Commentaries

Pharmacovigilance in Crisis: Drug Safety at a Crossroads

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ABSTRACT

Pharmacovigilance (PV) is under unprecedented stress from fundamental changes in a booming pharmaceutical industry, from the challenges of creating and maintaining an increasingly complex PV system in a globally diverse regulatory environment, and from unpredicted consequences of historical PV cost-reduction strategies. At the same time, talent availability lags demand, and many PV professionals may no longer be finding personal fulfillment in their careers. The situation creates risks for companies. Advantages and disadvantages of potential strategies to address this increasing problem at a corporate and industry level and in collaboration with regulatory agencies are discussed, as well as opportunities to adopt new technologies, including artificial intelligence and machine-learning to automate pharmacovigilance operations. These approaches would address burdensome and wasteful effort assuring regulatory compliance and free up resources to support the original mission of PV as an important public health activity and to reinvest in the development of new drugs. (*Clin Ther.* 2018;40:790–797)

Key words: pharmacovigilance, outsourcing, automation, artificial intelligence.

THE CHANGING PHARMACEUTICAL INDUSTRY LANDSCAPE

A fundamental shift in the drug development business has occurred in the last 2 decades. A proliferation of start-up companies has been fueled by venture capital, the realization of the scientific promise of genomics and biotechnology, and an opportunity to fill a productivity gap within Big Pharma. It is now a common model that drugs are discovered and researched by a small biotechnology company and bought, with or without the company itself, by a larger company: although the top 10 selling biotechnology products in 2017 are now marketed by a Big Pharma company, most had their origin at a start-up, small company or institute, and most of the remainder were discovered by a small company that subsequently grew big because of the product[1] (Table). The October 2017 report of the Massachusetts Biotechnology Council, MassBio,[2] identifies >425 pharmaceutical companies in Boston, Massachusetts, alone, and >66,000 employees in Massachusetts, a 28% growth in 10 years. With similar 10-year growth in Florida (291%), New York (135%), California (79%), New Jersey (64%), and Washington (51%), the start-up pharmaceutical industry is booming. Today's companies pursue treatments for hard-to-treat, rare diseases, often afflicting primarily children: between 2005 and 2015 the number of approvals of products for orphan indications more than doubled in the United States and the European Union.[3] These companies have become successful at bringing forward potential new medicines. The MassBio report recorded 367 products in Phase II, 98 in Phase III, and 20 filed, among companies in the Northeastern United States, a mean of 1 per company. Given this pace and productivity, a gap may be opening up between the talent demand of an estimated 500 departments of PV in the area, and the supply of available, experienced pharmacovigilance (PV) personnel.

PV is defined by the World Health Organization as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem.[4] Across the global community of jurisdictions, drug regulations in

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Table. Top 10 biotechnology drugs by global sales in 2017.

Product	Discovering Organizations	Marketing Organizations
Adalimumab	BASF and Cambridge Antibody Technology	Abbvie
Infliximab	Centocor	Janssen and Merck
Rituximab	IDEC	Biogen and Roche/Genentech
Etanercept	Immunex	Pfizer, Amgen, and Takeda
Insulin glargine	Sanofi-Aventis	Sanofi
Bevacizumab	Genentech	Roche
Trastuzumab	Genentech-UCLA	Roche
Pegfilgrastim	Amgen	Amgen
Ranibizumab	Genentech	Genentech and Novartis
Interferon beta-1a	Fraunhofer Institute and CinnaGen	Biogen and Merck

place for decades have governed the PV obligations of drug developers and marketing authorization holders to collect and analyze reports of suspected adverse reactions. Although this highly regulated environment is mature, it continues to evolve as new potential sources of PV data emerge because of digital health and the internet and as new regulations are implemented. The company's PV system must be able to handle and interpret an increasing stream of high-volume, low-quality information that is often incomplete and unstructured, sometimes based on medical opinion rather than scientific fact, and collected from multiple, diverse sources; then prepared to satisfy differing regulatory, company, and other requirements globally; and finally submitted within tight timeframes. PV requires meticulous attention to detail and consistency, with data necessarily housed and analyzed in complex systems that must continually evolve to keep up with changing regulatory requirements. PV is a high-pressure environment that requires expertise to identify signals of new hazards to patients and to prevent false signals triggering alarm.

For a start-up company preparing a marketing authorization application and launch, possibly internationally, there is little time to address PV system deficiencies. The urgency is exemplified by the observation that serious tolerability concerns are commonly present at the time of approval of orphan drugs,[5] making postapproval risk management activities and a Risk Evaluation Management Strategy probable. However, at the same time, hidden weaknesses in adverse event (AE) data management are liable to appear. These can be due to operational vulnerabilities. An example is the use of multiple databases at different clinical trial contract research organizations (CROs) that may not be mutually compatible and may have operated to differing standards and conventions but must support data pooling, subgroup analysis, and database reconciliation. Other problems include loss of institutional knowledge because of staff turnover before effective record taking and archival have been put in place and manual work practices that are not scalable to cope with increased serious adverse event (SAE) volume through late-stage drug development. PV after approval brings new data handling requirements, a probable large increase in case volume, global diversity, public awareness, and heightened scrutiny by inspectorates. Bringing a rudimentary PV system up to acceptable standards presents a major challenge and requires experience. Preparations must start long before the New Drug Application (NDA) or Marketing Authorization Application (MAA) is submitted.

DEMAND IS OUTSTRIPPING THE AVAILABILITY OF EXPERIENCED PV TALENT

It is an increasingly dire storyline in the last year that senior company PV positions are unfilled: the talent pool was sized to match the demands of the original, Big Pharma model. Although data on the number of vacant PV jobs are not readily available, a search on LinkedIn for director-level PV positions in the United States at the end of November 2017 returned 266 vacancies of which 61 were in the Greater Boston area. Some advertisements for heads of PV departments require a medical degree and specific

therapeutic area expertise gained over many years. It is unrealistic to expect that such PV leaders are plentiful. The last few years have witnessed a buyer's market in PV jobs, constrained only by willingness of candidates to relocate for work. Career advancement can be achieved by moving from one company to another, but moving frequently among companies interferes with experiential learning, and companies risk filling key PV positions with professionals who have not acquired substantive PV experience. Companies may consider hiring contractors and CROs and by offering PV positions as a 100% remote job. Relying on remote leadership can be successful up to a point but may leave a gap when PV inspectors call and underestimates the complexity of overseeing a well-functioning PV system. In such an environment, recruitment takes on new importance but may be slow or unsuccessful, jeopardizing the NDA and MAA. The expansion in numbers of companies together with a lagging PV talent pool create risk for the company and potential delay in bringing new medicines to patients.

FAILURE TO INVEST IN PHARMACOVIGILANCE PRESENTS RISKS

Lack of investment in PV presents several risks. First, approval of the MAA and NDA may be at risk if key PV elements are missing or substandard (eg, the PV System Master File, signal detection and management procedures, risk management planning, or integrated safety profile summaries and analyses). Second, the labeling (Summary of Product Characteristics or US Prescribing Information) that is approved may contain unnecessary or inappropriate safety profile content, affecting commercial success and providing inaccurate information for users. Third, different regulations apply after approval, and compliance with required reporting may be low, risking inspection findings, damage to company reputation and market value, or enforcement action.

The risks can be compounded by aggressive commercial strategies and efforts to enhance patient access: patient support programs (PSPs), market research, and related arrangements can generate large numbers of adverse events.

The PV system must be continuously updated to keep abreast of changes in regulatory requirements. In 2017, the European Medicines Agency (EMA) introduced new expectations for Eudravigilance access for signal detection.[6] Industry is preparing for the exchange of adverse drug reaction (ADR) reports with agencies through electronic gateways to a new standard (E2B[R3]).[7,8] In the last few years, the US Food and Drug Administration (FDA) reinforced that sponsors should submit ADRs rather than adverse events from clinical trials.[9,10] Both the EMA and FDA are engaged in bringing in the patient perspective and exploring the use of real-world data to inform risk-benefit evaluation for decision making[11–15] for which they are applying different frameworks in the European Union and the United States.[16,17] Finally, 2 new guidelines and 10 revisions to Good Pharmacovigilance Practice (GVP) modules became effective in 2017.[18] Lack of international harmonization of PV requirements is impactful. Monthly and quarterly joint FDA-EMA meetings focus on drug tolerability issues not processes.[19] In the 24 years since the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) published the first of the PV guidelines (ICHE2A to ICHE2F), requirements have diverged regionally, for example, because of updating of GVP and the FDA Final Rule, and new issues have emerged that would benefit from a common international standard, such as adverse events at social media sites or PSPs.

The PV system needs to be responsive to new AE information at all times. Publication of signals under review by regulatory agencies[20,21] might create adverse publicity even though the signal might be spurious or the health hazard easily managed. Biotechnological ingenuity that exploits advances in implantable medical devices, wearable technology, combination products, companion diagnostics, nanotechnology, and big data[3,22] may create challenges if a corresponding regulatory framework for handling PV is not yet in place. Societal pressure to accelerate and expand access to developmental products, including cell- and tissue-based products, through right-to-try laws,[23] the 21st Century Cures Act,[24] and recent initiatives in drug development, such as the Innovative Medicines Initiative,[25] may hinder a PV department's ability to respond to signals if preapproval clinical data have been collected to new standards and in fewer patients.

At the same time, agency inspectorates expect all companies to be conversant and compliant with the latest requirements, to have close oversight of service

providers and PSPs, to conduct signal evaluation and risk management and update labeling quickly, and to process all expeditable cases on time, for which achieving 98% to 99% is reportedly no longer adequate. Company PV systems are often centralized, yet inspections are conducted independently by the EMA, a national EU agency, and the FDA, each inspecting against different regulations. Common perceptions are that inspectors are not PV experts and a high turnover among inspectors contributes to inconsistent findings over time or from company to company.

UNINTENDED CONSEQUENCES OF MANAGING PV AS A COST CENTER

Labeling the PV department as a cost center in the early years of this century led Big Pharma to outsource much of the function to a location perceived to be cost-effective, commonly India. Introduction of an in-house risk management function staffed mostly by medically trained professionals introduced organizational separation between assessment of individual AE reports, and analysis of AE reports in aggregate. A consequence has been both a reduction and a fundamental change in the nature of the US PV talent pool. Managers interfacing with remote project coordinators across time zones, languages, and cultures replaced individuals who had performed PV operations in the United States. Ironically, after the transitions occurred, the original goal of reducing PV cost was undermined by the increasing cost of staff in (formerly) low-cost locations because of competition for local talent and by inherent inefficiencies of a remote workforce with little decision-making authority.

POTENTIAL STRATEGIES TO ADDRESS THE TALENT SHORTFALL

Rebuilding a depleted talent pool to satisfy the needs of the booming start-up industry presents several challenges. PV may have become less desirable as a career, lacking the glamor of research and development and the patient connection of medical affairs. Unpredictable, high peaks of urgent work, the need to satisfy changing regulatory requirements while maintaining constant inspection readiness, and the expectation of 100% compliance as a standard goal have added stress. Management can struggle to recognize and reward achievements in the absence of common, meaningful measures of success in an environment where identifying a potential safety hazard may be perceived as negative, and inspectorates focus on regulatory compliance rather than human health.

Attracting PV staff away from another company by offering increased compensation simply cannibalizes the talent pool and results in wage escalation. Enlarging the talent pool requires investment in education, training, and development, ideally through partnerships among pharmaceutical companies, educational institutes, professional bodies, and regulatory agencies, supported by fellowships, other financial support, and academic credentialing. Acknowledgement of the problem as industry-wide could support long-term training strategies under ownership by pan-industry representative bodies. Developing incumbents is a near-term, focused strategy that depends on internal mobility of employees and access to experienced trainers. It is feasible in larger companies, where providing development opportunities can be one component of a company staff retention strategy. The risk remains that the professionals, once trained, could be recruited by another company. Small companies that lack time or resource for a training program could instead leverage a seasoned PV consultant part or full time to act as safety department leader or adviser, under whose guidance the department can mature. This offers advantages of cost containment, engagement of junior staff, flexibility to adapt to changing corporate goals, and access to a network of external PV professionals.

ADVANTAGES AND DANGERS OF RELYING ON OUTSOURCED PV SERVICE PROVIDERS

Many companies, particularly start-ups and small companies, outsource the processing of SAE reports. Some also outsource signal detection and risk management. Outsourcing strategies seek economies of scale, global reach, and flexibility and may circumvent the need to hire PV expertise.

However, the symbiotic relationship between a CRO and a pharmaceutical company may be influenced by different business objectives. Success can be limited by a fragmented outsourcing strategy.[26] To deliver a cost-efficient PV service, CROs may operate in low-cost locations, where staff must be trained to the company's standards.[27] An oversight plan, regular auditing, and dedicated resource at both parties are

needed for an effective partnership,[28] with special attention at times of corporate change, a new procedure or staff turnover. Big Pharma PV staff can direct the CRO's processes and troubleshoot data management problems, but the same model may be less suitable for a small pharmaceutical company that lacks its own internal PV expertise. In such a relationship, the company can benefit from the CRO's experience of performing the same function for other client companies: the CRO may have expertise in PV gray areas, for example, handling adverse events detected in PSPs, during market research, or in clinical trials that require reporting to agencies in multiple regions. However, reliance on the CRO for decision making may be perceived to conflict with the company's retained accountability for PV. Inexperienced staff may misdirect the CRO, resulting in a detrimental effect on the PV system, and a future operational crisis may germinate undetected. Fixing the system can be resource intensive. Confusion due to inconsistent standards may lead to progressively greater dependence on the company's staff for decision making, eventually counteracting the cost-benefit of outsourcing. A fully outsourced PV system may not be suitable for a small pharmaceutical company handling a low to moderate volume of SAEs unless the CRO is also small and staff are matched in seniority to enable close collaboration.

COST AND PRODUCTIVITY OF PV

Gathering and organizing ADR reports is expensive. Simply putting in place arrangements to comply with regulatory reporting requirements for a Phase I program can cost ≥$100,000, even if no SAE occurs. The global cost of PV has been projected to be $6.1 billion in 2020,[29] an increase of $1 billion compared with the estimated amount spent in 2019. For context, the out-of-pocket cost of each new medicine brought to market was estimated by Tuft's University Center for Study of Drug Development in 2016 to be $1.4 billion.[30]

Although the necessity of a company department accountable for PV is unquestionable, its value is not measured with a metric that reflects the public health objective of PV. The World Health Organization recommends counting numbers of deaths and hospitalizations attributable to ADRs,[31] which may be appropriate in assessing the national health authority's PV activities but is less practical for a pharmaceutical company. The GVP module XVI anticipates that companies will measure the effectiveness of product risk mitigation activities,[32] although guidance on how to do this is only just emerging, with the ongoing collaborative European Network of Centres for Pharmacoepidemiology and Pharmacovigilance study on use of codeine, CODEMISUSED, being promoted as a pilot study.[33] For many years, compliance with regulatory reporting timelines has been the routine PV metric, reflecting regulators' expectations: the most recent Medicines and Healthcare Products Regulatory Agency annual report of inspections states their goal is "to examine compliance with existing EU and national PV regulations and guidelines."[34] However, among 6 critical findings and a mean of >4 major findings per inspection, reported from 37 inspections, none reported evidence of drug-induced harm.

Despite the enormous investment in PV, the yield of signals is low. The processing by Roche-Genentech of 80,000 adverse events in PSPs, including 15,000 deaths, failed to identify any new information affecting the safety profile.[35] At typical case processing costs, the likely cost of processing 80,000 cases would have been tens of millions of dollars. The lack of demonstrable correlation between time-bound reporting requirements and a benefit on public health is indicated by the observation that although the speed of identifying possible serious ADRs has increased progressively over time, the speed with which products have subsequently been withdrawn from the market as a result of a health hazard has not consistently changed.[36,37]

The low yield of new safety profile information from processing individual SAE reports is predictable. They often contain little more than the 4 minimum elements that validate a report: identifiable reporter and patient, suspect drug, and adverse event. Company personnel and CROs may conduct follow-up on tens or hundreds of thousands of SAEs each year, frequently with an uninformative response. Data are sometimes collected and processed with the primary objective of completing specific fields in the SAE database so the case can be submitted through the electronic E2B gateway to an agency. The FDA alone received 1.8 million adverse event reports in 2017.[38] However, despite well-known exceptions (eg, designated medical events, such as Stevens-Johnson

syndrome, and targeted medical events, such as Achilles tendon rupture), an individual case report rarely establishes causality, especially if it is a report of a common event with significant background prevalence in the treated population. FDA guidance on conducting a clinical safety review of a NDA considers such individual case causality assessments unnecessary and unhelpful,[39] yet it remains an expectation that every SAE undergoes a causality assessment.

Processing and interpreting a large and increasing volume of AE reports, each containing tens or hundreds of data points, precisely and quickly in an environment with little margin for error is not sustainable with existing procedures. The escalating cost of PV is disproportionate to its value and warrants reexamination. Resource required to comply with regulatory reporting requirements consumes precious, limited medical resources that could be deployed for signal identification and evaluation, risk management activities, or development of new medicines.

A BRIGHTER FUTURE: AUTOMATION WITHIN PV TO ELIMINATE OPERATIONAL INEFFICIENCIES

The process of collecting and processing SAEs has hardly changed in several decades. Individual case reports received by telephone, mail, fax, or e-mail are manually transcribed onto a SAE database, requiring recruitment, retention, training, and supervision of personnel, creation and maintenance of a quality management system, and continuous preparedness for inspections. Complexity is high, as is the risk of errors.

These limitations would be avoided by continuous, digitized, automated data management within a computerized system that leverages artificial intelligence, machine learning, and blockchain. Collection of all relevant information from the reporter at the outset could be supported by an artificial intelligence interface, reducing follow-up. Machine learning is an enabling technology in situations where it is not feasible to write an algorithm capable of handling every permutation and combination of data possible in a dataset, such as the processing of individual case AE reports: a computer can be trained to recognize, parse, and enter into the safety database all adverse event information presented to it in report forms and unstructured sources, such as e-mail. Artificial intelligence and machine learning could also enhance signal detection and management, for example, through the ability to detect disproportionate correlations among multidrug combinations, events, and SAE characteristics. Blockchain could assure data integrity during its transmission, reducing the need for quality control.

Only the medical reviewer's assessment of causality will test the adoption of these technologies. However, rejecting or imputing a causal relationship between drug and adverse event is based on probabilistic reasoning and pattern recognition that are subject to interreviewer variability because of different training, knowledge, experience, biases, and heuristics. Application of artificial intelligence could bring consistency and efficiency.[40,41] The IBM Watson artificial intelligence computer interprets clinical information and identifies treatment options consistently[42] and with the use of AI accelerated the diagnosis of a rare disease from weeks to minutes.[43,44] Quality and completeness of available SAE information are the likely limitations for successful causality assessment by artificial intelligence.

CONCLUSION

The PV profession is under duress. As a career it may have become unattractive and unfulfilling for many people for several reasons, including pressure of work and loss of a meaningful mission that resonates with the aspirations of PV professionals. Without addressing a talent shortfall and reversing the current emphasis on compliance with regulatory requirements, which do not add value to patients or public health, companies will find it increasingly difficult to adequately meet their PV obligations while developing and marketing potential new medicines. Although strategies to close the talent gap can be adopted in the short and medium term, a more substantial benefit will be seen with the development and implementation of automated PV solutions. The resulting efficiencies will address the talent shortfall and enable those working in PV to change focus from data management to a more worthwhile mission of ensuring that patients can use medicines effectively.

CONFLICT OF INTEREST

The author has worked for several pharmaceutical companies previously and is currently a consultant in PV at biotechnology start-up and small pharmaceutical companies. The author has indicated that he has no other conflicts of interest regarding the content of this article.

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