Safety Document Exchange in the Global Clinical Research Environment:

Secure, Cost-effective, and Well-connected

Not long ago, the public assumed that drugs approved as safe and effective by the FDA were, in fact, safe and effective. But a series of highly publicized product withdrawals and black box warnings given to marketed drugs in recent years has alerted the public and Congress that the FDA must give greater scrutiny to safety signals arising during drug development. As a result, the proper and timely reporting of Serious Adverse Events (SAEs) during clinical trials is under scrutiny.

The procedure for SAE reporting relies on multiple exchanges of information between sites and sponsors, often on different continents, in different time zones, using different languages. Exchanging information in this global environment is complicated and can increase the room for error. Inability for a site to communicate the case history to the sponsor, or for the sponsor to report the event to the other study investigators can increase the risk to other study patients and result in sponsor liability. And yet in this increasingly complex and regulated environment, companies continue to use traditional, non-secure methods for SAE reporting and notification: fax, email and overnight mail.

This whitepaper examines the benefits of an online alternative — a hosted, web-based portal that is simple to use, less costly than paper notification and able to instantaneously and securely disseminate safety reports to all stakeholders. In fact, using a web-based portal can save a large pharmaceutical sponsor or Contract Research Organization (CRO) thousands of dollars in overnight mail costs for a single trial, and millions of dollars for global safety reporting when many large global trials are running in parallel. It is a method that:

- Reduces the time frame for notification from days to minutes
- Reduces risk for both patients and sponsors
- Reduces delivery costs of safety reports and labor-intensive verification of receipts

Forward-thinking companies are embracing technology to reduce cost and increase efficiency in the global clinical trial environment. More and more, the costs of inaction, of not adapting to change, are exceeding the costs of implementing new operating procedures.

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Red Flag

At a meeting in fall 2009, the FDA's Center for Drug Evaluation and Research Director of Compliance Deborah Autor stated that her office is looking at a company's overall ability to meet FDA requirements as a possible indicator of whether the company should be a compliance concern. For example, Autor said that her office was noticing that poor quality of new drug applications or faulty Adverse Event Report systems tend to show a likelihood of poor compliance in other areas, such as cGMP (current Good Manufacturing Practice).

www.fdalawblog.net/fda_law_blog_hyman_phelps/2009/10/fda-compliance-directors-and-others-predict-where-the-fda-spotlight-will-shine.htm

Clinical Drug Development Today

The pressures on pharmaceutical and biotechnology companies to accelerate development timelines under tighter budgets and resource constraints has rapidly led to the proliferation of large, multinational clinical trials over smaller, locally-sponsored trials. The goal behind initiating these multinational trials is to increase access to treatment of naïve subjects by enlisting sites outside of major markets, and to drive cost savings through economies of scale. After a steep learning curve in the 1990's, most large pharmaceutical companies and CROs now have systems in place to capture the benefits of large, multinational studies while minimizing the headaches: hardware and IT infrastructure mismatches, requests for support in multiple languages outside of working hours, and regulators' queries from several countries arriving at the same time.

Some aspects of successful management of large, multinational clinical studies become ingrained through repetition and experience, such as training and support, while others, often critical processes, require constant oversight to avoid catastrophic errors.

Why the Urgency Around SAE Reporting in Clinical Development?

In clinical development trials, there are both immediate and longer-term needs that drive the urgency around SAE reporting. Sponsors and/or a Data Safety Monitoring Board evaluate SAEs and other important safety signals during ongoing trials to evaluate whether they are caused by the study drug. Investigators, Institutional Review Boards (IRBs)/Ethics Committees (ECs), regulatory agencies and subjects must be informed of these events, and subjects must be told if the drug poses a danger that they did not know about when the study began. The process of maintaining and disseminating accurate reports for each study and notifying all parties within a strict time frame is a labor and document-intensive, as well as costly endeavor for the sponsor.

The second significant factor in the renewed attention on safety reporting is the FDA's new focus on safety signal detection. In the past, companies collected SAE reports when the cases trickled in and then interpreted whether the event was a true signal or background noise. In this time of heightened awareness that FDA approval does not completely erase drug risk, companies are proactively designing programs to anticipate where safety issues might arise. The rapid and accurate collection of SAE information is the backbone of this safety surveillance system.

Are the Old Methods for Safety Document Distribution Working?

The process for managing SAE intake, review and report distribution within the strict time frame required is becoming more costly and labor-intensive, largely due to the increase in the number of investigative sites participating in studies and the global distribution of sites.

When a sponsor receives an initial SAE report, the clock starts ticking. Typically reports are phoned in or sent via unsecured email, which poses risks that reports go missing, go to the wrong recipient, or get lost in a stack of messages. Once received, the SAE report is evaluated by the sponsor's representative and a narrative is written to form the backbone of the SUSAR (Suspected Unexpected Serious Adverse Reaction) letter. The letter is then forwarded to regulatory agencies, investigators, IRBs/ECs and others for review within seven or 15 days of the event, depending on the severity of the event. Coordinating this communication can be difficult even when all documents are properly in place; consider the additional stress that arises if an addendum to an SAE report is misplaced midway through the evaluation.

Distribution of the SUSAR letter to investigators, IRBs/ECs, and CROs presents its own set of unique challenges. CROs or even the sponsor may have local country affiliates that must be included in the distribution flow. Safety letters being sent from the US sponsors' headquarters may have several routes — from sponsor directly to FDA; from sponsor to CRO to Western European sites; and/or from sponsor to Russian country affiliate and then to Russian sites, for example. The local country affiliate may need to add a cover letter in the local language before distributing the SUSAR letter, adding a step to the process and a new iteration of the document. The process becomes more complicated and costly when it comes to tracking and maintaining a record of which document version is being circulated, and when it was distributed. Failure to comply with the reporting timelines can jeopardize subject safety and result in penalties, lawsuits and damage to the company's reputation.

With the stakes so high, the traditional means of exchanging safety documents no longer make good sense, as the methods are either slow, costly or lack the ability to track receipt to the intended recipient.

- **Overnight mail**. At best, delivery is within 24 to 48 hours depending on the global destination. Concerns also exist around the inability to confirm receipt in large buildings and major medical centers: often a central receiving room signs for all courier deliveries, and then the packages are only distributed at a few set times throughout the day. The number of packages can be upwards of 200 per SUSAR and requires personnel to assemble and ship them. Estimating five minutes per package for packing and labeling, 17 man hours are needed to prepare overnight packages for a SUSAR being distributed to 200 recipients. The cost of using an overnight carrier in a scenario involving 200 packages can easily exceed US $4,000.
- **Fax**. Concerns here center on the inability to confirm that the intended recipient received the fax, and the delay within large organizations in fax distribution. If the Principal Investigator is out of town attending a medical conference (a common occurrence) and the fax is left in his mail box, the sub-Investigator covering the study may not learn of the new safety information until the Principal Investigator returns and gets through his mail. And there is an incidence of a SUSAR letter that was inadvertently faxed to a fast-food restaurant because someone mistyped the recipient's fax number on the cover sheet.
- **E-mail**. While email is the fastest and most convenient of the traditional distribution methods, most users don't consider the hazards associated with it such as choosing the wrong recipient from a pick list or misspelling the recipient's address. Emails can inadvertently be forwarded or sent to unauthorized parties; they can get caught in spam filters or be accidentally deleted. In addition, confirming the receipt of a SAE letter requires a follow up phone call which negates the convenience of email altogether. When dealing with confidential information regarding patient safety, security can't be a question. The lack of an audit trail report when using email to communicate sensitive safety letters leaves sites, sponsors and patients vulnerable.

Consider the Potential Impact of Delay in Safety Document Distribution

A 45-year-old woman in a clinical trial of a new antibiotic calls the site to report a mild rash. Site personnel instruct her to come to the study site if the rash does not improve in two days. Two days later she presents at the site with a patchy, blistered rash on her torso and face, which she says is spreading to her hands. Upon questioning, she reports she has had fever of 102 and malaise, headache, and eye pain with mild discharge for several days. She could have flu, or it could be a drug reaction called Stevens-Johnson Syndrome (SJS). SJS is a serious medical condition affecting young to middle-aged adults with a 3% mortality rate, induced up to 50% of the time by a drug reaction. The prodromal phase mimics a flu syndrome for several days, followed by a blistery rash that spreads from the face and trunk to the extremities, eventually involving up to 10% of the patient's skin. Patients are often treated at hospital burn units to prevent infection as skin sloughs. Typically, a skin rash does not alarm a physician, unless he/she is aware that the administered drug has been known to cause SJS. In that case, the drug is discontinued immediately and appropriate care is given to prevent exacerbation of the symptoms. In just two days that rash could have progressed to a life-threatening condition. Delays in reporting Serious Adverse Events to study investigators could impact the safety of other patients in the clinical trial.

While many investigative sites are interested in participating in clinical studies, the associated administrative burden can be a deterrent. Just as email, text messaging and instant messaging have surpassed phone calls as the preferred rapid communication among the technologically minded, sites participating in clinical trials welcome rapid, efficient methods of communication and document distribution to speed processes and decrease clutter. A recent poll of clinical study leaders and safety managers working at pharmaceutical companies and CROs confirmed that nearly 9 out of 10 respondents would be willing to try an online tool to manage a study. So with both sides ready and willing to move from paper to paperless technology, the decision seems easy.

But is "Going Paperless" Really Worth it?

"Going paperless" sounds good in theory, but the prospect of building, implementing and maintaining an internally supported solution from the ground up may not be feasible for a company struggling to sustain its pipeline in a challenging economic and regulatory climate. Though pharmaceutical companies' internal information technology (IT) departments have had success developing in-house software, over time it has become apparent that maintaining the software to evolving security standards and the need to integrate with new software has stretched internal departments. Another challenge posed by developing an in-house system is that credential management and end-user support fall on the sponsor. A better solution — one in sync with the industry's newest trend of concentrating on core competencies — is to look for a Software-as-Service (SaaS) solution where the burden of software management, maintenance and support falls on a neutral, third party provider. As pharmaceutical companies are experienced in relying upon strategic outsourcing partners, using a strategic partner to host a web-based portal for safety document exchange is a perfect fit.

Smart Use of New Solutions to Manage Safety Risk Globally

Innovative pharmacovigilance teams have started to move away from old methods of SAE reporting and safety letter distribution and begun working with new technologies, such as SaaS solutions, to improve efficiencies. SaaS solutions are increasingly attractive to large, global companies because they are web-based, hosted and supported by a third-party provider rather than the IT department of the sponsor or CRO. This means the solution provider owns the infrastructure, maintains the software with periodic updates, including enhancements to security features, and provides value-added services for the entire client/user base such as training sessions and a live, multilingual 24/7/365 help desk. This model requires no upfront capital investment on the part of the sponsor or CRO and so lowers costs and accelerates timelines. Outsourcing to a SaaS model frees up internal IT departments to focus on other segments of the business.

By choosing a portal solution from a SaaS provider with state-of-the-art online security features, a company can grant access to users inside and outside the firewall while maintaining strict access control. In addition, moving these previously manual and paper-based processes online allows the sponsor or CRO to maintain real-time distribution and access reports for all documents shared, helping maintain compliance and data privacy. Finally, using an online portal provides a single, centralized place of record to organize safety reports and SUSAR letters throughout the development of the compound, improving version control.

Early Adopters Calculate the True ROI

Based on sample industry data, a large pharmaceutical company could expect an annual **savings of up to $15M** when moving away from overnight mail to an online portal for SAE reporting. When a reportable SAE occurs within a large Phase III clinical study, the SUSAR letter must be sent to investigators at every site in any trial using that drug, as well as to their IRBs/ECs, any CROs involved, and regulatory agencies in any country with participating sites. So for a large development program running four large, multinational Phase III trials, plus open-label extensions and additional Phase I trials, a single SAE could necessitate distribution of a SUSAR letter to several hundred recipients. The following assumptions were used in calculating savings:

- 1,000,000 safety document distributions per year in a large global pharma company, or approximately 3,400 safety events being notified to approximately 295 recipients
- An average overnight delivery cost per package of $15 (assuming negotiated rates and local distribution)

Additional savings to consider when documents are sent online versus through the mail include the time needed to prepare the safety letter packages. The process of putting together the packages for distribution requires significant human resources. Using the same sample industry data and assumptions, the annual savings attributed to human resource costs is approximately **50,000 man-hours, or 24 full-time employees**. Again, here are some basic assumptions that were taken into consideration:

- 1,000,000 safety document distributions per year
- Three minutes to put together each overnight package (gather printed labels, stuff envelopes, affix labels to envelopes, and transport the envelopes to the mail carrier)
- This equates to 50,000 man-hours of work and 24 full-time employees a year to prepare document packages

By using a web-based portal for document distribution, SAE reports can be sent instantaneously to the distribution lists. Consider the following:

- Assume there are approximately 3,400 unique document packages and that it takes 10 minutes to upload to the online portal and associate the documents with the pre-set mailing lists. The time it would take to make those documents available to all appropriate parties could be calculated as 3,400 x 10 min = 566 man-hours of work or 27% of one full-time employee a year.

It takes 98% less time to distribute safety documents through an online portal than it would to prepare and send those packages via overnight carrier! When an SAE occurs generating a SUSAR letter, the letter can be uploaded into the system and with a few clicks of the mouse, distributed to all required parties along with an email alert, with confirmation of receipt and an auditable trail. Workflow capabilities allow for special handling requirements, for example, a cover letter in the local language can be added before the letter is distributed to the recipients. The risk of reporting delays are reduced because information can be passed in real time, rather than losing days as documents move back and forth through the mail system. By using a web portal, the costs and the time lag involved in safety document distribution and collection basically disappear.

Conclusion

To summarize, the globalization of clinical development studies has benefited companies by allowing better access to study subjects and the ability to get drug approval simultaneously in most major markets with just a few large trials. Most pharmaceutical companies and CROs initially experienced a learning curve to master the start-up of a large number of sites in as many as seven or 10 different countries, but now this has become the norm. In order to realize the benefits of these large multinational trials, hosted software for the exchange of documents such as SUSAR letters overcomes many of the problems of geography and language:

- **Web-based** — Broadband technology is widespread now, allowing all parties involved in safety document exchange to utilize web-based portals regardless of time zones or even holidays. Web-based applications can offer portals in local languages, a user-friendly added feature. An online solution ensures that everyone involved in managing safety has 24/7/365 access and the transit time for document exchange becomes instantaneous.
- **User Friendly** — With improved access to broadband even in developing regions, site personnel and those at local country affiliate offices have become more comfortable with web-based applications. With appropriate training and support, such as online tutorials, DVDs, presentations at investigator meetings, and a live help desk, implementing an online safety document exchange system is as easy as signing up for the latest new social networking site.
- **Secure** — A secure, web-based repository and exchange system facilitates companies' efforts to comply with regulations for the creation, transmission and retrieval of electronic documents, such as those described in FDA 21 Code of Federal Regulations (CFR) Part 11. It also enables companies to comply with HIPAA and European data privacy laws when exchanging sensitive medical information about an individual patient.
- **Cost-effective** — For companies conducting clinical development globally, even the most favorable ROI analysis for sending SUSAR letters via express mail shows the cost exceeds that of a web-based exchange. In addition, the soft cost benefits of a lightened work load for administrative staff and the peace of mind that comes with knowing SUSAR letters were delivered instantly and securely after sending, with notification of non-receipt in instances where letters were not delivered are viewed as desirable by most companies.

For companies receiving pressure from senior management, the board of directors, and Wall Street to develop novel drug therapies faster and cheaper, utilization of accepted and proven tools such as online portals to replace paper document exchange is no longer a choice but a necessity. Companies that continue to manage serious adverse event reporting by fax, overnight mail, and unsecured email are accepting unnecessary risks that their documents will be delayed, lost, or not received by the intended recipient. This increases the risk to study subjects, investigators and sponsors to unacceptable levels, when cheaper, faster, and better alternatives exist. Forward-thinking companies will not wait until a disastrous episode occurs before adopting new procedures to de-risk clinical development by using something as simple and widely accepted as an online portal for safety document exchange.

About IntraLinks

For more than a decade, IntraLinks' enterprise-wide solutions have been providing a secure, online environment where study teams, investigator sites, CROs and IRBs manage, track and store critical study documents. From site recruitment and study start-up, to study conduct and close-out, the IntraLinks platform can help improve operational efficiency and reduce time and costs while adding increased security and control to your process. More than 750,000 users across 90,000 organizations around the world rely on IntraLinks including, 10 of the top 10 pharmaceutical companies and 10 of the top 10 Clinical Research Organizations.

To learn how IntraLinks can transform your business by speeding up the clinical trial process, improving operational efficiencies and ensuring the secure exchange of your clinical trial documentation, visit **www.intralinks.com** or contact us at:

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