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SAE reporting: Europe goes online

Opening a gateway to e-reporting SAEs in Europe

The EudraVigilance gateway for centralised electronic reporting of serious adverse events is now open, but are pharma companies and national regulatory authorities ready to use it in the EU? **Liz Nowell**, **Alan Rawling** and **Dr Michael Bowden** review the new system and how companies can meet its requirements

The EMEA's implementation date (31 January 2003)[1] for electronic reporting of individual case safety reports (ICSRs) seems to have passed relatively unremarked. Perhaps this is not surprising in the light of an EMEA survey in September last year. More than 3,000 pharmaceutical companies were asked to assess their readiness for e-reporting of ICSRs via the new EudraVigilance system. By the beginning of November only 92 had replied according to the EMEA. Moreover, a review of EU national regulatory authorities' websites revealed little obvious mention of implementation plans for e-reporting. It seems that both the regulatory authorities and pharma are only just beginning to address the systems and processes they will need to put in place to meet the new e-reporting requirements.

Eventually the new system will affect clinical development in Europe. All clinical trial serious adverse events (SAEs) will be incorporated into the EudraVigilance database when the EU clinical trial directive comes into force in May 2004. Draft guidelines to support this legislation have been published. Unfortunately, at best, these can be described as unclear and in some instances appear to exceed the stipulations of the directive. It is unlikely that investigators and ethics committees will be able to accept e-ICSRs, and so paper systems may have to be maintained with this group for some time.

So why is the EMEA so keen to implement e-reporting across the EU? The existing paper-based systems have been in operation for many years. SAEs are either submitted on national reporting forms for those occurring in that country, or on CIOMS II forms for 'foreign' cases. These reports are then mailed or faxed to the appropriate national regulatory authority, in a manually coded format according to local standards. The data must then be entered again into each local pharmacovigilance system that requires an individual report. These paper-based approaches have many limitations. Apart from the risk of transcription errors resulting from multiple time-consuming data entry, differences in national coding and reporting requirements make it difficult to compare safety information from different sources. Moreover, data exchange between authorities

Benefits from e-reporting of SAEs

- Increased quality from reduced transcription errors and fewer duplicate reports
- Individual case data is immediately available after upload for signal/trend analysis and query generation during rapid alerts and evaluation of potential safety issues
- Reduced costs of processing paper and duplication of data entry for both pharmaceutical companies and the regulatory authorities
- Increased consistency globally via common coding standards and a standard format for submission of SAEs to multiple regulatory authorities
- Streamlined processes for managing pharmacovigilance information, and identification and classification of ICSRs (including management of duplicates and follow-ups, nullification of cases, identification of errors and acknowledgement of receipt)

during safety alerts can be slow.

Existing systems are also feeling the strain of the increasing volume of SAEs. For example, in 1998, the EMEA received 8,933 ICSRs for centrally authorised medicinal products; by 2001 this figure had risen to 34,334. It was forecast to reach 57,000 in 2002. The 2001 forecast of the number of ICSRs received for nationally authorised products was 267,000.[1]

The EudraVigilance system was set up partly in response to this burgeoning number of SAEs. It is ultimately designed to ease the reporting process and speed up the exchange of safety information between interested parties. Pharma companies will now be able to report SAEs via a single portal, the EudraVigilance Gateway, where the transactions are re-routed to the named recipients.

A similar system has been set up in the US, whereby manufacturers can submit ICSRs via the FDA ESTRI Gateway or by physical media to be included in the Adverse Event Reporting System (AERS). As yet, however, there is no deadline for companies to submit electronic ICSRs to the FDA AERS, which is currently receiving cases electronically from manufacturers on a voluntary basis. Both gateways acknowledge receipt of the transmission when it is successfully received and decrypted.

The ultimate goal for these centralised e-reporting systems is to promote the safe and effective use of medicines. They will enable regulators and pharma companies to extract data from their local pharmacovigilance database to be transmitted electronically in an internationally agreed format to one or many receivers where the information can be automatically processed and evaluated.[1]

The practical and technical aspects of how this will be achieved are discussed in a number of guidelines and websites covering electronic submission of SAE reports listed elsewhere.[2] One of the key guidelines is ICH E2B[3] which is the international standard for the transmittal of electronic safety data. This document has been revised as ICH E2BM[4] which clarifies and resolves issues raised in pilot studies. A total of seven European regulatory authorities and 17 pharma companies participated in three pilots that tested data transmission, validation and processing.

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Only the UK, Danish and Portuguese authorities were ready on 31 January to accept electronic SAE reports from companies that have completed pilot testing and are ready to move into the operational phase. In December 2002, several authorities suggested that they could be ready but it was unclear whether they meant ready to receive 'test' or 'live' data. Meanwhile, at least two authorities confirmed they would not be ready until later in 2003 or early 2004.

Implementing e-reporting of SAEs

Electronic transmission of ICSRs requires extensive preparatory work and testing by everyone involved. Companies will need to address the following areas before any electronic SAE reporting system can be successfully implemented.

•**Resourcing** – The IT resource and financial implications of switching to electronic submission of SAEs can be both expensive and technically demanding. A business decision needs to be made as to whether to allocate internal IT resource to establishing an E2B capability, at a cost to other projects and ongoing technical support, or whether it is more efficient to outsource to an external provider.

•**Planning** – The EU guidelines include a template implementation plan[5] (see www.eudravigilance.com) which recommends that pharma companies:

1 Assess current safety 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.
2 Set timeframes for testing and starting regular e-transmission of ICSRs. In Europe, companies need to notify the EMEA electronic transmission coordinator before the first submission of an e-ICSR, who will inform all parties accordingly. For the FDA, they must notify the AERS submission coordinator at aersesub@cder.fda.gov.
3 Map data items. Probably the most difficult and

International timetable for e-reporting of SAEs

January 2002	Mandatory date for the use of MedDRA for single case reports received electronically. MedDRA terms can be provided as either the text or code
January 2003	Mandatory date for the use of MedDRA for all adverse event reporting. MedDRA terms must be provided only as the codes
31 January 2003	Pharmaceutical companies will have completed a pilot test of electronic reporting with the EMEA or will at least have a plan in place
1 February 2003	Companies ready for electronic reporting for new cases to the EMEA
1 October 2003	Implementation date for e-reporting to the Ministry of Health and Welfare in Japan (marketed products)
31 January 2004	The EMEA additionally requires retrospective e-reporting of all expedited cases dating back to 1 January 1995. Companies will therefore need to convert all their legacy data to the E2B standard and transmit them to the EMEA.
Dates to be announced	Implementation date for electronic reporting to the Ministry of Health and Welfare in Japan (clinical trial products)
	Companies ready for e-reporting for new cases to the FDA. Awaiting publication of FDA final rule

critical aspect of preparing the files for e-transmission is mapping the database to the E2B or E2BM data set and developing the extract programs to build the specified DTD (document type definition file). The level of difficulty in performing these steps depends on how closely the current database resembles the E2B or E2BM data set.

4 Define the approach for uploading or downloading ICSRs.

5 Select a gateway product to interface with the EMEA/FDA. The EMEA is not endorsing any particular software but it is assessing pharma company interest in a free access web-based tool which can be used instead of reporting via the gateway. The tool has limitations – there are 250 fields to complete. As it is not possible to save cases, users need to complete the entire action without leaving their desk, or risk losing the data. If the ISCR is to be reported to more than one regulatory authority the submission details will have to be retyped each time. This method still requires double data entry as it is not possible to auto-populate the fields on the website directly from the company database, and this raises audit and archive issues. However, this option may be preferred by companies with low case volumes (five to 50 cases a year). This tool should be available soon, once the EMEA has finalised a training package for users. For companies with larger volumes several commercial providers of alternative gateway products exist, for example Cyclone Commerce, or dsGateway. The FDA currently uses the Templar product, but any compatible software is acceptable and US pilot companies are using several tools.

6 Determine a management procedure for follow-ups and duplicates.

7 Implement MedDRA. This may require a transition from existing coding dictionaries and significant recoding of data.

Once the implementation plan is finalised it can be sent with the declaration or letter of intent to the EMEA/national authority(ies). The EMEA will then review the plan with companies.

•**Testing the system** – The test procedures are outlined in the Joint Pharmacovigilance Plan for the Implementation of the ICH E2B, M1 and M2 requirements.[6] Once digital certification for Internet communication has been obtained and an interchange agreement has been signed (an agreement specifying the criteria for e-transmission of ICSRs) companies can exchange test data with the EMEA and national authorities. 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.

The EMEA is is assessing interest in a free access web-based tool which can be used instead of the gateway

The EudraVigilance database was set up to ease the SAE reporting process and speed up the exchange of safety information between interested parties

•**Validating the system** – Data validation is required to ensure the quality and consistency of data passing through the automated exchange process. Any SGML (standard generalised markup language) files generated for e-reporting will need verification that the file adheres to the syntax and document definition outlined in the ICH ICSR DTD[7] and that the file contains no data that violates the ICHM2[7] specification regarding data type, length, or valid values. Acknowledgement of receipt also needs validation. The FDA regulation 21 CFR Part 11 establishes accountability for information stored in electronic media and mandates control of access and access privileges within companies. According to the regulation, companies must create audit trails of who, when, and why anyone accesses stored records. Failure to comply can result in heavy fines and product withdrawal.

•**Piloting the system** – On successful completion of the test phase a pilot phase will take place, during which the existing regulatory reporting mechanism (usually mail and/or fax) will be maintained for about three months, although each authority may decide to shorten or extend this period. This will allow a comparison of the submitted data for consistency and quality assurance. 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. The FDA requires companies to submit a duplicate paper copy until the electronic file format has been validated.

•**The operational phase** – On successful completion of the pilot phase, operational e-reporting will replace the existing regulatory reporting mechanism. During the transitional period, various scenarios have been proposed.[1] These may include submitting an ICSR electronically to the EMEA and some member states, while simultaneously submitting a paper copy to national authorities that are still

To realise the full benefits and efficiencies all the players need to buy into the process, but this is unlikely to happen until e-reporting becomes mandatory

unable to receive e-reports, all within the 15-day reporting timeframe. The FDA has noted the importance of planning an alternative submission method for situations where the FDA system is unavailable. It has suggested either a MedWatch report on paper or adverse event data on CD or floppy disk.

Issues arising from implementation

The implementation and rollout of new technologies is never problem-free. Even within a single company it can take many months to get users to agree on the specifications and format of a new safety database. Attempting to implement such a system on a global scale across multiple companies and organisations only compounds the difficulties.

Two of the major issues for companies are the initial cost of implementation and the technically complex data format required, especially if the company does not have access to IT functions. In theory it would be possible to type an SAE in the required format, but the format is long-winded and intended for computer-to-computer transmission. Double data entry is required, as well as duplicated verification and so on, so this is only practical for companies with a negligible case volume.

Some companies may find their pharmacovigilance databases need to be re-programmed to be able to output data according to the ICH E2B/M2 specifications. The major commercial databases already comply but this is not necessarily the case with internally developed systems.

There are also practical problems in that companies will need to maintain compliance and quality while moving from a paper-based to an electronic system. They will need a (paper) backup mechanism in case the technology fails or is unavailable. Paper and electronic systems must be run in parallel until all the regulatory authorities, licence partners, CROs, ethics committees and investigators are able to accept e-SAEs

Another issue is the need to accommodate differing FDA/EMEA guidelines and standards. For example, the EMEA requires E2B files in XML format, while the FDA requires SGML. For MedDRA coding the EMEA insists all appropriate fields are coded as low-level terms, while the FDA requires coding of adverse events and indications at the preferred term level. The EMEA has not stated a required format for ICSR attachments, such as literature references, autopsy reports, or hospital discharge summaries, while the FDA needs these attachments to be submitted by physical media (floppy disk, CD-ROM, or digital tape) in portable document format (PDF). If the physical media route is chosen the pharma company needs to verify that the submission package has been received by tracking the delivery by the postal service or courier.

Although security and patient confidentiality issues arise even with paper systems, potential breaches may have more far-reaching effects with an electronic system. In the US, the Health Insurance Portability and Accountability Act of 1996 (HIPAA)[8] requires that all patient identifiable information must remain secured at all times – especially as it is transmitted between entities.

In parallel with the e-submission initiative, any computer system will need to comply with the quality demands of the 21 CFR Part 11 rule on electronic signatures and electronic records. If paper SAE reports were signed off on a cover sheet for instance, then the e-report ought to be signed electronically.

Approaches to implementation

There are three main options available to pharma companies as they plan their implementation of electronic SAE reporting. They can:

•**Develop a capability in-house**. For larger organisations with established pharmacovigilance and IT departments it makes sense to invest in developing the capability in-house. The advantages are that the experience is retained within the company, which retains full ownership of the process. The disadvantages are that resources may have to be diverted from other projects – not just during implementation but for ongoing support – and it may take time to train individuals in the new processes.

•**Use a hosted application from a software vendor.** For companies wishing to avoid the inevitable technical 'glitches' a hosted application solution from a specialist vendor may alleviate some of the headaches. However, although software vendors have the technical expertise, they may not be expert in 'good pharmacovigilance practice' and may need support from the pharmacovigilance team. The vendor is responsible for ensuring regulatory compatibility and compliance, including 21CFR Part11, and for maintaining an audit trail of the submission process. Minimal additional hardware/software purchases should be required and the solution should be implemented within weeks rather than months or years. The disadvantages are that the sponsor company does not develop internal IT expertise and needs to make a risk assess-

While software vendors have the technical expertise, they may not be expert in 'good pharmacovigilance practice'

It is time for pharma companies to address their electronic SAE reporting obligations and develop their e-pharmacovigilance strategy

ment of the stability of the chosen vendor. Moreover, hosting may be expensive where SAE volumes are high.

•Fully outsource e-reporting to a CRO or specialist pharmacovigilance company. This may be a solution for companies without the appropriate internal resource or infrastructure. These organisations can submit e-ICSRs on behalf of the marketing authorisation holder (MAH), but the MAH must provide the EMEA with a letter delegating this responsibility, and the provider will need to have a separate access to the EudraVigilance Gateway for each MAH it provides submissions for. Since minimal internal resource or expertise is required overheads are reduced and the service may be implemented quickly. The disadvantages are that the company does not develop expertise in-house and is subject to the stability of the provider. Cost is often raised as an issue with outsourcing, but the fully burdened costs of providing equivalent services internally are rarely calculated.

Outlook for e-reporting of SAEs

Successful electronic transmission of information relies on all parties agreeing to use common data elements and standard transmission procedures. In order to realise the full benefits and efficiencies all the players need to buy into and participate in the process, but this is unlikely to happen until e-reporting becomes mandatory. Maintaining parallel processes will increase workloads and make quality assurance and signal generation more difficult.

Since 31 January 2003, e-SAE reporting is a reality, not just a dream in Europe. And while the EMEA may not have expected total compliance on 1 February 2003, it will expect plans to be in place and for an increasing proportion of regulatory authorities and companies to become full participants during 2003. Like it or not, electronic SAE reporting has arrived and all the players need to be committed to making it work and to developing their e-pharmacovigilance strategy. GCPj

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