

# **Risk-based assessment of the possibility for falsification during post-marketing surveillance of medicines**

Angela Arsovska, Jelena Acevska, Katerina Brezovska, Hrisanta Godzo,  
Aneta Dimitrovska

*Faculty of Pharmacy, University of "Ss Cyril and Methodius", Mother Theresa 47, 1000 Skopje, Republic North Macedonia*

## **Introduction**

The prevalence of falsified medicines and the figures undoubtedly differ between countries (WHO, 2017); nonetheless it is necessary to establish an effective system for post-marketing surveillance of the quality of medicines on a national level, in order to monitor, detect and diminish the appearance of substandard and falsified medicines on the market (Pisani et al., 2021). In most low- and middle-income countries, post-marketing surveillance is often limited to sporadic sampling or the collection of medicine samples as part of routine inspections. This may be due to poor planning, unclear oversight objectives, and/or limitations in the methodology for sampling or analysis. This means that while regulatory agencies may spend significant resources on medicine sourcing and analysis, these efforts often result in poor quality data that cannot be used to make evidence-based decisions (PQM, 2018). Additionally, the limited capacity of quality control laboratories and large quantities of medicines that need to be analyzed suggest that a risk-based approach can prioritize activities accordingly (EDQM, 2020). Article 30 of the Guidance on the manner of quality control of medicines of Republic North Macedonia (Official gazette, 2021) stipulates that all segments of trade should be covered when sampling medicines for regular quality control and the geographical and demographic criteria should be taken into account as well. However, there is no targeted strategy for identification and subsequently sampling of medicines that, at some point, may be at a higher risk of being falsified.

The aim of this paper is to depict the critical aspects of market surveillance of medicines, which would facilitate the transition from a sporadic to a risk-based post-

marketing surveillance program for monitoring of the quality of medicines present on the market in our country.

## **Materials and methods**

A review of scientific literature in this area of interest and the current status of the scientific community was done to reveal advances in national methodologies to combat the possible falsification of medicinal products.

## **Results and discussion**

Pisani et al. have identified two approaches to active monitoring of medicine quality: case-finding and sentinel surveillance of medicines (Pisani et al., 2021). Case-finding efforts focus on trying to identify individual medicines that are likely to be falsified so that they can be quickly removed from the market. Sentinel surveillance is a form of continuous post-marketing surveillance designed to explicitly select samples of medicines from risky categories in reproducible ways over time, so that trends can be measured reliably.

Case-finding approach first defines risk factors relevant to public health (such as the active substance, brand of medicine, distribution chain, position on the market of the drug, geographical location etc.) and decides on indicators that would best describe these risk factors. Then, a risk score is assigned to each indicator (e.g., no risk, minimum risk, medium risk or high risk) and the risk scores are added to create a total risk index. Subsequently, medicines are sampled according to risk index and within a sampling matrix prepared according to the distribution networks of the country (Pisani et al., 2021).

Possible indicators for identifying risks could be: (i) Percent of change in the volume of public procurement or import of the medicine from year to year (shortage of a medicine indicates an opportunity for falsification); (ii) Patented medicines that are not included in the national health insurance scheme (patients are looking for alternative solutions that are more economically acceptable); (iii) Medicines with a small number of registered manufacturers (possible shortage); (iv) Brand medicines from a reputable company; (v) Medicines with a previous history of falsification; (vi) Medicines with known recreational or off-label use; (vii) Medicines with a high price compared to the median of the market for that molecule which also have a large volume of sales; (viii) Medicines that have been distributed by a company that has already been reported for distribution of suspected falsified medicines; (ix) Medicines that are mainly sold in places that are rarely subject to regulatory control, etc.

Sentinel surveillance approach, also encompasses establishing sentinel surveillance for falsified medicines beginning with defining risk factors and indicators that best describe them. However, no risk score is calculated; instead, proxy "sentinel groups" (or sentinel locations) are chosen, which are likely to contain the highest concentrations of falsified medicines. Then, a sample frame for each sentinel group is defined and a predetermined number of samples are tested over repeatable periods of time (Pisani et al, 2021). Examples of medicines that should be monitored over time can be: (i) Medicines with irrationally high demand (used for recreational purposes or have off-label use); (ii) Life-saving, but extremely expensive medicines (i.e., patented medicines that are not included in the national health insurance scheme); (iii) Medicines sold on unregulated internet platforms; (iv) Medicines that are widely used or have increased sales in specific situations (such as the COVID-19 pandemic); (v) Medicines sold in poor and hard-to-reach environments, etc.

Although post-marketing surveillance exists in various forms, there is currently no unified guidance on the form of national surveillance systems for detection of falsified medicines and there are no standardized methods for translating surveillance results into market-level estimates. Pisani et al.'s suggestions could be a solid starting point for building a national post-market risk-based surveillance scheme. In the short term, case-finding is likely to be a more attractive option as the advent of falsified medicines will emerge more quickly. This is true despite the fact that case-finding requires the collection of more data and is probably technically more difficult to implement. However, sentinel surveillance offers a more solid understanding of the extent of the problem, which would allow the health authorities to make assessments of the health and economic impacts of falsified medicines;

make additional investments in the implementation of regulatory control; plan and implement policies and programs to reduce the prevalence of falsified medicines; and monitor progress over time towards that goal.

In North Macedonia, it is crucial to start with targeted data collection regarding the procurement/import of medicines, sales of medicines, to seek out specific data from medicine dossiers, data from regulatory and police investigations and customs, to map out medicine distribution and sales chains etc. in order to have enough data to implement any of these or other approaches. This requires collaboration and joint action by the relevant competent authorities.

## Conclusion

Introducing a risk-based approach to the post-marketing surveillance program for monitoring the quality of medicines will facilitate better understanding of the possibility for occurrence of falsified medicines, and give insight for reliable quantification of the problem and monitoring of the effectiveness of interventions on the market.

## References

- European Directorate for the Quality of Medicines & HealthCare. 2007, revised 2020. Incorporation of a risk based approach in market surveillance testing at OMCLs. General European OMCL Network. <https://www.edqm.eu/documents/52006/71923/incorporation-of-RB-approach-OMCL-06-03-R11.pdf/6f898b2d-260e-a091-9cb3-da1fb07c51d0?t=1629095901198>
- Official Gazette of the Republic of North Macedonia. 2021. Guidance on the manner of quality control of medicines and the recognition of the analyzes of medicine lots. Official Gazette of the Republic of North Macedonia 37.
- Pisani, E., Hasnida, A., Rahmi, M., Kok, M. O., Harsono, S., & Anggriani, Y. 2021. Substandard and Falsified Medicines: Proposed Methods for Case-finding and Sentinel Surveillance. *JMIR public health and surveillance*, 7(8), e29309. <https://doi.org/10.2196/29309>
- Promoting the Quality of Medicines. 2018. Guidance for implementing risk-based post-marketing quality surveillance in low- and middle-income countries. <http://www.usp-pqm.org/sites/default/files/pqms/article/risk-based-post-marketing-surveillance-feb-2018.pdf>
- World Health Organization. 2017. A study on the public health and socioeconomic impact of substandard and falsified medical products. <https://www.who.int/publications/i/item/9789241513432>