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Drug Safety for Marketed Drugs:

in-depth report from an eyeforpharma conference

held in Amsterdam, 22–23 November 2005

Edited by Martin Fagan

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Drug Safety for Marketed Drugs:

in-depth report from an eyeforpharma conference

Edited by Martin Fagan

Executive summary

Safety surveillance has much to offer as a powerful knowledge-based tool capable of defending company products in the marketplace while conducting its primary function of safeguarding public health. However, this asset is not translating much beyond the cloistered walls of its practitioners in industry and health authorities.

Clearly, a formidable arsenal has been developed over time: a scientific conceptual base, legislation, data systems, sophisticated technological support – hard- and software – monitoring and analytical systems, quality controls with audit and inspection, and communication tools. The eyeforpharma conference on Drug Safety for Marketed Drugs, held in Amsterdam on 22–23 November 2005, demonstrated that, as a whole, this arsenal works. And yet there is a lack of awareness of its impact where it matters – the end user (the medical practitioner and patient).

This *Conference Insights* review comprises the highlights of a selection of presentations from the eyeforpharma conference, providing a platform for how and where the industry can improve drug safety. Crucially, it also outlines how companies can communicate the true and undoubted value of safety surveillance.

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Introduction

Safety practitioners are great at rousing each other to the clarion call of product defence, but are we actively nurturing links with all the right partners? Speakers and attendees at the eyeforpharma conference on Drug Safety for Marketed Drugs, held in Amsterdam on 22–23 November 2005, encompassed a broad mix, ranging from epidemiology, clinical development, pharmacovigilance, data management, clinical research organisations, health authority, information technology (IT) and management, including some involved in marketing. This mix reflects the interdisciplinary field of drug safety surveillance. However, the telling gap was the lack of a significant sales and marketing presence, which, considering the recent concerns over marketing 'spin' for licensed drugs, shows how this can influence and potentially damage the prospects of otherwise useful pharmaceutical preparations. Perhaps there are opportunities here to have a more holistic conference that challenges both the safety and marketing of drugs internationally. Drug safety and marketing are often seen as incompatible partners in drug companies, and are roles that are seen as directly combative. This should not be the case, and one hopes the recent moves by the UK Medicines and Healthcare Products Regulatory Agency to monitor and challenge drug company marketing will address this.

This 'them and us' position is well established. Marketing colleagues are the face of industry, interacting with the user community on a daily basis. Their primary focus may be on pitching treatment benefits, but gradually there is grudging acceptance that product safety is becoming a pressing issue for retaining market presence. The sea change apparent among company representatives actively co-operating with meeting adverse event reporting obligations would support this notion. Nevertheless, increased dialogue needs to be cultivated between safety and marketing, with the latter permitting more visibility for safety in the field and the former being less introspective. Perhaps the answer is to train the marketers in drug safety as part of an industry-wide move to address this issue?

Safety surveillance is strategic for product health and should not be seen as the harbinger of bad news. Clearly, marketing will continue to act as the corporate face of the industry. However, such communications can only be enhanced through closer interactions with safety colleagues who are fully equipped with updated information on the risk/benefit balance of products. In the paraphrased words of one speaker, Cinderella is fast becoming a princess; perhaps so, but only with Prince Charming motivated to sweep her out of obscurity into the limelight right by his side.

Martin Fagan
April 2006

About the editor

Martin Fagan is a Senior Executive Director with over 25 years experience in the healthcare, pharmaceutical, NHS (public sector) and data/IT/CRM industries, both in the UK and internationally. He has experience in start-up, rescue, organisational restructure, spin out and sales/marketing/business development in the pharmaceutical, B2B and IT industries, as well as in NHS supply. He also has extensive experience of commercial databases and patient data in clinical research, and knowledge of NPfIT and current NHS changes and opportunities through his current role as Vice President Market Insight Solutions for Infonetica.

Martin qualified as a toxicologist and, after a brief spell in research, progressed through the commercial arm in the pharmaceutical and supplies industries, including 4 years in Asia responsible for trade with over 10 countries. He established his own consulting company, Infozyme Consulting International, in 2001.

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Drug Safety for Marketed Drugs:

in-depth report from an eyeforpharma conference

Communicating value and the value of communication

Pharmacovigilance is not in the view of its real audience. As a consequence, the public remains to be convinced about the industry's protestations of responsible intentions on drug safety. Recent high-profile withdrawals of products from the market have seen industry and its regulatory overseers as targets for much hostility. When safety concerns emerge, and the expert and lay public are alerted, there is little on display of the structured drive in the background aimed at detecting threats to minimise harm from products. In fact, documentation of past activity is living proof of due diligence of independent, external inspection. It seems to me a potent metaphor for safety surveillance as an image booster for industry.

> *Documentation of past activity is living proof of due diligence of independent, external inspection*

Transparency matters and could be engineered by directly interfacing with corporate public relations engines. Certainly media communication training should be a prerequisite for key safety personnel. It is simply not adequate to provide bald factual information about safety concerns; these have to be placed in context for anxieties to be allayed. Confidence is increased when there is awareness that issues are being proactively managed and that interventions at the public level are merely a snapshot of ongoing safety activities. Claims of responsible intent must be backed by proof of legislatively determined due diligence and that evidence exists in safety departments. Public relations is crucial and there ought to be ways of communicating how resources are deployed on behalf of the user community in arriving at the final measures taken in protecting public health. This is necessary to complete the picture.

The following highlights of selected presentations from Drug Safety for Marketed Drugs, an eyeforpharma conference held in Amsterdam on 22–23 November 2005, clearly articulate the foundations for the way forward, extending beyond knowledge into communicating the true value of safety surveillance.

The importance of real-world data

The presentation of Dr John Parkinson (GPRD) was the first in a series of highly topical presentations to address the challenges of safety surveillance. Parkinson encouraged the industry to think creatively to find innovative risk management solutions that enable the balance of risk and benefit in the real world to be clearly understood and documented. This is essential, he said, given the current climate in which additional information postlaunch is now a regulatory requirement.

According to Parkinson, since post-launch usage occurs in patients previously excluded from the rigidly controlled environment of pre-launch trials (randomised controlled trials; RCTs), emphasis is placed on collecting real-world data. Following launch, the focus shifts from pre-approval issues of quality, efficacy and safety to effectiveness in treating illness in diverse age groups and indications, as the true benefits of a new drug become even more apparent in the face of multiple comorbid diseases and concomitant medication. These new variables, coupled with the sharp exponential rise in drug exposure post-launch, set the scene for the emergence of unexpected events not previously detectable under RCT conditions.

> *Since post-launch usage occurs in patients previously excluded from the rigidly controlled environment of pre-launch trials, emphasis is placed on collecting real-world data*

Concerns about perceived threat will inevitably arise in the early post-marketing phase. From the medical standpoint, undesirable adverse events are a threat to successful treatment, whereas industry may see clinical freedom beyond the limits of the product licence as a threat to continuing product availability within the marketplace. With both these perceptions in mind, Parkinson warned that safety surveillance must address these conflicting notions in order to maintain a satisfactory balance that promotes the benefits

	Randomised clinical trial	Real world
Study type	Phase 3	Phase 4
Patient numbers	100–>1000 (possibly >10,000)	10,000–100,000 (potentially >1,000,000)
Age (years)	35–55	0–115
Outcome	Efficacy	Effectiveness
Disease state	Single condition	Multiple comorbidities
Medication	Single drug	Multiple drugs with complex regimen
Compliance	High	Medium/low–poor
Persistence	Full	Low
Usage	Defined	Channelling
Adverse events (in thousands)*	Few	Tens/hundreds
Risk window	Short	Unlimited

*Principle of the rule of threes: 1000 study patients only ruled out 1 in 333 events and 10,000 patients rule out 1 in 3333 events.

Table 1. Contrasts between randomised clinical trials and the real world.

of medication through proactive risk management directed at minimising harm to the patient. Typically, said Parkinson, the current watchword in regulatory circles is "less about harm and more about extending knowledge by moving up the hierarchy of reliable evidence". This assures patient confidence with regard to clinical decisions surrounding treatment choices.

Detecting undesirable effects

Larger patient numbers improve the likelihood of detecting undesirable effects and it is at these real-world levels that regulators prefer to base assessments of risk. Identifying under-represented patient groups in pre-launch trials is, therefore, essential for guiding post-marketing safety assessment within a risk management plan for any given class of drugs. Table 1 summarises the contrasts between the two worlds.

Larger patient numbers improve the likelihood of detecting undesirable effects and it is at these real-world levels that regulators prefer to base assessments of risk

Pitfalls in the real world

Channelling

According to Parkinson, most new drugs are likely to suffer the effects of channelling in the first year after launch since new, higher-priced, more powerful drugs end up being used selectively in an attempt to improve prognosis. Channelling (the tendency of clinicians to prescribe treatment based on a patient's prognosis – as a result, comparisons between treated and untreated patients will yield a biased estimate of treatment effect) occurs because 'problem patients' who are unresponsive to existing drugs or prone to adverse drug effects are often the first to be placed on a newly launched product. Patients who are unresponsive to treatment are often potentially more ill and confounded by indication. Patients with a high susceptibility for adverse events, on the other hand, have a misclassification bias, as their prior history often goes undocumented or unrecognised as such. Such patients would not have been studied in pre-launch trials and adequate profiling would hinge on sufficient information being built from real-world data.

Parkinson also discussed 'exposure windows' – a series of prescriptions of variable duration. These may be associated with latent adverse events that go unrecognised. Furthermore, with chronic drug exposure, events may continue to occur for a lengthy period after discontinuation of the drug. The duration of this extended exposure window can be evaluated by repeat studies progressively lengthening the study period by a day and assessing changes in relative risk.

Usage in the real world

A further complication highlighted by Parkinson concerned that of drug usage in the real world. This may not always be strictly in accordance with the ideals of the product licence, and doctor and patient behaviour have to be taken into consideration in determining how far usage has diverged from the ideal. The doctor may have prescribed, singly or in combination with other drugs, dosing schedules that differ from the licensed posology. Equally, said Parkinson, patients don't always adhere to prescribed regimens and may, indeed, not be taking the medicine. These behaviours interact and may cause a drug's known profile to deviate from ideal conditions. It is therefore important that the granularity of a database

Attribute	Utility
Potency	Function of size; permits assessment of risk at levels set by regulators (e.g. 1:10,000, 1:50,000)
Generalisability	Indicator of true sampling, reflecting demographics such as location, age, gender and social class
Real-time proximity	Close real-time tracking of events
Granularity	Complete profiling to improve knowledge base on what types of patients are using a particular drug (applicable to channelling)
Expert support in data interpretation	Technical, medical and pharmacoepidemiological, with added benefit of contextual knowledge of local practicing physician
Access	Multilevel; to all sizes of companies
Validation	Well-grounded with good publication record
Non-automatic linkage of diagnosis	Often changes with disease course, therefore signs and symptoms preferable
Follow-up	Full access to additional/updated individual case information
Stability	Long-term availability

Table 2. Components of a sound database.

can describe quite accurately the types of patient taking a new drug in the early post-marketing phase.

Proactive surveillance: strategies and solutions

Elements of best practices for pharmacovigilance planning are set out in guidelines published by the European Medical Agency (EMEA).[1] This document forms the legal basis for enhanced pharmacovigilance within Europe. Clearly, said Parkinson, epidemiological tools are crucial for effective pharmacovigilance, and the industry would undoubtedly profit from funding this area at levels similar to those accorded to research and development. Enhanced pharmacovigilance based on large clinical databases, such as the General Practice Research Database (GPRD), is replacing historical practices centred around individual spontaneous case reports (ISCRs) of suspected adverse reactions. Parkinson noted the difficulty in discriminating between true safety signals and background noise from ISCRs, but added that clinical systems permit dynamic, ongoing interrogation of data. In the process, they have the ability to stop at any point to determine shifting needs, effect changes in planning and assess whether particular issues have been satisfied in order to focus on detecting new evolving signals. The components of a sound database are highlighted in Table 2.

Observational epidemiology

So what should pre- and post-launch observational epidemiology directed at gaining maximum knowledge about a drug include information on? Parkinson outlined the following:

- disease
- events
- comorbidities
- class compliance
- class persistence
- class and drug dosing
- drug combinations
- phenogenetic linkages.

Post-launch, the above information should, he said, facilitate proactive real-time tracking. This is useful for ongoing dialogue with regulators and gives context to potential flags from ISCRs in early marketing. As real-time tracking is based on true sampling, it provides more robust and accurate profiling for allaying or confirming concerns about an evolving safety signal.

Further insights into specific safety concerns identified by real-time tracking may be identified by signal hypothesis testing through prospective/retrospective observational studies

Post-marketing safety studies

Further insights into specific safety concerns identified by real-time tracking may be identified by signal hypothesis testing through prospective/retrospective observational studies. Effort should focus on the groups of patients likely to receive the drug. The appropriate age distribution usage groups should be targeted, as should special groups such as patients with liver and/or renal

Cohort study (traditional)	Case-control study (traditional)	Case crossover study (new)	PROBE* (new)
Studies exposure in cases versus controls to see nature of outcome in each arm: good, bad or no change	Studies outcome in cases versus controls and then looks back to see what treatment each arm received	Each case serves as own control with treatment switched on and off during period of disease	Clinical trial randomisation into database
Forward in time	Backward in time	Complex to run	Only intervention being prescription choice based on randomisation code
Difficult to find matched control	Difficult to find matched control		Time limit weeks to years
			No confounding or channelling problems

Table 3. Key elements of the four types of prospective/ retrospective observational studies.

*Prospective randomised open label with blinded endpoint.

dysfunction. The key elements of the four types of these studies are summarised in Table 3.

Reporting standards

Finally, Parkinson commented on the standard of risk management reports submitted by companies to regulators. They were, he said, highly variable and quite often failed to concentrate on the key areas of importance. The aim should be towards concise documentation (backed with appendices) highlighting key issues surrounding the product. These should be addressed within the context of switching such concerns into detailed understanding about identified risks and balancing them against the benefits of the product. Indeed, this would be entirely consistent with the common purpose of regulators and companies of safeguarding public health through responsible pharmacovigilance.

Are you truly aligned with regulatory expectations?

Insights into the aggregate findings of over 16 inspection audits looking at pharmacovigilance systems were shared by Dr Elliot Brown (Elliot Brown Consulting). These audits took place in four continents from generic, proprietary, biotechnology and 'big pharma' companies. Mind mapping tools were used to good effect in stimulating critical appraisal on whether drug safety data systems within individual companies were reliable and in keeping with required standards.

Brown pointed out that regulatory expectations are no longer merely about the timeliness of submissions of reports, but more about ensuring the adequacy of surveillance systems effective for monitoring the safety of products. Indulgence in *schadenfreude* on hearing about the failures of other organisations may, he said, be gratifying but really should prompt questions about internal perceptions of company practice to detect any hidden complacency that might impact on compliance. The integrated complex of tools that makes for an effective pharmacovigilance system may be interrogated by simplifying functions into basic management steps (Fig. 1).

Data quality underpins these functions and is maintained by quality management procedures implemented through standard operating procedures (SOPs), internal audit processes, training, quality control and documentation. Inspectors are particularly keen on viewing SOPs as these are central to defining how activities are conducted within an organisation. In the absence of full documentation there is no evidence that appropriate actions have been taken to fulfil regulatory standards. These are often found to be deficient at audit and give a negative impression of a company's handling of safety surveillance. Brown proceeded to ponder whether adverse events were actually being recognised. Procedures, he said, should be in place for ascertaining whether information on adverse events generated by unanticipated means is recognised as such. These could take the form of general medical enquiries for information on a particular clinical condition (e.g. thrombocytopenia) in association with a product; for example, a clinical investigator commenting about a serious adverse event, bypassing normal protocol channels. Alternatively, non-anticipated sources of potential adverse reactions may arise from product complaints or non-indexed medical publications circulating internally within companies (e.g. *Doctor, General Practitioner*). Procedures should also be in place for ascertaining whether there is a patient behind the particular circumstance, as should guidelines for appropriate documentation.

Are initial reports adequate?

So what needs to improve? For a start, Brown asserted that documentation of minimum identification criteria must be precisely stated within SOPs. In the case of

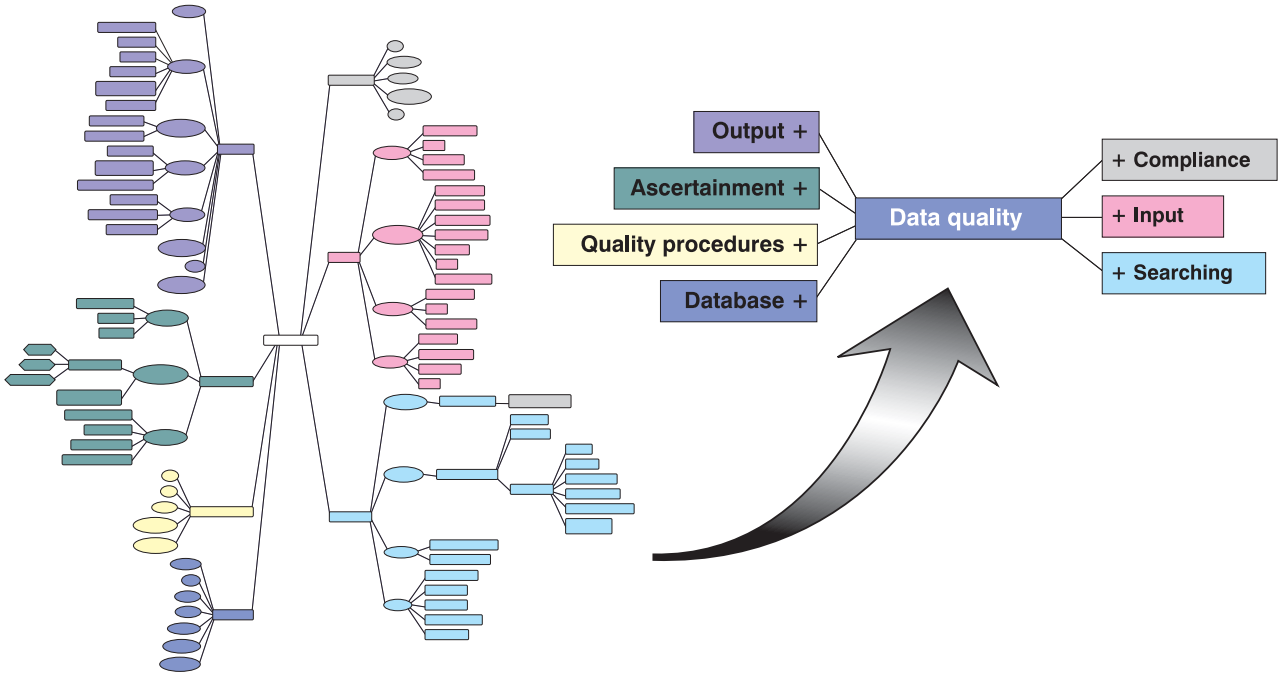

Fig. 1. The integrated complex of tools that makes for an effective pharmacovigilance system may be interrogated by simplifying functions into basic management steps. Adapted with permission from Brown (Elliot Brown Consulting).

specific demographic sets, clear definitions should be stated of what constitutes an elderly, middle-aged or paediatric patient. This enables assessment of whether special categories of patients are being identified in accordance with appropriate measures. Processes should be optimised to gain all necessary information on initial reporting through standardised forms, as there may be no prospect of a follow-up.

Follow-up itself often proves to be deficient on inspection, said Brown. The Council for International Organizations of Medical Sciences (CIOMS) provides useful templates for prioritising practices.[2] Records should state what distinguishes follow-up data from initial information.

The presentation went on to address issues such as data entry precision, MedDRA® (Medical Dictionary for Regulatory Activities) coding and the standardised crafting of narratives. Brown urged companies to provide adequate instruction to personnel involved in data entry processes. Variability in handling such issues was at the root of "unacceptable discrepancies" between source documents and database output found in the majority of audits. This, said Brown, needed to be eradicated. Data fields need to be clearly defined to ensure the accuracy of intended output, and greater care needs to be taken to standardise interpretations of debatable terms such as 'positive' or 'negative', 'dechallenge' and 'time to onset'.

With regard to MedDRA coding, Brown alleged that, 6 years since its adoption within general regulatory practice, many companies were still without adequate processes for assuring the appropriate coding of data. Common deficiencies at inspection, he said, include lack of coding manuals, incorrect version control, poorly configured browser capabilities, inadequate training and quality control, and continuing use of non-current codes. Where there is flexibility in regulatory guidelines (e.g. coding of diagnosis only versus diagnosis with signs and symptoms), care should be taken to adopt a single practice across a multinational organisation to ensure consistency of output in response to regulatory enquiries. The impact of inaccurate or inconsistent coding is huge, said Brown. It creates unreliable data that cannot be reproduced on request. Regulators expect clear descriptions on how MedDRA coding has been applied to evaluate the reliability of submissions, such as tabulated outputs within periodic safety update reports (PSURs).

Processes should be optimised to gain all necessary information on initial reporting through standardised forms

Equally, Brown shared a concern that many companies had no standard approach across data management sites for developing templates and work instructions for narratives. This was, he said, despite good guidance from CIOMS. He also pointed out that there is little guidance on translations or quality control. This means that there is often wide divergence, on audit, between company source data (e.g. records of initial telephone contact) and spontaneous reports generated from such material.

The presentation also questioned the reliability of searches and looked at how outputs of case reports should be presented. Brown advised that implementation of methods of searching for similar adverse events

should be procedural, following principles such as the guidelines issued by the Center for Biologics Evaluations and Research.[3] There must be capacity for producing searches of variable complexity at different hierarchical coding levels as well as multi-axial searches and standardised MedDRA queries. Medical knowledge must, he said, be an integral resource for building searches, particularly in response to regulatory demands. Full descriptions of search parameters in submissions defuse concerns about data manipulation. The quality of searches may be enhanced by limiting access to trained staff, detailing processes and ensuring that MedDRA searches are version-specific.

Full documentation is the key for satisfying regulatory doubts on compliance

Likewise, outputs of case reports should be presented in specific formats, both hardcopy and electronic. In PSURs, verbatim or coded terms are often lacking and the comments field is commonly underutilised for highlighting important issues surrounding causality assessment of a particular adverse event, such as chronology of events, concomitant medication and dechallenge and rechallenge outcomes. Tabulation formats must support signal detection, including cumulative listings and tables of serious unlisted events permitting flexibility of analysis at different MedDRA levels. Furthermore, output elements should be subject to centralised tracking to ensure regulatory requirements are being satisfied, and signalling detection processes should be fully documented to include meeting minutes that must be available company-wide and immediately accessible to audit inspectors on request. Metrics must be generated showing the timeliness and effectiveness of company processes and affiliate performance.

In summary, Brown stated that adherence to defined company SOP standards ensures compliance of internal quality assurance systems with regulatory standards. Regulations obviously take precedence and the strictest ones apply, particularly at audit. The only way to determine performance is by probing processes that may be invalidated by poor quality. Complacency, he said, leads to a false sense of security. Full documentation is the key for satisfying regulatory doubts on compliance.

German pharmacovigilance: legal basis

The legal frameworks surrounding pharmacovigilance systems in relation to German national requirements were looked at by Dr Jenny Müller (German Pharmaceutical Industry Association; BPI). Provisions in the German Medicinal Products Act (AMG) were adopted from the updated European Directive 2001/83/EC as amended in September 2005. Competent authorities in Germany responsible for oversight of medicines are:

- Federal Institute for Drugs and Medical Devices.
- Paul Ehrlich Institute.
- Competent Authority for Veterinary medicinal products.

Appointment of a qualified person in pharmacovigilance (QPP) within a company is designated in legislation on grounds of professional qualification and experience. Provisions are laid down under German law against parties causing endangerment to health in large numbers. These take the form of fines and imprisonment. Failure to appoint a QPP in accordance with legislation is an infringement punishable by law.

Specific obligations on safety surveillance

Although requirements for safety surveillance of human medicinal products follow EC recommendations, Müller highlighted a number of additional obligations that were specific to Germany (Table 4).

The obligations of German competent authorities in relation to risk management reflect EC recommendations enjoining wider cooperation with other agencies, the World Heath Organisation (WHO), medical professional organisations and pharmacovigilance centres. On top of this, Müller explained that a two-stage graduated procedure for risk re-evaluation exists, graded according to the potential impact of the hazard on public health, the higher stage requiring implementation of measures for risk minimisation. This graduated approach defines the parties involved as well as the risk, and details hazard procedures and measures to be implemented in such cases. It also describes mutual communication plans for informing the public, and defines criteria for routine and special meetings.

A two-stage graduated procedure for risk re-evaluation exists, graded according to the potential impact of the hazard on public health, the higher stage requiring implementation of measures for risk minimisation

Müller described the processes and measures required of marketing authorisation holders in Germany. Company risk minimisation measures are, she said, based on recommendations of the BPI. SOPs for risk situations must be in place detailing internal processes, contacts for responsible persons, mechanisms for safety committees, decision procedures and communication procedures. Proposed measures for minimising risk to

- Maintenance of records on numbers of recalls in case of blood products
- Submission of ISCRs on frequent/substantial individual abuse directly jeopardising human or animal health
- Inclusion of a scientific evaluation with all submitted ISCRs
- Submission of reports of any suspected infection (assessed as a serious adverse event) arising from contamination of human – or animal-derived – medicines outside the EU
- Quarterly searches of scientific literature cases of known substances
- Mandatory electronic reporting of all ISCRs
- Submission of expedited reports by trial sponsors on all suspected serious adverse events within and outside the setting of concerned trials and independent of market status, with a specific obligation to expedite reports to all relevant parties, including all investigators

Table 4. German requirements for safety surveillance of human medicinal products additional to EC recommendations.

the public should be stated, varying in impact from minor labelling changes to steps ultimately resulting in recall of a product from the market on quality or medical grounds. The QPP should fully record safety recommendations made to management, particularly pertaining to corporate level decisions on recall. The effectiveness of arrangements should be routinely re-evaluated to ensure certainty of implementation.

Risk communication

Timely and responsible communication promotes the image of a company in the public eye and must be conducted only with prior or simultaneous notification to competent authorities. Recall information should be adequate and based on a single endorsed corporate view disseminated in a format appropriate to the recipient; for healthcare professionals this is the 'red hand' letter (Fig. 2). This well-recognised symbol, said Müller, draws attention to mailings (postal, fax and electronic) on warnings about newly identified significant risks of medicinal products requiring immediate action for health protection. Information is also disseminated in weekly notices to doctors and pharmacists, and via television and radio, if urgent.

Müller pointed out that differences in the implementation of pharmacovigilance in German law and other European Union member states must be taken into account when designing pharmacovigilance systems. This, she warned, may lead to confusion of staff in multinational organisations. To combat this, structures must be defined to reduce the administrative load. Müller also cited the introduction of electronic transmission of information across Europe as being likely to expose additional challenges. Effort, she concluded, should be directed at developing legally binding provisions to eliminate parallel reporting and national discrepancies, with input from all interested parties.

Fig. 2. The 'red hand' – a well-recognised symbol used in Germany to draw attention to mailings on warnings about newly identified significant risks of medicinal products requiring immediate action for health protection.

Electronic transmission of information within the EC

Dieter Konrad (Boehringer Ingelheim) provided an overview of structures supporting electronic transmission of information within the EC. His presentation began with a look at EudraVigilance.

EudraVigilance

EudraVigilance is the main platform pertinent to pharmacovigilance activities. The platform consists of a family of databases, and has a range of functions (Fig. 3):

- It provides a **gateway** for improving regulatory compliance through standardised secure data transmission, enabling rapid communication between all relevant parties across Europe (European Agency for the Evaluation of Medical Products [EMEA]), competent authorities and Marketing Authorisation Holders (MAHs). Electronic submission eliminates data transcription errors and accelerates expedition of reports, enabling a common environment for receipt of safety data from multiple sources, including ISCRs, clinical safety and medical information. Access to MAHs by a specific company is restricted and there is no access to competitor data. Regulators obviously have freer access to the database contents.
- It has a **pharmacovigilance database management system** with fully automated functions supporting data interchange and interactive transactions on medicinal products and adverse reactions from multiple sources with tracking and querying capabilities suited to scientific, administrative and business aims.

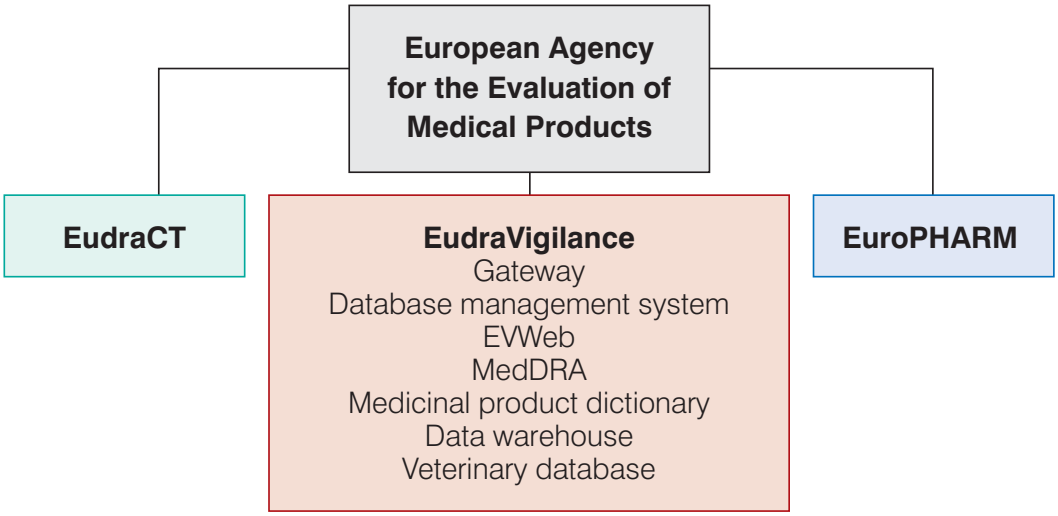

Fig. 3. European database platforms.

- The **EVWeb** enables secure data transmission for small and medium-size enterprises without International Conference on Harmonisation (ICH) E2BM-compliant systems.
- It has maintenance and support structures for updating and distributing **MedDRA** terminology under licence to all relevant parties.
- A **medicinal product dictionary** (EVMPD) collating standardised terminology on medicinal products (e.g. active constituents, routes of administration, formulations, concentration ranges) in hierarchical multi-axial structures allows automated data workflow, with facilities for quality control and audit processes. The process of building the dictionary has been fraught with problems as it has often been difficult to determine where responsibility rests for acquiring such information within companies. E2B requirements make it mandatory by law that information on developmental products be submitted to regulators, and more progress has been achieved there. However, post-marketing drugs do not have similar binding requirements for enforcement of cooperation.
- A pharmacointelligence **data warehouse**, reconsolidating transactional data from other databases, permits flexible, high-level interrogation of data in statistical analyses, data-mining and signal detection, and for risk management and drug information management studies. *Ad hoc* analyses may be conducted as well as queries on compliance and quality matters. Systems are being developed for text-mining tools to assist regulators in assessments of narrative discrepancies.
- It also has a **veterinary** database modelled along lines similar to the human system.

EudraCT

This database collates community-wide information on clinical trials, as required under European Directive 2001/20/EC. It permits full regulatory oversight of all activities surrounding trial conduct and investigational product development, and provides enhanced protection of clinical trial participants and patients through reporting requirements for suspected unexpected serious adverse events. Konrad pointed out that information on company investigation products has to be keyed in independently of the EVMPD, as the two databases are not linked.

Electronic submission eliminates data transcription errors and accelerates expedition of reports

EuroPHARM

This database is established for use by the general public for obtaining updated, authorised information on medicinal products available on package leaflets. The system is managed independently of pharmaceutical companies, and it should go public in the near future. There are plans for national translations other than English later in 2006, with the full production version available by 2007.

State of readiness

Konrad concluded that the European database project is massive in its scope and, as such, it is not yet sufficiently synchronised for routine use. This should become a reality as soon as the current testing phase is completed.

Using technology to gather and communicate safety data

Simon Sparkes (Aris Global) addressed the key drivers of investment in technology solutions for enhancing safety surveillance. According to Sparkes, increasingly sophisticated systems are required to fulfil the industry's need to satisfy multiple pressing demands. Challenges

faced include growing public awareness toward safety, global regulatory demands for full electronic reporting, streamlining operations for efficiency gains, cost reductions in the face of rising work volumes, proactive surveillance, risk management and demonstration of compliance.

Recent responses from an IT customer survey indicate that safety departments place a high premium on systems that support timeliness, measurability, clarity and quality. These factors are, said Sparkes, essential for improving global operational efficiencies, meeting evolving regulatory compliance requirements, inspection readiness and global premier pharmacovigilance practices. Indeed, premier pharmacovigilance is seen as the definitive means of establishing confidence in safety activities that is demonstrable to consumers, managers, investors and government. Software solutions must, therefore, be versatile and able to integrate, with the capacity to support the distinct pharmacovigilance functions of case intake, case handling, expedited reporting, periodic reporting, clinical safety and signal detection (Fig. 4).

This presentation affirmed that systems should be capable of triaging case sources (i.e. safety, medical inquiries and product complaints) and determining suitability for E2B compliance. According to Sparkes, most companies are evolving from Citrix-mode dependency to web-based data collection systems with remote access permitting use by licensed partners and affiliates. Such systems allow semi-autonomous access to affiliate organisations in keeping with specific local needs for ISCR entry and expedited submissions, which can be tracked by central units through informed authority updates. Sparkes highlighted the promise of the electronic data capture (EDC) of cases which, he said, had the potential for minimising the need for reconciliation with clinical trial databases. However, Sparkes felt that the real value of automating case intake rests in the facility for gateways to import E2B documents. There are minor technological challenges associated with this in the shape of version control after document alteration through assessment updates and distinguishing follow-up information from initial content.

Sparkes also looked at the value of workflow automation and automatic case distribution. Workflow automation in case handling, he said, promotes efficiency, regulatory compliance and adherence to SOPs and timelines. What's more, communication tracking is assured through systems supporting the generation of standard letters and automatic reminders, and case narrative construction can be sped up and standardised by means of autonarratives. Other nominated benefits include configurations for coding MedDRA, the WHO-Drug Dictionary (WHO-DD) and EVMPD, and fields for case assessment, compliance metrics, quality checks, alert notifications and database searching.

In addition to this, Sparkes pointed out that automatic case distribution promotes operational efficiency in meeting specific local considerations of affiliates.

Crucially, it permits algorithms for E2B modules with regards to complying with potential regional discrepancies in submissions to central regulatory bodies such as the EMEA, the US Federal Drug Administration and the Japanese health authority.

Automatic case distribution promotes operational efficiency in meeting specific local considerations of affiliates

Sparkes' presentation also underlined the merits of periodic reporting and integration with EDC portals, and highlighted how software solutions can facilitate multialgorithm automated signal detection. In the case of periodic reporting, semiautomated systems offer solutions such as templates for interdepartmental input into PSURs which also support scheduling and tracking of PSUR commitments. These templates can be configured for multipurpose reporting obligations such as EU Clinical Trial Documents and annual safety reports. In addition, clinical-to-safety database transfers through integration with EDC portals enables the bridging of heterogeneous database environments. Reconciliation of safety and clinical databases can be conducted in accordance with user-defined variables. Despite the encouraging progress made in applying IT solutions to enhance pharmacovigilance practice, Sparkes concluded that some issues remain unresolved.

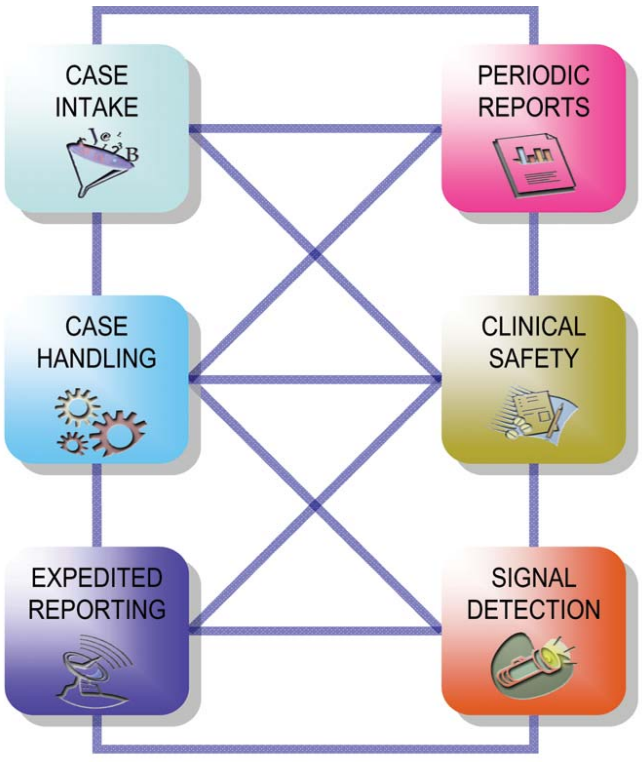

Fig. 4. Key pharmacovigilance functions and activities. Reproduced with permission from Sparkes (Aris Global).

There are cost implications as its niche value does not attract the support of large vendors. Furthermore, shifting legislation and the emergence of new technologies soon make compliant systems obsolete, with a need for reinvestment in updated systems. For the vendor, he said, this is not altogether unwelcome as there is the ever-present challenge of developing fully integrative solutions versatile enough to handle diverse requirements.

The place of registries in product surveillance

The search for practical tools for enhancing risk management programmes has led to increasing use of registries by companies to support systematic prospective surveillance of treatment in the post-marketing setting. Dr Nawab Qizilbash (Oxon Clinical Epidemiology) looked at the role patient registries play in risk management. Registries fall into three broad groups: disease, drug and pregnancy. Although impractical for routine safety surveillance, according to Qizilbash, they permit evaluation of important signals identified from ISCRs and other sources against covariate risk factors affecting adverse outcomes such as dose, exposure history and patient characteristics. Additional resources include a bank of outcome information not available in large automated database resources as well as information from physician records, hospital summaries, pathology reports and vital statistics. Qizilbash admitted that there are some disadvantages – registry numbers are limited, there is no non-disease control group, and variations in data capture and quality exist – but these are, he believed, surmountable.

So what considerations should be made for risk management planning? Qizilbash advised that, since risk management plans are generally product specific, care must be taken to find the right type of registry matching specified goals. Logistical aspects of timing, accessibility and costs must be considered, meaning that proactive decisions for registry inclusion within company plans are primarily driven by marketing and development strategies. It may be necessary to implement rapid exploratory studies to enable efficient collection of high-quality data to satisfy questions raised by regulators either in late development or in the early stages of marketing. Registries are readily adapted for this purpose and the appropriateness of their design may contribute towards safety competitiveness.

In the course of registry data collection all identified adverse events are documented and transmitted to the company involved

Qizilbash further explained how the process works, stating that in the course of registry data collection all identified adverse events are documented and transmitted to the company involved. Comparative listings can then be generated between adverse events arising from the registry and those in the company safety database, with discrepancies being resolved by follow-up through the registry or directly with the prescriber. Data testing can then be performed through propensity score analyses with adjustment of covariants using methods similar to those used in epidemiological observational studies. According to Qizilbash, registry modes have the added advantage of supporting automatic links between the adverse reaction and other associated patient data. Key benefits accruing from registries in safety evaluation compared with safety databases are summarised in Table 5.

The cipher code

An exposé of the highly complex topic of optimising medical terminology coding for effective data retrieval and analysis provided one of the high points of day one of the conference. Although now widely adopted for general use with pharmaceuticals, MedDRA nevertheless continues to pose challenges to users at both input and output levels.

	Safety databases	Registries
Data source	ISCRs	Patient records (hospital)
Method	Retrospective	Prospective
Data type	Limited	Multisource
Covariants data	Poor	Rich
Diagnostic tests	Lacking	Detailed
Real-time proximity	Reporting time lag	Rapid adverse event identification with direct transmission to company
Reporting conditions	Variable content and quality	Investigator engagement
Safety evaluation application(s)	Signal detection	Fulfilment of risk management obligations Detailed characterisation of adverse events

Table 5. Key benefits accruing from registries in safety evaluation compared with safety databases.

Dr Reinhard Fescharek (Bayer Healthcare) outlined these challenges. The problems, he said, stemmed from the unique way the coding system was developed, which created certain difficulties in conducting effective searches for analytical purposes. The answer, said Fescharek, lies in the configuration of company databases to support the storage of multiaxial coding channels, which will enable the merging of split terminologies from separate hierarchies when searches are performed. Furthermore, to ensure the capture of all necessary data related to the medical concepts under scrutiny, certain considerations must be factored throughout the whole exercise.

MedDRA design considerations

What are these considerations?

Primarily, MedDRA data entry is built round a repository of lowest-level terms (LLTs) matching reporter terms verbatim. The huge numbers and lack of discriminatory power of LLTs are, said Fescharek, unhelpful for analytical purposes. LLTs are linked to preferred terms (PTs), which are defined medical terminology concepts with high specificity or granularity. This characteristic reduces the level of interpretation required to maintain synonymity with verbatim terms. The sheer multiplicity of terms describing similar medical conditions at PT levels is equally problematic, particularly when grouping terms efficiently during searches. Moreover, databases coded originally using less granular coding systems and converted into MedDRA will reflect the lower specificity of the legacy coding system. In situations where non-specificity of legacy coding fails to accurately reflect verbatim terms, re-coding from source data during MedDRA conversion may be necessary to support the accuracy of future analyses. These practical considerations engender a need for expert advice on MedDRA in determining database structure in relation to hierarchies, storage allocations of terminologies, secondary assignation of system organ classes (SOCs), evolving coding practices and data migration from non-MedDRA based systems.

Although now widely adopted for general use with pharmaceuticals, MedDRA nevertheless continues to pose challenges to users at both input and output levels

The advice?

Caution must be taken in maintaining the consistency of methods employed for data retrieval and presentation. The selection of multiple coding terms (i.e. diagnosis with signs and symptoms) for a single medical condition increases term counts. On the other hand, coding for diagnosis only reduces term counts. Comparison of adverse event profiles between products, said Fescharek, should be based on the same methodology, as observable differences in event profiles are likely to be spurious, arising from discrepancies in term counts. Likewise, search queries should be constructed from the same version of MedDRA, and updates to the appropriate MedDRA version must be performed prior to use of new data.

HLGT: Cardiac arrhythmias

- HLT: Cardiac conduction disorders
- HLT: Rate and rhythm disorders NEC
- HLT: Supraventricular arrhythmias
- HLT: Ventricular arrhythmias and cardiac arrest

Table 6. An example of HLGT and HLT levels in MedDRA. HLGT and HLT levels should be viewed as an additional tool for data retrieval and presentation, as they provide clinical grouping of terms.

Considerations arising from hierarchical construction

The concept of hierarchies (high-level group terms [HLGTs] and high-level terms [HLTs]; Table 6) in MedDRA is to enable retrieval across several levels of clinically grouped terms aimed at identifying potential clusters for signal detection purposes. However, Fescharek emphasised that hierarchies are built as multiaxial structures with HLTs distributed across multiple HLGT terms, and HLTs and HLGTs in turn across several SOCs. Hence the classification of bullous conditions (HLTs), a related set of specific medical diagnoses, under several HLGTs covering inter-related conditions in which bullous diseases may manifest as part of a larger clinical syndrome. These, in turn, require allocation to different SOCs indicative of the fact that bullous conditions arise in various organs (e.g. skin, gastrointestinal tract, nervous system). This arrangement supports flexibility of data retrieval by different routes to ensure a reasonable first approach to data capturing. Hierarchies sit within each other and so multiaxiality impacts at lower levels as well. It is for this reason that MedDRA allocates PTs to one primary SOC. Representation in other SOCs is regarded as secondary to prevent multiple counting. Clinical conditions are then retrievable and grouped as functional medical attributes such as aetiology, system or site.

Caution must be taken in maintaining the consistency of methods employed for data retrieval and presentation

Fescharek pointed out that there are sections of MedDRA that do not support multiaxiality. Investigations are one example of a stand-alone SOC. PTs in such SOCs may be missed as they may not be identified as

clinical concepts. It is important therefore to recognise that analysis by SOC alone may be misleading and that stand-alone SOCs and secondary pathways must be checked for complete optimisation.

According to Fescharek, the construction of MedDRA evidently introduces the potential for underestimating the size of a clinical concept arising from its granularity and through possible splitting as a consequence of multiaxial algorithms. As such, conclusions based on inappropriate use of search parameters may be misleading. Guidance in the form of standardised MedDRA questions (SMQs) is now available from the joint efforts of CIOMS and the ICH. SMQs are concept-based searches built from groupings of terms (at various hierarchical levels) from one or more SOC relating to a defined medical condition or area of interest. They are relevant to specific drug safety issues and permit subsearching, algorithm design and other usage options.

MedDRA deciphered

In his conclusion, Fescharek had words of comfort for perplexed users of MedDRA and offered the following tips:

- Optimisation for best results of MedDRA rests on sound knowledge base of terminology design to guide choices for appropriate data presentation.
- Standard-term based queries may identify clusters of adverse events or other issues for in-depth assessment using secondary path analysis and SMQs.
- *Ad-hoc*/in-house queries should be adopted for issues not covered by officially released SMQs and fully documented; potentially they could be submitted to the ICH for adaptation into official SMQs.
- Presentations of adverse events should group related events to ensure that true occurrence rates are not obscured. Remember groupings by PTs can be a challenge as narrowness in grouping may result in frequent underestimations, whereas too broad a grouping may hide the existence of specific problems.
- Secondary pathways must always be taken into account.
- Calculation of indices based on dictionary hierarchy groupings alone should be complemented by SMQs.
- Search strategies should be documented to aid regulatory assessment of analyses, and to permit reproducibility and consistency of approach.
- Version control descriptions must be validated.
- ICH guidelines[4] should be referred to as a matter of course.

Benefits of electronic data capture

The basics of applying EDC systems to company clinical safety workflows were addressed by Dr Johann Pröve (Bayer Healthcare). His presentation used information gathered from over 200 phase 1–4 transcontinental studies in anti-infective, cancer, cardiovascular, erectile dysfunction and hyperlipidaemia indication settings. According to Pröve, EDC is rapidly replacing traditional paper-based methods for the collection, handling and processing of all clinical trial data. Benefits of EDC are outlined in Table 7.

EDC is rapidly replacing traditional paper-based methods for the collection, handling and processing of all clinical trial data

Pröve highlighted how EDC systems can store a wide range of safety data, including adverse events, laboratory results, patient questionnaire data, medication data, demographics and clinical investigation results. Subsets of these data are relevant to different departmental interests (safety, medical, data monitoring boards, study managers and external boards). Tools must, he said, support the needs of these users in rapidly conducting reviews of safety data, and take the form of listings, correlation diagrams, Excel®-based formats and standardised customised reports. Rules are also determined for agreeing thresholds for numeric data, flagging outliers of interest and for usage of coding lists such as the WHO-DD, SNOMED CT® (Systematised Nomenclature of Medicine Clinical Terms) and MedDRA.

The management of external safety data

The presentation also looked at the management of external safety data – non-company resources such as hospital central laboratory tests and results of clinical investigations – and how merging such data into company systems increases the options for where merging should take place. Should it occur in EDC data, a clinical database management system or a statistical environment (SAS)? Furthermore, said Pröve, owing to potential technical discrepancies between internal and external systems, data may require conversion before merging can take place. He also warned of software issues of incompatibility between systems, making automated merging error prone. These challenges require in-house solutions in order to provide comprehensive datasets to interested parties.

In addition, there is also a tendency for discrepancies to arise between safety data stored in clinical and drug

- Eliminates human errors from data entry and streamlines workflow, permitting efficiencies by balancing increases in volume capacities against costs
- Validation can be performed at data entry, facilitating accuracy of records
- Ease of collection permits cross-functional evaluation both internally by monitors, data managers and safety personnel, and externally by clinical investigators
- Data are efficiently organised for ease of different types of analyses, including safety and statistical options
- Ease of reconciliation of clinical trial safety data with pharmacovigilance systems is facilitated
- The migration of contents from other portals and database systems (e.g. E2B inbox and laboratory data from central sources) may be a route for increasing integration with company databases

Table 7. The benefits of EDC.

safety databases, stemming from the independent processes underlying data entry in both settings. Pröve advised that these discrepancies necessitated a process of serious adverse event reconciliation through cleansing of the clinical safety database, a process that with paper-based systems would be quite cumbersome. On the other hand, he said, EDC makes serious adverse event reconciliation easy, with programmes for comparing such information and other data efficiently. Serious adverse event and coding discrepancies are readily highlighted and errors corrected. Queries and responses can also be easily transmitted and tracked between investigators and sponsor.

EDC makes serious adverse event reconciliation easy, with programmes for comparing such information and other data efficiently

Pröve concluded that the ultimate aim is that EDC will support the transfer of all serious adverse events and related data to the E2B inbox in sponsor clinical and pharmacovigilance safety databases. Electronically available safety data can then be moved to the case report production environment by a safety expert, with coding done centrally. Follow-up information would be managed electronically, enabling minor effort only in future serious adverse event reconciliation.

Enhancing drug safety knowledge management

The highlight of day two of the conference was, without doubt, the transatlantic telepresentations on knowledge management in drug safety. During the course of these interactive panel discussions, Sidney Kahn (Pharmacovigilance & Risk Management, Inc.) looked at why a knowledge management approach is needed, Jim Averback (Life Science Integration Partners) addressed confidence in safety strategies, A Leander Fontaine (Pharmiceutics) focused on terminology and communications strategy, and Peter Elkin (Mayo Clinic) tackled decision support strategies.

The sessions were moderated by Barry Hardy (InnovationWell). Hardy spoke extensively about the need to gather a community together to review information and to spread communication. He cited the eloquent example of the 'ferryman' of Basle, the knowledge the river gave the ferryman regarding life, and his ability to communicate this while ferrying people across the river. In a pharmaceutical context this knowledge includes the sharing of information across research groups, the production and presence of best knowledge in decision-making situations to deliver improved outcomes, and the flow of knowledge across disciplinary and organisational walls. Hardy developed the theme that there are four characteristics of the internal review groups in the sharing of pharmacovigilance information: they are pervasive, informal as well as formal, involve explicit and tacit knowledge-sharing (particularly the experience and understanding held in people's heads not in information systems) and, finally, that they have connections throughout people in the organisation.

Optimising use of these networks is most likely to enable better knowledge sharing and questioning of the facts available, with best decisions being made based on the best knowledge available.

Developing these themes, Kahn examined the processes involved in developing a knowledge management approach, highlighting in particular why we need such an approach and what the benefits are. Kahn noted that public and regulatory agencies are now more aware than ever before as to the risks and benefits of drugs, and that the commercial outcomes of some widely publicised events are well known. He also highlighted the debate raised by statistical reviews of adverse reactions (which can suggest real issues with well-known medical compounds), which in reality are not as onerous as the statistics would suggest. This, he said, shows the absolute need for a good knowledge management strategy. The end goal should be the ability to track the safety of a medicine while at the same time providing reassurance to the public and regulatory authorities alike. This may also translate into some protection from liabilities for the drug industry.

Averback highlighted current public concerns arising as a combined result of the increased media scrutiny of drug companies, which has led to a drop in confidence in them, and the very public cases of apparent lack of risks associated with some preparations. Knowledge management, said Averback, is one, but not the only, solution by which to increase the ability to communicate risk/benefit balance and to better inform and build confidence. The benefits for a drug company vary depending on the degree of openness they follow, but the overall need to communicate more fully through a standardised model is paramount.

Fontaine expanded upon this strategy to provide more information to the public and regulators alike, exploring issues surrounding the need to understand each other and avoid the potential for miscommunication, particularly between manufacturers and regulators, and also healthcare providers. Do patients and consumers understand the issues and similarly the role played by the media? Are the media representing a true objective picture? Fontaine argued that although the terminology used by the regulators may be fully understood by the regulators, these terms may have totally different meanings when used by the public or the media. Fontaine proposed that common approaches to terminology would lead to a confident strategy regarding drug safety.

Elkin spoke on the 'ontology'-driven approach to drug safety and the need for good education programmes, both for the physician and the public. To achieve this, he said, a good systems-driven approach, with common and regularly reviewed nomenclature, is essential. In addition, Elkin noted that in some parts of the world it is becoming mandatory to give tests before administering drugs. This is because genomic differences can result in reduced metabolism and increased bioavailability of the drug, with potential overdosage outcomes in some gene types. Capturing all this information in a standardised format and then making it accessible to all interested parties in an open and holistic way can, said Elkin, be the best possible outcome for risk management. Here technology can assist.

In the roundtable discussion that followed, questions were raised as to the usage of handheld technology, such as Palm and iPod (Podnostics), and the ability to use these technologies not only to store relevant information concerning drugs, but also for video conferencing and expert help via video links, etc. This is clearly a future trend. The Mayo Clinic, in particular, is at the forefront of the development of these adjuncts to assist the physician. Recent developments in third-generation Universal Mobile Telecommunications System technology will again make the spread of information relevant and timely, and be able to assist physicians in treating patients or finding information on adverse reactions. Another point of interest concerned the use of programmes such as Medic-to-Medic,[5] where the care pathways involved allow both for the correct treatment protocols to be followed in an auditable way and for capturing information that can be used for monitoring best practice. These programmes are now being integrated into basic student training in medical schools, together with recent developments from the Connecting for Health™ Programme in the UK.[6]

Conclusion

The whole area of risk management and drug safety is of key importance given recent highly public cases. It is gratifying to see the industry is taking this matter very seriously and beginning to share data, even that which has yet to be published, and is also investing heavily in new technological solutions to assist in the tracking and identification of safety issues. The wider use of longitudinal real-life data, such as those from GPRD, and technology to investigate hypotheses and thus new investigation pathways, will inevitably open areas for debate and question, but a fair, objective and open debate can only increase the confidence of the public in the pharmaceutical industry.

In addition to the new knowledge management solutions discussed at this conference, the development of better care pathways for the treatment of disorders and the technological innovation involved is beginning to bring long-awaited results. It is close to impossible for front-line physicians to remember every interactive permutation of possible issues with a drug, and these technological solutions can only serve to make the safety and management of the treatment of disease better. It only remains now for the drive made by the industry in safety to be reflected by the marketing arms in the companies, and this alone would make an interesting conference agenda for the future.

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Bioinformatics and Drug Safety

A KeywordPharma **Expert Review** by **John Hammond**

Published February 2006

ThePharmYard product code kwp005

ISBN-13: 978-1-905676-04-0

In this Expert Review, John Hammond examines how genetic analysis can be useful in designing drug regimens. It outlines where the best gains for drug safety can be made and how genotyping can help form part of the solution.

Executive summary

Establishing the safest and most efficient drug regimen for a patient can be a trial-and-error process that can, in some cases, place patients at risk. Variability in response to certain drugs between different patients has major implications for the pharmaceutical and healthcare industries.

The ability to determine the correct drug and dosage for therapy at the outset would contribute significantly to drug safety. It would also lead to a more economical use of drugs, with potential savings for healthcare providers.

It is becoming clear that variability in drug response may be inherited. With the application of genetic analysis, DNA analytical techniques and pharmacokinetics, it has become possible to identify the genes, and the proteins which they encode, that are involved in drug responses.

This Expert Review, *Bioinformatics and Drug Safety*, looks at how to identify the genes involved in drug response, characterise the variants and devise a convenient means of identifying variants in a patient. It shows how genetic analysis can be a useful tool in designing the drug regimen for the best risk/benefit, and makes a case for genotype testing prior to prescription, and for genotype determination as a part of the clinical trial process.

Contents

About the author

John Hammond graduated in Biochemistry and Soil Science from the University of Wales, following this with research for an MSc in the same subject. He was later awarded a DPhil in fungal biochemistry from the University of Sussex. He worked as a government research scientist at the Glasshouse Crops Research Institute, and then at Rothamsted Experimental Station for 17 years, working on fungal and plant biochemistry, molecular biology and genetic manipulation, and authoring over 40 research papers. He has also held visiting research fellowships at the University of California, King's College, London and the University of Surrey.

After leaving full-time research he was appointed senior lecturer, and later reader, in molecular genetics at the North East Surrey College of Technology. In these positions he developed and taught courses on molecular genetics, biotechnology and DNA technology for undergraduate and postgraduate students. As well as continuing with part-time lecturing in medical and molecular genetics at the college, he now writes on molecular and genetic aspects of medicine, and constructs websites and online learning materials for healthcare companies, as principal of Bioupdates Consultants. He is a Member of the Institute of Biology and a Chartered Biologist.

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Edited by Dr Peter D Stonier

Published by John Wiley & Sons

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