mining should be formally evaluated with directed pharmacoepidemiologic studies (e.g., new-user active-comparator cohort study).[5]

In 2017, the FDA released the *Sentinel Initiative: Final Assessment Report*, which outlined how the agency planned to modernize the process of postmarketing drug safety surveillance, including through implementation of TreeScan and other data-mining tools.[16] In Canada, the Drug Safety and Effectiveness Network (established by the Canadian Institutes of Health Research) created CNODES, the Canadian Network for Observational Drug Effect Studies, in 2011, which is able to access data for millions of patients across the country. CNODES now plays an essential role by conducting pharmacoepidemiologic studies in response to requests from Health Canada. A natural extension of this work would be the incorporation of TreeScan or another data-mining technique to advance the current process of pharmacovigilance in Canada with the ultimate goal of preventing adverse events.

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THE "CON" SIDE

It has been suggested that the dawn of pharmacovigilance occurred in 1848, when a young English girl died after undergoing chloroform-induced anesthesia.[1] As a result of this and other anesthetic-related deaths, *The Lancet* established a commission exhorting all doctors to report any deaths associated with anesthesia. Formal systems were established in the United States in 1906, after the *Pure Food and Drug Act* was passed. Its successor, the *Federal Food, Drug, and Cosmetic Act* (1938), ruled that the safety of all drugs should be demonstrated before marketing.

The wake-up call of the thalidomide tragedy occurred in the 1950s, the first example of an effective licensed medicine having widespread, serious adverse effects. First marketed in 1956 in West Germany as a sedative and hypnotic, thalidomide was also strongly promoted to treat nausea in early pregnancy. Ultimately, it was prescribed in 46 countries, including Canada. Somewhat ironically, though, the US Food and Drug Administration (FDA) withheld approval because of a lack of evidence of safety in pregnancy, as identified by Dr Frances Kelsey (a Canadian doctor working for the FDA as a pharmacist).[2] In 1959, the first cases of congenital deformities—involving not only limbs but also internal organs—were reported. Initially, the manufacturers denied the possibility of any causal association, but the evidence became overwhelming and the drug was withdrawn: in Germany and the United Kingdom in December 1961, and in Canada in March 1962. This was not in time to prevent the estimated 10 000 cases of affected children worldwide,[3] including more than 100 in Canada.[4] Had there been in place systems of pharmacovigilance to indicate a link between medicine taken by the mother and effects on her unborn child, actions could have been taken earlier to alert doctors to the potential risks.[5] The disaster triggered the establishment, worldwide, of national systems of licensing and safety monitoring for all medicines.

In Canada, legislation regarding the control of new drugs was reinforced in late 1962,[2] and the Canadian Adverse Drug Reaction Information System was established in 1965. Now, consumers, health care professionals, and product manufacturers can report suspected adverse events to the *Canada Vigilance Adverse Reaction Online Database* (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html).

In the United Kingdom, 1963 saw the establishment of the Committee on Safety of Drugs (renamed the Committee on Safety of Medicines in 1970), and in 1964 letters were circulated to all doctors and dentists asking them to report "any untoward condition in a patient which might be the result of drug treatment". This was the precursor of the current Yellow Card Scheme, so called because in its original incarnation, reports were prepared on a yellow card. Indeed, these yellow cards are still used, although much of the reporting is now done online. Since the scheme was introduced, reporting rights have been given to other health care professionals, initially nurses and pharmacists and now any health care professional. In 2004, patient reporting was introduced, on the assumption that it would increase the number of reports and lead to earlier detection of signals. There were concerns that patient reports might be less valid, and hence create false signals from background noise, but this has not proved to be the case.[6,7]

International collaborations were also established, increasing the sample size of exposed individuals. In 1968, the World Health Organization (WHO) instituted its Programme for International Drug Monitoring.[8] Participation has grown from an initial 10 countries to about 150 countries, all of whom are eligible to submit reports of adverse reactions associated with medicinal products to the program's global database, VigiBase. In 2001 the European Agency for the Evaluation of Medicinal Products and the European Commission developed a single European database, EudraVigilance, to which all member states must submit any details of "serious" reports, as defined by the Council for International Organizations of Medical Sciences.[9]

Currently, although there are differences between national schemes in terms of eligibility to report and what to report, all of the above approaches, however systematically introduced, whether voluntary or mandatory, depend on a system known as spontaneous reporting. This has been much criticized for under-reporting, even in countries where reporting is mandatory, such as Sweden, France, and Italy. Indeed a systematic review of 37 studies conducted in 12 countries suggested a median under-reporting rate of 94% (range 6%–100%).[10] In Canada, although more than 90% of pharmacists and 63% of physicians were aware of how to report an adverse reaction, this proportion was reduced to just 55% for health professionals overall.[11]

Despite a certain level of under-reporting, this is not the time to abandon a well-established system that has prevented another disaster on the scale of thalidomide. Because of the level of detail requested at the point of reporting, generation of an adverse event signal need not necessarily result in withdrawal of a useful drug, but there will be warnings about use. For example, a warning might refer to contraindications, such as the recent restriction of domperidone to people over 12 years of age,[12] because of a lack of evidence of benefit in younger children, or the recommendation that gabapentin not be prescribed to patients with respiratory risk factors.[13] Some warnings may relate to drug-drug interactions, such as the interaction between fluconazole and citalopram causing serious cardiovascular events, or food-drug interactions, such as the interaction between grapefruit juice and a range of common medicines.[14] Sometimes a medicine will be withdrawn completely; examples have included both prescribed medicines (e.g., rosiglitazone, because of cardiovascular effects[15]) and non-prescribed over-the-counter or herbal medicines (e.g., *Aristolochia* in Chinese medicines, because of renal failure).[16]

As premarketing safety assessments become more rigorous and well informed, we can hope that drug withdrawals will become less common. However, premarketing exposure to a drug is limited to perhaps hundreds of people, and it remains likely that rare and potentially fatal events may only be identified once thousands of people are using the drug. Any system can always be improved, but that is no reason to discard it. Efforts are needed to increase professional and public engagement with current spontaneous reporting systems. Approaches could include better education, individualized feedback, multiple reporting routes, and local initiatives. New approaches linked to big data may also provide complementary information but should not replace current systems.

In Canada, the *Protecting Canadians from Unsafe Drugs Act*, also known as Vanessa's Law,[17] will strengthen Canada's ability to collect information and make decisions about potential health risks from treatments. It is now mandatory for hospitals to report serious adverse events related to drugs and devices within 30 days after first documentation of the event (reporting by manufacturers was already mandatory). Multiple reporting routes are available. As experts in medicines, pharmacists must ensure adherence with the new law, so that patients can continue to take medicines as needed, in the knowledge that effective surveillance systems are in place.

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ON THE FRONT COVER

Sherbrooke Lake, Yoho National Park, British Columbia

This image of a serene, glistening lake, with Cathedral Mountain in the background, was captured by June Chen while she was en route to Mount Niles in August 2017. June is a clinical pharmacist with the University of Alberta Hospital in Edmonton. She practises on the cardiac intensive care and cardiovascular surgery units. During the summer months, she enjoys hiking in the mountains, and all-year-round, she likes to dance contemporary jazz.

The *CJHP* would be pleased to consider photographs featuring Canadian scenery taken by CSHP members for use on the front cover of the Journal. If you would like to submit a photograph, please send an electronic copy (minimum resolution 300 dpi) to publications@cshp.ca.