

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.

.....
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.

©PI

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

©PI

Translated from *Rev Prescr* October 2001; 21 (221): 705-706

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).

.....
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

© PI

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.

© PI