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.
departments and commercial operations. 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™.

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;

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

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

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.

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
Look-alike sound-alike drug name confusion: trastuzumab emtansine

Look-alike sound-alike drug names may be responsible for as many as one in four error reports received by surveillance programs. Not only brand names but also International Nonproprietary Names (INNs) may be subject to look-alike sound-alike confusion, including those for complex products manufactured with new technologies. This article looks at reports of confusion between trastuzumab and trastuzumab emtansine, action taken, and possible future measures that could mitigate the risk of confusion and protect patient safety.

Introduction
Drug name confusion has been well documented in recent years as a contributing factor to the burden of health care-related harm to patients around the world. In particular, look-alike sound-alike drug names have been identified as a significant risk for the occurrence of medication errors. Some estimates suggest that look-alike sound-alike name confusion is responsible for as many as one quarter of error reports received by surveillance programs such as the Institute for Safe Medication Practices (ISMP) Medication Error Reporting Program in the United States. (1) Recognition of the potential for error caused by similar drug name pairs has prompted regulatory authorities, patient safety organisations, the pharmaceutical industry and health professionals to develop strategies that seek to lower the risk of error while acknowledging challenges in the provision of health care. Health Canada recently revised its Guidance Document on the Review of Drug Brand Names (2) to provide greater direction to the pharmaceutical industry on the processes to follow when determining the potential for proposed names to be confused with those of other products on the Canadian market. Similarly, the FDA’s process for name review was developed from initiatives that aim to minimize the potential for medication errors. (3) These documents and processes address drug brand names under the authority of the regulator in granting approval for the marketing of health products.

International Nonproprietary Names (INN) may also be subject to look-alike sound-alike confusion. Unlike brand names, these names are selected by the WHO’s INN Programme. Many of the drug name pairs on ISMP’s list of confusable names are INNs. (4) In addition, the complexity of biological products and the application of technologies such as nanotechnology and pegylation has led to the use of drug names that pose challenges for error-free communication across all stages of the medication use process.
Trastuzumab and trastuzumab emtansine

In 2013 regulators including Medsafe, the FDA, and Health Canada issued safety communications (5, 6, 7) alerting health professionals to the potential for medication errors based on look-alike sound-alike confusion between two nonproprietary names1, trastuzumab (78) (40) and trastuzumab emtansine (103) (65). The communications directed health professionals to use the respective brand names of Herceptin® and Kadcyla® throughout the medication use process in order to reduce the risk of name confusion.

Trastuzumab emtansine (103)(65) represents the first example of an antibody-active drug conjugate for which the monoclonal antibody portion – trastuzumab – was previously marketed as a separate compound. The two INNs are both in use concurrently within health facilities. Differences in dose and treatment schedule (conjugate used at ±50 % of the antibody dose) make the correct use of these products critical. The Lists of Recommended and Proposed International Nonproprietary Names published by the INN Programme indicate that there are other monoclonal antibodies which may be available in the future both with and without conjugates, such as indusatumb (112)(74) / indusatumab vedotin (112)(74) and vorsetuzumab (107) (69) / vorsetuzumab mafodotin (107)(69). Antibody-drug conjugates have also been developed in which the same antibody is conjugated with different cytotoxic agents (e.g. cantuzumab mertansine (105)(65) and cantuzumab ravnatins (105)(66)). The number of look-alike and sound-alike INNs for monoclonal antibodies will naturally increase, with a corresponding greater risk of name confusion.

The examples in Table 1 illustrate that confusion between the antibody and the antibody-drug conjugate as well as between antibody-drug conjugates with

### Table 1. Sample list of antibody-active drug conjugates

<table>
<thead>
<tr>
<th>INNs</th>
<th>Active moieties*</th>
</tr>
</thead>
<tbody>
<tr>
<td>trastuzumab emtansine (103)(65)</td>
<td>Emtansine</td>
</tr>
<tr>
<td>vorsetuzumab mafodotin (107)(69)</td>
<td>Mafodotin</td>
</tr>
<tr>
<td>denintuzumab mafodotin (111)(73)</td>
<td></td>
</tr>
<tr>
<td>lorvotuzumab mertansine (103)(65)</td>
<td>Mertansine</td>
</tr>
<tr>
<td>cantuzumab mertansine (105)(65)</td>
<td></td>
</tr>
<tr>
<td>cantuzumab ravnatins (105)(66)</td>
<td>Ravnatins</td>
</tr>
<tr>
<td>indatuximab ravnatins (105)(67)</td>
<td></td>
</tr>
<tr>
<td>anetumab ravnatins (109)(71)</td>
<td></td>
</tr>
<tr>
<td>coltuximab ravnatins (109)(71)</td>
<td></td>
</tr>
<tr>
<td>brentuximab vedotin (103)(65)</td>
<td>Vedotin</td>
</tr>
<tr>
<td>enfourtumab vedotin (109)(71)</td>
<td></td>
</tr>
<tr>
<td>polatzumab vedotin (110)(71)</td>
<td></td>
</tr>
<tr>
<td>pinatuzumab vedotin (108)(70)</td>
<td></td>
</tr>
<tr>
<td>lifastuzumab vedotin (110)(72)</td>
<td></td>
</tr>
</tbody>
</table>

* See reference (8)
either the same antibody or the same drug/toxin is possible. Errors relating to antibody-drug conjugates (cantuzumab mertansine (105)(65) vs cantuzumab ravtansine (105)(66)) could theoretically be even more dangerous than confusion between the antibody and the antibody-drug conjugate where toxicity or adverse effects are mainly related to the incorrect dose or lack of effect.

Antibody-active drug conjugates are named in accordance with the naming policy of the INN Programme in which a separate, second word identifies the conjugate. (9) Changing the order of the words so that the conjugate appears first would not mitigate the risk of name confusion as some drugs/toxins are conjugated to more than one antibody. In the case of trastuzumab emtansine (103) (65), regulators and healthcare providers have proposed strategies to address the possibility of confusion. These include the addition of a prefix (ado-trastuzumab emtansine) as well as specific prescribing, dispensing, labelling, systems and storage requirements.

**FDA experience – does the addition of a prefix prevent errors?**
During clinical trials prior to market authorization in the United States, four patients inadvertently received trastuzumab emtansine at 6 mg/kg instead of trastuzumab. It was reported that all four patients developed Grade 2 thrombocytopenia and increased liver transaminases. In one case a Holter monitoring 18 days after the error showed asymptomatic ventricular extrasystoles. The following day, the patient died. The cardiologist did not believe that the extrasystoles contributed to death. No autopsy was performed. (10)

As a result of these medication errors, the FDA took the step of modifying the approved nonproprietary name of the conjugated compound to ado-trastuzumab emtansine. The effectiveness of the addition of the prefix in preventing name confusion errors is difficult to determine at this date. Reports published shortly after the approval indicated that there were inconsistencies in the terminology used in U.S. drug information references as well as in health information systems, with some publications displaying the prefix ‘ado’ and others omitting it. It was postulated that health professionals may have encountered difficulties in accessing key information or placing orders for the drug. (11) Unilateral use of this strategy may also make cross-referencing of data or information retrieval by other regulatory authorities or organizations difficult. For example, some Canadian databases such as those used by poison control centres may rely on content from U.S.-based sources, and delays in retrieving information may occur if users do not enter the ‘ado’ prefix as part of their search criteria. The continued use of the ‘ado’ prefix may pose a challenge in light of the possibility of new conjugates as well as new monoclonal antibodies.

**Roche/Genentech Global Safety Database**
At the request of the INN Programme, Roche/Genentech performed a search of their Global Safety Database for post-market reports of medication errors between the two substances. The search looked for reports of (ado)-trastuzumab emtansine entered in the database until 21 February 2015 under the MedDRA High Level Group Term (HLGT) “Medication Error”. Although there was a lack of detail in the data provided, three
cases reported in the U.S. are suggestive of product confusion. A mix-up between trastuzumab and ado-trastuzumab emtansine cannot be excluded.

**EMA data**

According to the assessment report for marketing authorization from the EMA, “six cases of medication error occurred in the clinical trials. Of these 4 were due to a confusion between trastuzumab emtansine and trastuzumab. The medication error occurred with a product labeled for clinical trials, which had no tradename or specific distinguishing features to differentiate the two products.” Clinical consequences from these errors are not provided in the report. (12)

The post-market data from Roche/Genentech indicates that a total of 12 medication errors involving trastuzumab emtansine were reported until 21 February 2015 in the following countries of the European Union: Germany (7), Greece (2), United Kingdom (2) and Denmark (1). No further details regarding the role of name confusion were provided.

**Health Canada data**

As regards Canadian data, three cases were reported to Health Canada until March 31, 2015. The first report was received as a communication prior to the market authorization in Canada of trastuzumab emtansine under the brand name Kadcyla® in October 2013. The communication identifies the potential for selection errors during ordering, computer order entry, compounding and programming IV pumps.

The second report received describes a near-miss incident in which trastuzumab emtansine (Kadcyla®) was selected at order entry in the pharmacy software instead of trastuzumab (Herceptin®). The error was caught when the label generated by the computer was being checked for accuracy. The reporter indicated that limitations in systems had prevented the consistent use of the brand name as per the Health Canada safety communication.

The third report outlines a sequence of events that led to a patient receiving trastuzumab instead of trastuzumab emtansine. The prescription for trastuzumab emtansine was correctly entered into the pharmacy software and verified by the pharmacist. During compounding the technician inadvertently mixed the order using vials of trastuzumab and then labelled the product as trastuzumab emtansine. At the time of the incident, labels generated by the computer used only the nonproprietary name and did not include the brand name. The pharmacist did not catch the error and the drug was then given to the patient labelled as trastuzumab emtansine although it contained trastuzumab.

Later a technician observed extra stock of trastuzumab emtansine in the fridge, and the error was detected. The reporter stated that the same situation had occurred a week or so prior, but had been intercepted by the pharmacist before the patient received the drug.

The patient did not suffer any adverse effects from the error and was rescheduled to receive trastuzumab emtansine the following week, eventually resuming the originally planned schedule of administration on a three-week cycle.

The report revealed that the following changes were implemented as a result of the error and the near-miss:

- The order of the name in the pharmacy software was switched so that the brand name appears first (e.g. Kadcyla® – trastuzumab emtansine)
Labels affixed to the IV bags now include the brand name in addition to the INN.

The two medications are now stored separately.

A high-alert\(^2\) colour-coded label has been added.

Additional risk mitigation strategies have been proposed to support the safe use of \textit{trastuzumab} and \textit{trastuzumab emtansine} including the following: (13)

- Recommended dosing and dose limits should be programmed into software at the point of order entry.
- Automated alerts and warning labels should remind practitioners that the medications are not interchangeable.
- Use of the brand names in addition to nonproprietary names should occur at each stage of the medication use process.

The market authorization holder has also provided training materials and other resources to health facilities to help minimize the risk for name confusion.

\textbf{Conclusion}

The influence of under-reporting on the voluntary reporting of medication errors and adverse effects is such that the rate of occurrence of these events cannot be effectively determined. The true incidence of errors between \textit{trastuzumab} and \textit{trastuzumab emtansine} is therefore not known, although the reported cases highlight the potential for serious harm from medication errors resulting from name confusion.

For the future, healthcare providers should continue implementation of a system-wide set of standard risk mitigation strategies that acknowledge risks at each stage of the medication use process. Challenges such as software limitations and diversity of processes will need to be addressed in recognition of the continued development of antibody-drug conjugates and the increased complexity of look-alike sound-alike name candidates. The use of brand names in addition to nonproprietary names for these antibody-drug conjugates during prescribing and dispensing as well as clearly distinguishable packaging and labelling would be key to preventing medication errors. Promotion of the INN as a standard for drug nomenclature is also important to ensure that health professionals understand its role and application. Other strategies such as the addition of a prefix or a suffix (e.g. a 4-letter biological qualifier) require further evidence of their effectiveness as patient safety measures.

\textbf{References}


\(^2\) High-alert medications are drugs that bear a heightened risk of causing significant patient harm when they are used in error.


