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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;▮:▮▮▮–▮▮▮)

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 place for decades have governed the PV obligations of drug developers and marketing authorization holders

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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

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