



TRANSLATED FROM LA REVUE PRESCRIRE

Reorienting European Medicines Policy

Background

European regulations on medicinal products, adopted during the 1960s and 1970s, have had a major positive impact in European Member States. In particular, they have obliged national policy-makers to create effective drug control and monitoring infrastructures designed to improve health care quality and patient safety, and also to stimulate healthy competition among drug manufacturers.

The European Medicines Evaluation Agency (EMA) was created in response to the call for greater European integration. More resources and more independence were expected to bring greater transparency and harmonisation.

But, discreetly, by a thousand cuts, EMA has been driven away from its primary mission as a safeguard of European citizens' health. The pharmaceutical industry now has its foot firmly in the door.

Strangely, EMA is part of the Enterprise Directorate General rather than the Health and Consumer Protection Directorate of the European Commission. It now receives most of its funds directly from the drug companies. The administrative open door known as the mutual recognition procedure has been institutionalised and a shroud of secrecy has descended. The European pharmacovigilance system has not fully materialised, and most of the data obtained in this field have remained in a black box.

Ever more pressing, the pharmaceutical lobby, supported (and sometimes preceded) by the Enterprise Directorate, has been making strenuous efforts to ensure that the European Directive on medicines

for human use are changed to suit the best interests of industry.

Its overriding objective is to make the European market even more permissive, with permanent marketing authorisations granted more rapidly and more easily, with no need to show therapeutic advance; no regular postmarketing reappraisal of the risk-benefit ratio; no public explanation of EMA decisions; no comparative assessments on which to fix prices more reasonably; and direct-to-consumer advertising of prescription-only drugs under the guise of "information".

We are publishing a series of documents and reviews on current European pharmaceutical policy, aimed at helping individual citizens and policy-makers to reach well-founded conclusions.

Among these papers you'll find a detailed description of the European Medicines Evaluation Agency (EMA) website, notably underlining its fake transparency.

We offer a description of the instruments and institutions of European pharmaceutical policy, and a review of the current activity of EMA, the cornerstone of the system. We identify a number of strong points and institutions that should be maintained, but we also identify strategies that are being used to drive the system away from its primary objective: public health.

We also report on the proposals of Directive and Regulation of the European Commission Enterprise Directorate (on behalf of a pharmaceutical lobby group), and the positions of various patient and consumer organisations and professional bodies.

Contents

- Background 1
- A call to national and European policy-makers2-3
- Editorial: A free hand4
- Pharmaceutical policy is now decided at the European level5-7
- European pharmaceutical policy is turning its back on public health 8-10
- An industry-serving pharmaceutical policy 11-13
- Towards a medicines policy that supports basic public health needs14-15
- Internet16-20
 - *Drugs agencies have a duty to inform*
 - *EMA: fake transparency*
 - *FDA: an example of transparency*
 - *FDA MedWatch*

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A CALL TO NATIONAL AND EUROPEAN POLICY-MAKERS

Putting european drugs policy back on tracks

It is vital to restore European pharmaceutical policy to its rightful public health context, for the individual and collective benefit of European citizens, by restoring independence and transparency throughout the system.

If the pharmaceutical industry is to remain dynamic and efficient in the long term, it must be actively re-directed towards true public health needs and therapeutic advance, both in Europe and throughout the world.

We call on members of the European Parliament, ministers of the Council of Europe, and European Commissioners to reconsider the policies outlined in the draft Directive and Regulation on medicinal drugs prepared by the European Commission's Enterprise Directorate.

In the interests of public health, we call them to adopt new priorities.

Our demands are the following:

Public health before industry. *Medications being a cornerstone of any health policy, national and European regulatory bodies charged with authorising new drugs and postmarketing surveillance must be directly accountable to national and EU health authorities.*

Thus,

- European Union health ministers, and not industry ministers, must, in conjunction with the European Parliament, decide European pharmaceutical policy and all relevant Directives and Regulations;
- The European Medicines Evaluation Agency (EMA) must become part of the Health and Consumer Protection Directorate General instead of the Enterprise Directorate General.

Financial independence. *Given the massive economic stakes, it is essential that the structures and personnel charged with drug registration and control be financially independent from pharmaceutical companies.*

Thus,

- The budgets of EC Member States and of the European Union itself must rapidly be increased to cover the full operating costs of national and European medicines agencies;
- Fees paid by drug companies for marketing applications must be attributed to Member State and EU coffers, and not directly to the medicines agencies concerned, in order to avoid conflicts of interest;
- These fees must be re-adjusted in such a way as to encourage manufacturers to choose the European centralised marketing procedure for products they wish to sell throughout the European Union;
- All conflicts of interest of agency personnel and outside experts must be declared regularly, accessible on the Internet, and be taken into account in practice.

Free access to scientific data. *Drug-related matters must not be an exception to the obligation of transparency in national and European institutions. Indeed, this information is required to ensure optimal use of drug therapy prescribed to European citizens. It is also a moral duty to render public the results of clinical research in which thousands of citizens volunteer to participate.*

Thus,

- National and European medicines agencies must be re-organised to ensure that the public and health professionals have access to detailed and referenced reports of the scientific information on which their decisions are based, whether positive or negative. This must apply not only to national, centralised and mutual recognition procedures, but also to postmarketing data (pharmacovigilance, comparative studies of drug benefits, drug errors, etc.).

Universal and strict centralised procedure. *The measures taken since 1995 to harmonise and concentrate resources through the creation of the European Medicines Evaluation Agency (EMA) and the European centralised marketing authorisation procedure must be continued and amplified.*

Thus,

- The mutual recognition procedure must be phased out as rapidly as possible, in favour of an efficient and transparent centralised procedure for all drugs intended to be marketed in more than one European Union Member State;
- The European Medicines Evaluation Agency budget must be considerably increased, so that this cornerstone of European pharmaceutical policy has the means to fulfil its responsibilities in terms of expertise, independence, transparency and surveillance;
- The time allocated to examine marketing applications (both national and European) must not be systematically shortened. Agencies must have the time necessary for thorough critical assessment of these applications, with



the overriding aim of protecting patients. This time should only be shortened in strictly defined situations involving serious diseases for which no treatment is available;

- Periodic re-examination of marketing authorisations, both national and European, must be strengthened and actually applied. This re-assessment must focus not only on efficacy and side effects, but also on the overall value of individual drugs in light of new data and new therapeutic options (drug and non drug).

Quality information for rational use. *Rational drug use, especially the prevention of side effects and medication errors, requires that citizens and health professionals be adequately informed.*

Thus,

- National and European authorities must take all the necessary measures to ensure that European citizens and health professionals have access to reliable information. That means information independent of drug companies, well documented and referenced, comparative, and designed in transparent manner, on diseases and available treatments, together with preventive, diagnostic and screening tools, and their correct use;

- International nonproprietary names rather than trade names must be adopted as the main medicine identifiers throughout the European Union, by regulators, patients and health professionals;

- Drug companies must be strongly encouraged to improve the information in patient leaflets and on drug packaging;

- Drug advertising must be tightly regulated in all Member States: advertisements for non prescription drugs must be approved before their release; direct-to-consumer advertising of prescription-only drugs must be banned; advertisements targeting health professionals must be controlled retrospectively; and effective sanctions must be applied rapidly to all offenders.

Transparency in drug cost. *Drugs can serve a public-health oriented policy only if they are universally accessible and if their prices are compatible with health budgets.*

Thus, in order to deal with the current spectacular increase in drug prices,

- National and European policy-makers must undertake strict studies of drug production costs, and particularly the true cost of biomedical research and development;

- The European Union, and its individual Member States, must create adequately funded bodies capable of sponsoring, co-ordinating and stimulating clinical research aimed at answering the numerous questions that are left pending by industry-sponsored studies;

- They must also create institutional structures designed to provide patients, health professionals, organisations paying for medicines with clear, synthetic, referenced, up-to-date comparative drug information on which to base rational choices among available therapeutic options.

Several years of sustained effort are required.

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Reference documents

The following documents are essential for a thorough understanding of the current debate on European medicines policy.

- “The ISDB Declaration on Therapeutic Advance in the Use of Medicines” Paris, 15-16 November 2001. The Declaration puts patients’ needs at the forefront, and separates real advance from mere “innovation”.

Available in several languages on the ISDB website: www.isdbweb.org

- “Helsinki Declaration: Ethical Principles for Medical Research Involving Human Subjects” World Medical Association 2000 edition. News treatments must be assessed in comparison with reference options (whenever available) rather than against placebo.

Available on the ISDB website: www.isdbweb.org

- “Uppsala Declaration: Statement of The International Working group on Transparency and Accountability in Drug Regulation” (1996), by Health Action International and Dag Hammarskjöld Swedish Foundation, Uppsala, 11-14 September 1996. How to tackle obstacles to transparency and public control of official measures involving medicines.

Available on the ISDB website: www.isdbweb.org

- “Erice Declaration: On Communicating Drug Safety Information” (1997), by (among other parties) the Uppsala Monitoring Centre on adverse drug reactions, under the aegis of the World Health Organisation (WHO). What regulatory authorities should do to carry out their mission in terms of information to professionals and the public?

Available on the ISDB website: www.isdbweb.org

- “Penser et prescrire en DCI: une bonne pratique professionnelle” (la revue *Prescrire* n° 209); “Les médicaments génériques”. Prescribing and dispensing medicines under international nonproprietary names (INN) or generic names is a first step towards rational use of drugs.

Available in French only, on request.

- “Prix des médicaments remboursables: quelle logique ?” la revue *Prescrire* n° 222 and 233.

Available in French only, on request.

A free hand

In this supplement we review the performance of the European Medicines Evaluation Agency (EMA), and the European drugs policy.

Time is pressing, as draft Directive and Regulation will be submitted for adoption by the European Parliament and the Council. These drafts are prepared and sponsored by Enterprise Directorate of the European Commission, on which EMA has so far depended.

We believe, like many other independent observers, that EMA's performance is not that good. And things may get even worse over the next seven years if the current drafts, which are supported by a powerful industrial lobby, are adopted.

Some hold that the European community is a technocratic juggernaut that disregards its own citizens' interests and stifles national vitality.

We believe this is far from the truth. On the contrary, harmonisation is an effective way of optimising scientific and human resources, and European institutions are not ill-designed and sclerotic, but open to public influence.

The real problem is one of public apathy: who, apart from drug companies, is monitoring, and trying to influence, European pharmaceutical policy?

So it is hardly surprising that this policy is increasingly industry-oriented, or that EMA has been linked to Enterprise Directorate General (and not Health and Consumer Protection Directorate General), and receives most of its funds from industry (like most national medicines agencies). Medicines are now seen as simple goods serving the European economy, rather than as a cornerstone of citizens' health. A "free market" policy that disregards public health regulations will be detrimental to European citizens.

This trend is not inevitable. It is not too late to act. We can, and must, demand that change serves the public interest first and foremost. The pharmaceutical industry must not be given a free hand to ride roughshod over the rest of society.

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REORIENTING EUROPEAN MEDICINES POLICY



Pharmaceutical policy is now decided at the European level

For about a decade now, pharmaceutical policy has been decided and organised mainly at the European level, within a context of international harmonisation. Some national responsibilities persist, but they are almost all governed by rules that apply throughout the European Union.

A firm grasp of the functioning of European institutions is therefore

required to understand the new legal framework of the countries in which we live and work.

First, a short glossary.

• **Marketing authorisation.** Marketing authorisation allows a drug company to sell a proprietary (industrially manufactured) drug. Europe currently has three types of marketing authorisation:

National marketing authorisation is granted by a national medicines agency, on the basis of an application file, after approval by the national licensing authorities. This form of authorisation is only valid in the country in which it is granted;

European centralised marketing authorisation is granted by the European Commission, after examination of the file by the European Medicines Evaluation Agency (EMA) and taking into account the opinion of the European Commission for Proprietary Medicinal Products (CPMP). This marketing authorisation is valid in all EC Member States;

Marketing authorisation by mutual recognition (also known as the decentralised procedure) is granted by national medicines agencies through recognition of marketing authorisation initially granted by another Member State. This latter Member State is known as the Reference Member State (**a**), because it builds up the assessment report that is submitted for recognition by other Member States. EMA is kept informed of the procedure by the company, but the CPMP is only consulted when arbitration is required between Member States.

• **EMA (European Medicines Evaluation Agency).** Created by a European Regulation in 1993, and in operation since 1995, EMA is based in London. It co-ordinates the scientific resources provided by the different Member States for assessing and monitoring human and veterinary drugs.

EMA has no deciding power, but offers an "opinion" to other ►►

.....
a- "Rapporteur country", now called "Reference Member State", i.e. the country which initially granted marketing authorisation within the mutual recognition procedure should not be confused with "rapporteurs" and "co-rapporteurs", who are CPMP members working within the framework of the centralised procedure. The latter are responsible for analysing drug assessment files on behalf of their CPMP colleagues. They act as members of a European expert Committee, not on behalf of their countries of origin.

Distribution of roles within the European Union

- **European Council: impetus and direction of general policies.** Each Member State is represented by the head of government (or head of state) and minister for foreign affairs.

- **European Parliament: shared legislative power and budgetary power.** The European Parliament has legislative power (in conjunction with the European Council), budgetary power and control power. It is composed of members of the European Parliament, who are elected by European citizens for 5-year terms of office. This is the only EC institution that meets and debates in public.

- **European Council: shared legislative power.** The Council (of ministers) of the European Union is also a legislative body (in conjunction with the European Parliament). It includes one ministerial representative from each Member State, and its composition can vary according to the issue in hand. Drug related matters can be discussed by ministers of health or industry according to the decisions taken.

- **European Commission: sole legislative initiative.** The European Commission is the only EC institution with the right to propose new legislation. It prepares legislation, in principle in keeping with the large directions laid down by the Council of the European Union. The draft Directive and Regulation now being discussed were prepared by the Enterprise Directorate General of the European Commission. The European Commission is also the European Community's executive body, responsible for ensuring that

community treaties and decisions are enacted. It employs about 20 000 staff.

- **Advisory committees.** The Economic and Social Committee, which comprises three groups (employers, workers and miscellaneous activities), has a consultative role. For example, it organised a consultation on the drug regulation now undergoing discussion. The Committee of the Regions, created with the aim of bringing European institutions closer to the citizen and comprising local and regional representatives, also has a consultative role.

- **Directives and Regulations.** The scope of Directives and Regulations is defined by article 249 of the European Treaty:

« In order to carry out their task and in accordance with the provisions of this Treaty, the European Parliament acting jointly with the Council, the Council and the Commission shall make regulations and issue directives, take decisions, make recommendations or deliver opinions.

A regulation shall have general application. It shall be binding in its entirety and directly applicable in all Member States.

A directive shall be binding, as to the result to be achieved, upon each Member State to which it is addressed, but shall leave to the national authorities the choice of form and methods.

A decision shall be binding in its entirety upon those to whom it is addressed.

Recommendations and opinions shall have no binding force. »

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Further information

European Communities. "Annuaire interinstitutionnel – Qui fait quoi dans l'Union Européenne?" Office des publications officielles des Communautés européennes, Luxembourg 2002. Besides general information on EU institutions, this directory contains lists of all Members of Parliament and of the different institutions. All this information can also be accessed via the Europa server of the European Parliament (see below).

- Sauron JL "L'application du droit de l'Union européenne en France" La Documentation Française Collection Réflexe Europe, Paris 2000: 135 pages.

- The ABC of Community Law "Borchardt KD" – Fifth edition. European Communities 2000; European Commission, Directorate - General for Education and Culture - Publications Unit, rue de la Loi - Wetstraat 200, B-1049 Brussels (available in all EC languages).

Website:

-European Parliament
<http://www.europarl.eu.int> (mostly in all EC languages).

-European Union online
<http://www.europa.eu.int/inst-fr.htm> (mostly in all EC languages).

► European institutions (mainly the European Commission, which grants or refuses marketing authorisation, and Member States for pharmacovigilance matters).

EMEA has a number of consultative committees (mainly the CPMP) and expert groups composed of members seconded by the different Member States.

In 2001, EMEA employed 208 salaried staff (2002 estimate: 251), and its budget was 65 866 000 euros (2002 estimate: 70 547 000 euros), 69% of which came from taxes and fees paid by companies to have their marketing application files examined (1).

- **CPMP (Committee for Proprietary Medicinal Products).** The CPMP is one of EMEA's consultative committees. The CPMP currently comprises two experts from each Member State, chosen for their experience in drug assessment and appointed for a renewable period of three years. These experts are scientific experts, not political representatives of their countries of origin.

The role of the CPMP is to offer an opinion on drugs intended for human use, through the centralised procedure. It also arbitrates in disputes over mutual recognition.

The CPMP is assisted by working

groups on efficacy, safety, pharmacovigilance, biotechnics, blood-derived medicinal products, and phytotherapy, among others. In addition to EMEA, another committee is now responsible for giving opinions on orphan drugs (Committee for Orphan Medicinal Products).

- **EPAR (European Public Assessment Report).** EPARs are EMEA publications on drugs that have been authorised through the centralised procedure. They are supposed to reflect the assessment file submitted by the manufacturer, its analysis by



the CPMP, and the reasons underlying the CPMP's opinion. In fact, these brief documents have been expurgated of all data considered confidential from a commercial or industrial point of view, and are approved by the manufacturers concerned before being released to the public.

EPARS relate only to marketing authorisations granted through the centralised procedure. No assessment report is available on products that are refused marketing authorisation. Similarly, none of the numerous decisions taken through the mutual recognition procedure give rise to EPARS.

• **SPC (Summary of Product Characteristics).** Attached to the marketing authorisation, these "identity cards" recap the state of knowledge on a drug when marketing authorisation is granted, and are revised after each five-yearly re-appraisal of the assessment file.

Drafted by the manufacturers, SPCs are submitted along with the marketing application. They are finalised when marketing authorisation is granted, and are translated (European marketing authorisation only) into the different languages of the European Union.

The SPC is written according to a standard layout. Further information can be added throughout the lifetime of a drug, such as warnings on side effects that were not identified during the initial assessment phase.

The SPC contains the information that companies must mention on all advertising aimed at health professionals (such as brochures, adverts, and monographs in a datasheet compendium).

Another annex to the marketing authorisation (now called Annex III) sums up the information contained in the SPC in plain language. This annex forms the basis for compulsory information in the patient leaflet.

• **Blue box.** This is the information box, surrounded by a blue line that figures on the packaging of preparations approved through the centralised procedure. It carries information specific to Member States where the product is marketed. This includes the drug's legal status (e.g. classification of controlled substance) and any restrictions on its

prescription (these elements are not yet fully harmonised within the EU).

• **European marketing authorisation number.** When a product is granted European marketing authorisation through the centralised procedure, the marketing authorisation number (which can be found, for example, on the packaging or in the SPC) is composed of the following elements:

-the letters "EU", for European Union;

-the number "1" or "2", according to whether the drug is designed for human use ("1") or veterinary use ("2");

-two figures corresponding to the year of initial authorisation (95 for 1995, etc.);

-three figures corresponding to an identification number given to each drug;

-three figures for each product in the range, corresponding to its formulation, dose strength and package contents.

For example, EU/1/97/031/044 corresponds to the human drug NeoRecormon[®], in injectable form, 6 000 IU per syringe, sold in boxes of 6 syringes, and authorised in 1997 through the European centralised procedure.

• **ICH (International Conference on Harmonisation for technical requirements of registration of pharmaceuticals for human use).** The ICH process was launched in 1990, driven by the regulatory authorities and pharmaceutical industries of the United States, Europe and Japan.

The aim is to harmonise marketing authorisation procedures by adopting common recommendations for drug evaluation and similar administrative procedures.

Through international conferences held every two years, and especially the work of a 14-member committee supported by industrial and administrative experts, ICH has seen more than a hundred common recommendations adopted by pharmaceutical firms and medicines agencies

This rapid harmonisation is welcome because it saves time and money (for example, fewer redundant clinical trials and animal studies). However, there is also a risk that international requirements for drug

evaluation will be reduced to the lowest common denominator.

Health professionals and patient organisations have made virtually no contribution to this process, which should be monitored closely (by consulting the website of a major medicines agency such as EMEA) and opposed when necessary.

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I- The European Agency for the Evaluation of Medicinal Products "Work Programme 2002" 18 December 2001: 62 pages ("Annex 1 - EMEA establishment plan 2000-2002" pages 42-43; "Annex 2 - EMEA budget summaries 2000-2002" page 44).

..... Further information

Key information on European pharmaceutical regulation can be obtained from the following sources:

• History of the construction of European drug legislation: Campion G "Clefs pour l'Europe du médicament" Éditions de Santé, Paris 1996: 251 pages.

• Current EC drug regulations; definitions, concepts, and list of current texts: Brunet P "Dictionnaire of the main reference terms - Pharmaceutical law in the European Union" Éditions de Santé, Paris 1999: 236 pages.

• Marketing authorisation procedures in theory and practice: "La réglementation des médicaments dans l'Union Européenne - Volume 2A. Avis aux demandeurs - Médicaments à usage humain" Office des publications officielles des Communautés européennes 1998: 175 pages.

• Current European texts (Directives and Regulations) and proposed amendments to these texts: European Union website <http://europa.eu.int/eur-lex>

European pharmaceutical policy is turning its back on public health

It is on the basis of its practical impact at the Member-State and pan-European levels that current European pharmaceutical policy should be judged.

Is the policy transparent? Is it part of a coherent overall public health policy? Does it aim to strengthen the responsibilities and roles of the different players (patients, health professionals, regulators and manufacturers)?

Readers of *la revue Prescrire* find answers to these questions in each issue of the journal, and especially in our year-end reports. We have often criticised the French medicines authorities for their administrative secrecy, the secrecy of postmarketing studies, and the weaknesses of their drug pricing policy.

At the European level, our readers will have noted that:

- centralised marketing authorisation does not always mean therapeutic advance (1-3);
- the European Medicines Evaluation Agency (EMA) is financially dependent on fees paid by pharmaceutical firms to balance its budget (a)(4);
- EMA, as illustrated by its website, is lacking transparency towards citizens and health professionals alike (5);
- current European regulations hinder effective price controls on drugs at the member-state level (6,7).

We are not the only organisation to denounce the current inadequacies of national and European measures driving pharmaceutical policy away from its initial objectives. Here are three other examples.

ISDB: minimal agencies

At its creation, EMA undertook to guarantee transparency, in the same way as all other European institutions, in line with the spirit of the Charter of Fundamental Rights of the European Union (b)(8). EMA made systematic publication of public assessment reports (EPARs) on drugs authorised through the centralised procedure the cornerstone of its communication policy.

These documents, which include about ten pages of useful scientific data, were supposed to be written by EMA then released to the public and updated regularly.

Independent European drug bulletins belonging to ISDB (the International Society of Drug Bulletins) initially praised this initiative, and proposed ways of further improving to the EMA (9).

Following the deteriorating quality of EPARs, the European ISDB group published a detailed study of nine consecutive EPARs (September 1996 to August 1997), which it then extended to cover all EPARs published in 1999 and 2000. These studies compared the information distributed by EMA and that collated by ISDB members. The results were very negative: the EPARs were not harmonised, reliable or correctly updated (10,11).

The *Prescrire* staff that analyses the files of new drugs considers that things have now got even worse. EMA has no documentary resources independent of drug companies (c). In many cases, analysis of EPARs suggests that these documents are totally or mainly written by the firms themselves, or edited by copying and pasting from the firm's application (d). Too many EPARs are vague or even inconsistent. In addition, irregular publication of their updates on the EMA website means that their value is highly uneven (5).

EPAR are only released for drugs authorised through the centralised procedure, yet the bulk of products are approved through the totally secretive and increasingly popular mutual recognition procedure, which gives rise to no usable centralised information. Hardly any national agencies make public the results of their evaluation, even when they operate as rapporteur (the Netherlands recently introduced a few exceptions).

Worrisome results of an independent survey

The results of a 5-year follow up

and analysis of the European regulatory system published by two British researchers provides food for thought during the run-up to the submission of the draft Directive and Regulation for approval by the European Parliament (e)(12).

John Abraham, a sociology professor and head of the Centre for Research in Health and Medicine at the University of Sussex, and Graham Lewis, a consultant in international drug regulations, examined, between 1994 and 1999, European bodies handling medicines-related matters, together with the role of individual member states.

Their work, funded principally by the British Council for Social and Economic Research, was based on interviews with staff in about fifty industrial organisations and administrative bodies in European Member States (especially Germany, the United Kingdom and Sweden – countries with strong pharmaceutical industries), and on the numerous published and unpublished documents they were able to gather.

The authors first recall the economic, sociological and political context in which the European pharmaceutical system was built up. They then describe its functioning, illustrated by a number of examples. They con- ►►

a- In 2002, the industrial contribution to the EMA budget rose to 69.46% (ref 14) from 53% in 1998 (ref 4).

b- The transparency principle figures in the Citizenship Chapter of the Charter, in articles 41 (Right to a good administration) and 42 (Right of access to documents) (ref 8). A Regulation on access to documents, adopted in 2001, came into effect on 3 December 2001, and provides for application of the transparency principle (ref 15).

c- It must be stressed that EMA is not the only medicines agency in this position. For example, the French agency for health product safety does not have solid industry-independent documentary resources that it can use systematically to analyse both the literature (including independent journals) and the conclusions of other drugs agencies worldwide.

d- According to EMA internal procedures, EPARs are sent to the firms concerned, for their opinion, before publication. We recommend that EMA states how and by whom EPARs are actually written, and who gives the pass for press.

e- A 243-page textbook with more than 400 references reports the results of this work, and represents a major source of information on European drugs policy (ref 12).



Quoted from: *The Lancet* – Volume 358, Number 9275 – 07 July 2001

CPMP members' standpoint

EMEA under DG health control. "EMEA is located in an industrial institution of the European Commission (initially called Directorate General [DG] III, now called DG Enterprise) despite the fact that its mission is "to promote the protection of human health ... and of consumers of medicinal products". Public health should be the fundamental concern of EMEA because it is the final outcome of improved availability of medicines (...). If public health issues were paramount, EMEA approval of new drugs would depend on their benefit to patients, and would be granted only for well defined indications after extensive research (...)."

For a financially independent EMEA. "Financial support for EMEA comes from two sources: a European Community grant, and the fees EMEA charges industry for the assessment of dossiers and other services. EMEA is forced to compete with national agencies for these fees, because – apart from biotechnology products – industry can apply to these agencies via the decentralised procedure, and hope to obtain approval with greater ease than through the EMEA. To eliminate this conflict, all applications for the European market should be made to one agency, the EMEA."

EMEA should be allowed to do its own research (or to contract research out to third parties) to confirm or disprove data reported by industry. EMEA should also be equipped to deal with pharmacovigilance, to review drug use, and to make active investigations rather than relying on spontaneous reports and secondhand data.

Europe should acknowledge the need for the EMEA to take on these new roles, and supply the substantial investment that they would require. EMEA is still much smaller than the US Food and Drug Administration, although it covers almost double the population of its transatlantic cousin. If the European Community's grant were adequate, fees paid to EMEA by industry would be a small proportion of its income, and allow the agency to be free and independent".

Experts must be independent, not judge and jury. "It is unusual for the same organisation and especially the same individuals--ie, CPMP members--to advise industry about the best

way to develop a drug, to decide on approval of that drug, and, in appeal cases, to decide on approval for a second time. Scientific advice should not be a systematic activity, and should be given more on the CPMP's initiative than at the request of companies. If the CPMP were to give a negative opinion on a drug, it should not be able to change its opinion on the same dossier within a mere 120 days. Appeals should only be possible for serious reasons, such as deliberate misuse of information in the dossier. The appeal should be judged by an independent group of experts who come from outside the CPMP.

Assessment of the dossiers could also be improved. One of the two CPMP rapporteurs is normally suggested by the company. This situation is difficult to condone. A company would be unlikely to select its rapporteur from CPMP members who are thought to be critical (...). In addition, a report by an independent expert is a required part of the dossier.³ In practice, these "neutral" experts tend to extol the virtues of the new drug rather than give a balanced view of its pros and cons. A summary of the dossier prepared by the company would be a less hypocritical document (...).

Industry can stop the procedure several times, for several months if required, but the CPMP must follow a rigid schedule. The CPMP should be allowed equal flexibility in the timing of the assessment process".

Comparative assessments are lacking. "European Union legislation repeatedly states that drugs should be assessed for their quality, efficacy, and safety. However, this statement has been interpreted and acted on as if each drug were to be made available in a therapeutic vacuum. Industry has determined that once quality is acceptable, efficacy is suggested even if not shown, and safety raises no serious concerns – any drug should be allowed on the market. The apparent aim of industry is to produce a European catalogue from which physicians, or even in some cases patients, can select which medicine to use, and national health services can select drugs to be reimbursed. However, if there is no way of making valid comparisons between products, how can physicians or patients make informed choices?"

This point is made in several guidelines, including the E10 document of the International Conference for Harmonisation last year, that medicines should be tested against comparative drugs rather than placebos. These guidelines generated a strong reaction from the European Federation of Pharmaceutical Industries and Associations, which stated that for legal, scientific, and public-health reasons "quality, safety, and efficacy must remain the only criteria to assess the applications for marketing authorisation (...)."

Few therapeutic areas and indications exist, besides rare diseases, for which there is no treatment; in these cases only must placebo be used rather than an active comparative drug (...)."

Drug cost overlooked. "Despite regular appeals to take economic aspects into consideration and contain health-care costs, the CPMP works in an ideal world in which there are no financial limits on new drugs (...)."

SPCs are not comparative. "However, in these summaries, drugs are described as if they were the only ones on the market; comparisons should be made with other drugs with a similar mechanism of action that are available for the same indications (...). Distribution of the summary among physicians should be done by national authorities (...)."

Lack of Transparency. "Information on withdrawn applications is confidential, and no data are made public. Public health interests would be served by publication of such data. Therefore, either no withdrawal should be allowed after preliminary assessment, or the essential characteristics of any drug whose application has been withdrawn should be reported (...)."

If a drug is not approved or rejected unanimously, the minority view is lost along the route to making the committee's opinion on the drug public. Reports of all views in all documents, including the summary of product characteristics and the EPAR (European Public Assessment Report) would enable people to make up their own minds. Although votes are needed to reach a decision at the regulatory level, the majority decision does not necessarily represent the truth".

Mutual recognition too lax. "The decentralised system seems to contribute more to the free movement of pharmaceutical products in the European Union than to patients' interests (...)."

Re-assessment of authorisations is needed. "Public health interests would be better served by an updated analysis of the drug's benefit-risk profile (...)."

► *Following of page 8* cluded that the tendency to produce and to authorise ever more drugs, increasingly rapidly, was overshadowing public health considerations.

They also analysed how medicines agencies compete with one another in a context of still inadequate harmonisation, and noted that they are financed mainly by the pharmaceutical industry, with the sole exception of the German agency which, at the time of the survey, received "only" 40% of its funds from industry. Like EMEA, national agencies mainly live off the taxes and fees paid by companies seeking marketing authorisations.

The two researchers also recalled the dangers inherent in the lack of independence of many scientific experts involved in the drug evaluation process. Finally, and above all, they described a total lack of transparency in the drug regulation, and the authorities' failure to explain their decisions.

The impact of these trends on European countries with smaller pharmaceutical industries is only briefly mentioned. A continuation of this survey would be welcome during this period of European expansion.

Severe criticism by CPMP experts calling for regulations adapted to public health requirements

Silvio Garattini, a director of the Italian Mario Negri Institute, a clinical pharmacology research centre with universally recognised expertise, especially in the cardiovascular field, is a CPMP member. Together with Vittorio Bertele, another expert at the Mario Negri Institute who is also a CPMP expert, he published in the *Lancet*, in July 2001, a detailed analysis of the weaknesses of the European medicines system, and proposed a series of amendments (13). The inset on page 9 contains parts of their analysis.

The two experts concluded that "centralisation of at least one part of the marketing authorisations at the EMEA is satisfactory, and should be gradually

increased, with the aim of unifying the approval, monitoring, and policies on medicinal products, including pharmacovigilance and review of drug use. The institutional location of EMEA should be changed so it reports to the directorate of public health, not industry. Approval of new drugs must involve comparative assessments. More criticism is needed in the approval of new drugs. To defend patients' interests, companies cannot be allowed to release drugs with the sole aim of obtaining a slice of the market. The increasing power of the pharmaceutical industry requires an equally strong counterpart to ensure that drugs continue to be beneficial to patients, and are not just a profitable business."

Conclusion: urgent reform is necessary

Seven years have passed since the creation of EMEA and effective implementation of European pharmaceutical policy. It is time to draw lessons from this experience.

EMEA, depending on DG Enterprise, cannot properly serve European public health interests. On the contrary, it behaves mainly as an administrative service for the pharmaceutical industry.

European institutions have started to revise the Directive and Regulation on medicines. The Council of Europe has repeatedly stated that pharmaceutical policy must be part of a welfare protection system at the service of patients; that rational drug use must be promoted; and that new therapies offering patients real advance must be developed.

The draft modifications proposed by DG Enterprise would only worsen the pro-industry bias of the current policy in the short term. They disagree with the Council of Europe's guidelines, and carry major risks, both for patients and, in the long run, for the European pharmaceutical industry itself, by facilitating the marketing of drugs that provide no tangible therapeutic advance.

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- 1- Prescrire Rédaction "Nouveaux médicaments à AMM européenne: cotation Prescrire en 1999" *Rev Prescr* 2000; **20** (202): 60.
 - 2- Prescrire Editorial Staff "EU centralised procedure does not mean a drug is innovative" *Prescr Int* 2001; **10** (52): 53.
 - 3- Prescrire Editorial Staff "Our judgements on products approved through the centralised procedure in 2001" *Prescr Int* 2002; **11**(58): 60.
 - 4- Prescrire Editorial Staff "Funding of Medicines agencies" *Prescr Int* 2000; **9** (46): 34.
 - 5- see pages 17-19 of this issue.
 - 6- Prescrire Editorial Staff "The real beneficiaries of European drug policy" *Prescr Int* 2002; **11**(58): 34.
 - 7- Prescrire Editorial Board "Prix des médicaments remboursables: quelle logique? Deuxième partie - Prix proportionnels à l'innovation: principe raisonnable, maigres résultats" *Rev Prescr* 2001; **21** (223): 859-863.
 - 8- Charter of Fundamental Rights of the European Union (2000/C 364/01) 18 December 2000: 22 pages.
 - 9- Bardelay D "ISDB Euro-group relations with EMEA" *ISDB Newsletter* 1999; **13** (1): 4-5.
 - 10- International Society for Drug Bulletins "ISDB assessment of nine European Public Assessment Reports published by the European Medicines Evaluation Agency (EMA)" 26 June 1988: 12 pages.
 - 11- ISDB European Group "The failings of the European Medicines Evaluation Agency" *ISDB Newsletter* 2001; **15** (1): 11-13.
 - 12- Abraham J and Lewis G "Regulating medicines in Europe - Competition, expertise and public health" *Routledge, London & New York* 2000: 243 pages.
 - 13- Garattini S and Bertele V "Adjusting Europe's drug regulation to public health needs" *Lancet* 2001; **358**: 64-67.
 - 14- EMEA "Work programme 2002 - Annex 2 - EMEA budget summaries 2000-2002" 18 December 2001: 44.
 - 15- "Règlement (CE) n°1049/2001 du Parlement européen et du Conseil du 30 mai 2001 relatif à l'accès du public aux documents du Parlement européen, du Conseil et de la Commission" [Editor's note: also applies to all agencies created by these institutions] *Journal Officiel des Communautés européennes*, 31 May 2001: L145/43 - L145/48.

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An industry-serving pharmaceutical policy

The framework texts of European drug policy have undergone multiple amendments over the last four decades. Directive 65/65/EEC (1965) laid the groundwork for the definition of medicinal products and for the principle of marketing authorisation, which is now obligatory for all pharmaceutical preparations (i.e. industrially prepared drugs). Similarly, Directives 75/318/EEC and 75/319/EEC defined the foundations for analytical assessment of the pharmacological, toxicological and clinical properties of new drugs prior to their market release.

The current versions of these texts are Directive 2001/83/EC (26 November 2001) and Regulation 2309/93 (22 July 1993).

The Council of Europe's desire to protect public health has not been respected

The creation of the European Medicines Evaluation Agency (EMA) in 1995, and its early marketing authorisation and pharmacovigilance activities, were important steps in the implementation of European legislation on medicinal products. Seven years on, it is time for the European authorities to draw lessons from this experience and to adapt current regulations accordingly. The Council of Europe's position on this need for change was developed at the Lisbon Conference on medicines and public health in April 2000 (1).

Taking into account current trends in the pharmaceutical market, the Council underlined the need to identify drugs with real added therapeutic value, to scrutinise drug costs in order to ensure more rational use, and to develop drug information resources that are independent of the pharmaceutical industry.

The Council considered it vital to identify drugs bringing real therapeutic advance, not only to protect the consumer, but also to promote a healthy pharmaceutical industry (1).

These objectives were restated at the Ghent conference on health in Europe in December 2001, towards the end of the Belgian presidency of the European Union. It was also recommended that the public health

dimension be taken into account more effectively by the relevant European institutions (2).

The European Commission empowers "Enterprise Directorate General" (DG Enterprise).

The European Commission, via DG Enterprise – on which EMA is dependent – has drawn up a draft reform of European drug regulations. [Note that the Commission is the only European body able to initiate such changes (see pages 6).] The two draft texts, on drugs for human use (one Directive and one Regulation), have been in the discussion stage since 2001, with a view to their adoption by the European Parliament and the Council of Europe in late 2002 (3,4).

These draft texts are accompanied by two particularly interesting documents – a Memorandum clarifying the rationale behind the texts (5), and a document on likely impact of the proposed modifications on the drugs industry (6).

DG Enterprise has chosen its camp.

The impression given by the Memorandum is that DG Enterprise has simply ignored the numerous criticisms that have arisen from both within and without EC institutions. The same applies to key guidelines of the Council of Europe. This impression is confirmed when one reads the document on the industrial impact of the proposed changes, and also the draft Directive and Regulation (3-6).

For example, DG Enterprise seems to base its opinion of the EMA's first five years of operation only on an audit done in 2000, at the Commission's request, by Cameron-Mc Kenna and Andersen Consulting. The Memorandum refers to comments made by the interested parties (Member States, drug companies, pharmaceutical industry organisations, physician and pharmacist organisations, and patient and consumer groups) (5), but it fails to mention the documents in which these parties' opinions are expressed. It also mentions none of the documents critical of EMA that we examined on pages 8-10.

The Memorandum underlines DG Enterprise' wish to take into account ongoing changes in the industrial

landscape, such as globalisation. DG Enterprise considers that current regulations are unsuitable, and that they risk isolating Europe and weakening its pharmaceutical industry (5).

Double language

Some of the main objectives stated in the Memorandum are mutually incompatible:

« – to provide a high level of health protection for the people of Europe and tighter surveillance of the market;

– to complete the internal market in pharmaceutical products taking account of the implications of globalisation and to establish a regulatory and legislative framework that favours the competitiveness of the European pharmaceuticals industry sector;

– to meet the challenges of the future enlargement of the European Union;

– to rationalise and simplify the system as far as possible, thus improving its overall consistency and visibility, and the transparency of procedures and decision making» (5).

The Memorandum then summarises each of the points on which DG Enterprise proposes modifications. It is highly instructive to compare what is said on each of these points in the Memorandum (5); in the document on the impact on the proposed modifications on the pharmaceutical industry (6); and in the proposed Directive and Regulation that is shortly to be submitted to the European Parliament and Council of Ministers for approval.

Easier marketing authorisation.

The Memorandum states that the quality of the scientific debate (on marketing application files) must be maintained when Europe expands to 20, 25 or 28 Member States (5). It briefly mentions the importance given by the Council of Europe to the identification of drugs that have substantial added therapeutic value relative to existing options, but states that regulations are not the appropriate way of achieving this aim.

The document on the industrial impact of the proposed changes states that firms will be able to obtain marketing authorisation more ►►

Dangers of the mutual recognition procedure

Marketing authorisation by mutual recognition (also known as the decentralised procedure) is granted by national medicines agencies on the basis of initial approval by another Member State. This "Reference Member State", establishes an assessment report that is then submitted for "recognition" by the other EU countries. The European Medicines Evaluation Agency (EMA) is kept informed by the firm, and the Commission for Proprietary Medicinal Products (CPMP) is only called on to arbitrate if one or more Member States refuse to recognise the initial marketing authorisation.

A "transient" procedure that persists. This procedure was initially understood to be transient, pending full operation of the centralised procedure (for a description of this procedure, see page 5). Yet the mutual recognition procedure has developed over the years, and, little by little, become institutionalised under the impetus of some national medicines agencies and drug companies. And the draft Directive of DG Enterprise proposes, at length, to maintain manufacturers' right to use this procedure, and even to facilitate it.

There follows a list of fundamental objections to the mutual recognition procedure, which carries inherent risks for public and individual health (1,2).

A particularly secretive system. As responsibility for marketing authorisation is diluted in the mutual recognition procedure, and as transparency is not obligatory, the data on which national agencies

base their decision to grant marketing authorisation are not made public (with occasional exceptions (a)).

True, this secrecy is shared by almost all national marketing authorisations in Europe, but the mutual recognition procedure is its most blatant illustration.

A "marketplace" for marketing authorisation. Most national medicines agencies are funded, totally or mainly, by the fees paid by drug companies to have their marketing applications examined (b) (3). It is therefore crucial, for their financial existence, that these agencies are appreciated by their clients, i.e. firms, who might otherwise opt for the centralised procedure.

Needless to say, drug companies are only too pleased to see national agencies competing with one another for their custom.

Down-grading of requirements. Firms will naturally choose those agencies which have the least stringent requirements and/or which examine applications most rapidly (the two are not always but often linked).

National agencies compete on the basis of their "flexibility", as specialists say (in fact, their pliability) (4). And each national agency is linked to all the other national agencies within the framework of the mutual recognition procedure: if a given agency voices too many objections, other agencies may "seek revenge" when the country in question is rapporteur, making it less attractive to its potential "customers".

Lack of harmonisation in decisions and expertise. In the mutual recognition procedure, the criteria on which decisions are based are not standardised, and the level of scientific expertise varies from one national agency to another, as do the independence and critical capacities of national experts. Companies are naturally quick to exploit these differences in their own best interests.

When a drug is intended for sale in more than one Member State, European health would be best served by the removal of the mutual recognition procedure, after a short transition period, in favour of a reinforced, efficient and transparent centralised procedure.

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a- For the moment, only the Netherlands have made tentative steps towards transparency in this area. Representatives of the Swedish agency have suggested publishing assessment reports, but nothing has yet come of this project. French law makes it obligatory to publish such reports (art. L.5311-1 of the Code of the public Health), but is not implemented.

b- In a 1999 survey, only the German agency received more than half its funds from the public budget; industry funding nevertheless amounted to 40% of its budget (ref 2).

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1- Garattini S and Bertele V "Adjusting Europe's drug regulation to public health needs" *Lancet* 2001; **358**: 64-67.

2- Abraham J and Lewis G "Regulating Medicines in Europe - Competition, expertise and public health" Routledge London - New York, 2000: 243 pages.

3- Prescrire Editorial Staff "Funding of medicines agencies" *Prescr Int* 2000; **9** (46): 34.

4- Bouzy C and Abadie E "L'Europe du médicament" *Rev Prat* 2002; **52**: 510-514.

► rapidly; that suppression of five-yearly re-evaluations will save time and money; and that the mutual recognition procedure, whose flexibility is appreciated by drug companies, will be maintained (6).

The proposed Directive and Regulation recommend:

- that the risk-benefit ratios of new drugs should continue to be assessed without any need for a comparison with existing reference treatments (yet this makes it impossible to identify drugs with real therapeutic added value);

- that the period allowed to examine marketing applications (for both national and mutual recognition procedures) be cut from 210 to 150 days (this would be unlikely to improve

the quality of the scientific debate (a));

- that a fast-track procedure be created for "innovative" drugs (the term "innovative" is not defined). In our view such a procedure should be reserved for exceptional situations, such as new drugs likely to bring major therapeutic advance in life-threatening diseases without adequate treatment;

- that the current five-yearly re-evaluation of marketing authorisations be suppressed, and that the principle of permanent, once-and-for-all approval be adopted, whatever the assessment procedure followed;

- that the mutual recognition procedure be facilitated: most disagree-

ments would no longer be arbitrated by the CPMP, but by a small, autonomous "facilitating" group representing the Member States involved in the dispute (3,4).

Cheap, secretive pharmacovigilance. The Memorandum speaks of maintaining a high level of drug safety, and better management of pharmacovigilance crises (5). But the document on the likely industrial impact of the proposed changes states that the proposed reinforcement of pharmacovigilance will not cost firms money, as they already have the necessary system (6). It is hard to see exactly how pharmacovigilance would be reinforced.

The proposed Directive and Regu-



lation in fact call for minimal changes in this area, mainly requiring firms to prepare pharmacovigilance reports on their products every 3 years instead of 5 years at present (b)(3,4). Note that the creation of a European pharmacovigilance database presently touted as a major advance by DG Enterprise and by the pharmaceutical industry, has been one of EMEA's tasks since 1995: it is therefore nothing new. In addition, this database is not accessible yet to health professionals or patients.

Generic drug development hindered. The Memorandum claims it will be easier to market generics (5). But the document on the industrial impact of the proposed changes states that harmonisation of data protection periods will delay requests for "light" marketing authorisation procedures by generics manufacturers (6).

The proposed Directive and Regulation in fact recommend a lengthening of data protection periods, which is an obstacle to the marketing of generics (3).

Direct-to-consumer advertisement facilitated. The Memorandum is very clear on this point, recommending a pilot phase during which three drug classes will be able to be advertised directly to the public (5).

On this point, which has been hotly debated in recent months, the proposal in the Directive is less explicit than that in the Memorandum, using the word "information" instead of "advertising". But as the relevant proposals are found in the section of the Directive devoted to advertising, it is clear they are not referring to independent information (3).

Transparency of procedures and decisions: half-promises. Greater transparency of procedures and decisions is announced in the Memorandum (5) but is not even mentioned in the document on the industrial impact of the proposed changes (6).

In contrast, transparency is mentioned in the proposed Regulation, which state that expurgated assessment reports on drugs authorised via the centralised procedure should be published (but this is already the case with EPARs, of uneven quality: see page 8); and that an appropriate

level of transparency should be guaranteed by the adoption of rules ensuring public access to non confidential information (4). Somewhat vague terms for a draft regulation.

Industry first

In short, although the Memorandum, which precedes the proposed Directive and Regulation, hints at public health (5), the proposals themselves are mainly designed to strengthen the short-term competitiveness of pharmaceutical companies (3,4). The annex on the likely industrial impact of the proposals confirms this impression, as it reassures firms that the proposed texts will have only a limited impact on their activity (6).

Similarly, the conclusions of the G10 – an informal group with strong industry representation, convened by the European Commission to examine the draft proposals – confirms that the pharmaceutical industry welcomes the proposed changes with open arms (c)(7).

It is hardly surprising that some organisations of health professionals, patients, consumers, together with organisations paying for medicines, are extremely worried about the impact of these proposed measures on European public health. They have drawn up in many European countries joint counter-proposals aimed at preserving the initial spirit of European regulations, namely strict assessment of new drugs, active pharmacovigilance, tight controls on drug promotion, and a transparent pharmaceutical policy dedicated to public health (see page 14).

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a- 210 days may seem long. But when one examines all the steps involved, the time actually left for thorough study of a marketing application is in no way excessive. For example, in the centralised procedure, rapporteurs have no more than 70 days to prepare their report.

b- Currently, PSURs (periodic safety update reports) must be submitted to the relevant authorities (national or European) by the marketing licence holder every six months during the first two years, then once a year for three years and every five years thereafter. These reports are supposed to comprise data on sales volume, the numbers of prescriptions and of patients exposed to the drug, and adverse events known to the firm. The reports must, in principle, be accompanied by the results of trials conducted to complete the safety assessment. In practice, it is impossible to know what PSURs actually contain because they are not publicly available, at either the national or the European level.

c- The G10 is composed of 13 members: two members of the European Commission (DG Enterprise and the DG Health and Consumer Protection), five ministers, three representatives of manufacturers' organisations, the president of GlaxoSmithKline Europe (the leading European pharmaceutical group), one representative of mutuality health insurers, and one patient representative (ref 7,8).

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1- 2281st Council meeting – Health "Follow up to the Lisbon-Conference on medicinal products and public health – Conclusions" Luxembourg 29 June 2000: 8-9.

2- Mossialos E et al "The influence of EU law on the social character of health care systems in the European Union – Report submitted to the Belgian Presidency of the European Union – Final version" Brussels 19 November 2001: 60-80.

3- "Proposal for a Directive of the European Parliament and of the Council amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (Text with EEA relevance)" 2001/0253 (COD): 87-119.

4- "Proposal for a Regulation of the European Parliament and of the Council laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (Text with EEA relevance)" 2001/0252 (COD): 14-57.

5- "Explanatory memorandum" preceding texts 2001/0253 (COD) and 2001/0252 (COD): 77-86.

6- "Impact assessment form. Impact of the proposal on businesses, particularly on small and medium-sized enterprises (SMEs)" 68-75 (Directive) and 126-133 (Regulation).

7- Albanese V "Compétitivité industrielle en Europe. Le G10 émet 14 recommandations" *Pharmaceutiques* 2002; 96: 36-39.

8- European Commission "High level group on innovation and provision of medicines. Recommendations for action" G10 Medicines -Report - 07 May 2002: 30 pages.

Towards a medicines policy that supports basic public health needs

After carefully scrutinising the DG Enterprise' complex draft modifications of the Directive and Regulation on medicinal products (see pages 11-13), various organisations and high-ranking persons throughout the European Union have launched a counter-lobbying operation. Here are some examples.

Independent journals

The International Society of Drug Bulletins (ISDB (a)), has intervened in many European institutions (b).

ISDB stressed the specific role of the different players of the health care system in the field of drug information. In particular ISDB:

- 1- calls for the development of independent information sources on therapeutics;
- 2- denounces repeated major abuses of drug advertising towards health professionals;
- 3- considers that these past abuses automatically disqualify drug manufacturers from providing information to the public;
- 4- recommends the continued ban of all direct-to-consumer advertising of prescription drugs throughout the European Union;
- 5- considers that drug manufacturers have already enough on their hands, with the need to improve their drug packaging and patient leaflets. (1).

ISDB also denounces the negative impact of accelerated marketing authorisation procedures (shorter assessment periods, or unjustified use of accelerated procedures), as well as the continuation (instead of the disappearance) of the complex and opaque mutual recognition procedure, and the intention to suppress the current 5-yearly re-examination of marketing applications, which is poorly enforced at present (2).

CPMP members

In an open letter dated 25 February 2002, nine expert members of the Committee for Proprietary Medicinal Products (CPMP) belonging to seven countries (Finland, Iceland, Italy,

Norway, the Netherlands, Portugal and Spain), addressed members of the European Parliament who will vote, in late 2002, on the proposed changes to the European Directive on medicinal products (3).

The letter lists current problems and laments the fact that EMEA currently serves the interests of the pharmaceutical industry rather than European public health. They especially denounce:

- the fact that EMEA depends on of the Enterprise Directorate of the European Commission rather than the Health and Consumer Protection Directorate;
- EMEA funding by the pharmaceutical industry to the tune of 70%;
- EMEA secrecy regarding its goals, data, and some of its decisions, whereas the Charter of Fundamental Rights of the European Union and European Regulation n°1049/2001 (on access to documents) provide for greater transparency;
- the fact that marketing authorisation is granted for many drugs that are only equivalent, or simply "not inferior", to those already on the market, for reasons that are not made public;
- the short period that experts are given to prepare their opinion of applications, which are often difficult to assess rapidly because of the lack of comparative data, among other reasons.

Consumers organisations

The non governmental organisations Health Action International (HAI (c)) and the European Public Health Alliance, a group of European non governmental bodies (EPHA (d)), organised an international symposium on direct-to-consumer advertising of prescription drugs (Brussels, 10 January 2002) (4).

HAI and EPHA issued a joint statement. Here are a few extracts :

« This meeting clarified a number of points:

• **People want objective information on prescription medicines.** Everyone emphatically agreed that the public needs

access to balanced, comparative, relevant, up-to-date, accurate and unbiased information on pharmaceuticals and non-pharmaceutical treatments but only DG Enterprise defended their proposal (to advertise prescription medicines).

• **No one claims responsibility for the commission's proposal.** No one could say who exactly is driving this proposal. DG Enterprise said that this proposal was based on expectations expressed by patient groups but it could not name a single patient group supporting this proposal.

The director of the European Federation of Pharmaceutical Industries and Associations (EFPIA) claimed that they have no position on DTCA and representatives from AstraZeneca, Novartis and Merck Sharp & Dohme, who attended, offered no comment.

It became clear that some national health policy makers (such as the Dutch Ministry of Health) reject DTCA but want to improve the quality and accessibility of information about medicines (which does not require any change in legislation).

• **There is evidence that direct-to-consumer advertising of prescription medicines threatens public health.** (...)

HAI and EPHA demand that the EU: « - Reject this proposal in its current form, as it does not uphold the Community's Treaty obligation to ensure a high level of public health in all of its activities as set out in article 152 of the EU Treaty. Neither does it conform to the WHO's Ethical Criteria for Medicinal Drug Promotion as agreed on by all WHO member states in 1988.

- Vigorously enforce the present legislation with review, sanctions, and thorough monitoring of promotion to health professionals and the general public.

- Develop a robust consumer information and education strategy to ensure that people receive and can use quality, objective information on medicines. Specifically,

- Improve the quality of patient information leaflets to make them more reader-friendly, comprehensive, and understandable.

- Encourage the provision of independent and comparative information about medicines for health professionals and the public. Furthermore, promote



regular independent testing of the effectiveness of medicine information in educating and informing professionals and the public.
(...)

Medicines in Europe Forum

The aim of the Medicines in Europe Forum, created in March 2002 in Paris, is to provide information to all those concerned by European pharmaceutical policy, and to propose amendments to the draft Directive and Regulation of the European Commission (e).

Here are some of the reasons underlying its creation (5).

«• Medicines are not mere consumer goods.

Medicines are used by people who are either sick or have risk factors for a particular disease. All medicines, whether used therapeutically or preventively, have potential adverse events. In addition, the medicines market is captive: patients take drugs when required, not by choice; they are not mere consumers. For these reasons, approvals of new medicines must be thoroughly assessed; known and potential side effects must be actively monitored; and health professionals and citizens must have access to thorough and reliable information on the medicines they may be called on to prescribe, dispense or use. (...)

• **Reducing the time for assessing a marketing application from 210 to 150 days (see article 17 of the proposed directive) means the quality of assessment cannot be guaranteed.** It takes time to evaluate pharmaceutical, toxicological and clinical data on new drugs, and the process cannot be accelerated without compromising on quality. The experience of experts working with national agencies or with the European Medicines Evaluation Agency shows that it is already difficult to comply with the current period of 210 days. (...)

The accelerated procedure should be reserved for exceptional circumstances, such as medicines likely to offer a significant benefit for patients who have no alternative treatment. (...)

• **Given the rate at which new scientific knowledge now accumulates, medicines must be re-assessed regularly (contrary to article 24 of the proposed directive).**

Re-assessment of adverse drug reac-

tions in the light of new pharmacovigilance data is essential to guarantee patient safety and rational use.

It's also important to re-assess the comparative benefits of different drugs in the light of new international data so that patients can always be prescribed the most effective treatment. (...)

• **Drug safety cannot be ensured if pharmacovigilance is passive and secretive (see articles 101-107 of the proposed directive).** EMEA already collates spontaneous notifications of adverse drug reactions, but what purpose do the data serve if those most directly concerned – health professionals and patients – don't have access to them? The database of adverse drug reactions must be accessible on request, and so must pharmacovigilance reports. (...)

Above all the European Medicines Evaluation Agency must create an independent and proactive pharmacovigilance system. It must be given the means to conduct prospective surveys, in collaboration with the agencies of EU member states and those of other countries. (...)

• **Three principles must be reinforced.** (...) Three principles need to be reinforced in all sections of the proposed directive and regulation if European citizens are to be given every public health guarantee:

– **The principle of transparency.** (...) Secrecy now prevailing at the European Medicines Evaluation Agency and in most national agencies is an obstacle to rational drug use. Transparency must be improved if patients and health professionals are to regain confidence in this key organisation, and if these interested parties are to join force for improving rational drug use.

Real patient representation in the EMEA (articles 58, 50.3 and 51.1 of the proposed regulation)

Representatives of patients must be allowed to participate actively in all EMEA consultative bodies.

Article 58 must provide for balanced representation of patients and drugs companies on the EMEA Management board, as well as transparent procedures for selecting these representatives.

– **The principle of independence.** (...) The proposed directive and regulation must restore key guarantees of independence. Community funding of the EMEA must be increased substantially to reinforce its independence and to provide it with the means required for its role and responsibilities to be fulfilled.

– **The principle of harmonisation.** A

considerable effort has already been made to harmonise the regulation of medicines in Europe. But much remains to be done in the field of pharmacovigilance at the European and international levels, and also to improve marketing authorisation procedures. While the centralised procedure has a good performance in terms of harmonisation, the mutual recognition procedure is still chaotic, and its quality is highly variable. In addition the mutual recognition procedure is not trustworthy because it is totally opaque. (...)

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a- Created in 1986, the International Society of Drug Bulletins (ISDB) is an international network of drug bulletins that are independent from the pharmaceutical industry. Its web address is www.isdbweb.org

b- Its representatives participated in the Conference on European Integration and Health Care Systems: a Challenge for Social Policy, organised by the Belgian presidency of the European Union (Ghent, 7-8 December 2001, (ref.1)), and also in the consultation by the European Economic and Social Committee on "What are the consequences of the EU commission's proposals on the health of EU citizens, and especially on drug safety?" (Brussels, 6 March 2002), (ref.2).

c- Health Action International (HAI) is a network of some 150 consumer groups and bodies focusing on health and development in over 70 countries. Its web address is www.haiweb.org

d- European Public Health Alliance (EPHA) represents more than 80 organisations and non governmental organisations involved in health matters. www.ephha.org

e- The Medicines in Europe Forum, created in Paris in March 2002, groups together family organisations, consumer groups, patient groups, mutual insurance systems, and health professional organisations. E-mail: samia.nabi@prescrire.org

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1- Bardelay D - European Group of the International Society of Drug Bulletins "Information for consumers" European integration and health care systems: a challenge for social policy" Ghent 7-8 December 2001: 8 pages.

2- International Society of Drug Bulletins "About the proposals of the EU Commission (COM 2001-404 Final) regarding drug approvals and pharmacovigilance" European, Economic and Social Committee, Brussels 6 March 2002: 8 pages.

3- Group of 9 experts of the Committee of Proprietary Medicinal Products "Dear Members of the European Parliament – Proposed amendments to the EU pharmaceutical legislation" Milan 25 February 2002: 2 pages.

4- Health Action International – European Public Health Alliance "Joint Statement on the proposed relaxation of the EU Ban on direct to consumer advertising of prescription medicines" 28 January 2002: 3 pages.

5- Medicines in Europe Forum "Platform" March 2002.

DRUGS AGENCIES HAVE A DUTY TO INFORM

National drugs agencies must guarantee the transparency of their decisions, and have a duty to inform not only political authorities and the pharmaceutical industry, but also health professionals and citizens (1).

The most appropriate medium through which to convey this information to the public is now the internet: costs are minimised; daily updates can be made; and decision-making can be traced.

The quality of drugs agencies' websites reflects the quality of their work, and their willingness and capacity to inform and thereby fulfil their public health mission.

First impressions of websites are usually based on their user-friendliness, i.e. accessibility, rapidity, compatibility with popular browsers and software, and layout.

In particular, all information posted on drugs agency websites must be regularly updated, and dates on which information is posted must be clearly stated.

What matters most, however, is whether these sites provide clear answers to legitimate questions on national drugs policies.

The criteria we used to evaluate drug agency websites are listed on page 10. They may not be comprehensive, but they represent the bottom line.

We regularly assess websites of regulatory agencies and other important websites in our French edition.

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1- "Statement of the International Working Group on Transparency and Accountability in Drug Regulation" Uppsala, 11-14 September 1996 Available on the ISDB website : www.isdbweb.org



Prescrire's criteria for assessing drugs agency websites

1- Organisation of the agency

- Organisational flow chart: positions and contact details of managerial personnel; lists of experts; conflicts of interest.
- Calendar of meetings, with precise minutes, and whether or not meetings are open to the public.
- Detailed annual activity reports.
- Board of Directors' reports; financial controllers' reports; etc.
- Budgets.

2- Regulatory matters

- All regulatory texts defining the role and objectives of the agency, its commissions and its task forces.
- All decisions and recommendations signed by the directors.
- Lists of generics, drugs with special status, controlled drugs (opioids), blood-derived products, etc.
- List of banned advertisements, with the reasons for prohibition.

3- Assessment reports

- Summaries of Product Characteristics (SPC), including information for professionals, patient information leaflets and pack labelling, with precise details of any wording changes.
- Assessment reports submitted in support of applications for marketing authorisation (with dates of drafting and submission, clearly mentioning updates (a)).
- Reports of discussions by commissions and specialised task forces (or transcrip-

tions of recorded meetings).

- Register of ongoing and completed clinical trials. Comparative assessment of drug cost-effectiveness: work of ad hoc commissions; access to all reports made by these commissions, to evaluations of « services rendered » relative to other available products, and the reports on which they are based.
- Clinical guidelines; vaccination calendars; etc.

4- Pharmacovigilance

- Pharmacovigilance decisions, and the data on which they are based: alerts, warnings, packaging modifications, batch withdrawals (industrial problems), circulars (to manufacturers, pharmacovigilance centres, health professionals, etc.), market withdrawals and suspensions of marketing authorisation.
- Changes to SPCs relating to adverse effects, interactions, pregnancy, warnings, restricted indications, dose regimens, overdose, special clinical settings.
- Reports of completed pharmacovigilance surveys.
- Reports of commission meetings on pharmacovigilance, pharmacodependence, drug interactions, pregnancy and breast-feeding, etc.
- Drugs subject to special monitoring (list of ongoing surveys, lists of monitored drugs).
- Pharmacovigilance bulletins (national and regional pharmacovigilance centres).

- Reports of spontaneous notifications by prescribers and pharmacovigilance studies
- List of pharmacovigilance and pharmacodependence centres, etc.
- Downloadable notification forms for reporting adverse effects (for drugs, medical devices, herbal products, etc.).

5- Consumption, Usage, Pricing

- Data on consumption.
- Data on usage: non compliance, dependence, off-licence indications, prescriptions not observing the SPC.
- Market withdrawals, stock shortages.
- Regularly updated details of price of drug reimbursed by the public health insurance system.

6- Other products

- Drugs agencies' responsibilities are rarely limited to proprietary medicinal products: their websites must also, depending on regulations and the missions of the different institutions, include:
- extemporaneous preparations made in community or hospital pharmacy;
 - medicinal plants;
 - blood-derived products;
 - medical devices;
 - dietary products.

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a- For instance the European Public Assessment Reports (EPARs) of the European Agency, and Drug Reviews of the US Food and Drug Administration. No such reports exist in France.



EMA: fake transparency

<http://www.emea.eu.int>

The European Medicines Evaluation Agency (EMA) is responsible for assessment of the quality, efficacy and safety of human and veterinary drugs within the European Community.

EMA's chief missions are the following: –co-ordination of drug assessment (European centralised marketing authorisation procedure) and scientific arbitration of disputes arising from mutual recognition of national marketing authorisation (European decentralised procedure);

–co-ordination of European pharmacovigilance;

–co-ordination of drugs industry inspection activities, especially verification of Good Manufacturing Practices, Good Laboratory Practices and the Good Clinical Practices.

EMA also offers scientific advice on the conduct of preclinical and clinical trials.

During its first six years of activity, EMA appraised 339 centralised marketing applications for human pharmaceutical preparations, approving 194 of them. During the same period, EMA registered 1399 applications made through the mutual recognition procedure and arbitrated in 10 disputes. Finally, the Agency examined 5 240 proposed modifications of licensing terms.

Strengths

The EMA website provides two useful categories of document.

European Public Assessment Reports (EPAR). EPARs on drugs approved through the centralised procedure are made public, together with any subsequent revisions (section: Human Medicines; subsection: Product information\Authorized products: <http://www.emea.eu.int/htms/human/epar/epar.htm>).

EPARs are based on published clinical trials but also mention a number of unpublished trials.

Initially, EPARs were published as a single document and only in English, and some of the older EPARs are still only available in this language. EPARs currently comprise eight independent sections ("modules"). The choice of this layout is not explained. Modules 1, 3, 4 and 5 are almost always translated into 11 languages, and module 2 is occasionally translated. Module 4 corresponds to the

summary of product characteristics (SPC) and modules 3 to the leaflet. Modules 6, 7 and 8, which deal with the scientific discussion, the different evaluation steps and any postmarketing assessments, are only available in English.

Pre-licensing opinions. On 1 April 2001, as a result of lobbying by citizens and professionals, EMA agreed to publish summaries of the opinions reached by the Committee for Proprietary Medicinal Products (CPMP) on initial marketing applications for human medicines. These "summaries of opinion" are placed online on the day the opinion is reached, whether it is positive or negative, and can be downloaded from <http://www.emea.eu.int/htms/human/opinion/opinion.htm>. Once marketing authorisation has been granted (or refused) by the European Commission, the summary is deleted from the EMA website and replaced by the European public assessment report (EPAR) compiled by the CPMP (for a description of this procedure, go to <http://www.emea.eu.int/pdfs/human/opinion/163501en.pdf>).

Yearly EMA activity reports are also posted online at <http://www.emea.eu.int/htms/general/direct/ar.htm>

Purely cosmetic transparency

No detailed reports of CPMP meetings are available. The EPARs and CPMP opinion summaries posted on the web only represent the tip of the administrative iceberg.

Secrecy of the mutual recognition procedure. Assessment reports relating to mutual recognition procedures, which are by far the most numerous, are not published on the EMA website. Approximately 2 500 drugs that were approved through the decentralised procedure (either before mutual recognition, or post-marketing modifications of licensing terms) are listed on another site (European Product Index, <http://mri.medicines.com/prodidx/>), but only the public assessment report for one of these drugs is available at this address.

The EMA website has no hypertext links to assessment reports or summaries of product characteristics generated by the 15 member states' proper mechanisms.

No references, vague dating. EPARs for drugs authorised through the cen-

tralised procedure are posted online, but only as abstracts. EPARs rarely provide references of the published clinical trials on which EMA scientific discussions are based.

Revised texts are posted online, but they are not dated and the changes are not highlighted.

Minimal pharmacovigilance data.

EMA is responsible for pharmacovigilance of all drugs used in the 15 member states of the European Community, yet hardly any pharmacovigilance data are available on its website.

In 2001 EMA posted only seven product safety warnings concerning drugs already marketed in Europe (Product safety announcement), and four withdrawals of marketing authorisation.

Neither the pharmacovigilance issues discussed by EMA nor reports of meetings on adverse drug reactions are released to the public.

EMA does not offer health professionals the possibility to receive e-mail alerts or notifications of centralised withdrawals or suspensions; this information can only be obtained by clicking the red "Product alert" button on the website's homepage.

EMA does not provide downloadable side effect notification forms. The website simply gives the name, telephone number and e-mail address of the person to contact (00 44 20 7418 85 92, noel.wathion@emea.europa.eu).

Other pharmacovigilance data are scattered among the different pages of the website or are embedded within assessment documents. For example, the EMA position statement on the risk of venous thrombosis linked to "third-generation" oral contraceptives is located in the Press-Orientated Information pages. Changes to EPARs that are made in response to new pharmacovigilance data are not identified as such: to obtain this information the visitor must consult each revised EPAR, one by one, comparing each revised paragraph in the different versions.

EMA is not currently responsible for medical devices and materials.

A labyrinth

"User-unfriendly" is the term that best describes the EMA website. Users' computers must be capable of handling the Java programming language. According to EMA, Windows users can only visit the site properly if they have Internet ►►

► Explorer version 5 or Netscape Navigator version 4.7 or later. Macintosh users must be equipped with Netscape Navigator version 4.7: all Internet Explorer versions for Mac give poor results. Other flaws are the use of hierarchical pull-down menus and tiny characters, and the fact that only the top of each page appears on-screen.

Navigation tips

Although bulky, the site map provided on the homepage is nicely done: it gives a good idea of the site layout and provides direct links to the different pages.

News. The "Just Published" page provides a list of all new documents posted on the site; it is updated daily and presented in reverse chronological order (<http://www.emea.eu.int/whatsnewp.htm>). Users wanting to keep themselves informed of EMEA news should bookmark this page.

The website of DG Enterprise (unit F2, European Commission) – the interface between EMEA and the European Commission – provides rapid access to European regulatory and pharmaceutical information.

Drugs register. The Pharmaceuticals site map (<http://dg3.eudra.org/F2/sitemap.htm>) can be used to access the EC human drugs register (drugs marketed through the centralised procedure only) and the orphan drugs register ("Register" page). The former register can be searched either in alphabetical order of proprietary names, or by chronological order (but not by therapeutic class or international non proprietary name). In both cases, all the drugs are listed on a single page. Clicking a name (blue hypertext link) leads to the SPC and the patient information leaflet, in the language of one's choice.

Search index. The internal search index on the EMEA website offers two search modes ("EMEA new Web" and/or "EMEA Web"). The old EMEA server (EMEA web), whose internet address was closed in February 2001, still contains some EPARs that have not been transferred to the new site. Note that the two search options can be selected simultaneously.

Site created in 1995

Editor(s). The European Medicines Evaluation Agency (EMA), created on 1 January 1995, has its offices in London. EMA is a "community agency", i.e. a permanent European public body. It is attached to the European Commission Enterprise Directorate General (DG Enterprise).

EMA, legally represented by its chief executive officer, has a management board composed of 34 members (two representatives per Member State, two representatives of the European Parliament, and two representatives of the European Committees).

EMA has three scientific commissions that are responsible for preparing opinions on questions relating to the assessment of human and veterinary drugs.

The Committee for Proprietary Medicinal Products (CPMP), is composed of 30 members (two per Member State), and meets monthly. Another committee gives opinions on orphan drugs only (Committee for Orphan Medicinal Products, or COMP).

The CVMP, or Committee for Veterinary Medicinal Products, is charged with assessing drugs for veterinary drugs.

The EMA organigram (undated) is available, and a list of CPMP members can be obtained at <http://www.emea.eu.int/htms/aboutus/cpmp.htm>. The visitor seeking regulatory texts defining the role and objectives of the agency and its committees is directed to Eudralex, on the "Pharmaceuticals" website of DG Enterprise, at <http://dg3.eudra.org/F2/eudralex/index.htm>.

An overview of European drug legislation and the respective roles of the different institutions (Commission, DG Enterprise, EMA, etc.) can be downloaded from http://pharmacos.eudra.org/F2/pharmacos/docs/b_rochure/pharmaeu.pdf. Finally, users should know that the EMA website is only one of six EC sites on medicinal products in Europe. All these sites can be accessed via the Eudra portal at <http://eudraportal.eudra.org>.

Funding. In 1999, 2000 and 2001, EMA funding broke down approximately as follows: 25% from a European Community grant, 70% from industry fees, and 5% from "other sources" (2001 EMA report, downloadable from <http://www.emea.eu.int/htms/general/direct/ar.htm>).

Companies must pay 200 000 euros to have their marketing authorisation applications evaluated by EMA, plus 20 000 euros for each supplementary dose strength and/or formulation, and 5 000 euros for each supplementary formulation or dose strength.

EMA scientific opinions cost companies from 30 000 to 60 000 euros according to the number of expert categories involved.

Advertising. None.

Fate of users' personal data. No personal data are requested.

Editorial policy. The EMA code of conduct (<http://www.emea.eu.int/pdfs/general/admin/Conduct/3767499FR.pdf>) stresses that all work done by the agency is highly confidential. The management board, committee members and experts undertake, in writing, to exercise total lifetime discretion. However, the same code of conduct

stresses the importance of making public all information likely to affect the health of European citizens.

The EMA website only represents the tip of an information iceberg, as it only contains documents and information that EMA has decided to make public, in concert with the respective drug companies.

The result of this "conflict of interest" is an inadequately clear editorial policy and a confusing transparency policy. Explanatory paragraphs scattered around the EMA website describe the types of documents and data that the Agency has decided to make available to European citizens and health professionals, but the reasons underlying these choices are rarely given. Some documents state that transparency is a major concern for EMA (see, for example, the report of the workshop entitled "A clear step forward: Transparency at the EMA" available at <http://www.emea.eu.int/htms/general/manage/ar.htm>). The External Catalogue of EMA Documents (<http://194.81.125.53/EMEAApps/dbCat/OraExternalCatalogue.htm>), which has its own search engine and contains all the documents generated by EMA since 1 December 2000, categorises documents according to their degree of confidentiality, as P (public document), Rt (document under temporary embargo, clear title), Ct (confidential, clear title), R (temporary embargo, masked title) and C (confidential, masked title). Thus, the 109 drug assessment reports produced by EMA in 2001 all have masked titles ("Assessment Report of a Product") and all are classified confidential (C). So much for EMA transparency: all the full versions of scientific assessments, including those for authorised drugs, remain confidential. Furthermore, European Public Assessment Reports (EPARs) – summaries of the full scientific reports drawn up in concert with the company concerned – are not routinely given Public Document status (P): a large number are under temporary embargo with masked titles (R), and some are classified confidential (C). Somewhat paradoxical for a "public" report! Manufacturers even have the right to withdraw their application files just before the CPMP gives its opinion: in this case the results of the scientific assessment remain confidential (more than 50 files have withdrawn before the CPMP opinion since 1995).

The full version of the CPMP opinion on a given drug – on which the European Commission bases its final decision to grant or not to grant marketing authorisation – also remains confidential. Only summary opinions is released to the public, and only for initial marketing applications (CPMP opinions on subsequent revisions are not routinely made public).

Furthermore, when a drug is authorised on the basis of a majority opinion within the CPMP, the scientific arguments of the dissenting minority are never made public.

One would expect confidentiality to apply only to industrial manufacturing processes, yet many preclinical and clinical data are also shrouded in secrecy.

EMA rarely states its reasons for granting temporary or permanent confidentiality status to certain documents produced by its commissions.

Update policy. Some EPAR sections ("modules")



are regularly updated; this is notably the case of module 8, which describes measures taken once a proprietary drug has been released onto the European market. The file describing each authorised drug states which modules have been revised and indicates the number (but not the date) of the last revision. The nature of revisions is only rarely stated in the relevant texts: there is no introductory note, and no special labelling (i.e. italics, boldface, highlighting or underlining) that would help the reader to identify the changes in a revised document.

Last, but not least, the space provided (at the bottom of each EPAR module) for the date of the last update is systematically empty. The European public is being abused...

Author(s). More than 3 000 European experts are seconded to EMEA by the fifteen member states to prepare the scientific assessments on which the EMEA's two scientific committees base their opinions.

The names of these European experts, classified by country, are available online at <http://www.emea.eu.int/pdfs/aboutus/ExpertsCo.pdf>. Their fields of expertise and declared conflicts of interest are not mentioned, but "can be provided on request".

Information last verified on 7 March 2002

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FDA: an example of transparency

<http://www.fda.gov>

The Food and Drug Administration (FDA) evaluates the risks and benefits of health products (drugs, medical devices, screening tests, etc.) and monitors the safety of foodstuffs and some consumer products that carry a potential health risk (portable phones, microwave ovens, etc.).

The FDA website is well designed and currently provides online access to some 140 000 administrative or technical documents.

Each main FDA department has its own subsite on the FDA server.

Strong points. The home page makes it easy to access the information sought, with separate internal links to pages for:

- consumers, patients, health professionals, manufacturers, journalists, women, elderly people and children (Information for);
- publications (Reference room);
- news (FDA news);
- product types (Products FDA regulates);
- clinical trials, commissions, surveillance, etc. (FDA activities);
- FDA contact pages: to report a problem, request a public document, etc. (Let us hear from you).

Departments with their own subsites include:

- **Center for Drug Assessment and Research (CDER)**, which is responsible for assessing new drugs in terms of manufacturing quality, efficacy, safety and information leaflets, and gives its opinion on whether a new product warrants marketing authorisation in the US. The CDER home page can be found at <http://www.fda.gov/cder/index.html>

- **Center for Biologics Assessment and Research (CBER)** is responsible for evaluating the efficacy and safety of therapeutic products of microbiological, plant, animal or human origin, such as blood and blood products, vaccines, monoclonal antibodies, enzymes and interferons, genes, xenografts, allergens, etc. Laboratory tests for infectious agents are also dealt with by CBER. The home page can be found at <http://www.fda.gov/cber/index.html>

- **Center for Devices and Radiological Health (CDRH)** is responsible for assessing the safety and efficacy of medical devices (prostheses and orthoses, blood glucose monitors, surgical robots, etc.), and the safety of radiation-emitting devices (microwave ovens, video screens, cellular phones, radiological equipment, etc.). American surveillance data on

materials, including public alerts, are gathered together under the heading Postmarket issues. The CDRH home page can be found at <http://www.fda.gov/cdrh/index.html>

- Medwatch (see inset page 20) is a general FDA department responsible for pharmacovigilance and materials surveillance; the home page can be found at <http://www.fda.gov/medwatch/index.html>

- **Center for Food Safety and Applied Nutrition (CFSAN)** is charged with monitoring the safety of foodstuffs consumed by the American population (with the exception of meat, poultry and eggs). The prevention of foodborne illnesses is thus one of its main responsibilities. CFSAN is also responsible for the safety of food additives and dietary supplements, milk formulas and other foods used for human therapeutics, and cosmetics. The CFSAN home page can be found at <http://vm.cfsan.fda.gov>

Limitations. The FDA has the legal obligation to make available on its website the information it holds. The limitations of the website reflect those of the FDA itself.

In brief. The web page entitled FDA Manuals and Publications provides easy access to all the documentation present on the site. The different types of document are classified and can be accessed via a short list of key words given in alphabetical order. Each FDA department also offers a specific list of its online documents.

Three search modes are provided at the bottom of the home page: a precise plan of the site (Site map), an A to Z key word index (A-Z index) and an internal search engine (Search). Information contained in the site's database cannot be accessed using these three search modes: each database must be searched individually.

The home page for health professionals (Health professionals) has links to all the FDA website pages likely to interest them: this is a time-saver for the health professional who just wants to browse.

The visitor seeking specific information can use the advanced search mode (Advanced Search) to find all the pages containing a string of closely related or unconnected words, and can choose to search the entire text or simply the titles and/or keywords. A specific search can be made for documents posted online the previous day or week. The information contained in databases cannot be accessed in this way. The user is advised to type words entirely in lowercase or uppercase letters, and to place each ►►

► word inside quotation marks to optimise the search (click on Search tips for more details).

Users can subscribe to various mailing lists (FDA News Digest, FDA Consumer, MedWatch "What's new", etc.). Links to these services are found at the bottom of the home page (Subscribe to FDA's E-mail lists).

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Site created in 1995

Publisher(s). US Food and Drug Administration. Funding is stated. The site is financed by FDA, whose provisional budget for 2002 is \$ 1 414 391 000 (approximately 40% from the public coffers and 60% from industry dues).

Advertising. None.

Fate of users' personal details. FDA states that it never communicates to third parties any personal information volunteered, such as e-mail addresses, which must be given to subscribe to FDA mailing lists, or personal details required to identify surveillance problems.

Update policy. New documents are posted online each day. Documents published on the FDA website are updated regularly and modifications can be posted daily.

Author(s). The FDA employs 9 000 people, including chemists, microbiologists, clinicians, veterinarians, lawyers, biomedical engineers, health inspectors, pharmacy inspectors, etc., and also has a number of advisory committees comprising experts in the various areas the FDA covers. The authors of online documents may be agency employees or outside experts.

Information last verified on 19 August 2001

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MedWatch

The FDA safety information and adverse event reporting program

<http://www.fda.gov/medwatch/index.html>

MedWatch is the name of the FDA's safety information and adverse event reporting program for drugs, biological products, medical devices and dietary supplements sold on the US market.

Strong points. Pharmacovigilance alerts and new warnings on adverse effects are readily accessible.

The Safety Information section provides pharmacovigilance alerts and explanatory documents (letters, reports, etc.). It has five subsections, entitled biological products, dietary supplements, drugs, medical devices, and "miscellaneous".

A brief summary of pharmacovigilance data appears on screen, with hypertext links to detailed documents, circulars addressed to health professionals, reports, etc. Alerts are archived by year and in alphabetical order.

All modifications to summaries of product characteristics (SPC) for drugs marketed in the US are published online. These modifications cover all the different sections of the SPC, i.e. adverse effects, precautions for use, warnings, contraindications, indications, dosage and mode of administration, and interactions, as well as clinical pharmacology, oncogenicity, etc. The new text is marked clearly in bold, underlined characters. A hypertext link is provided if the text containing the data that led to the modifications is available on the FDA website. SPC modifications

are archived by date and in alphabetical order.

The standard adverse effect form can be downloaded. Health professionals and members of the public can notify adverse effects online.

The MedWatch site encourages comments and questions on product documents and reports, and provides an online form for this purpose.

One section provides a list of product or batch withdrawals, each accompanied by the reason. Most involve manufacturing problems (inappropriate packaging, failure to respect good manufacturing practices, etc.), illegal copies – which are relatively frequent in the United States (identifiers are provided), batch withdrawals of blood-derived medicinal products (identification of a risk factor in a donor, such as an infection, ongoing drug therapy, an underlying health disorder; and labeling errors, etc.), and lack of conformity of medical devices.

Weak points. MedWatch only covers drugs marketed in the United States. A drug marketed elsewhere may also be available in the United States but may have a different brand name, indication or dose strength.

Short-cuts. The What's New page shows the last two weeks' alerts. Automatic e-mail alerts can be received by subscribing to the MedWatch mailing list.

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