Safety of medicines

The WHO Collaborating Centre for International Drug Monitoring

Detecting and addressing medicines-related problems is critically important for patient safety. As the manufacture and supply of medicines becomes more globalized, so too should the approaches to monitoring the safety of vaccines and medicines. WHO, through its Programme for International Drug Monitoring, works with the Uppsala Monitoring Centre (UMC) to maintain the world’s single global repository of data on adverse drug reactions and to promote good pharmacovigilance practices in Member States.

Background
Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (1). Although all medicines are rigorously tested in clinical safety and efficacy trials before they are made publicly available, most of the safety data on medicines only becomes known once the products are on the market. Continued monitoring in real world settings, where medicines are used in conjunction with other products, among different patient populations and in patients with multiple illnesses, is therefore critically important.

WHO promotes medicines safety in Member States in several ways. The organization develops normative guidance with a focus on low- and middle-income countries, supports countries in implementing best pharmacovigilance practices, and communicates regulatory decisions and safety signals for medicinal products at a global level.

WHO Programme for International Drug Monitoring
An important part of WHO’s medicines safety work is the Programme for International Drug Monitoring (PIDM). The WHO PIDM members submit Individual Case Safety Reports (ICSRs) into a global database.

The ICSRs submitted by member countries are managed by the WHO Collaborating Centre for International Drug Monitoring, known as the Uppsala Monitoring Centre (UMC)1. With over one hundred staff and consultants, UMC carries out a wide range of activities to support and promote patient safety through effective global pharmacovigilance practice. The centre maintains relationships with hundreds of individuals, institutions, professional societies, research units, government

1 www.who-umc.org

This article is based on the Annual Report 2015 of the Uppsala Monitoring Centre (UMC) (2). We thank Paula Alvarado and Lembit Rägo for their useful input.
UMC receives a sustained flow of guidance through the WHO Advisory Committee on the Safety of Medicinal Products (ACSoMP) and WHO-appointed UMC Board members.

A global database
The core repository of ICSRs submitted globally is the VigiBase™ database, which is developed and maintained by the UMC on behalf of WHO.

In December 2015 there were 122 WHO PIDM member countries and a cumulative total of over 11 million ICSRs submitted to VigiBase (Figure 1), including more than one million reports from low- and middle-income countries. From 2017, VigiBase will receive ICSRs transferred by the European Medicines Agency (EMA) on a daily basis (see also page 57).

UMC has developed a range of data management and analysis tools in support of VigiBase, notably the web-based ICSR management system VigiFlow™ – provided free of charge to WHO PIDM members as a limited-access version enabling electronic ICSRs reporting – and the search and analysis tool VigiLyze™.

In 2015, aggregated safety data from VigiBase became accessible to the public through the launch of VigiAccess™ 2.

Research
With VigiBase as the sole global database of safety information, the detection and dissemination of signals of suspected drug safety concerns is a major focus of UMC’s work. A total of 42 signals were detected, assessed and published in 2015.

Identifying safety signals is rather like finding needles in haystacks. The UMC’s research team is continuously seeking new and better ways of recognizing medicinal problems early in order to protect patients. Some examples include:

- detecting syndromes, when more than one ADR is reported and there is a need to group reports with similar ADR profiles;
- finding risks in specific populations (paediatrics, vaccines, geographical regions);
- highlighting case series with sufficient information for assessment;
- detecting signals in electronic health records;

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2 www.vigiaccess.org
• developing software to analyze free-text narratives in case reports;
• detecting substandard drugs; and
• exploring the potential of social media as a source of patient risk information. Members of the UMC’s research team contribute to professional meetings and research conferences and have won international awards for their work.

UMC also contributes to external collaborative projects. Examples include the PROTECT project aiming to strengthen the benefit-risk monitoring of medicines in Europe by developing and validating new signal detection methods, the SALUS project aiming to develop tools and protocols for mining and analyzing real-time patient data from heterogeneous electronic health records, and WEB-RADR, which aims to leverage mobile-phone reporting and find ways to analyze social media for pharmacovigilance purposes.

In 2009–2013 UMC coordinated the Monitoring Medicines project, a multi-regional pharmacovigilance and public health effort funded by the European Commission (3). This project was developed by WHO and brought together diverse parties to develop methods, tools and guidelines for pharmacovigilance and resulted in significant synergies. Its outputs illustrate how pharmacovigilance activities can serve to detect, assess, understand and prevent not only adverse reactions to medicines, but also threats to patient safety caused by other drug-related problems such as product quality deficiencies or inappropriate use of medicines (Table 1).

Table 1. The Monitoring Medicines project: addressing medicines-related safety issues

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<th>Stated objectives</th>
<th>Outputs</th>
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| 1. Support and strengthen consumer reporting of suspected adverse drug reactions (ADRs) | WHO handbook (4)  
Online reporting system (used in six pilot countries, offered free of charge to all VigiFlow users) |
| 2. Expand the role and scope of national pharmacovigilance centres to identify, analyse and prevent medication errors | WHO handbook (5) |
| 3. Promote better and broader use of existing pharmacovigilance data for patient safety | Methodology for detecting drug dependence in spontaneous adverse drug reaction databases (6)  
Methodology for detecting substandard or counterfeit medicines (7) |
| 4. Develop additional pharmacovigilance methods to complement data from spontaneous reporting systems | Publication on WHO strategy for collecting safety data in public health programmes (8)  
Cohort event monitoring (CEM)  
Targeted spontaneous reporting (TSR)  
Clinical use of pharmacovigilance data  | Web-based data management tool CemFlow (used in Belarus, Kenya, Nigeria, Tanzania and Zimbabwe)  
WHO handbook on pharmacovigilance of medicines used for tuberculosis (9)  
Web-based database and risk assessment tool in antiretroviral therapy, available at www.hivpv.org |

Source: Adapted from: (3).  
Terminology and coding tools
The data collected in VigiBase are also the source of the content for the WHODrug™ Dictionary portfolio. This UMC resource aims at optimizing the global analysis and reporting of medical product information during the whole life cycle of a drug. WHODrug is mandated in Japan and recommended in the United States for concomitant medications in clinical trials. It is regularly updated with new releases and components to support its use in specific contexts. The 2015 releases include an Enhanced version produced in collaboration with IMS Health, the Cross Reference Tool Japan and the Cross Reference ATC 5.

A mapping bridge has been developed between the WHO Adverse Reaction Terminology (WHO-ART) and MedDRA, the standard terminology of the International Council for Harmonization (ICH). For the future UMC is seeking to collaborate with ICH towards one global terminology solution for both regulatory and pharmacovigilance purposes.

Support activities
Training
UMC carries out training activities in member countries on a wide range of topics including signal detection, the use of data management tools, communications skills and safety reporting processes. Its platform of partners includes the WHO Collaborating Centres in Ghana, Morocco and the Netherlands, the International Society of Pharmacovigilance (ISoP), Jagadguru Sri Shivarathreeswara (JSS) University in Mysore, India, and the Asia-Pacific Economic Cooperation (APEC) among others.

In 2015 UMC organized or participated in pharmacovigilance training courses in Asia, Africa, South America and Europe. Two major events were the 17th annual pharmacovigilance training course held in Uppsala with participants from 28 countries, and the first Asia-Pacific Pharmacovigilance training course in Mysore, India, organized in collaboration with JSS University.

In addition, UMS held webinars on a range of topics in five languages and launched a YouTube channel providing access to over 150 training sessions.

Advocacy
In 2015 UMC launched its first public campaign, Take&Tell™, encouraging patients to tell their health professionals about adverse effects. This innovative and unique campaign raised much interest around the world and was taken on board by a number of national pharmacovigilance centres and other major organizations. It thus achieved its aims to raise global awareness of the importance of pharmacovigilance and to change the way people view the process of taking medicines.

Technical support
UMC provides individual technical support in response to hundreds of – often complex – enquiries and search requests every year. More than 170 search requests from external and internal stakeholders were received in 2015.

Information base
The UMC regularly produces a range of guidelines, manuals and support materials on specific topics such as adverse drug reaction (ADR) reporting forms and data management tools, and makes them

3 www.takeandtell.org/
available in the Publications section of its web site. Its quarterly newsletter “Uppsala reports” celebrated its 70th edition in July 2015. UMC also maintains a collection of links to resources available elsewhere, such as pharmacovigilance guidelines produced by member countries and the websites of their regulatory authorities.

Conclusion
The steady growth of membership in WHO PIDM, the high attendance at UMC training events, the increasing uptake of its core tools and the improved quality of reporting by a number of members show that the Programme is reaching a wider audience of patients and health professionals. Many low- and middle-income countries have become active contributors to the WHO PIDM. And at the 2015 annual meeting of WHO PIDM member countries, India proposed to make its Pharmacopoeia Commission the first WHO collaborating centre for pharmacovigilance in the region - a promising development, particularly as many low-cost generic medicines supplied internationally originate in India.

Safer medicines, safer use of medicines and safer patients are high priorities for the world. The results achieved under the WHO PIDM are difficult to quantify, but clearly they have contributed to enhancing pharmacovigilance practices and building a global safety culture. If this work is kept up, it can bring the world closer to UMC’s vision of a place where where all patients and health professionals make wise therapeutic decisions in their use of medicines.

References