Focus Article

Electronic SAE reporting – are the players ready?

By Liz Nowell, Health Decisions Ltd
Dr Alan Rawling, Assured Information Systems
Dr Michael Bowden, Health Decisions Ltd

Introduction

Pharmacovigilance, or drug safety, has traditionally been an independent, self-contained function in many pharmaceutical companies, its primary role being to meet regulatory requirements. However, with increased focus from the international regulatory authorities and organisations such as the International Conference on Harmonisation (ICH), this role is changing, and pharmacovigilance is increasingly taking a central role as a valuable source of information about the use and tolerability of the company's products.

The volume of pharmacovigilance data, both in terms of number of individual cases and contributing organisations is increasing annually. This has led to the expectation that replacing the current paper based processes with an electronic methodology will introduce efficiencies that will improve public safety and reduce the cost overhead for marketing and support of pharmaceutical products in the European Community and beyond.

This paper examines the current position of the key regulatory authorities with a focus on Europe due to its imminent implementation of electronic serious adverse events (SAE) reporting and notes that the significant implications for smaller companies and those without e-capable IT Departments make compliance expensive and technically demanding.

The current practice of paper transmission of SAEs to regulatory authorities as single case reports and the subsequent re-keying of data upon receipt is time consuming, potentially inaccurate and totally inefficient

Table 1: Regulatory documents covering electronic submission of SAEs

- ICH E2B Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports[1] (now modified to ICH E2BM [2001])
- ICH M2 Electronic Standards for the Transfer of Regulatory Information (ESTRI)[2]
- Commission Directive 2000/38/EC (an update of Directive 75/319/EC)[3]
- Council Regulation (EEC) No. 2309/93[4]
- Notice to Marketing Authorisation Holders Pharmacovigilance Guidelines (January 1999)[5]
- Note for Guidance Regulatory Electronic Transmission of Individual Case Safety Reports (ICSRs) in Pharmacovigilance (2002)[6]
- Joint Pharmacovigilance Plan for the Implementation of the ICH E2B, M1 and M2 requirements related to the electronic transmission of Individual Case Safety Reports in the Community[7]
- Notice to Applicants, Volume 9[8]
- FDA Guidance for Industry – Providing Regulatory Submissions in Electronic Format – (excludes vaccines)[9]

Why report electronically?

The volume of adverse event reports handled by pharmaceutical companies is increasing – one large, global manufacturer that we have worked with is seeing its case volume double in number every 18 months. Part of this is due to new product releases and increased sales volume, but a significant proportion is thought to be related to a cultural trend towards increased reporting by healthcare professionals and consumers.

The number of participants – regulatory authorities, organisations such as the World Health Organisation (WHO), and pharmaceutical company licensing/marketing partners that require access and copies of individual SAE reports is also increasing.

As a consequence, the current practice of paper transmission of SAEs to regulatory authorities as single case reports and the subsequent re-keying of data upon receipt is time consuming, potentially inaccurate and totally inefficient. The FDA's mission to "promote and protect public health" is not met by such an outmoded practice. To overcome this, the regulatory authorities and pharmaceutical industry have been working through ICH to replace paper reporting of SAEs with electronic transmission and routing of Individual Case Safety Reports (ICSRs). This is close to fruition in Europe where the implementation date has been set as January 31, 2003. Japan will follow later in 2003 and the FDA is expected to announce a date soon.

What are the advantages?

There are benefits to be gained on both sides:

For regulatory authorities:

- Cost reduction – for example the FDA is known to employ 100 outsourced contract data entry staff to re-key paper safety reports. Most of these would not be necessary with e-submissions. It will be interesting to see whether the cost savings are passed back to the pharmaceutical companies in terms of reduced licence fees
- Quality – reduced need to verify data against the original copy after data entry; data will be coded by the submitter giving a common basis for analysis
- Speed – case data are immediately available for signal/trend analysis and query generation
- Consistency world-wide – access to a global safety profile via a common standard will improve the quality of decision making.

For manufacturers:

- Provides a single standard format for manufacturers to submit SAEs to multiple regulatory authorities
- Reduce duplication of data entry and cost of processing paper copies between affiliates and their headquarters, and between partners (other pharmaceutical companies and Contract Research Organisations [CROs])
- Reduce transcription errors from multiple data entry, and duplication of reports, therefore quality of information should improve
- Speed of transmission of individual cases during rapid alerts/safety issues.

What are the issues?

The implementation and roll-out of new technologies is never problem-free. Within a single company it can take many months to get the users to agree on the specifications and format of a new safety database; attempting to implement this on a global scale across multiple companies and organisations only compounds the complexity (see Table 2).

The legal framework

Unsurprisingly, there are a number of guidelines covering electronic submission of SAE reports, and the implementation of a data processing network and a database for pharmacovigilance, a selection of which are listed in Table 1). The key documents are ICH E2B – the electronic report format for Individual Case Safety Report (ICSR) submission, and ICH M2 (ESTRI), which defines the "transport vehicle" and security and format definitions. Two useful websites are *www.ifpma.org* – the "definitive" source of all ICH documents, and *www.eudravigilance.org*

Table 2: Major issues in switching to electronic submission

- Initial cost of implementation – particularly for smaller companies
- Technically complex data format required – again an issue particularly for smaller companies and those without access to IT functions
- In theory it would be possible to type an SAE in the required format, but although the format would be readable it is long-winded and intended for computer-to-computer transmission. Manual data entry would require double data entry, duplicated verification etc and is practical only for those companies with a negligible case volume
- Pharmacovigilance databases need to be re-programmed to be able to generate an electronic reporting capability based on the ICH E2B/M2 specifications. The major commercial databases already comply but this is not necessarily the case with the vast number of "home grown" systems
- Need to maintain compliance and quality while moving from a paper-based to an electronic system.
- Still need (paper) back-up mechanism in case technology fails/is unavailable
- Security/patient confidentiality issues (an issue present even with a paper system) HIPAA[12] legislation requires that all patient identifiable information must remain secured at all times – especially as it is transmitted between entities
- Electronic signatures – if the paper reports were signed off eg, on a cover sheet, then the electronic report ought to be signed electronically
- In parallel with the e-submission initiative, any computer system will need to comply with the quality demands of the FDA's 21 CFR part 11 rule on Electronic Signatures and Electronic Records
- Need an audit trail of the entire submission process, including uploading the file, sending the file, and receiving message receipt and ICSR acknowledgements
- ICSRs need to be coded using MedDRA – the e-submission requirement mandates the use of this ICH-driven terminology
- CRO contracts and licensing agreements will need to specify an E2B, M2 and MedDRA component
- SOPs may need to be revised to incorporate the electronic reporting process

Common terminology

In addition to all the guidelines, policies and procedures, electronic SAE reporting uses a lot of technical language. A glossary of some of the more common phrases is listed in Table 3.

When does it start?

The expectation from the EMEA is that companies will have completed a pilot test by January 31, 2003 and will be ready for electronic reporting for new cases from February 1 onwards.

However, this is not legally enforceable. The EMEA recognises that there will be a transitional phase, but "hopes" that all companies will at least have a plan in place by that time. In addition, the EMEA requires retrospective electronic reporting of all expedited cases dating back to January 1, 1995. Companies will therefore need to convert all their legacy data to the E2B standard and transmit them to the EMEA by January 31, 2004.

The Ministry of Health and Welfare in Japan has set a date of October 1, 2003 for

EMEA expects that companies will be ready for electronic reporting for new cases from February 1, 2003

Table 3: Glossary of common terms

DTD Document Type Definition	Hierarchical representation of the information contents of a document utilised by SGML. It defines each element of the ICSR being transmitted together with the relationships between various data elements
EDI Electronic Data Interchange	Transfer of data electronically in a secure environment between two authenticated parties
ESTRI–Gateway Electronic Standards for the Transfer of Regulatory Information	A data exchange service which consists of all core standards and functionality required for supporting the ICH standards (eg, Simple Mail Transfer Protocol SMTP)
EUDRANET	A network linking the EC, the EMEA and national competent authorities to allow rapid and secure exchange of information between members
EUDRASAFE	A secure document delivery system accessible through the Internet. Companies may use EudraSafe to submit case safety reports to the EUDRA mailboxes of the national regulatory authorities and the EMEA
EUDRAVIGILANCE	The EU pharmacovigilance system for electronic exchange of ICSRs and PSURs, providing a centralised database of adverse reactions occurring both within and outside the EU. EudraVigilance is EMEA's new European data-processing network and database management system for the exchange, processing and evaluation of expedited Individual Case Safety Reports (ICSRs)
GATEWAY	A device or program which accepts information into a network from an external source
ICSR Individual Case Safety Report	A report of a serious adverse drug reaction in an XML/SGML format
MedDRA Medical Dictionary for Regulatory Activities	The internationally agreed medical terminology (ICH M1) designed to support the classification, retrieval, presentation and communication of medical information
SGML Standard Generalised Mark-Up Language	An international standard for documents which supports multi-lingual characters
XML	Extensible Markup Language, a subset of SGML

marketed products, with no date yet for clinical reports, while in the USA industry is awaiting publication of a final rule from the FDA.

The mandatory date for the use of MedDRA for single case reports received electronically was January 2002, and for all adverse drug reaction reporting is January 2003.

In view of these imminent deadlines we contacted the national regulatory authorities within Europe to establish their ability to accept electronic SAE reports.

Among the responses we received, only one regulatory authority, (INFARMED – Portugal) confirmed that it is ready to start receiving electronic ICSRs; several anticipate that they will be ready by January 31, 2003 (but is that ready to receive "test" data or "live" data?); and at least one authority admitted it would not be ready until later in 2003.

Are we actually harmonising?

On the surface the answer to this question is "yes". However, there are significant differences in expectation and requirement between Europe and USA. Table 4 suggests that there has been an "agreement to disagree" in several areas.

EMEA

The first joint pilot meeting on electronic transmission took place in April 1999. The first pilot exercise began in November 1999, ran for 12 months, and involved seven European regulatory authorities and 17 pharmaceutical companies. In later pilots, five pharmaceutical companies (Astra Zeneca, Bayer Vital, Lundbeck, Merck Sharp & Dohme and Roche), the EMEA, the UK Medicines Control Agency, and the Irish Medicines Board submitted test data, with the main focus being on testing the safety message transmission and the subsequent data validation and processing.

The EMEA has established a Joint Implementation Group, which meets quarterly and provides a forum for discussing strategic and practical issues regarding the implementation of electronic transmission in Europe. An update on the pilot activities in the other ICH regions (US and Japan) is also provided during each meeting. Participation is open to all pharmaceutical companies having a medicinal product authorised in the European Union and allows companies to participate at an early stage, even if they are not yet ready to start the actual testing with the EMEA[10].

The procedure for commencing electronic transmission of ICSRs within Europe is as follows[6]:

1. Contact the EMEA Electronic Transmission Co-ordinator, who will inform all parties accordingly
2. Send Letter of Intent and Implementation Plan. A template is available at *www.eudravigilance.org*
3. Review of Implementation Plan – discuss with the EMEA
4. Obtain EudraVigilance Gateway certification for Internet communication

Table 4: Comparison of EU and US acceptable formats

	EMEA	FDA
E2B Data format	Version 2.1 November 2000	Currently using version 2.0; just moving to version 2.1; will accept both for the time being
E2B File format	XML	SGML
MedDRA version	5.0 (latest version)*	4.0 (15 months old)
MedDRA coding level	Low Level Term	Preferred Term
MedDRA coded items	All appropriate fields	Adverse events and Indications only
Attached files eg, lab results, x-rays etc	No provision in ICH for this data type	Pdf file required

* NB version 5.1 has been released in September 2002 and this is expected to be the preferred version for EMEA.

EudraVigilance Gateway is a single gateway for the whole of Europe for rapid and secure electronic exchange of pharmacovigilance data

5. Test phase – following the procedures outlined in the Joint Pharmacovigilance Plan for the Implementation of the ICH E2B, M1 and M2 requirements[7]
6. Sign the Interchange Agreement – an agreement specifying the criteria for Regulatory Electronic Transmission of ICSRs
7. Operational pilot phase – Commences on successful completion of the test phase. During the operational pilot phase, the currently established regulatory reporting mechanism will be further maintained for a period of three months; each authority may decide to shorten this period or extend it. This will allow comparison of the submitted data and ensure quality assurance and data consistency. The EMEA requires a paper copy of each submitted ICSR in parallel with the electronic version for the first six months of regular electronic submission
8. Operational phase – on successful completion of the operational pilot phase electronic reporting will replace the currently established regulatory reporting mechanism.

EUDRAVIGILANCE

The first production version (release 5.0) of EudraVigilance was launched by the EMEA on December 5, 2001. Further development to extend system functionality is scheduled during 2002/2003. The main functional components of EudraVigilance are[9]:

1. EudraVigilance Gateway, a single gateway for the whole of Europe for rapid and secure electronic exchange of pharmacovigilance data. This will allow Marketing Authorisation Holders (MAHs) to report to a single point within the Community from where the transactions are re-routed to the specified Member States as well as Iceland, Liechtenstein, Norway, the EMEA and the European Commission. The Gateway is considered a hub and all connections for both the pharmaceutical industry and regulatory authorities are known as spokes
2. EudraVigilance database management system (DBMS) for the collection and effective analysis of pharmacovigilance data. The regulatory authorities have access to the database via the established secure network EudraNet and it is planned to give restricted access to the pharmaceutical industry via secure connection over the Internet as the next step[10]
3. EudraVigilance Standard Terminology, with main focus on the Medical Dictionary for Regulatory Activities (MedDRA) and a Medical Product Dictionary. The deadline for pharmaceutical companies to submit simplified product information for the dictionary is September 20, 2002.

The EudraVigilance website (*www.eudravigilance.org*) includes a questionnaire to all pharmaceutical companies to assess readiness for electronic reporting.[11] No deadline has been established for completing this questionnaire although, together with submission of a Letter of Intent, it is important for EMEA planning purposes, since a great number of companies will be testing their systems at the same time. The questionnaire also provides an opportunity for companies to express their concerns and address MedDRA, Gateway, ICH and Drug Dictionary implementation issues in a systematic way.

EMEA submission tool

The EMEA is not endorsing any particular software for electronic transmission of ICSRs. The "internal" version of the tool that EMEA is currently using is basically a simple Internet screen, which can browse your local directory to find the XML file to be sent. Once identified, the "post" button will send the file to the EMEA. Another screen allows users to read acknowledgement messages returned by the EMEA gateway.

This software is currently being extended by EMEA with a view to making it available to all manufacturers. No mention is made of charges and the implications to date are that there will be none. Such a tool will be ideal for low case volumes. Where larger volumes exist several commercial providers of alternative gateway products exist, eg Cyclone, dsGateway, who are quoting in the region of $30,000 per annum for a two-user system.

Impact for Contract Research Organisations

The EMEA has confirmed that CROs can submit electronic ICSRs on behalf of a MAH, but the MAH must provide the EMEA with a letter from the person responsible for pharmacoviglance delegating this responsibility. For submissions through an ESTRI Gateway CROs will need to have a separate access to the

EudraVigilance Gateway (a different certificate) for each MAH for whom they will be providing submissions.

FDA

The current FDA AERS system has around five customers currently active and is receiving about 15% of cases by volume electronically. Companies need to submit a duplicate paper copy until the electronic file format has been validated (Docket 92S – 0251). Prior to the first submission of an electronic ICSR, companies need to notify the AERS submission coordinator at *aersesub@cder.fda.gov* .The FDA currently uses the Templar product for its gateway, but is not endorsing the product. Any compatible software is acceptable and the pilot companies are using several tools.

ICSR attachments (literature references, autopsy reports, or hospital discharge summaries) need to be submitted by physical media (floppy disk, CD-ROM, or digital tape) in Portable Document Format (pdf).

Once a submission reaches the EDI Gateway and is successfully recognised and decrypted, an EDI Gateway acknowledgement will be returned to the sender.

The current procedure includes a manual review to "clean" the data. For example, companies can code using MedDRA 5.0 even though AERS uses 4.0. This is reconciled by the FDA after receipt. Even with this manual review the FDA reports much faster input speeds with electronic reporting – two days versus one week for paper reporting.

The FDA has noted the importance of planning an "alternate submission method" for situations where the FDA system is unavailable and has suggested either a MedWatch report on paper or adverse event data on CD/floppy disk.

Ministry of Health and Welfare, Japan

The MHW makes reference to ICH on its website and has published a guideline for electronic submission of ICSRs.

An E2B implementation plan

As we have discussed, the IT resource and financial implications of switching to electronic submission of SAEs can be both expensive and technically demanding. The first need is to evaluate the current pharmacovigilance business process within the company and assess current database(s) for E2B (and other regulatory) capability, including headers, trailers, electronic signature, encryption and ability to exchange data not only with regulatory authorities, but also licence partners, CROs and other third parties.

The next step is to prepare an implementation plan. The European guidelines include template plans[7] (and *www.eudravigilance.com)* which essentially address the following aspects:

- Evaluate and address deficiencies in current system capability
- Set timeframes for testing and start of regular electronic transmission of ICSRs
- Determine methods of communication with other parties
- Map of data items
- Define approach to upload/download of case safety reports
- Select gateway product for interface with the EMEA/FDA
- Determine management procedure for follow-ups and duplicates
- Implement MedDRA.

Once the implementation plan is finalised it can be sent, together with a "Declaration of Intent" to the EMEA/National Authority(ies). Once digital certification for Internet communication has been obtained you can exchange test data with the EMEA and National Authorities including acknowledgement of receipt. Throughout the entire submission process an audit trail needs to be maintained including uploading the file, sending the file, through to receiving message receipt and ICSR acknowledgements.

A solution for smaller companies without the appropriate internal resource or infrastructure is to outsource their pharmacovigilance operations to a Contract Research Organisation – a subject for a paper in its own right.

Conclusion

In conclusion – are we ready for paperless pharmacovigilance? Successful electronic transmission of information relies on the definition of common data elements and standard transmission procedures.[1] However, until electronic reporting becomes mandatory it is unlikely that all companies will participate; until all compa-

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nies participate in a common process the possible efficiencies will not be realised. It is interesting to note that of around 3,500 companies in Europe that the EMEA has identified that will need to report SAEs electronically, only around 20 have performed any testing to date.

The January 2003 deadline is fast approaching and there is still a lot to do. While few companies are totally ready for e-submissions, many are making plans. However, it is believed that the majority are either at the start of this activity or have ignored it to date. The EMEA may not expect total compliance on February 1, 2003 but does expect plans to be in place at that time and for an increasing proportion of companies to come "on stream" during 2003. The question the reader must answer is – ''as a player in this process, is your company ready?''

Authors

Liz Nowell is the Pharmacovigilance Manager at Health Decisions Limited, a global Contract Research Organisation.
E-mail: *lnowell@healthdec.com*

Alan Rawling is Managing Director of Assured Information Systems who developed PV-Works™.
E-mail: *alan.rawling@assured.co.uk*

Dr Michael Bowden is the Managing Director of Health Decisions Limited.
E-mail: *mbowden@healthdec.com*

References

1. Maintenance of the ICH Guideline on Clinical Safety Data Management including the Maintenance of the Electronic Transmission of Individual Case Safety Reports Message Specification (ICH ICSR DTD Version 2.1).
2. ICH M2 Recommendations on Electronic Transmission of Individual Case Safety Reports Message Specification.
3. Commission Directive 2000/38/EC (an update of Directive 75/319/EC).
4. Council Regulation (EEC) No. 2309/93, articles 24 and 51, paragraph c.
5. CPMP/PhVWP/108/99 Notice to Marketing Authorisation Holders Pharmacovigilance Guidelines (January 1999).
6. EMEA/H/31387/01/FINAL Note for Guidance Regulatory Electronic Transmission of Individual Case Safety Reports (ICSRs) in Pharmacovigilance March 1, 2002.
7. CPMP/PhVWP/2058/99 rev 1 Joint Pharmacovigilance Plan for the Implementation of the ICH E2B, M1 and M2 requirements related to the electronic transmission of Individual Case Safety Reports in the Community.
8. Notice to Applicants, Volume 9, Part III – EU Electronic Exchange of Pharmacovigilance Information.
9. CDS018\CDERGUID\4153DFT FDA Guidance for Industry – Providing Regulatory Submissions in Electronic Format – Post-marketing Expedited Safety Reports (excludes vaccines).
10. EudraVigilance: the new Pharmacovigilance System in the European Union, brochure at *www.eudravigilance.org*
11. Evaluation of the Status of the Implementation of the Electronic Transmission of Individual Case Safety Reports for Medicinal Products for Human Use Authorised in the European Union in accordance with the Centralised, Mutual Recognition and National Procedure.
12. Federal Health Insurance Portability and Accountability Act of 1996.