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The Internet and Drug Safety

What are the Implications for Pharmacovigilance?

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Abstract

Use of the Internet is becoming widespread throughout the world. Its use in the domain of drug safety and pharmacovigilance is spreading rapidly. Governments and industry have taken the lead in developing extensive web sites. The US Food and Drug Administration (FDA), the European Agency for the Evaluation of Medicinal Products (EMEA) and other agencies have developed sites containing enormous amounts of information both on pharmacovigilance in general and on specific drugs in particular. Under the US 'Freedom of Information Act' the FDA has put major parts of its adverse event database on line. Regulatory documents are also available from the FDA site or from hyperlinks described in the site. The US Center for Drug Evaluation and Research updates its site most days and maintains a free automated e-mail announcement service of these updates. Similarly, the EMEA updates its site frequently and publishes extensive material including regulatory documents, guidelines, European Public Assessment Reports on newly approved medications and other useful information. A free update service by e-mail is also available. Although English is the primary language used on the EMEA site, some of the information is available in other languages.

Pharmaceutical companies are not using the Internet for pharmacovigilance yet. Rather, the Internet is being used for promotion of their products and for informing consumers on general information on diseases, for financial and investor data and for employment opportunities, etc. Other organisations such as lobbies, consumer groups and medical journals are also beginning to use the Internet.

The electronic transmission of safety information, using the standards developed by the International Conference on Harmonization, is currently being tested for the transmission of individual patient adverse event information between companies and governments. In addition, the FDA has begun to accept adverse events from healthcare providers and consumers directly on line using an electronic version of its MedWatch form. It is expected that these developments will change the nature of the way pharmacovigilance is carried out.

Significant issues will arise from this including privacy concerns. The European Union's 1995 directive on 'the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC)' went into effect in October 1998. The enabling legislation now being passed by the member states will produce significant changes in the way companies and

governments handle individual patient data in order to assure the privacy and protection of individuals.

The Internet has already begun to have an impact on the way drug safety and pharmacovigilance are being carried out. This impact has not been felt directly but rather as a fallout from areas that are using the Internet heavily such as advertisers and groups establishing chat rooms or discussion forums. In addition, various governmental groups are beginning to define the requirements for electronic data transmission, initially using physical media (e.g CD-ROMs, diskettes) but eventually by using direct Internet or Internet-compatible electronic transmission. The impact of the Internet is expected to be felt in the next 2 to 5 years in all areas touching drug safety. The changes will be felt by consumers, healthcare practitioners, governments and industry.

Since this entire area is changing from moment to moment, this article will attempt to sketch out earlier uses of the Internet, issues involving electronic transmission of data, the current status of the Internet, initiatives underway and proposed and, finally, possible future directions. There is very little in the printed literature regarding the Internet and drug safety.[1,2]

1. Technical Aspects: Selected Definitions

1.1 The Internet, The Net, The World Wide Web, The Web

The terms the Internet, the Net, the World Wide Web (WWW) and the Web are all used more or less synonymously though in fact the Internet ('the Net') encompasses several elements, one of which is the World Wide Web. The Internet is a rapidly expanding network of over 2.2 million servers[3] that are attached to each other either full-time or part-time, and is used by over 60 million people with the typical user spending over 6 hours a week on the net.[4] The WWW (which became publicly available in January 1992 with its first and only original server) is one part of the Web but is now used by many people as a synonym for the Internet.

1.2 Intranet

An intranet (anyone, any company or organisation can set one up) is a secure information-sharing network that uses Internet architecture and whose members are limited to the users of a particular group. This 'network' of users can be local ('local area network' – 'LAN') or separated by distance ('wide area network' – WAN). The network is protected by a computer (a 'firewall') that does not allow 'nonmembers' (i.e. those without a password whether outside or inside the organisation) to get onto the network. An intranet can be simply defined as a company owned and controlled Internet, with no 'extra-company' access.

1.3 Electronic Mail

A electronic mail or e-mail is a system whereby messages, files, text, data, audio, video and other computer files can be sent from one user to another user in a different company, organisation or network instantaneously (at least in theory) over the Internet. E-mail software and a connection to the Internet are required. There is generally no cost associated to the sender or receiver for each message. Rather, costs are incurred for connection to the entire Internet through an Internet Service Provider (ISP). Currently, costs are generally charged for time spent connected to the Internet (either hourly or a flat fee) and are higher for speedier connections (e.g. T1 or cable modem connections) than for slower connections (telephone modem or ISDN connections). Thus, there is no cost per message or cost per number of recipients of the message as there would be for regular postal mail ('snailmail'). Enormous numbers of recipients can receive a message with minimal or no incremental cost to the sender for each additional recipient.

1.4 Validation

Validation is a process that involves developing documented evidence that a computer system is developed according to quality software engineering principles, that it provides the functional capability required by the users of the system and that it will continue to do so over time.[5] Validation is (or should be) required for all new computer systems. Governments are beginning to make this obligatory by issuing guidances and regulations. The US Food and Drug Administration (FDA) released 'General Principles of Software Validation' Guidance for Industry on 9 June 1997. This document is available at www.fda.gov/cdrh/comp/swareval.html.

1.5 Electronic Signature

An electronic signature (digital signature) is an electronic or digital code that can be attached to an electronically transmitted message that uniquely identifies the sender. Like a written signature, the purpose of a digital signature is to guarantee that the individual sending the message really is who he or she claims to be (also known as 'authentication'). There are a number of different encryption techniques to guarantee this level of security.[6] The FDA has already issued regulations on 'Electronic Records; Electronic Signatures; Final Rule.'[7]

2. The Internet and the Pharmaceutical Industry

2.1 Drug Safety

Currently, the major pharmaceutical uses of the Internet are for advertising, promotion and communication with consumers. Most major pharmaceutical companies have developed websites. In a survey performed in early 1998 by one of the authors (BC), while a member of the Pharmaceutical Research Manufacturers of America's Clinical Safety Surveillance Committee, it was shown that Internet usage is widespread amongst pharmaceutical companies. The results of the survey can be summarised as follows.

1. All the companies surveyed had websites.[1] The companies and their website addresses are as follows:
- Alza (www.alza.com)
- Amgen (www.amgen.co)
- Hoechst Marion Roussel (www.hmri.com; www.managedcaredigest.com; www.healthoutcomesresearch.com; www.hmrpharma.com; www.cardisense.com; www.anzemet.com)
- Roche (infodesk.roche.com)
- Astra Merck (www.astramerck.com; www.gerd.com)
- Knoll (www.basf.com)
- Lilly (www.lilly.com and several others)
- Merck (www.merck.com)
- Warner Lambert Consumer Products (www.warner-lambert.com)
- Organon (www.organon.nl)
- Pfizer (www.pfizer.com)
- Rhône-Poulenc Rorer (www.rp-rorer.com)
- SmithKline Beecham (www.sb.com)
- Schering-Plough(www.myhealth.com/index.html; www.sch-plough.com)
- Dupont Merck (www.dupontmerck.com)
- Janssen (www.mentalwellness.com and more on the way plus sites outside the US)
- Biogen (biogen.com)
- Proctor & Gamble (www.pg.com)

2. Half of the companies had separate websites for US and non–US residents.

3. Most websites contained promotional material, medical information, product listings and copies of the annual report. Many websites had research and development information, job listings, prescribing information for healthcare professionals and a field in which questions can be submitted to the company.

4. About 25% of the companies had separate homepages for patients and healthcare professionals.

5. Almost all companies had legal disclaimers indicating that the information was intended for res-

1 Please note that all website addresses [Universal Resource Locators (URLs) in this document are subject to change].

idents of a particular country or that the information was supplied 'as is' with no warranties or that the information does not replace a physician's medical advice, etc.
6. About 40% of the companies' safety departments had their own internal (intranet) homepage.
7. No companies had chat rooms at the time of the survey.
8. The company-sponsored homepages are routinely monitored for incoming messages or e-mail (where possible) either by external companies or by internal employees. Frequency of monitoring varied from daily to every 4 to 5 months.
9. Only 2 companies scanned the entire Internet on a periodic basis for adverse events related to their products. If misinformation (or even disinformation) is found few companies attempt to correct it or track it down to the source.
10. Most companies are receiving adverse event case reports via e-mail or message fields on their websites even though they do not wish to receive case reports this way and some even expressly discourage such reporting. When adverse event reports are received they are treated in the same way as other adverse events with follow-up and reporting to governmental health authorities if appropriate. Most companies do not like to use e-mail for follow-up due to the unsecured nature of the communication.

2.2 Advertising and Promotion

One of the largest areas of Internet use by pharmaceutical companies is for advertising and promotion. This is a controversial area which many governments are examining closely and are concerned about because the Internet has no boundaries. It is as easy to connect to a site locally as it is to connect to a site across the other side of the world. Hence, local or national legal restrictions on advertising and promotional claims which are more easily enforceable in regard to print, radio or television, are very hard to enforce on the Internet.

Various governmental agencies have reminded the public and the industry that current laws and regulations are applicable to advertising and promotion on the Internet. The UK Medicines Control Agency (MCA) has recently done so.[8] The MCA noted that the European Community Directive 92/28/EEC[9] is applicable to the Internet. The FDA has also reminded the public and industry that all advertising and promotion regulations apply to the Internet.[10] Another area of controversy has been hyperlinks in corporate websites (hyperlinks give the user the ability to navigate from one document on the WWW to another). The new document connected to by the hyperlink could be on the same website currently being visited, or on a website across the world. Due to the dynamic nature of websites, which can change daily, a hyperlink to another website which has acceptable content today may have unacceptable content tomorrow. Thus, pharmaceutical companies have taken a conservative stance tending to avoid hyperlinks since off-label claims, unacceptable safety data or similar problematic information may appear on the link unbeknown to the referring company. The FDA has indicated this is an issue that they are considering addressing,[10] although nothing has appeared as of yet.

2.3 Non-Governmental Organisations

Several of the major pharmaceutical organisations and professional organisations have homepages which, in some instances touch on safety matters. Organisations and their website addresses are as follows:

- International Federation of Pharmaceutical Manufacturers Association (http://www.ifpma.org/)
- Drug Information Association (http://www.diahome.org/index.htm)
- Pharmaceutical Research Manufacturers of America (http://www.phrma.org/) – the industry organisation of US pharmaceutical companies
- International Society of Pharmacoepidemiology (http://www.pharmacoepi.org/)
- Health Action International (http://www.haiweb.org) – a collection of worldwide consumer and public interest groups that have the goal of assuring that 'all

drugs marketed should be acceptably safe, effective, affordable and meet real medical needs'. Health Action International 'also campaigns for better controls on drug promotion and the provision of balanced, independent information for prescribers and consumers'. There are also many hyperlinks.

3. Journals

Various journals dealing in drug safety (among other areas) have established homepages on the Internet. Some contain full articles or article abstracts on line that also appear in the print version of the journals. These journals include, but are not limited to, the following:

- International Journal of Pharmaceutical Medicine (www.thomsonscience.com/pm/)
- Drug Information Journal (www.diahome.org/English/dhp5a.htm)
- Pharmacoepidemiology and Drug Safety (www.interscience.wiley.com/jpages/1053-8569/)
- Drugs/Drug Safety/Reactions Weekly (www.adis.com/frames.html or www.adis-usa.com)

4. Governmental Initiatives

4.1 The US Food and Drug Administration

The US FDA has set up a very complete and detailed website (www.fda.gov). Its homepage has several links to internal FDA sites including those for human drugs, biologicals, animal drugs, foods, cosmetics, devices, toxicology research and MedWatch. Several sites will be discussed here.

4.1.1 MedWatch

The MedWatch programme was set up by the FDA to enhance the post-marketing surveillance of drugs, biologicals and devices on the US market and encourages healthcare professionals to be aware of and report adverse events to the FDA and/or the manufacturer. The website (www.fda.gov/medwatch) describes the programme, gives instructions on how consumers and healthcare professionals can report adverse events and includes a downloadable copy of the MedWatch form. The site also contains a copy of the MedWatch form which can be submitted directly on the Internet to the FDA with encryption. The form may also be downloaded for submission by fax or mail. The website also contains copies of 'Dear Doctor' letters sent by the FDA as well as listings, by drug, of all label changes related to safety of marketed products. A free automated e-mail update service is available from MedWatch. Finally, this site also contains various FDA publications directed at both consumers and healthcare professionals relating to safety plus several technical articles on safety reporting aimed primarily at physicians and for whom continuing medical education (CME) credit is available.

4.1.2 Center for Drug Evaluation and Research

Each of the FDA's major divisions is also represented with a homepage. The Center for Drug Evaluation and Research (CDER), the division handling drugs, has an extensive homepage (www.fda.gov/cder) which has several subdivisions. There is a description site which contains information about the division, including a copy of its policy manual, organisational charts, information on the drug review process and more. This site also contains an invitation to receive daily or weekly e-mail updates of new material appearing on the site.

The Drug Information site has information on new drugs as well as a database (in several zipped files) of over 1 million adverse events received by the FDA in its Spontaneous Reporting System from 1969 to October 1997. Although difficult to set up and navigate this is, nonetheless, a remarkable resource that is available to everyone and contains adverse events reported to the FDA on all marketed drugs available in the US.

Other sections in the CDER homepage include extensive listings of regulations applicable to drugs in the US plus a link to another governmental sites with the entire Code of Federal Regulations. There are other sections with news and information (www.fda.gov/cder/whatsnew.htm), some of which are updated daily!

4.1.3 Center for Biologic Education and Research

Similar to the CDER site, the Center for Biologic Education and Research (CBER) site

(www.fda.gov/cber) has extensive information on the division, on product safety recalls, on safety reporting information particularly in regard to vaccine reporting, a publication section where various documents can be downloaded, faxed or e-mailed and a section on conferences and current news (www.fda.gov/cber/whatsnew.htm).

4.1.4 Freedom of Information Reading Room

This site (www.fda.gov/foi/foia2.htm) contains an extensive listing of the documents available to the public under the US Freedom of Information Act. Documents can be downloaded directly.

4.2 European Agency for the Evaluation of Medicinal Products

The European Agency for the Evaluation of Medicinal Products (EMEA) site (www.eudra.org) is very extensive and has many internal sites which include sections on information about the EMEA and its organisation, news updates, a forum for discussions, a search facility and an area for feedback to the EMEA. Also available are Committee for Proprietary Medicinal Products (CPMP) press releases, statements, product listings, guidelines, position papers, European Public Assessment Reports (EPARs) – which summarise much of the scientific information available on newly approved medicines/procedures) plus similar information from the Committee for Veterinary Medicinal Products (CVMP) and the EMEA itself. The information is available (usually) in multiple languages though English predominates. There are extensive links to other medically related sites (commercial, scientific and others) and to other health authorities that have websites. The EMEA maintains a subscription service accessible from the site which allows subscribers to receive updates on breaking news and information. This site may be of great interest to professionals and authorities in developing countries as a resource which easily provides a great deal of information on new and old drugs.

4.3 European Safety Agency Sites

4.3.1 Portugal

The site of the Instituto Nacional da Farmacia e do Medicamento (Infarmed) gives a general description of the agency and its missions (www.infarmed.pt). It is available only in Portuguese.

4.3.2 Sweden

The site of the Swedish Medical Products Agency (www.mpa.se) gives information about the agency plus approved products, treatment recommendations, press releases, statutes, guidelines, regulations and other information including a large hyperlink section. It is available in Swedish and English (though some pages are only in Swedish).

4.3.3 UK

The site for the UK's Medicines Control Agency (http://roof.ccta.gov.uk/mca/mcahome.htm) is an extensive site with much safety information including a link to the Committee on Safety of Medicines website, which has information on its activities, the 'yellow card' system, current and back issues of *Current Problems in Pharmacovigilance*, 'Dear Doctor' and 'Dear Pharmacist' letters, etc. There is information on licensing and post-licensing including lists of black triangle medications, licensing and enforcement (Good Medical Practice and Good Laboratory Practice) information and more.

4.3.4 Australia

The site (www.health.gov.au/tga/) of the Australian Therapeutic Goods Administration (TGA) has information on the various duties of the TGA. Also included are copies of the Australian Adverse Events Drug Bulletin along with other governmental publications related to drugs and devices. The Australian Ministry of Health Site is: www.health.gov.au.

4.3.5 Canada

The site for Health Canada Online (www.hc-sc.gc.ca/english/index.htm) has a listing of Regulations and Policies, a News update section, and sections on Public Health and related Factors. This site is available in English or French.

4.3.6 Japan

This site (www.mhw.go.jp/english/index.html) is available in English and Japanese and is maintained by the Ministry of Heath and Welfare. There is not much information on drug safety, but it does include a descriptive section on the Ministry of Health and Welfare itself, along with health related statistical summary information.

4.3.7 Other sites

The FDA maintains an extensive list of hyperlinks to ministries and health authorities at: www.fda.gov/oia/agencies.htm. Most of these sites do not cover pharmacovigilance in any detail.

Some other governmental sites are listed below. They are in English unless otherwise specified (all were accessed on 21 December 1998):

- Argentina National Administration for Drugs, Food & Medical Technology: www.anmat.gov.ar/principal.html (in Spanish only)
- Austria Ministry of Labor, Health & Social Affairs: www.bmags.gv.at/ (in German but an English version is apparently being prepared)
- Belgium Ministry of Social Affairs, Public Health and Environment: www.health.fgov.be/en/welcome_homepage-en.htm
- Brazil Ministry of Health: www.saude.gov.br/ (in Portuguese only)
- Columbia National Institute of Vigilance of Drugs & Food: http://www.sinpro.gov.co/invima/indice.htm (in Spanish only)
- Costa Rica Ministry of Health: www.netsalud.sa.cr/ms/ (in Spanish only)
- Ecuador Ministry of Public Health: www.salud.org.ec/index_ms.htm (in Spanish only)
- Egypt HealthNet: www.idsc.gov.eg/health/
- France Ministry of Health: www.sante.gouv.fr/index.htm (only in French)
- Germany Federal Institute for Drugs & Medical Devices (BfArM): www.bfarm.de/gb_ver/ (in German and English)
- Guyana Ministry of Health: www.sdnp.org.gy/moh/
- Hong Kong Department of Health: www.info.gov.hk/dh/
- India Ministry of Health and Family Welfare: www.nic.in/mohfw/
- Indonesia Ministry of Health: www.depkes.go.id/english/
- Israel Ministry of Health: www.health.gov.il/code_eng/rashi.html
- Italy Ministry of Health: www.sanita.interbusiness.it/ (only in Italian)
- Korea Food & Drug Administration: www.kfda.go.kr/main1en.htm
- Lebanon Ministry of Health: www.public-health.gov.lb/
- Lithuania State Medicines Control Agency: www.vvkt.lt/defaeng.htm (in Lithuanian and English)
- Mexico Ministry of Health: www.ssa.gob.mx/ (in Spanish only)
- Morocco Ministry of Health: www.sante.gov.ma/ (in French)
- New Zealand Medicines & Medical Devices Safety Authority: www.medsafe.govt.nz/indexother.htm
- Nicaragua Ministry of Health: www.ops.org.ni/ (in Spanish only)
- Peru Ministry of Health: www.digesa.sld.pe/ (in Spanish only)
- Philippines Department of Health: www.medsafe.govt.nz/indexother.htm
- Singapore Ministry of Health: www.gov.sg/moh/
- South Africa: www.gov.za/dept/health/index.html
- Spain Ministry of Health & Consumers: www.msc.es/ (only in Spanish)
- Thailand Ministry of Public Health: www.moph.go.th/
- Turkey Ministry of Health: www.health.gov.tr/

4.4 World Health Organization Monitoring Centre (Uppsala Monitoring Centre)

The World Health Organization (WHO) Monitoring Centre (also known as the Uppsala Monitoring Centre) in Uppsala, Sweden collects adverse event data from around the world. The centre maintains a database of adverse event reports which can be accessed on line. The centre's site

(www.who.pharmasoft.se/home.html) also contains other information on their publications including adverse event coding.

4.5 International Conference on Harmonisation

The International Conference on Harmonisation (ICH) was formed in the early 1990s to harmonise product development and registration in the European Union (EU), Japan and the US. Membership comprises regulators and industry representatives from these regions. Four international meetings have been held and numerous guidelines and reports have been issued. Many deal with the safety of pharmaceuticals and can be found on this site (http://www.ifpma.org/ich1.html) under the 'Efficacy' headings (not the 'Safety' sections which deal with pre-clinical testing).

5. Electronic Data Transfer

The ICH and the various governments supporting ICH have indicated their desire to move to a paperless (or at least a less paper) world in which adverse event case data will be submitted electronically.

The FDA has stated that it intends to require the electronic submission of all postmarketing safety reports, precoded in ICH-M1, using the ICH-E2B format encased in ICH-M2.[11] To this end several documents have been developed which define the content and format for the electronic transmission of individual case data.

The European Commission Directorate General for Industry, the EMEA, the EU national regulatory agencies and the European Commission Joint Research Centre are jointly developing the EudraNet to provide EU national health authorities and the pharmaceutical industry with certain generic functions such as electronic mail and file transfer plus specific network based applications for market authorisation and post-market control. The system will also be used for the dissemination of regulatory information.[12]

In particular, the EudraWATCH system is creating a pharmacovigilance database at the EMEA. This will allow downloading of serious adverse drug reports from the national pharmacovigilance centres, manual entry of reactions received by the EMEA and query and report generation for data analysis. It is also hoped that industry would be able to transfer data to this system at a future date.[13] It is hoped that the EudraWATCH system will be up and running between the EMEA and the 15 EU member states in 1999.

5.1 Standards for Safety Data

Several documents have been published by ICH and describe standards for safety data collection, transmission and coding. These are as follows.

5.1.1 E2B Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety

This document applies to safety data from both pre- and postmarketing, (i.e. from clinical trials and spontaneous reporting) and has reached step 5 (implementation) in the ICH process. It standardises and identifies the data elements of individual case reports for adverse events and adverse drug reactions regardless of source and destination. It is meant to be used for the electronic transmission of safety data between databases, such as company to government or government to government or company to company.[14,15] This document is available at: www.ich.org/ich5e.html#Safety. It has been adopted by the CPMP for the EU[16] and has been published in the US Federal Register.[17] The FDA has indicated that it plans to have adverse event data submitted to its new Adverse Event Reporting System (AERS) using the E2B guideline[18] and a pilot programme is underway using E2B for transmittal of data from 2 pharmaceutical companies to the FDA. Other companies have been invited to join an expanded pilot programme.

5.1.2 M2 Multidisciplinary Group 2 – Electronic Standards for the Transfer of Regulatory Information

This group was established to evaluate and recommend open and non-proprietary standards for the transfer of data electronically that will meet the requirements of industry and government authori-

ties. These recommendations cover structured and personal messaging, electronic data interchange (EDI), data definitions to incorporate structured data formats like SGML, security, data integrity, authentication and more. This guideline can be downloaded at www.ich.org/ich5.html.

5.1.3 M1 International Medical Terminology/ Medical Dictionary for Regulatory Activities

The Medical Dictionary for Regulatory Activities (MedDRA) has been developed to serve as a single dictionary of terminology for the classification, retrieval, presentation and communication of medical information throughout the entire life cycle of a product. It will replace multiple dictionaries now in use and it will be available in several languages. Further information on M1 is available on the ICH site: www.ich.org/ich5m.html. The FDA has indicated that MedDRA will be a part of its AERS system (www.fda.gov/cder/aers/concept.htm). A maintenance organisation is being enlisted to maintain the coding system, distribute it, assign new codes, etc. It is expected that MedDRA will be available in early 1999. Discussions are already underway on the impact that MedDRA will have on adverse effect reporting, product labelling and submission of dossiers (New Drug Applications or the equivalent) to health authorities.[19]

6. Privacy

Whatsoever things I see or hear concerning the life of men, in my attendance on the sick or even apart therefrom, which ought not be noised abroad, I will keep silence thereon, counting such things to be as sacred secrets.

Oath of Hippocrates, BCE 400

On October 24, 1995 the EU issued a directive on 'the protection of individuals with regard to the processing of personal data and on the free movement of such data' (95/46/EC). This directive was to be put into law (making clear any exemptions) in each of the member states by October 24, 1998. Although several states have already enacted enabling legislation this has not yet happened in all member states. Legislation is expected in additional states in 1999.

The directive and national laws are aimed not only at the pharmaceutical industry but at all industries and entities that deal with documents that involve data privacy issues. This will include banking, commerce, healthcare, trade union issues, etc.

A copy of the directive in English and other languages along with other information on data privacy is available on the website: 193.91.44.33/legal/en/dataprot/directiv/directiv.html.

Non–EU countries have varying levels of data protection. The US does not have such clear privacy protection though various laws and proposals are being discussed. In some cases, laws on privacy vary from state to state within the US. Websites that deal with data protection and privacy include:

- 193.91.44.33/legal/en/dataprot/dataprot.html
- www.cnil.fr/ (this site is mainly in French; however, there is an interesting section on how a user can be traced while on the Internet)
- www.epic.org/privacy/medical/
- http://elj.warwick.ac.uk/elj/jilt/dp/

The EU directive covers the following points.

- Data, processed both manually and automatically (i.e. by computer), must protect the 'fundamental rights and freedoms of natural persons, and in particular their right to privacy with respect to the processing of personal data'.
- Data processing in a third country (i.e. non-EU) must not diminish the protection of EU citizens' privacy. That is, data from the EU that comes to the US, for example, must still adhere to EU privacy protection standards when processed in the US or elsewhere.
- The subject or patient's consent must be obtained for processing of data and EU member states can put limits on the extent of use of this data outside the EU. 'The transfer of personal data to a third country which does not ensure an adequate level of protection must be prohibited.'
- Each country is to create a 'controller' which is a person or public agency to 'determine the

purposes and means of the processing of personal data'.
- The data collected must be accurate and a system must be in place to allow for correction of erroneous data.
- The data must be kept in a form which permits identification of the subject for no longer than is necessary. Countries shall lay down appropriate safeguards for storage periods.
- Any processing of health data must be under national laws which clearly protect the confidentiality of the data.
- The data subject must be told where the data is going (e.g. a pharmaceutical company), the purposes of its use and the subject must have access to it and the right to rectify it. For scientific research, some exceptions can be made at national levels; however, there must always be appropriate safeguards.
- Safeguards must be enacted to protect the personal data from accidental or unlawful destruction or accidental loss, alteration, unauthorised disclosure or access in particular where the processing involves the transmission of data over a network. This section is designed to include protection from 'hackers' – people who enter other people's databases either for sport or for malicious reasons.
- The controller in each country must know the purpose of the data processing and the proposed transfer of this data to third countries.
- The processing operations will be 'publicised' and a register kept by the controller that can be inspected by anyone.
- Legal remedies shall be made available to individuals for any breach of their rights and damages.
- Member states will inform each other of countries with inadequate protection.
- Trade associations are encouraged to draft national codes of conduct and submit them to the national authorities for approval.
- Each member state must set up an independent supervisory authority to monitor data protection. It will have investigative powers including access to the data and the processing operations and it will have the power to collect all information it deems necessary. These national authorities in the EU will cooperate with each other.
- A working party made up of the supervisory authority from each EU country is set up and will exchange information with each other. It reports to the Commission and may make recommendations to the Commission which may take action to protect individuals' privacy. It will publish an annual report.

The implications of this directive are such that pharmacovigilance (and other) researchers must get specific patient or subject consent for the specific uses of the data or stop collecting/processing certain specific demographic data which could allow identification of the patient. That is, data must be anonymised with loss of certain information such as data pertaining to age, gender, ethnic background, race, sex life and certain other health information. The European Federation of Pharmaceutical Industries and Associations (EFPIA) has drafted a voluntary code of conduct for the industry which is currently under evaluation. Other organisations are considering a similar step.

Unless exemptions are granted for pharmacovigilance data, it might be necessary to stop sending this data to countries that do not have adequate privacy protection (specifically the US which does not have the EU level of protection) or to remove all identifiers from individual patient data (anonymisation).

There are significant implications of the directive and the resultant new legislation and regulation being developed. Significant protection of patients' rights in the transmission and processing of data will be required for safety data transferred electronically unless exemptions are granted. This will require various combinations of encryption, anonymisation, limitation on the data collected in the first place or in the data retained after initial processing since the data to be transmitted under E2B standards clearly include personal data that falls under the EU directive. The implications for signalling, epidemiology and pharmacovigilance

are being explored. This is an evolving area and much will change over the next few years.

7. Synthesis

The number of initiatives going on is voluminous and somewhat confusing. The impact of the Internet can be summarised as follows.

7.1 Dissemination of Data

The web is now allowing the movement of known health information, whether accurate or not, immediately and rapidly. Governments as well as many other institutions (e.g. WHO Uppsala Monitoring Centre, universities, medical centres, individual physicians, activist groups, news organisations, pharmaceutical companies, etc.) are disseminating data to consumers, healthcare professionals, activists, other governments and anyone else who chooses to log on to a website. Techniques are now being developed by software manufacturers, advertisers and others to target specific audiences for the receipt of certain data. In addition, search engines are becoming more sophisticated. It is expected that surfers of the web will be able to find the data they need faster and with more precision as these techniques develop.

The ability to download files permits users to obtain and manipulate enormous amounts of data with minimal effort. Entire databases (e.g. the FDA's database of adverse events) can be downloaded and analysed using various software tools rapidly and inexpensively.

As with many advances, this presents a double edged sword. Data can be misused and misinterpreted either in benign (erroneous) or malevolent manners. Data can be changed and redisseminated without telling future recipients of the data about the changes made. Data integrity and validation issues still need to be addressed. Unlike printed material for which an original document can exist, be stored in a library and represent the definitive and unchanging source document, web material is dynamic and ever-changing, often with no traces of changes evident. In addition, web sites and data can totally disappear with the click of a mouse removing the source material. Clearly, this field is still in dynamic flux as new techniques and ground rules evolve. For safety data, it remains to be seen whether the dissemination of (often unvalidated) adverse event data will further public health or merely raise premature fears on the safety of drugs before reasoned and thoughtful scientific conclusions can be drawn. For promotion and advertising, it is likely that rules will be laid down restricting what can be said on the Internet. This too is a dynamic area as the Internet seems to be overlapping with telephony, radio, television and even printed media ('newspapers on the web'). It would not be surprising to see in a few years various 'electronic boxes' around the home and office capable of delivering television, radio, telephone calls, printed media and more. Commercial enterprises will be in the forefront of these developments for promotion and advertising. How governments will react, particularly since the Internet makes national borders and jurisdictions irrelevant, remains to be seen.

7.2 Collection of Data

An area that appears to be somewhat more 'controlled' regarding adverse event data involves the collection of data. With appropriate firewalls, wide area networks, encryption and various other security measures, data can be easily and rapidly ('real time') transmitted from governments to governments, governments to companies and clinical investigators to sponsors. Since data collection can be done without its general availability to the surfing public, it is likely that this area will develop rapidly and efficiently. It is likely that confidentiality issues will remain contentious as new laws and initiatives advance and this may tend to limit some uses of the Internet for data collection and data sharing.

7.3 Communication

This area, related to the two areas discussed above, has already produced enormous changes in the way people communicate. Chatboxes (chatlines) now allow people, either one-on-one or in groups, using

one or more languages to communicate with each other in real time. Translation software may one day allow websites and typed conversation to be translated as it happens. Other interesting issues have arisen in chatboxes in which a guest answers questions. In regard to dissemination of drug information by a pharmaceutical company, it is necessary that only approved labelling information (e.g. approved indications or adverse events) for that country be given to a questioner on chatbox. Yet this may prove to be difficult or impossible since users are usually anonymous and their country of residence is not determinable.

The use of e-mail also allows a message to be disseminated in a one-to-many (if not nearly a one-to-infinite) manner. The risk of transmission of incomplete, wrong or malevolent data clearly has increased and the ability to correct it has decreased.

> *A lie can travel halfway round the world while the truth is putting on its shoes*.
>
> Attributed to Mark Twain.

A more positive use of the Internet involves bilateral communication of safety data between licensing partners or governments and corporations or governments and governments. If the proposed standards from ICH (M1, M2, E2B) are adopted and used the ability to transmit safety data will be significantly enhanced.

7.4 Future Developments

Making predictions is always dangerous, but there is a large possibility that the Internet will change the way the safety business is done. Although there will be changes in the way data is entered, transmitted and communicated, the most exciting prospects seem to lie in the ability to use the Internet to analyse data and draw conclusions in regard to the safety of medications and devices with the goal of improving public health. With the creation of large databases in North America, Europe and elsewhere along with the move to standardised coding (MedDRA), the ability to do real time on-line searches to detect and evaluate safety signals and perform complex and rapid pharmacoepidemiological evaluations may be greatly enhanced. The continued standardisation of drug labelling around the world (with country to country differences declining) would also be likely to follow.

8 . Conclusion

The Internet and all of the 'fallout' from the Internet are going to produce major changes in the way the world functions. More traditional uses of the Internet (e.g. commerce, financial analysis/ summary, news and newsgroups, and even multi-company extranets whereby partner companies can access a common set of information, etc) are now becoming more prevalent. Books such as *Unleashing the Killer App: Digital Strategies for Market Dominance*,[20] and websites such as Microsoft's Research site (http://research.microsoft.com) are just beginning to touch on potential long term strategies and uses for Internet technology. 'Phase-shifting' (the next generation of video-conferencing where each conference attendee sees all the other attendees on his or her PC screen) and further futuristic refinements such as holographic images will surely arrive also. 'Portal' access (configurable and personalized user access to the Internet) is also now starting to be developed.

Mr John Chambers, the president of Cisco Systems, a major technology company, recently stated that:

> *The Internet will change how people live, work, play and learn. The Industrial Revolution brought together people with machines in factories, and the Internet revolution will bring together people with knowledge and information in virtual companies. And it will have every bit as much impact on society as the Industrial Revolution. It will promote globalisation at an incredible pace. But instead of happening over 100 years, like the Industrial Revolution, it will happen over 7 years.*[21]

Pharmacovigilance, too, will be touched by these changes. We live in electronically exciting times.

References

1. Pines W. The challenge of the Internet. Drug Inf J 1998; 32: 277-81

2. Cobert BL, Silvey J. The internet, adverse events and safety. Int J Pharm Med 1998; 12: 83-6
3. Zakon RH. Hobbes' Internet Timeline v4.0 [online]. Available from: URL: http://info.isoc.org/guest/zakon/Internet/History/Hit.html [Accessed 1999 Jan 6]
4. Cyberatlas Demographics [online]. Available from: URL: cyberatlas.internet.com/big_picture/demographics/demographics_index.html [Accessed 1999 Jan 6]
5. Brown E. Straight talk: what is validation? PROTOCOL, A Validation Industry Quarterly Newsletter, Spring 1996. Bridgewater (NJ): Taratec Development Corporation (data on file)
6. Digital signature [online]. Available from: URL: www.pcwebopaedia.com/digital_signature.htm [Accessed 1998 May 4]
7. US Code of Federal Regulations: 21 Chapter 1 Part 11 Electronic Records; Electronic Signatures [online]. Available from: URL: http://www.access.gpo.gov/nara/cfr/cfr-table-search.html [Accessed 1998 Dec 21]
8. MCA News. UK Mail, 103, 4 (September/October 1997)
9. EC Council Directive 92/28/EEC Concerning the Advertising of Medicinal Products for Human Use. Official Journal of the European Communities, 1992, L113, 13 [online]. Available from: European Union Document Delivery Service http://eudor.eur-op.eu.int/ [Accessed 1998 Dec 21]
10. FDA Internet Guidance. The Pink Sheet 1997; 59 (21); 7
11. Center for Drug Evaluation and Research. Reporting regulations and guidances [online]. Available from: URL: http://www.fda.gov/cder/aers/regs.htm [Accessed 1998 Dec 21]
12. DG III-E-3Telematics Projects in Pharmaceuticals and Cosmetics [online]. Available from: URL: www3.is.eudra.org/telemat/index.htm [Accessed 1998 Dec 21]
13. Eudranet & EudraWatch Project Progress Report (January 1998, Issue 5) [online]. Available from: URL: http://www3.is.eudra.org/telemat/pdf/en319.pdf [Accessed 1998 Dec 21]
14. De Cremiers F. Efficacy Workshop, ICH 3. The Regulatory Affairs Journal, 1996 May: 360
15. Brown L. Highlights and achievements of ICH 4. Good Clinical Practice 1997 Sept/Oct; 4 (5): 25-30
16. E2B Clinical Safety Data Management: Data Elements for Transmission of Individual Case Reports. CPMP/ICH/287/95 [online]. Available from: URL: www.ich.org/ich5e.html#Safety [Accessed 1998 Dec 21]
17. International Conference on Harmonisation; Guidance on Data Elements for Transmission of Individual Case Safety Reports. US Federal Register 1998; 63 (10): 2396-2404
18. Center for Drug Evaluation and Research. AERS: concept of operations [online]. Available from: URL: http://www.fda.gov/cder/aers/concept.htm [Accessed 1998 Dec 21]
19. White C. A preliminary assessment of the impact of MEDDRA on adverse event reports and product labeling. Drug Inf J 1998 32: 347-62
20. Downes L, Mui C, Negroponte N. Unleashing the killer app: digital strategies for market dominance. Cambridge (MA): Harvard Business School Press, 1998
21. Freidman, T. The Internet wars. New York Times 1998 Apr 11; Sect. A: 11

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