Ticking time bomb: Poorly managed product safety

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Abstract

A key paradigm of the pharmaceutical industry has changed. With increased attention towards ensuring the safety of drugs and medical devices, the ability of firms to conduct risk management based on high-quality pharmacovigilance (PV) – starting early on in clinical development – is becoming increasingly important to the successful marketing of pharmaceutical products. Indeed, the repercussions of recent litigation regarding the Cox-II class of compounds are just an example of how safety management will continue to impact the marketability of both existing and future drugs and medical devices. Firms without satisfactory safety data handling and reporting operations in place are now vulnerable to significant business risks with potential long-term drug safety issues. While this has often been considered a necessity, a small proportion of companies have actively pursued excellence in this area.

Companies are taking different approaches to address the increasing demands in this area – from focusing on efficiency to driving higher levels of rigorousness in their PV practices. PRTM various has identified a number of key practices common among firms demonstrating excellence within PV. Results of a pioneering study of 23 top Western and Japanese pharmaceutical companies confirm that, overall, the industry has yet to achieve both a high-level of quality and productivity in firms' PV operations. As the burden for conducting efficient, effective PV becomes increasingly difficult, senior management will seek targeted improvement strategies in order to balance a high level of efficiency with a high level of rigorousness among their safety data handling practices. With this in mind, this article seeks to demonstrate how a company can most effectively comply with ever-changing requirements, strategically improve the thoroughness of the practices within their PV operations and achieve greater efficiency. In addressing these challenges, top management will be focusing a greater amount of attention on one more thing – pharmacovigilance.

Keywords: *product safety, pharmacovigilance, adverse events, risk management, drug safety, surveillance*

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INTRODUCTION

A significant paradigm shift is under way in the life sciences industry. Unlike sales, marketing, and R&D, however, we hear about this topic only when there is a problem. The subject is the 'unglamorous' area of product safety or pharmacovigilance (PV). For those unfamiliar, PV is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.[1]

In the last few years, we have all been increasingly overwhelmed by news of product recalls such as Merck's Vioxx and Guidant's pacemakers[2] as well as reports of significant litigation related to safety problems with various medical products. And while we fight the daily battles to win market share with such tools as pricing, samples and promotions, the spectre of poorly managed product safety lurks in the background – just waiting to trump all of our good work in the market.

Fortunately, the implication of product safety problems on business has raised awareness of the significant role that product safety plays in the marketability of products. Firms without satisfactory safety data handling and reporting operations are now vulnerable to significant business risk. And this, in turn, means that companies need to change the way they think about product safety and risk management. The ability of firms to plan

for and conduct risk management based on high-quality product safety data handling – starting early in clinical development – is essential to successfully market both drugs and devices.[3]

Unfortunately, at the same time that the media has focused on life sciences companies, transformation in the area of product safety has been slow at best. Those who are seeking improvements in this area are adopting approaches that vary from improving productivity to increasing the rigorousness of internal practices.

A view into the PV practices of the pharmaceutical industry should, therefore, prove enlightening. Results of a study of 23 top Western and Japanese pharmaceutical companies (including four of the top five global pharmaceutical firms) provide a window into industry practices in this area. For example, even among firms handling approximately the same number of case reports, striking differences exist in how they handle and report adverse events. A closer inspection of internal practices exposed varying levels of rigour in their PV practices (representing recommendations and regulatory requirements from the International Conference on Harmonisation (ICH),[4] Council for International Organisation of Medical Science (CIOMS),[5] and the US Food and Drug Administration (FDA),[6] EU European Medicines Agency (EMEA) and Japanese Ministry of Health, Labor and Welfare (MHLW)[7] regulatory agencies.

The key for pharmaceutical firms in particular and, we believe for medical product firms in general, is to balance a high level of rigorousness with efficiency among their safety data handling staff in order to achieve both high-quality and productivity in their product safety organisations.

SURVEY METHODOLOGY

The survey was sent to the head of the product safety departments at over 50 firms in order to:

- help participants improve their operations by comparing their internal policies, processes, systems and resources against other global and domestic firms;
- capture emerging trends and issues in order to help participants manage in the quickly evolving environment of PV.

Participants received a complementary analysis and report of the study results in return for taking part in the survey. Responses were received via mail from 23 firms, including 4 of the top 5 global firms. Overall, participants included the following:

- 11 global Western firms;
- 7 Japanese firms that serve the global and domestic market;
- 5 Japanese firms that serve the Japanese market only.

Questions from the 40-page survey, offered in both English and Japanese, covered every aspect of PV, including each company's policies, processes, organisation, systems and performance measurements. Some examples are:

- How does your product safety management department obtain additional or follow-up information for spontaneous reports from the reporter?
- How many different times in the review process do you perform quality control on your safety database with report forms?
- What percentage of your individual post-marketed spontaneous case reports receive a medical review by a physician (either in-house physician or outsourced)?
- Does your safety data management

department utilise standardised, well-defined performance measures to evaluate the effectiveness of safety data handling?

- How are the individuals that handle post-marketed spontaneous reports within your product safety management department grouped?

WHAT IS PRODUCT SAFETY?

The product safety function develops and maintains comprehensive safety profiles of products by evaluating adverse side effects (ie adverse event [AE]) reported by patients in clinical trials and in the post-marketing environment, as well as any other information relevant to drug safety. For each adverse event received by your company, an assessment must be made of the seriousness, expectedness and causality of that adverse event and the drug in question. 'Serious' is defined in the regulations as an adverse experience that is fatal or life threatening, a persistent or significant disability/incapacity that requires or prolongs hospitalisation, or is a congenital anomaly/birth defect. An unexpected event is defined as an adverse event that is not listed in the current labeling for the drug, including events related to an event listed but differing from the event in severity or specificity.[8]

In properly collecting, evaluating and reporting this information to regulatory authorities, product safety departments will typically conduct the following activities (Figure 1):

- Collect and evaluate AE and other drug safety relevant information.
- Create and maintain AE database for analysis.
- Conduct periodic trend analyses of AE databases to identify AE of concern (ie signals), possible drug interactions and/or high-risk populations.
- Prepare safety reports summarising and analysing AE case trends and any other possible safety risk to support regulatory submissions and management decision-making.
- Develop an external communication strategy plan.

WHY RAISE AN ALARM?

One might expect that daily references to product safety failures in the business press would serve as sufficient warning to the industry. While this is true, it seems that change is slow to take effect. In fact, the operational transformation of life-science organisations often evolves much more slowly than similar changes in non-regulated industries. Survey results clearly indicate a cause for concern. One-third of the survey participants claimed a 'high' risk of reporting expedited adverse events late to relevant regulatory authorities (eg 15-day 'alert' reports for unexpected, serious adverse events for post-marketed drugs). Furthermore, nearly 40 per cent indicated a 'high' risk of misjudging the seriousness or expectedness (separately) of an adverse event.

Interestingly, the data show that, as the

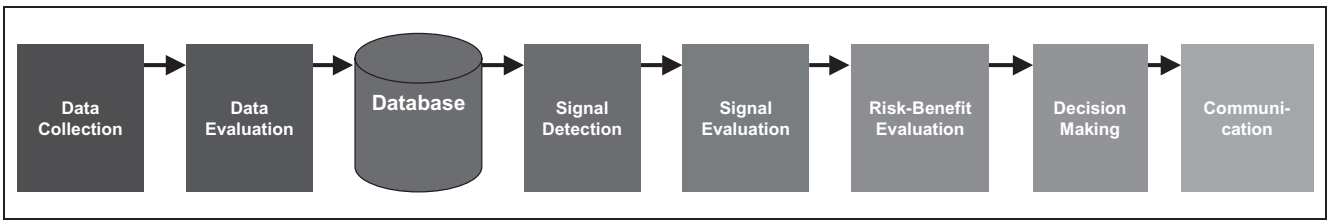

Figure 1: An overview of the PV process for a product safety department

number of product safety case reports handled per employee increases, the perceived risk of non-compliance (eg poor data quality, reporting delays) tend to increase dramatically across firms. As shown in Figure 2, aside from noted exceptions (circled), the greater the number of reports handled per employee, the greater the perceived risk of non-compliance. The noted exceptions, however, represent firms either clearly in control of operations or at high risk without acknowledging it. The three exceptions, all Western pharmaceutical firms, have historically experienced a relatively large number of adverse event case reports, when compared to other firms in the study.

The majority of survey participants seem to agree on the primary causes of these risks. Insufficient or unclear information from the person reporting the adverse event is considered the top cause of risk to both adverse event reporting and data quality. Participants, however, pointed internally to the next two culprits: insufficient quality control checks and insufficient resources.

In addressing these deficiencies, funnelling much-needed resources away from R&D into safety data handling is not an attractive option for most companies in an investment environment that increasingly focuses on the development pipeline. Senior management expects product safety managers to find effective, but efficient, methods to improve adverse event reporting and data quality with few to no additional resources.

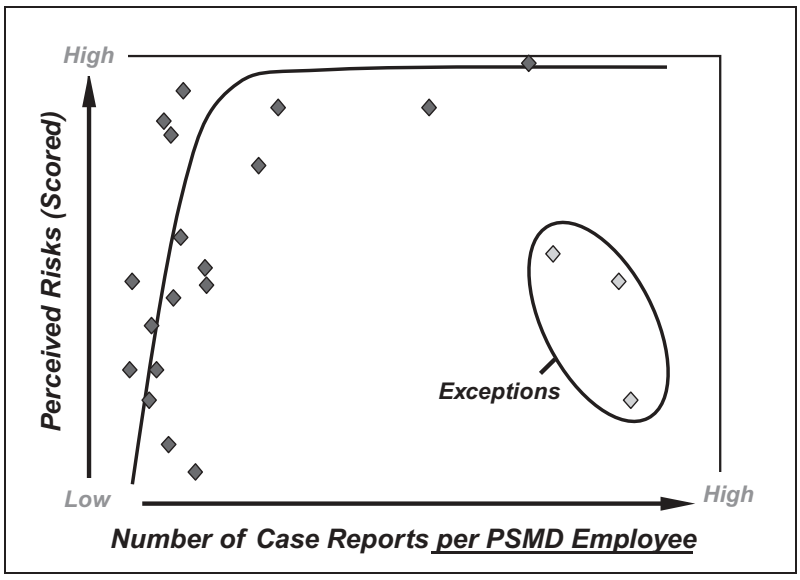

Figure 2: The degree of risk (non-compliance) perceived by participants compared to the number of case reports processed per product safety staff member (including outsourced staff)

WHERE DO WE GO FROM HERE?

Identifying the highest priority improvements requires a clear understanding of your organisation's capabilities – or lack thereof. Any sincere effort to significantly improve PV operations requires an understanding of one's current level of productivity (ie the number of case reports handled per product safety staff) and rigour in managing PV. No participant reported both high levels of productivity and rigour in their PV practices. Rather, participants fell into three primary groups (Figure 3):

- (A) those who must improve productivity while maintaining their level of PV;
- (B) those faced with the challenge of increasing both productivity and their level of rigour in PV; and
- (C) those who must improve their level of rigour in PV while maintaining productivity.

Interestingly enough, those in Group A were primarily European and Japanese firms operating globally while those in Group C were primarily of North American companies. Group B comprises Japanese companies operating solely in Japan, where they are not exposed to the same rigour as their Western counterparts. Clearly, firms in Group A (high rigour, low productivity) face a different challenge from those in Group C (lower rigour, high productivity).

The framework for assessing one's strength and weaknesses, however, is the

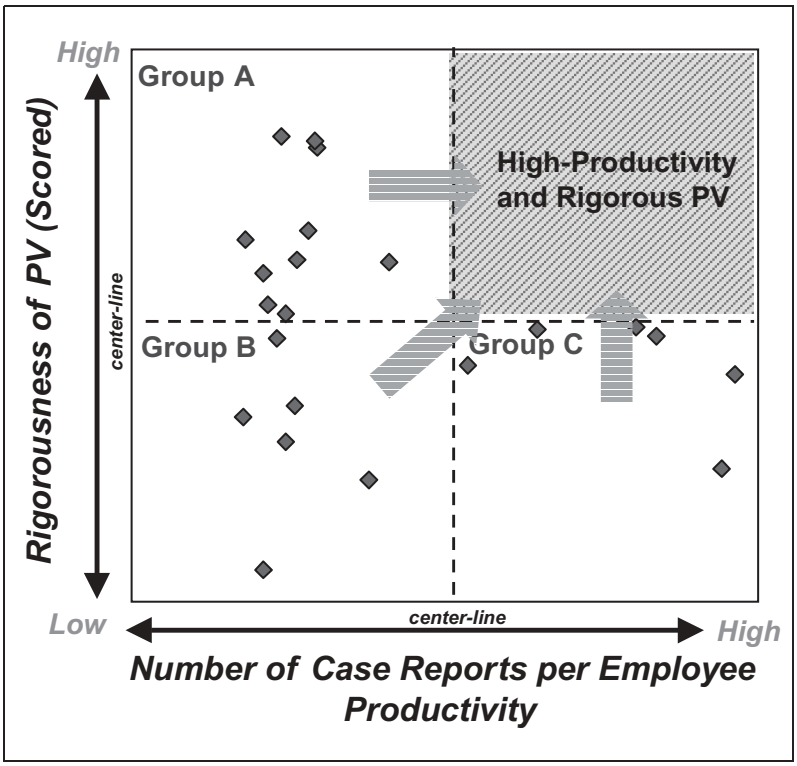

Figure 3: The level of rigorousness of a firm's PV practices compared with the number of case reports processed per product safety staff member (including outsourced staff)

same. Product safety managers, with support from senior management, must make strategic improvements among the four key areas of operations (Figure 4): (1) Processes and procedures, (2) Information technology, (3) Organisation and decision-making and (4) Performance measurements.

Within each area, key questions should be addressed, such as:

- **Processes/procedures**: Do you have well-documented, centralised, efficient, scalable processes that are standardised to promote effective AE case report tracking?

- **Information technology**: Do you have a single, validated safety database for both clinical and spontaneous reporting with E2B functionality (electronic transmission of safety data results) and real-time tracking; single, standardised, semi-automatic MedDRA (the Medical Dictionary for Regulatory Activities) coding dictionary?

- **Organisation/decision-making**: Do you have a centrally managed PV department, strong communication linkage with regulatory and other departments; fully aligned skill sets; documented, integrated, continuous training programmes and modules; flexible resources and effective workload management?

- **Performance measurements**: Do you utilise metrics to proactively identify improvements; continuous monitoring of critical metrics in 'real time' to balance workloads, ensure on-time reporting; average reporting precedes agency deadline and timeline for business partners?

Interestingly, significant differences were reported by survey participants in each of these fundamental areas of operation.

Processes/procedures

The medical review of case reports represents one key process that can be used to both improve the level of rigour, as well as operational efficiency. A critical practice, the medical review of case reports (eg seriousness, expectedness), seems to vary greatly among participants, based on the percentage of incoming case reports that receive a medical review versus the percentage of agency reports receiving a medical review.

Surprisingly, over half the survey participants indicated that both a low number of case reports (the reportability assessment) (eg 5 per cent) and agency reports (eg 8 per cent) actually receive a medical review by a physician or trained designate. From a risk standpoint, they may not be able to ensure that potential medical issues have been recognised by the company. On the other extreme, only 24 per cent of participants indicated that *all* reportability assessments *and* regulatory agency reports receive a medical review. Given the large number of case reports

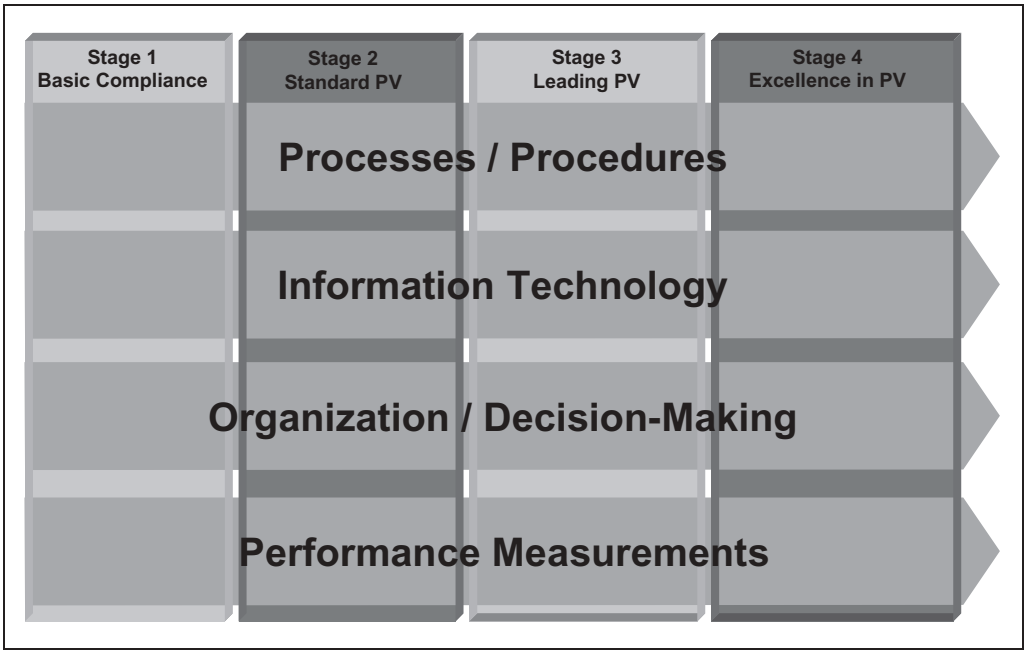

Figure 4: A staged business process maturity model for excellence in PV

that firms typically handle, only firms with unusually large staff or unusually small numbers of reports might afford the high utilisation of the skilled resources required to medically review every report.

Some firms, though, have taken a strategic approach to medical review, treating the reportability assessment as a 'compliance check', while focusing resources on the medical review of regulatory agency reports. These firms indicated that while nearly all agency reports undergo a medical review, only a small percentage of case reports undergo a medical review for the reportability assessment (eg 10 per cent). These firms suggest that there may be a more strategic approach to the utilisation of physicians and medical designates, highly prized resources within a clinical research organisation.

Information technology

In order to effectively handle a reported adverse event, the information technology that a firm selects often imposes predefined work process on product safety. While participants reported dramatically different times for case report handling and reporting depending on which system they used, there was no discernible correlation between a particular system and a level of rigour or efficiency.

According to participants, AE systems meet their expectations for data quality and regulatory submissions, but fail to meet their expectations for cycle-time reduction or user efficiency, requiring significantly more resources to process data and generate reports (Figure 5). Viewed another way, the system can satisfy a company's need to store safety data and report electronically to regulatory authorities, but cannot help management drive significant improvements in efficiency; conversely, the system may reduce overall productivity.

Not surprisingly, participants expressed frustration with their lack of freedom to further configure/customise their system, which was reported as the greatest problem reported by participants with their AE systems. Those participants who deal with foreign affiliates also reported having trouble with the

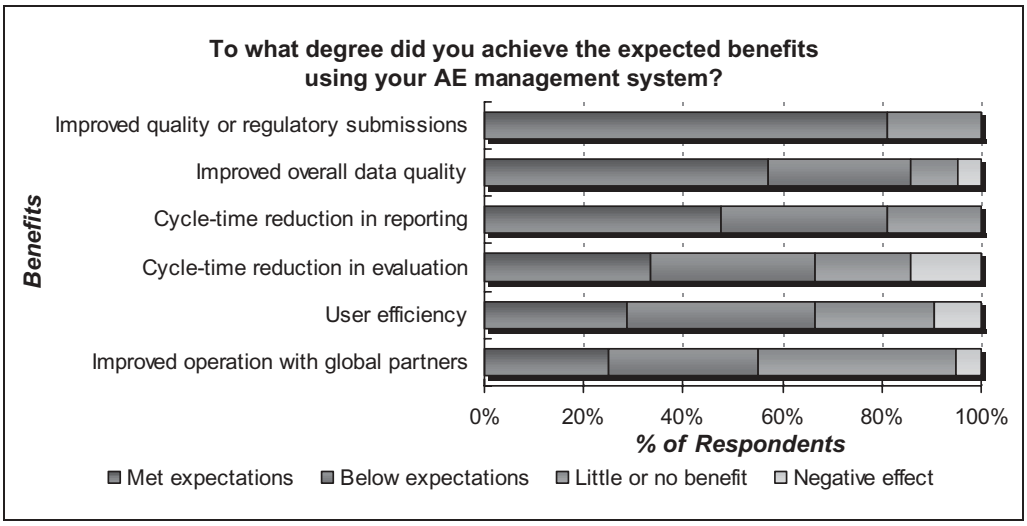

Figure 5: Expected benefits from AE management systems

performance of translation functions and the time required to draft foreign affiliate reports.

Organisation and decision-making

According to survey participants, the biggest organisational challenge facing safety data handling departments today is finding a sufficient number of qualified staff. Consequently, over 90 per cent of participants utilise temporary staff to process post-marketing spontaneous reports. Temporary employees are able to take on product safety's most time-consuming activities (data entry, quality control checks, etc.) without appearing on a department's headcount for full-time employees. Contract employees, on the other hand, are employed under long-term (1–3 years) contracts that preclude benefits as a company employee. Only half the participants (43 per cent) reporting the employment of contract employees, a significantly lower utilisation rate than temporary staff.

Overall, every participant reported the use of either contract employees, temporary staff, or a combination of both for the processing of post-marketed spontaneous reports. 'Cost' and 'temporary increases in workload' represent the two most frequently reported reasons for using outsourced staff (Figure 6), providing further support for their use as additional resources for time-consuming activities in the short- to medium-term.

Performance measurement

As many management pundits would say, 'you get what you measure'. This adage certainly applies for a critical process such as handling product safety data. In the survey, a small percentage of participants (10 per cent) reported the establishment of standardised performance measures in order to enable management to evaluate the effectiveness of their safety data department. Where performance measures and internal reports are in place, they allow management to collect broad measures of performance (eg quality, time, productivity). No doubt, the inability of firms to customize and configure their AE systems (see IT above) inhibits firms' ability to monitor and measure their internal business processes.

Nevertheless, for the 10 per cent of participants who do use standardised performance measures, management has the ability to evaluate the effectiveness of safety data handling. These metrics (Figure 7) can be used to measure and monitor the time required to complete major steps in the process or the time

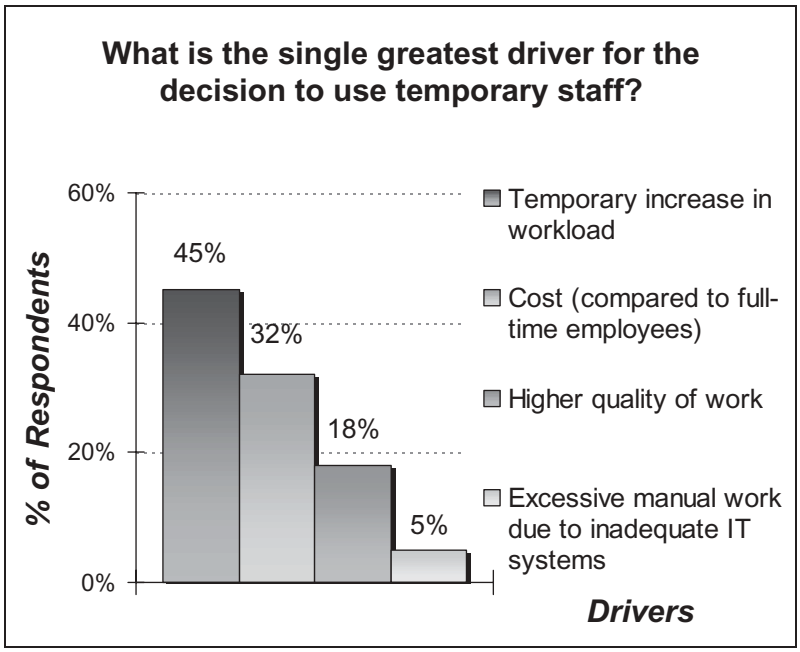

Figure 6: The use of temporary staff

required to complete reportability assessments and reports, both for the FDA and business partners (jointly marketed or licensed drugs require the sharing of reported AE information among each other). Performance reports, can be regularly collected internally (on a daily, weekly, monthly or annual basis) in order to monitor how well your staff is processing cases.

EFFICIENT AND EFFECTIVE PRODUCT SAFETY IS RISK MITIGATION

The ultimate goal for any firm's product safety department is to understand and monitor the safety profiles of their products in order to minimise or prevent the occurrence of adverse events (eg identifying potential at-risk populations, drug–drug combinations, etc.). This represents a challenging task, one that can consume a large amount of resources if product safety is to effectively identify signals and minimise 'unexpected' adverse events from occurring. Furthermore, effective risk management is essential to minimise exposure to regulatory and public claims of negligence and unwanted legal actions.

Given the trends identified previously, firms must strive for greater rigour and productivity in their product safety operations (Figure 8). Focusing too much attention on productivity can result in poor data quality, missed signals and late

Performance Metrics		Performance Reports
Efficiency / Productivity	Time required to complete data entry of case reports	List of reportable cases that have not yet been reported to the FDA or your business partner (not past the due date)
	Time required to complete the reportability assessment of case reports (following data entry)	List of any cases that were reported late to the FDA or your business partner
	Time required to create an FDA or business partner report	List of any cases that are currently overdue to the FDA or your business partner
	Number of case reports completed in a certain time	List of any reports that have not yet been assigned to an individual for assessment
Quality	Number of corrections to case reports	
	Number of acknowledgement errors received	

Figure 7: Performance metrics and reports

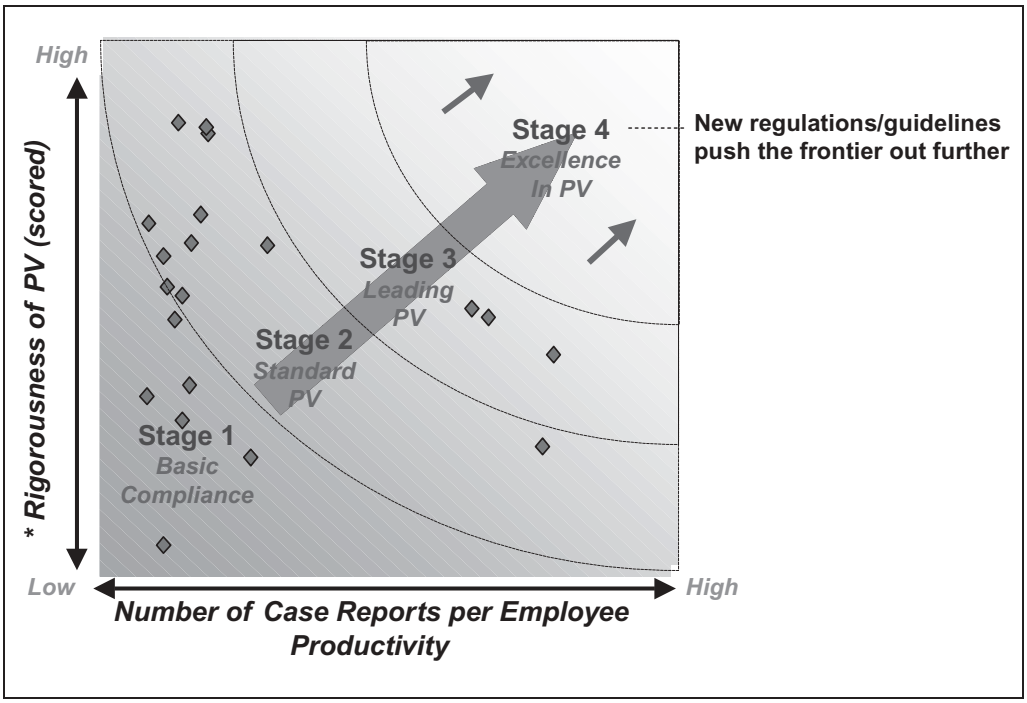

Figure 8: The level of rigorousness of a firm's PV practices compared with the number of case reports processed per product safety staff member (including outsourced staff)

reporting. At the same time, too much focus on rigour can result in excessive headcount struggling to maintain inefficient, redundant processes. Both of these scenarios limit a firm's ability to manage product safety or PV. Excellence in product safety/PV requires management attention to both. As new, more stringent regulations increase pressure on these organisations, the frontier for excellence will continue to move further out, requiring continuous improvement from PV operations.

The time-bomb of poor product safety can be diffused only with efficient, effective PV. This burden, though, is becoming increasingly heavy. As such, senior management must devise improvement strategies in order to balance efficiency with rigorousness. Product safety departments will need to develop innovative solutions to improve their processes/procedures, IT, organisation/decision-making and performance measurements. In addressing the product safety challenge, top management needs to focus a greater amount of its attention on product safety – not just as a supporting business activity, but as a core element of a comprehensive solution for the market.

References and notes

1. World Health Organization (2002), 'The importance of pharmacovigilance: Safety monitoring of medicinal products', WHO, Geneva, Switzerland, p. 7.
2. Long, D. (2006), 'Documents show Guidant failed to alert docs to malfunctions', *Med. Device Daily*, Vol. 10(110), p 1.
3. US FDA, 'CDER: Premarketing Risk Assessment' (URL: http://www.fda.gov/cder/meeting/riskManageI.htm [accessed 12th June, 2006]).
4. For examples see ICH Guideline for Clinical Safety Data Management (E2A) and ICH Guideline for Good Clinical Practice (E6).
5. Lumpkin, M. (2005), 'CIOMS V: Pragmatic approaches to some current challenges in pharmacovigilance (URL: http://www.fda.gov/cder/present/dia-nice2000/dianice2/[accessed 12th June, 2006]).
6. For examples see 21 Code of Federal Regulations 310.305 Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications; 21

Code of Federal Regulations 312.32 IND safety reports; 21 Code of Federal Regulations 312.33 Annual reports; 21 Code of Federal Regulations 314.80 Postmarketing reporting of adverse drug experiences (Pharmaceutical Products); 21 Code of Federal Regulations 600.80 Postmarketing reporting of adverse experiences. (Biological Products); Expedited Safety Reporting Requirements for Human Drug and Biological Products (FDA Final Rule), *Federal Register*, Vol. 62, No. 194, 7th October, 1997.

7. For examples see The Pharmaceutical Affairs Law, Article 64–5-2, Paragraph 1, No. 1, 1–1, 1–2, 1–3 and No. 2, 2–1, 2–2, 2–3 (27th March, 1997); The Pharmaceutical Affairs Law, Article 66–7, Paragraph 1, No. 1, 1–1, 1–2 and No. 2, 2–1, 2–2, 2–3, 2–4 (27th March, 1997); The Pharmaceutical Affairs Law, Article 77–4-2 (27th March, 1997); The Pharmaceutical Affairs Law, Article 80–2 (27th March, 1997).

8. 21 CFR §314.80(a).