Pharmacovigilance’s Growing Influence

Pharmacovigilance will always be about protecting patients, but the discipline is rapidly evolving into something greater than regulatory compliance. Increasingly, pharmacovigilance has a central role to play in product development and product management activities and in influencing portfolio decisions. With that in mind, ProductLife Group recently posed some searching questions to a cross-section of life sciences industry leaders, who are observing and being affected by changes in their daily roles. Here are six of the main trends they identified.

The Growing Emphasis on Quality
In recent years, inspections by health authorities across Europe have taken issue with serious deficiencies in a number of companies’ pharmacovigilance quality systems. As a result, organisations have had to invest more resources in their safety departments and systems. "Quality is the priority. You must have good-quality data, and inspections are increasing," said Julia Appelskog, qualified person for pharmacovigilance (QPPV) and head of pharmacovigilance at Bluefish Pharmaceuticals. But there’s an upside. “Although this creates challenges, it also helps us achieve a better system and better processes because business leaders understand now how important pharmacovigilance is and are allocating more resources.”

There’s a balance to be struck, however. “With more audits than ever before, it can feel as though we’re feeding a hungry compliance animal rather than focusing on patient safety,” said David Ferguson, head of international pharmacovigilance at Shire Pharmaceuticals. The worry is that all of this regulatory rigour could detract from “the nuts and bolts of patient safety data,” he suggested.

Breaking down silos and establishing better cross-functional collaboration between pharmacovigilance and quality operations has also become of greater concern at many companies. “There are expectations by inspectors that there should be a good quality system and a good pharmacovigilance system and that the processes should be aligned,” said Lesia Tontsak, director of pharmacovigilance at Allergan. When it comes to having to align and standardise activities globally, including those handled by affiliates, the challenge multiplies, she said.

That includes managers at affiliates, where there must also be processes in place to ensure that any safety information gets communicated into the central function. Overall accountability ultimately rests with pharmacovigilance at headquarters, however. A strong and connected relationship between pharmacovigilance and quality is also essential for maintaining a high-level perspective, according to Mariska Kooijmans, head of drug safety and pharmacovigilance international and EU QPPV at Amicus Therapeutics, who works closely with the head of pharmacovigilance quality. “This enables us to map the systems and make sure there is integration,” she said. “The quality group has to be part of pharmacovigilance decision-making and vice versa.”

The question of responsibility for pharmacovigilance becomes more involved as the boundaries blur. Skire’s Ferguson said a pharmacovigilance system can touch almost any department in a pharmaceutical organisation. “One of the biggest challenges has been to create an understanding across the whole organisation that pharmacovigilance is a system for which others have responsibility as well,” he said.

For small companies, the quality requirements can, however, be among the most challenging aspects of pharmacovigilance, according to Laura Dalsasso, regulatory affairs office and pharmacovigilance manager at E-Pharma. The evaluation of a pharmacovigilance system tends to be outsourced, thereby creating its own set of complications “because you have to audit your partners, and if several partners are involved, you have to spend time preparing agreements with each partner,” she said. E-pharma markets only a limited number of packages so that it can avoid a sunset clause, but the company is still required to maintain a full pharmacovigilance system for evaluating the safety data of those products, which is time-consuming and resource-intensive.

Risk-benefit Balancing that puts the Patient at the Centre
A growing emphasis on balancing the risk–benefit ratio requires companies to consider any benefit in terms of what it means to patients, as opposed to a scientific endpoint of efficacy. “It’s about what your drug brings to the party,” said Shire’s Ferguson. “For example, a cholesterol drug might demonstrate that it lowers cholesterol levels, but benefit is about answering such questions as, Do patients live longer? What’s the cost? and, Does your drug work better than others currently out there?” he said.

The risk-benefit profile, too, isn’t static, which adds to the workload. Beyond the point of clinical trials, any new data is almost exclusively safety data, Lesley Wise, managing director of Wise Pharmacovigilance and Risk Management, said. “That means pharmacovigilance or medical safety has to be driving the risk-benefit discussion.” For some products, conditional approval is given with a requirement to conduct post-authorisation efficacy studies and post-authorisation safety studies. “Regulators want drugs on the market; they want innovation,” said Cheryl Key, head of practice PV platform services/principal medic at ProductLife Group. They also have to make sure that what’s authorised is safe for patients.

Pharmacovigilance and its Influencing of Strategic Decisions
The more complete and reliable the picture being developed by pharmacovigilance activities, the greater the value to a business strategically. A clearer view of safety can have a bearing on whether a company should proceed with acquisitions, for instance.

Allergan’s Tontsak said companies are now increasingly bringing in safety experts at the earliest stages of potential acquisitions to help assess target products or companies. “It doesn’t make sense to bring in a product that isn’t safe and will cost in the long run with lawsuits or from pulling the product from the market,” she said.

For that reason, Shire’s Ferguson said he is surprised that pharmacovigilance usually doesn’t automatically have a full seat during the due diligence process. “It’s often assumed it will be all right until you hear it’s not,” he said. “But you’ll never hear that until you go out and ask the question.”

Reimbursement is another area where safety must play a more prominent role. Kooijmans at Amicus said that ensuring reimbursement for a product requires a focus on health economics,
including risk-benefit data, during a drug’s development plan. At Bluefish Pharmaceuticals, senior management seeks advice from pharmacovigilance before deciding to initiate a new product registration. “We’re asked what the implications will be for risk minimisation activities, whether a post-authorisation safety study might be required, and what the potential costs are,” Appelskog said.

Superior Safety that Offers Competitive Advantage

One commercially interesting trend is the potential to use safety as a differentiator against other brands.

Amicus’s Kooijmans used to work at Biogen, which recently had its first product approved for an orphan indication (nusinersen as a treatment for spinal muscular atrophy) because its safety profile was better than that of the product that had been approved earlier, which led to a superior risk-benefit profile. Her current company, meanwhile, has been granted approval for an oral drug for treating Fabry disease, Galafold, which was found to be easier to tolerate and had fewer side-effects, compared with already approved and marketed IV treatments.

“A product like that diminishes the risk side but also assists on the benefit side because the patient doesn’t have to go to the hospital to get an IV and can instead simply take a pill,” she said. “For companies focused on me-too products, having a safety focus would be a good approach because if you aren’t developing targeted, personalised medicine, you have to think about the two other areas to make your drugs stand out: better or safer or both.”

Wise said that when a company is looking to differentiate on safety, those activities will be part of the clinical development plan, which is usually managed by clinical rather than safety – particularly at smaller or midsize companies. In larger companies, medical safety – as distinct from the operational aspects of pharmacovigilance – is firmly embedded in clinical development. “Using safety as a differentiator is an argument in the risk-benefit of a product,” Wise said. “If your risk-benefit is positive because your risks are lower but the benefits are the same, that’s an important thing to know when you’re going into a risk-benefit discussion.”

Global Pharmacovigilance Becoming More Complex

The European Medicine Agency’s (EMA’s) good pharmacovigilance practice is being watched closely by other regional markets, which are likely to adopt many of the same principles in time but with their own emphases and tweaks, which creates more work for global players. Bluefish’s Appelskog points out the importance of good and ongoing dialogue, which is well established at EMA. “I’m concerned that with Eurasia and the Middle East, good pharmacovigilance practice will be brought in without discussion or willingness to adapt,” she said. “A lot still has to happen to agree on standards.”

Other complexities include the requirement to have a responsible person for pharmacovigilance, even in markets where a product might not be marketed. “Shire works in the area of rare diseases, and it might be we don’t even have a single patient in a small country such as Cyprus, but because we have Europe-wide marketing authorisation that is applicable to all European Union member states, we’re legally obliged to have a responsible person for pharmacovigilance in that market,” Ferguson said.

One potentially troubling development is that the QPPV, which was traditionally a European role, is now becoming a requirement in more markets, Wise said. “That raises questions about who that QPPV is going to be, because on one hand, few QPPVs would be willing to take responsibility in markets outside Europe, given the legal liabilities, but because there’s only one pharmacovigilance system, it doesn’t make sense for a global company to have multiple QPPVs,” she said.

From a wider global safety perspective, PLG’s Key said it is important to have a safety-monitoring system in place when launching products in emerging markets. For example, one company that conducted clinical studies in Africa into an antimalarial drug struggled to collect patient information from even the more advanced sites. PLG’s Anelli added, “You can imagine how impossible it will be when it comes to getting information from patients in the field.”

Roles and Skills that may need Redefining

Finally, Wise said, pharmacovigilance leaders must develop the business skills needed to play full roles in clinical risk-benefit decision-making and the strategic skills to match the responsibility of driving the evolution of a pharmacovigilance department that is a moulded part of the R&D organisation.

The management of affiliates has become another priority for pharmacovigilance heads, says Shire’s Ferguson. In the past, in the hiring of a safety person in an emerging market, those roles would have focused on operational activities, such as receiving adverse events, doing the translation, entering the data into the database, and ensuring the events were reported to the authorities on time. “Now I’ve brought those operational activities into the centre and hired third parties to manage them,” Ferguson said. “The skill set I need from someone now at the affiliate has changed: I look for people with pharmacovigilance and quality experience. I need people who can ensure compliance, who know about the regulations and how they affect everything we do.”

The role of the QPPV has also evolved: today quality assurance is the primary concern, Amicus’s Kooijmans said. “When I started out in a QPPV role, the focus was more on discussing the minimal safety side with regulators. Now it’s much more on being ready for inspections, making sure your system works, and keeping the pharmacovigilance system master file up-to-date. That attracts different people to pharmacovigilance,” she said. “Equally, heads of safety require more of a business background because of the growing importance of health economics, so there’s a shift from the medical side towards a different breed of drug safety people.”

With so many changes taking place, the QPPV and heads of pharmacovigilance have to be able to apply innovative thinking to solutions, Appelskog said. That in turn requires more collaboration, she concluded, pointing to the stakeholder platform introduced by EMA that facilitates intraorganisational discussion.

As 2017 gets into its stride, the intensifying focus on pharmacovigilance will make for an interesting study.

Cheryl Key

Cheryl is the Head of practice PV platform services/principal medic at Product-Life Group. Cheryl has more than 15 years of drug safety experience in working with pharmaceutical and biotech companies, for contract research organisations, and for regulatory authorities. Cheryl has a medical degree from Charing Cross and Westminster Medical School, Membership of the Royal College of General Practitioners, a diploma in pharmaceutical medicine and Membership of the Faculty of Pharmaceutical Medicine and is on the Specialist Register at the General Medical Council for Pharmaceutical Medicine.

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