globe, 13 Nov 2000, p. A1.

7- Brundtland, GH, Statement at GAVI symposium, Oslo, Norway, 13 June 2000., http://www.who.int/director-general/speeches/2000/20000613_oslo.html.

8- Summary of GAVI strategy from its webpage: <http://www.unicef.org/gavi>

9- GAVI information, 26 Jan 2001, <http://www.who.int/vaccines/aboutus/gavi.htm>

10- Global vaccine fund commits US\$150 millions in vaccines and funding over five years to 13 developing countries, press release, WHO, 20 Sept 2000, <http://www.who.int/inf-pr-2000/en/pr2000-GAVI13.html>

11- The initial 13 countries include: Cambodia, Côte d'Ivoire, Ghana, Guyana, Kenya, the Kyrgyz Republic, Laos, Madagascar, Malawi, Mali, Mozambique, Rwanda, and Tanzania.

12- See GAVI, October 2000. Detail of first disbursement from the Global Fund for Children's Vaccine. <http://www.vaccinealliance.org/reference/1stdisburs.html>. The Global Fund will provide three sub-accounts for:

1. the development of immunisation services as part of the health system
2. introduction of new and under-used vaccines and associated safe injection equipment
3. research and development of vaccines for diseases which are prevalent in developing countries.

The last account is not yet operational. The first two sub-accounts are only open for the 74 countries with per capita income below US\$1,000/year. Countries with an immunisation coverage below 50% can only request support from the first sub-account - they are not entitled to funds for new and under-used vaccines.

13- Compulsory licensing is a provision in the global trade agreement on intellectual property rights (TRIPs) that can help address the negative effect of patent monopolies. Compulsory licensing is the granting of a license to a third party without the consent of the patent holder. It can be issued on various grounds including public health. The patent holder receive remuneration for the license. Compulsory licensing is a legal option within the TRIPs agreement.

14- Donnelly, J. 2000.

15- Ibid.

[Reprinted from Health Action International web pages http://www.haiweb.org/pubs/hailights/mar2001/mar01_lead.html ; see related article in the BMJ 2001; 322: 754 (31 March)]

Kusuri-no-check-wa-inochi-no-check goes on the web <http://www.npojip.org/>

The first Japanese drug bulletin for the public has launched its website, in Japanese and English. For more details regarding this emerging bulletin, see February Newsletter on page 19.

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

La revue Prescrire and its balance sheet

Being financially independent of drug companies means ISDB bulletins are dependent on someone else: subscribers, consumers' organisation, public funding, non-profit bodies, the World Health Organisation, etc. *La revue Prescrire* is totally dependent on subscribers, and it has published its balance sheet annually (see March issue) for many years.

La revue Prescrire is published by a non profit organisation (*Association Mieux Prescrire, AMP*) comprising doctors and pharmacists. The journal is accountable to its subscribers (represented in *AMP*) who actually control the journal through their annual and renewed subscriptions. As a company, the journal and the staff depend on subscribers who need to be informed of the use of their money.

Should your bulletin make budget and financial matters public, please could you let us know. In this largely opaque domain of medical information, transparency of accounts of ISDB bulletins is an asset.

REMINDER Correct dating of reprinted articles

Do not forget to specify clearly the date of first publication of articles in original bulletins when reprinting or translating them in your bulletin. If a bulletin has editions in other languages, specify the date of first publication in the original language. Indeed, experience has shown that subsidiaries of multinational drug companies can use the delay between first publication and reprint publication (sometimes over 1 year) to cause trouble to the reprinting bulletin. They can argue that new evidence has not been taken into account in the reprinted article. Correct dating is a safeguard against these troubles.

Drug representatives under scrutiny in Italy

As reported in *Ricerca & Pratica* 2000; 16: 231-237 (Italy), a group of general practitioners examined the organisation and contents of visits by representatives. They designed a set of rules:

- limiting the number of visits
- banning counterinformation on competing molecules
- banning gifts or incentives
- monitoring the quality of the information delivered.

This Italian experience can be added to others, like the *No free Lunch!* organisation in the USA (see ISDB Newsletter, February 2001, page 3), and *Prescrire's* reps monitoring network in France (see ISDB Newsletter, October 2000, page 8). *La Lettre du GRAS* in Belgium is also keeping a watch on drug advertising (see ISDB Newsletter, May 2000, page 2), as well as the Medical Lobby Appropriate Marketing internationally.

We would welcome reports on similar initiatives.

THE DRUG AND THERAPEUTICS BULLETIN - WHY NOT ZANAMIVIR?

Here is an article reproduced from the February 2001 issue of *DTB*.

In 1999, *Drug and Therapeutics Bulletin* (*DTB*) and the National Institute for Clinical Excellence (NICE) concluded independently that zanamivir (Relenza) should not be used in managing patients with influenza (1,2). Recently, after reviewing further evidence, NICE revised its position regarding use of zanamivir in 'at-risk' adults: it now recommends that, under specific circumstances, the drug should be prescribed for patients at risk who are able to start treatment within 48 hours of the onset of influenza-like symptoms (3). We disagree with this revised advice (4) for reasons we explain here.

NICE guidance

NICE is charged with providing the NHS in England and Wales with independent advice on the effectiveness and cost-effectiveness of selected health technologies, including medicines, devices, diagnostics and procedures. NICE bases its guidance on appraisals that are conducted by external agencies and reviewed by the Institute's standing Appraisal Committee.

The revised zanamivir Guidance

The revised guidance for zanamivir (3) was published on 21 November 2000. The

detailed appraisal of the drug (comprising an initial Health Technology Assessment Report (5) plus a Supplement (6)) was published 3 weeks later on the Internet (at www.nice.org.uk). The guidance is intended for "at-risk adults", whom it defines as those whose age (65 years or over) or underlying medical problems (e.g. chronic respiratory disease requiring regular medication, significant cardiovascular disease, diabetes mellitus, being immunocompromised) puts them at particular risk of experiencing more prolonged and/or severe illness, or of developing complications, as a result of an influenza virus infection (3).

Key evidence

The revised advice appears to be based primarily on meta-analyses of data pooled from six randomised placebo-controlled trials of zanamivir, involving "some 800" at-risk patients (3,6). Only one of the trials was conducted specifically in at-risk patients (a recently published study (7) involving 525 patients with asthma or chronic obstructive pulmonary disease). The guidance makes three key statements about the collated evidence (3):

- "In the overall pooled analysis of at-risk individuals, the duration of symptoms of influenza is reduced by 1.2 days (95% CI 0.1 to 2.2) from about 6 to 5 days in the ITTP [intention-to-treat population]."
- "Overall zanamivir reduced the ►►

► absolute risk of complications requiring antibiotics in the ITTP by 6% (95% CI: 0 to 11%).”

• “No reliable data are available as to the impact of the use of zanamivir on hospitalisation rates or mortality.”

Problems with the evidence

Most of the trials used in the pooled analyses (6) did not specifically recruit at-risk patients. Indeed, such individuals (identified using a variety of ‘at-risk’ criteria) formed only a small minority of participants in these studies (5,6). The pooling process combined data from these potentially unrepresentative subgroups with results from a trial restricted to at-risk patients, and the robustness of the resulting analyses is therefore questionable.

It is also arguable whether ‘complications requiring antibiotics’ (as highlighted in the revised guidance (3)) is a reliable proxy measure of serious outcomes of influenza, such as hospitalisation or death. Such complications may be relatively minor (e.g. sinusitis or tracheitis), and it is not clear from the appraisal report what proportion of all the at-risk patients in the pooled analysis had more severe complications (e.g. pneumonia)(6). Nor is it clear exactly what criteria were used for initiating antibiotic therapy (5,6). Also, none of the trials in the pooled analysis assessed ‘complications requiring antibiotics’ as a primary outcome measure. This and the “considerable heterogeneity” of zanamivir’s effect on such complications in the studies (6) further limits the robustness of the meta-analysis. In any case, the estimated reduction

in complications requiring antibiotic use (6%, 95% CI 0–11%)(3,6) does not reach conventional levels of statistical significance.

The suggestion that zanamivir shortens symptom duration (by about 1 day) in at-risk patients is not a compelling reason for prescribing the drug, given the small size of this benefit and the unconvincing evidence that such treatment helps prevent serious outcomes of influenza. Also, no published trial has assessed directly how zanamivir’s effect on influenza symptoms compares with that of symptomatic therapy, such as paracetamol or ibuprofen, taken regularly throughout the illness.

Potential conflicts to be considered

The current summary of product characteristics (SPC) for zanamivir suggests that the drug has unproven efficacy in at-risk patients (8); this seems at odds with, and is not mentioned in, the revised NICE guidance (3). The SPC also refers to the risk of bronchospasm with zanamivir, particularly in patients with asthma or chronic obstructive pulmonary disease; again, this issue is not discussed in the revised NICE guidance.

NICE has proposed that zanamivir could be supplied directly by nurses and community pharmacists working to Patient Group Directions (PGDs)(3). This suggestion must be weighed against advice from the NHS Executive (9), which warns that great care should be taken to ensure that any inclusion of antimicrobials in a PGD “is absolutely necessary and will not jeopardise strategies to combat increasing resistance.”

Conclusion

Despite guidance given by the National Institute for Clinical Excellence (NICE) and having considered the data published by the Institute, we believe that, on current evidence, zanamivir should not be used in the NHS for treating patients with influenza; this includes those at particular risk of developing complications of the infection.

[M=meta-analysis; R=randomised controlled trial]

1- Zanamivir for influenza. *DTB* 1999; 37: 81-4.

2- National Institute for Clinical Excellence. *Guidance to the NHS on zanamivir (Relenza)*. October 1999. [Now published as *Old Guidance – Zanamivir (Relenza)*. Available: <http://www.nice.org.uk>].

3- National Institute for Clinical Excellence. *Guidance on the use of zanamivir (Relenza) in the treatment of influenza*. Technology Appraisal Guidance - No. 15. Available: <http://www.nice.org.uk> [21 November 2000].

4- *Treatment Notes*. *DTB* 2000; 38: 96.

5- Burls A, Clark W, Stewart T et al. *Zanamivir for the treatment of influenza in adults*. Health Technology Assessment Report. Available: <http://www.nice.org.uk> [12 December 2000].

6- Burls A, Clark W, Stewart T et al. *Zanamivir for the treatment of influenza in adults*. Supplement to the Assessment Report. Available: <http://www.nice.org.uk>

7- Murphy KR, Eivindson A, Pauksens K et al. Efficacy and safety of inhaled zanamivir for the treatment of influenza in patients with asthma or chronic obstructive pulmonary disease. A double-blind, randomised, placebo-controlled, multicentre study. *Clin Drug Invest* 2000; 20: 337-49.

8- *Relenza*. Summary of product characteristics, UK. GlaxoWellcome UK Limited, June 2000.

9- *Patient Group Directions [England only]*. Health Service Circular: HSC 2000/026. NHS Executive, August 2000.

TREATMENT NOTES FROM DTB

Drug and Therapeutics Bulletin (*DTB*) in the UK has been producing independent advice for doctors and pharmacists for 40 years. Now, more than ever, patients desperately need access to similar information too. So, two years ago, *DTB* set about filling this gap. The aim was to adapt *DTB* articles into patient-friendly versions. These are intended to be distributed to patients in the context of a consultation with a health care professional, as an independent resource for the patient

but also to support the message of the health care professional.

How Treatment Notes was developed

Before launching *Treatment Notes*, the *DTB* team spent 6 months looking at what makes good patient information. As well as working out how best to present scientific information in patients’ terms, they also examined how language, font size and style, colour, pictures and other layout issues can

be used to enhance readability. The first few pilots were tested in focus groups with patients and with health care professionals, after which every aspect of the leaflets was examined again in detail.

By January 2000, the first titles were launched. Since then 14 have been published in all:

Fighting flu

When and how to lose weight

Inhaled steroids for children with asthma

Which Pill?

Taking and stopping antidepressants
Postnatal depression
Helping children with constipation
Bandage treatment for leg ulcers
Worried about falls?
Medicines to help you stop smoking
Operations for heavy periods
Polycystic ovary syndrome
When your child has epilepsy
Helping your heart

Every leaflet goes through a rigorous production process: each one is tested with patients; its circulated to as many as 80 people for comments, including specialists, GPs, pharmacists, nurses, patient groups and drug companies; and every fact is double-checked against original sources.

How are Treatment Notes being received?

So far, 110,000 copies of *Treatment Notes* have been sold. Orders are coming from a variety of places, with hospital specialists and GPs being the main purchasers. Community pharmacists can also subscribe through an arrangement with their national organisation. The size of orders has ranged from one pack of a single title to bulk orders from local GP groups or health authorities. National Health Service (NHS) libraries are also buying the leaflets for distribution to patients.

The most popular titles are those on antidepressants and anti-smoking treatments. Last year, *Fighting flu* – one of the very first *Treatment Notes* – was commended in the British

Medical Association patient information awards.

What next?

As *Treatment Notes* go from strength to strength, DTB hopes to make them available more widely across the NHS – perhaps electronically or through bulk deals for paper copies. Four more titles are planned for this year (possible topics include chlamydia, hyperactive children and female incontinence) and more for 2002.

All *Treatment Notes* are available for review purposes only on www.which.net/health/dtb/treatment.html.

For more information, contact Emily Sowter, Editor of *Treatment Notes* (emily.sowter@which.co.uk).

LA REVUE PRESCRIRE

ESSENTIAL DRUGS CONCEPT: STILL VALID

When used correctly, a selection of well-assessed drugs with good risk-benefit ratios is sufficient to meet most medical needs

The “essential drugs” concept emerged more than two decades ago, and was materialised in 1977 by a list of reference drugs published by the World Health Organisation (WHO) (1). Criticised by some, the concept has stood the test of time in numerous countries worldwide (2).

Far from being a simplistic idea only relevant to third-world countries, the essential drugs concept can serve as a cornerstone of both public health policy and individual medical and pharmaceutical practice.

A reference list of essential drugs

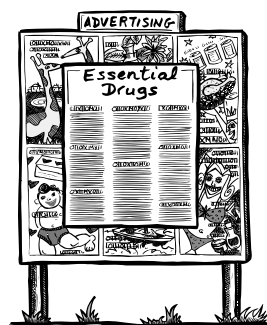
The essential drugs concept is based on a simple fact: a restricted number of safe and effective drugs, of high quality and reasonable cost, can meet the major health requirements of a large proportion of the world population. This was the basis for the strategy presented by the WHO director general to the World Health Assembly in 1975, with the aim of solving the problems posed by medicinal drug availability and use in poor countries (1).

Attempts had already been made to ratio-

nalise the plethora of drugs that had invaded national markets, most notably in Egypt in the 1950s, Sri Lanka in 1960, and Mozambique in 1975 (a)(3-5). Experience acquired in these countries contributed to refining the essential drugs concept, which was materialised by the publication, in 1977, of the first WHO “model list” of essential drugs (1).

A well-adapted list covering major needs. The choice of drugs to be included in the list was presented in confidence to an expert committee of academics, doctors and pharmacists from every continent. The committee’s proposed list was considered provisional, aiming at a common core of fundamental needs with universal relevance and applicability. It was realised that the essential drugs list would have to take into account the entire range of local conditions if it was to meet the practical health requirements of the largest number of people (1).

Each country had to define its own list according to local requirements and possibilities, using the WHO model list as a basis for this difficult exercise. To enable requirements to be identified systematically, and to facilitate comparisons among available drugs, the expert committee designated drugs by their international non proprietary names (INN), and categorised them into therapeutic classes. The committee also recommended that essential drugs lists should only include medicines for which adequate



evidence was available, based on controlled (comparative) studies: note that this was a new concept at that time (1).

An evolving list. The selection process was designed to be continuous, taking into account changes in individual countries’ priorities as well as financial/technical capabilities, and therapeutic progress (1). The 1977 list contained 208 substances available in various pharmaceutical formulations. The list has been revised over the years, and the latest (11th) version, published in December 1999, listed 306 substances (see inset page 92).

The 10 consecutive revisions introduced 173 new substances and removed 70 from the initial list (6,7). The expert committee justified the changes made at each revision with brief notes in the annex of each new list. However, more detailed information ►►

► on the reasons for the committee's choices was demanded by health professionals, who considered that the list should serve as a tool for reflection, rather than being adopted directly by different countries (8).

Relatively few of the drugs added over the years have emerged from recent therapeutic advances: most were added because of changes in assessment of their usefulness in various health settings (b)(9).

Conflicts over the choice of some drugs arose within the WHO expert committee, as reflected by the fact that some drugs introduced in a particular revision were subsequently removed (and sometimes reintroduced) in later revisions (c,d).

In 1995 the overall structure and evolution of the WHO model list were judged relevant by outside observers, who considered that the list met health requirements in a rapidly changing context and served as a basis for countries and organisations faced with very different conditions (e)(10).

A list central to health programmes. To encourage collective adoption of the essential drugs concept, national lists must be fully integrated into the health care system (1). It must serve as a guide for pharmaceutical procurement, prescription, training and information for health professionals, and health education, within a precise regulatory framework (1).

The WHO list is limited to essential drugs for two reasons. The first is to satisfy the health requirements of the bulk of the population through more efficient use of available resources. Countries that pioneered the essential drugs concept, through better stock management and competitive procurement (4,5) made substantial savings.

The second aim is to rationalise drug use, by eliminating useless and potentially harmful products, facilitating training of health professionals, and encouraging the publication of concise, thorough pharmaceutical information provided by impartial sources (1).

More than 150 countries now have national lists of essential drugs; unfortunately, the lists are not always known, accepted and used by all health professionals (2,11,12).

Simple concept, difficult to apply

The introduction of an essential drugs policy requires changes at every level of the drug supply system. The reforms take time and require technical infrastructure, funding and legislative measures sustained by a strong political will. They may affect vested interests or habits of many groups and individuals, and may meet strong resistance.

Supporters and adversaries. The essential drugs strategy rapidly emerged as a battle campaign for WHO, the list of 200 essential drugs serving as its main weapon (13). Some failed to perceive the concept behind the first model list of essential drugs, focusing their criticism on individual drug choices (14).

The pharmaceutical industry retaliated immediately on publication of the list, judging the economic and medical arguments forwarded by WHO, and considering the essential drugs policy to be a threat to its interests and a hindrance to research and innovation. Some health professionals considered the list an infringement on their freedom of prescription (14,15). WHO was accused of introducing a dangerous, utopic concept launched by desk-bound physicians (15).

Supporters of the essential drugs concept committed themselves to applying it in various poor countries, at the level of "primary health care", another innovative concept at that time (f). They received moral, technical and/or financial support from international organisations, bilateral or multilateral co-operative groups, and humanitarian agencies (16).

The International Consumers Union campaigned for the essential drugs policy and against the pharmaceutical industry's promotional ventures (16).

In an attempt to reconcile the different viewpoints, WHO organised a large conference on "rational drug use", leaving the essential drugs concept on the backburner (17).

A strategy subject to political whims. In each country the decision to limit the number of drugs distributed by the public sector, or those refunded by health care providers, depends on various state authorities (health, trade, finance, industry, etc.). This is a political decision, and that is why the implementation of the concept has encountered certain practical difficulties.

Changes of government or policy have led to the discontinuation of essential drugs programmes in countries such as Sri Lanka and Bolivia (4,18).

External pressure against essential drugs policy was exerted in some countries as in Bangladesh (19) and, more recently, South Africa (20).

Application limited to public health care bodies. Drug shortages affect all the public health care services in poor countries, because of inadequate pharmaceutical budget and poor management (21). Priority for implementing the essential drugs concept has, therefore, been given to the public sector, mainly through primary health care centres and generally in rural areas (16, 22).

Currently, WHO reports that 71 countries use an essential drugs list for pharmaceutical procurement by the public sector (2).

The private pharmaceutical sector, which, in most poor countries, has a predominant position and offers a wide range of preparations, has not been affected (21,23). WHO has never formally recommended limiting the number of drugs supplied by the entire pharmaceutical sector (24).

Attempts have been made to introduce essential drugs policies in the private sector, especially in Latin America and French-speaking African countries, by the use of generic drugs (25,26). But it is difficult to promote two different concepts simultaneously to health professionals and citizens who are aware of neither. The generic drugs concept, the main goal of which is to reduce costs, has often superseded the essential drugs concept based on rational drug use (27).

Spread the word! Restricted to the public sector and virtually ignored by lecturers in university hospitals, the essential drugs concept has been promoted and applied too sparingly (28). When available, national lists of essential drugs have been distributed almost exclusively to primary health care centres.

Most of the information and advertising received by physicians and pharmacists, both in hospitals and in the private sector, has been generated by the pharmaceutical industry (23).

WHO strongly promoted the essential drugs policy to decision-makers and health professionals involved in programmes supported by various organisations (16). However, this dynamic approach was criticised, sometimes even within WHO, by those arguing that WHO's mission should be limited to coordination and technical support (16). These opponents are now less noisy and, for some years now, WHO essential drugs recommendations have been extended to countries of the former Soviet bloc (2).

Essential drugs and funding. Poor countries committed themselves to essential drugs policies under the pressure of economic crisis (21). Funding obtained for the implementation of such programmes lead to the public pharmaceutical sector being relaunched and rationalised (g). To ensure sustainability, funding systems based on end-users were started in some countries. The sale of generic essential drugs in public hospitals put an end to the illusion of free supply and, in general, to shortages too (21).

Despite the cost reductions achieved by the use of generics, the cost of some drugs remains too high for many people, given the

lack of health insurance systems in many countries (29).

Globalisation, and especially World Trade Organisation (WTO) agreements on patents, may further hinder access to some essential drugs (30). So far, national pharmaceutical industries in countries which have not signed international patent agreements such as Argentina, India and Thailand, have been able to produce legally recent drugs (still protected by patents). This is why some recent antibacterial, antifungal and antiretroviral drugs are available in these countries at prices far below the international price of the original proprietary product (30).

Global patent enforcement will dry up this alternative source of recent drugs. Hence the importance for poor countries of adopting legislation that includes WTO provisions allowing them to exploit commercial competition (e.g. parallel imports and compulsory licencing) (30).

Lessons for the present and future, worldwide

In 1977 the International Federation of Pharmaceutical Manufacturers Association (IFPMA) was appalled by the WHO director's statement that the essential drugs concept was valuable for industrialised countries too, in which the cost of drugs was an increasing burden (15). Yet this opinion is now universally accepted, with the increasing adoption of generic drugs and the containment of drug spending. Experience in poor countries has become a source of useful information on essential drugs for countries in both hemispheres.

From essential drugs to rational drug use. Given the plethora of available drugs, choices must be made according to context and on the basis of reliable data, as recommended by the WHO in 1977. The original selection criteria are still valid and applicable at all levels, as is the need for continuous reassessment of existing choices.

Likewise, the advantages of using international non proprietary names are now well documented (31), and drug classification in therapeutic classes is universally accepted.

Many individual professionals have long since adopted an approach based on essential drug selection principles. Examples cited in the literature 10 years ago include formularies for general practitioners, drawn up by groups of GPs with specialist assistance (32). Clearly, the best way to adhere to such formularies, individually and collectively, is to be part of the process by which they are drawn up. Indeed, the lack of prescriber par-

ticipation in the original design and revision of the essential drugs list has proved to be a major obstacle to its practical adoption (28).

Local hospitals can draw up drug lists corresponding to local requirements and acceptable to all.

"Rational use": an attitude to be developed. Irrational prescribing has been shown in many studies done in first- and third-world countries alike (33). It is clearly difficult to modify prescribing and dispensing habits acquired over the years. Students must therefore be "immunised" against the unwarranted influences they will encounter in their professional practice, such as pressure from patients, all forms of advertising, and irrational prescribing by their peers. Education about such rational prescribing is not yet available in medical schools (33).

New educational methods are being adopted in various countries, such as Canada and The Netherlands, with the aim of developing future prescribers' capacity to choose among treatments and to critically assess new drugs on an ongoing basis. A Guide to Good Prescribing has been published to this effect (34). These methods have been tried and tested in rich and poor countries alike, as part of the WHO action programme for essential drugs (35). Student pharmacists could benefit from a similar approach, notably to develop counselling to patients.

"Therapeutic need". According to the WHO recommendations published in 1977, new drugs should only be included in the list of essential drugs if they have a clear advantage over previously chosen drugs (1). The pharmaceutical policy of Norway has long been considered as a model: the "need clause" used to be followed for marketing authorisation, in order to limit the number of drugs and drug combinations with no real therapeutic value. The same notion had to be taken into account by hospital pharmaceutical committees (36).

Currently, the concept of therapeutic need is barely mentioned in marketing authorisations granted by European and American drugs agencies. This is reflected by the large proportion of new drugs that we score as "Nothing New" in our New Products column, following a thorough analysis of the clinical files; this was the case of 1 427 (63%) of the 2 259 preparations we reviewed from 1981 to 2000 in la revue Prescrire. We also considered that 56 new preparations reviewed during the same period were "Not Acceptable". By ignoring the concept of therapeutic need, health authorities allow the interests of the pharmaceutical

industry and public coffers to override the patient's best interests.

[Adapted from la revue Prescrire March 2001]

a- In Egypt, the number of preparations on the national market fell from 22 000 to 3 000 between 1952 and 1961 (ref 3); in Sri Lanka in 1960, the number of preparations in the private sector fell from 4 000 to 2 100, and the national formulary consisted of 500 drugs designated by their INN (ref 4); in Mozambique in 1975, the number of preparations fell from 13 000 to 2 600 in the private sector, and the national formulary comprised 430 drugs designated by their INN (ref 5).

b- Of the 120 new drugs added to the list between 1977 and 1990, only 16 were recent drugs, such as valproic acid, captopril, etoposide, calcium folinate, ivermectin, ketoconazole, praziquantel, timolol eye drops, etc. (ref 9).

c- For example, glibenclamide was the first oral antidiabetic drug to be included in the list. In 1983 it was described as "replaceable"; still present in 1985, it was no longer "replaceable"; in 1988 it was replaced by tolbutamide; then, in 1997, tolbutamide was removed from the list and glibenclamide was reinstated. Other examples are amodiaquine, an anti-malarial removed in 1979, reintroduced in 1983, and again removed in 1988; mupirocin, an anti-infective ointment, which was included in the list in 1989 and removed in 1993. Note that the composition of the expert committee was changed at each revision (ref 9).

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WHO ESSENTIAL DRUGS, EXCEPT FOR THE POOR...

In 1977 the World Health Organisation (WHO) published its first list of essential drugs: approximately 200 drugs with good risk-benefit ratios covering most medical needs in both hospitals and the community, in the North and the South.

The WHO stressed the fact that the drugs this first list contained were available in generic form, and were therefore affordable. As well as supporting rational prescribing, the list encouraged containment of drug expenditures, unlike the advertising industry which favours unnecessary prescription and consumption of costly new drugs.

During successive revisions, some drugs that were still protected by patents, and were therefore expensive, found their way onto the list. They remain a very small minority,

as high cost is generally an exclusion criterion for items on the WHO list. This is why antiretroviral drugs are not on the current list. The WHO explains this position in the following way: "Zidovudine and nevirapine have been shown to reduce or prevent mother-child transmission of HIV infection. This is the only indication for which they are included here (...). Triple therapy is beyond the budgets of most national drug programmes, and therefore HIV/AIDS treatment policies must be decided at country or institutional level" (1).

The cost criterion is useful when choosing among drugs with equivalent therapeutic effects. But it is difficult to understand why some drugs for which there is no alternative are excluded from the list on the grounds of cost alone.

The retail prices of drugs bear little relation to their production costs. Like national authorities and individual health professionals, the WHO should not be influenced by the financial policies of drug companies, at the expense of the patient.

On the contrary, it is up to the WHO, as a United Nations agency, to ensure equitable access for all patients to all essential drugs. If need be, this must mean defying financial lobbies.

[Adapted from *la revue Prescrire March 2001*]

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