Quality and Safety of Medicines

WHO project for the surveillance and monitoring of SSFFC medical products

The existence of substandard/spurious/falsely labelled/falsified and counterfeit (SSFFC) medical products is not a new phenomenon, but is increasingly recognized by WHO Member States, regional groups and various international organizations as representing a significant threat to human health.

The right to safe, efficacious, quality medicines which are affordable is a fundamental human right. In some low income countries access to healthcare facilities is limited; for those fortunate enough to reach a facility they should be able to have trust and confidence in the medicines they receive. Often, this is not the case and with tragic consequences. However, this situation — which was once regarded as an issue solely affecting low and middle income countries — now impacts all. The vast profits to be made through the high demand and large turnover of medical products is a powerful driver for those engaged in the manufacture, distribution and supply of SSFFC medical products.

The rapid increase in connectivity to the Internet has also effectively opened up global markets to the distribution of SSFFC medical products. Whilst enabling access to medicines, it has also encouraged a culture of self-diagnosis and self-prescribing. Unregulated web sites have been seen in some parts of the world as a key source of SSFFC products: an issue which is impossible to regulate effectively and cannot be dealt with by one country in isolation.

Worryingly, incidents involving SSFFC products are frequently reported from hospitals, clinics, pharmacies and licensed entities within the regulated supply chain — precisely the places where patients should have the highest level of confidence that the medicines they receive are safe and effective. Every incident damages confidence in health systems, medicines and healthcare professionals.

Despite this situation, there is no accurate global assessment of the scope, scale and harm caused by the issue. Much anecdotal information exists, but there is a lack of clear, validated, reliable evidence. Some excellent surveys have been conducted in various parts of the world. However, these reports are often short-term, restricted to limited geographic areas and may concentrate on specific therapeutic categories. They are frequently used to extrapolate an estimate of the global threat which is less than sound and commonly challenged. Policy makers require reliable evidence upon which to base sound decisions concerning the allocation of finite resources to tackle this damaging issue in a proportionate way.

Surveillance and monitoring

In 2010, WHO began to re-examine existing methods and systems of collecting data concerning SSFFC medical products. A rapid alert system had been developed in the Western Pacific Region but was not being regularly used. During 2011, two consultative meetings were held in Kiev, Ukraine and Kuala Lumpur, Malaysia. National regulatory authorities from the respective regions were asked to participate and
agree on methods to encourage the reporting of incidents.

Building upon the good work started in the Western Pacific Region, a new surveillance and monitoring system was designed utilizing the submission of a clear, concise and structured Rapid Alert Form to encourage a more systematic method of reporting. The objective of the project is to significantly improve the quantity and quality of data enabling detailed analysis and validation of incidents.

**Rapid Alert Form**
Following further consultation, an electronic Rapid Alert Form was designed. This template contains what is considered to be the minimum amount of information for WHO to conduct an initial risk assessment. Some of the data fields are mandatory and failure to complete these fields will prevent the document from being forwarded to WHO.

The Rapid Alert Form contains a hidden language recognition code. This enables the form to be completed in one language and automatically translated to English when downloaded into a data base retained at WHO Headquarters. The Rapid Alert Form is currently available in English and a French Version is being tested. It is planned to make Spanish, Russian, Arabic and Mandarin versions available.

The form is provided as a template to trained focal points within national regulatory agencies. Once the mandatory fields are completed, the document can be saved and sent as an attachment via e-mail to rapidalert@who.int. Focal points are encouraged to send any photographs, laboratory reports or other relevant documents as attachments.

Once sent, the originator will receive an automated message confirming receipt and notifying them that they will be contacted by WHO within 72 hours. (In cases where adverse reactions are reported this is 24 hours).

**SSFFC data base**
On arrival at WHO, the details contained on the Rapid Alert Form are automatically downloaded and will populate the SSFFC data base. The system will immediately identify duplicate reports. For example, it will recognize if the specific batch/lot number of a medical product has been previously reported and will also match a range of other details. This allows cross matching of incidents and enables WHO to put Member States in contact with each other if dealing with linked incidents.

At WHO, staff within the Quality and Safety of Medicines Team will also receive automatic notification of the arrival of a rapid alert. They will conduct an immediate risk assessment with a focus on the current threat to public health and the need to communicate the incident to any other countries which may be affected. Sharing of information is only conducted following consultation with the originator of the report.

**Review and analysis**
WHO staff will make contact with the originator of the Rapid Alert either by telephone or e-mail and ask some additional questions. They will start to populate the data base manually with any further information obtained from the originator. The data base contains over 250 fields which can be cross searched in any combination, permitting detailed analysis. The areas explored in more detail contained within the data base include: suspect product details, laboratory analysis, impact on public health, risk communication, dissemination, method of distribution, method of discovery, means and route of import or export, details of who is responsible for any investigation, details of internet distribution, cost of medical product, photographs of product and free text comment and analysis areas.
During this process, an analyst will be looking for a range of characteristics in order to make a final classification of the case. Those characteristics include:

- Unauthorized attempt to visually imitate the licensed, authorized or approved product.
- Attempt to mislead any person concerning product ingredients.
- Incorrect, misleading or missing information as to the place of origin or manufacture.
- Falsification of safety or security features.
- Falsification of batch number, date of manufacture or expiry dates.
- Falsification of any other aspect of packaging.
- Falsification of license status, registration, authorisation or approval information on packaging.
- Falsification of accompanying documentation.
- Was the product concealed or misdeclared during shipment?
- Was the product stolen or diverted?

**Final classification**
Most cases should be closed within 90 days and classified. The final classification is designed to separate substandard medicines caused by genuine manufacturing error from incidents that demonstrate a clear intention to deceive a patient, consumer, healthcare professional, or anybody else that the product is the genuine article.

This final classification ensures that future trend analysis is based upon the comparison of similar incidents. Reports sometimes suggest that a product is falsified when in fact it is substandard due to an honest manufacturing error. It is only after validation has been sought from the originator that a final classification can be carried out.

**Training workshop and pilot study**
Following the consultation process, ten Member States agreed to participate in a pilot study. They are: Cambodia, Croatia, Georgia, Indonesia, Kyrgyzstan, Malaysia, Philippines, Russia, Ukraine, Viet Nam.

In September 2012, the first 3-day SSFFC training workshop was hosted in Manila by the Philippines Food and Drug Administration and held at the WHO Regional Office. The focal points from the ten pilot countries together with their immediate managers attended and participated in five exercises involving recent SSFFC incidents. The USA and China sent observers from their respective regulatory agencies who fully participated in the workshop. At the conclusion of each exercise, delegates were required to complete and submit the Rapid Alert Form to WHO. This training was immediately followed by the pilot study.

This took place between September 2012 and January 2013. Forty reports involving 72 medical products were reported during this period concerning 30 active pharmaceutical ingredients. The pilot study was designed to thoroughly test the system and identify scope for improvement. A number of refinements were made to both the Rapid Alert Form, to improve ease of completion, and the data base, to facilitate better analysis.

**Challenges**
Incidents involving SSFFC medical products are hard to detect. It can be difficult to identify the harm caused by the SSFFC product in a patient who is already suffering from a disease. However, WHO is working closely with the WHO Collaborating Centre in Uppsala to develop methods for mining data
Case Study

In May 2013, WHO issued a drug alert relating to an antimalarial medicine circulating in Western and Central Africa which contained no active pharmaceutical ingredient. This branded product is a WHO prequalified medicine and was being distributed as part of the Global Fund AMFM programme. The genuine product is a reliable, trusted and effective medicine sought after in many sub-Saharan countries as an effective treatment for malaria. A German nongovernmental organization reported to WHO that samples they had recovered in Cameroon had failed mini-lab screening and had been sent to a WHO prequalified laboratory in Kenya for further analysis. Testing confirmed that the sample contained no active pharmaceutical ingredient. Further investigation with the genuine manufacturer of the medicine revealed that the same medicine bearing the same batch number had been seized in Angola as part of a World Customs Organization operation. A second batch of the same medicine had also been recovered during market surveillance in Benin and Nigeria. Recent information also suggested that at least two falsified batches containing no active pharmaceutical ingredient were currently circulating in Western and Central Africa. Initially, WHO issued a warning to all national regulatory authorities requesting increased vigilance. WHO was satisfied that a current and credible risk had been clearly identified which led to the publication of a WHO international drug alert to all Member States and publication on the WHO web site.

relating to unusual clusters of reports of a lack of efficacy or adverse reactions in patients which may be caused by sub-potent SSFFC medical products. That work is on-going but pharmacovigilance reporting is seen as a potentially useful source of information.

Next Steps
WHO is confident that a robust and reliable system is now in place to receive reports on incidents suspected to involve SSFFC medical products. Three further training workshops are planned for 2013 in Nigeria, Tanzania and Tunisia, which will bring regulatory, pharmacovigilance and laboratory experts together.

Since the conclusion of the pilot study, reports have continued to be submitted to WHO from a number of different sources. Over 130 products have now been reported and are undergoing review and analysis. A number of cases have led to serious adverse reactions including fatalities.

WHO wishes to make the Rapid Alert Form available in more languages and to engage more Member States in use of the system. Closer links with pharmacovigilance reporting will be developed. Further collaboration with WHO prequalified laboratories will be encouraged. Extending the Rapid Alert Form to other stakeholders including procurement organizations, nongovernment organizations and other relevant stakeholders is under consideration in an effort to achieve a more complete assessment of the situation.

Conclusion
Once sufficient reports are received within the database, WHO will be in a position to report validated findings on a geographic or thematic basis. Reporting should begin to identify supply chain vulnerabilities and the finished medical products and active pharmaceutical ingredients most at risk of falsification and misrepresentation. This reporting will influence recommendations for market surveillance, increased vigilance and the development of sound strategies to minimize the risk from SSFFC products.