* 1. INTRODUCTION AND OVERVIEW
* **The need for evidence**

The presence of substandard and falsified medical products in countries and their use by patients threatens to undermine progress towards meeting the Sustainable Development Goals. Such products may be of poor quality, unsafe or ineffective, threatening the health of those that take them. The problem of substandard and falsified medical products continues to increase, as globalized manufacturing and distribution systems grow ever more complex. That complexity heightens the risk that production errors will occur, or that medicines will degrade between factory and consumer. Increasing demand for medicines, vaccines and other medical products in almost every country, in addition to poor supply-chain management and the growth of e-commerce also creates opportunities for falsified medicines to be introduced into the supply chain.

Unfortunately, reliable information on the true public health and socioeconomic impacts of substandard and falsified medical products is sparse. A stronger evidence base is needed to help prevent, detect and respond to substandard and falsified medical products, and the public health threat they represent. “The lack of understanding of the public health and economic costs has frustrated efforts at making the argument that investments in strengthening regulatory systems are a good buy and has prevented countries from understanding and acting on the problem in their own settings” *(1)*.

Establishing the magnitude of any disease or public health challenge depends on having clear definitions. In the field of substandard and falsified medical products, such definitions have been lacking. The media, the general public and even some academic researchers have used words such as “fake” and “counterfeit”, often interchangeably with other terms. The World Health Organization (WHO) previously used the catch-all term “substandard, spurious, falsely-labelled, falsified and counterfeit medical products”, although the various terms were interpreted differently by different Member States *(2)*. Most controversially, the term “counterfeit” was sometimes used in some jurisdictions to refer to medicines that infringed patents or other intellectual property rights.

In 2012, the World Health Assembly established the Member State mechanism to provide oversight, strong commitment and political will from Member States and WHO on this issue from a public health perspective. Intellectual property considerations are explicitly excluded from its mandate and the Member State mechanism works on agreed prioritized activities designed to fill specific data gaps on key technical issues, including the standardization of definitions. In May 2017, the World Health Assembly endorsed the definitions suggested by the Member State mechanism, which are shown in Box 1 *(3)*. Although these definitions are now clear, they have only recently been agreed and comparing studies published before achieving this consensus is not straightforward.

**Box 1: WHO definitions of substandard, unregistered/unlicensed and falsified medical products** *(3)*

For many years, the response to this important threat to public health was embroiled in a discussion of complex definitions that meant different things to different people. Reflecting this complexity, until May 2017, WHO used the term “substandard/spurious/falsely-labelled/falsified/counterfeit medical products”. The WHO Member State mechanism on substandard and falsified medical products was tasked with revising these definitions to ensure that they were based on a public-health perspective, with no account taken of intellectual property concerns. Based on these deliberations, the World Health Assembly, which governs WHO, adopted the following definitions:

**Substandard medical products**

Also called “out of specification”, these are authorized medical products that fail to meet either their quality standards or their specifications, or both.

**Unregistered/unlicensed medical products**

Medical products that have not undergone evaluation and/or approval by the national or regional regulatory authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

**Falsified medical products**

Medical products that deliberately/fraudulently misrepresent their identity, composition or source. *Source:* Appendix 3 to Annex, World Health Assembly document A70/23, 2017.

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**5** CONCLUSION

**The impact of substandard and falsified medical products is important to understand** and is summarized in Box 5 (adapted

from Newton et al. *(18)*).

**Box 5: Impact of substandard and falsified medical products**

**Health impact**

* adverse effects (for example toxicity or lack of efficacy) from incorrect active ingredients
* failure to cure or prevent future disease, increasing mortality, morbidity and the prevalence of disease
* progression of antimicrobial resistance and drug-resistant infections
* loss of confidence in health care professionals, health programmes and health systems

**Economic impact**

* increased out-of-pocket and health system spending on health care
* economic loss for patients, their families, health systems and manufacturers (and other actors in the supply chain) of quality medical products
* waste of human effort and financial outlay across the health system, further straining resources, staff and infrastructure
* increased burden for health care professionals, national medicine regulatory authorities, law enforcement and criminal justice systems

**Socioeconomic impact**

* lost income due to prolonged illness or death
* lost productivity costs to patients and households when seeking additional medical care, the effects of which are felt by businesses and the wider economy
* lack of social mobility and increased poverty

**Quantifying the public health and socioeconomic impact of substandard and falsified medical products is possible, but it needs consistent use of guidelines to reduce variability.** Studies may use different definitions and sampling and

testing strategies even when they are investigating similar therapeutic categories. Information that would allow for better comparison (for example sampling characteristics, or providing more details on API concentrations) is often not reported. Just as the problem of substandard and falsified medical products may be diminished by greater and more effective application of standards in production and supply chain management, the problem of the evidence base might be diminished by increased use of standards in data collection, analysis and reporting.

Besides being based on clear definitions, robust estimates of the prevalence of disease, behaviours or products depend largely on two factors: sampling that is representative of wider populations or markets, and testing that has a known sensitivity and specificity. Some relevant standards already exist – for sampling and reporting, for example – and others, including those on testing methods, are under development. The consistent use of guidelines and other technical documents, such as those listed in Box 6 should, over time, reduce variability, so that further studies contribute to more consistent and comparable data globally. The use of these technical documents is to be encouraged; however, they can only be used if the resources to support data collection and analysis are available.

**Box 6: WHO guidelines and technical documents**

**Subject**

The definitions of substandard, falsified and unregistered/unlicensed medical products

Draft guidance on testing of suspected falsified medical products

Testing of suspect substandard and falsified medicines

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**There must be consistent data and strategic information gathering.** This study has illuminated some of the importantinformation gaps that impede our ability to understand the exact nature and extent of the threat posed by substandard and falsified medical products. Annex 5, adapted from Pisani *(29)*, outlines the main data sources identified by this study and also lists data sources that were excluded, including because the data were not always publicly available and/or they included intellectual property considerations. All have advantages and disadvantages, including in terms of resources required, and all are most useful when used in combination. Potentially rich data sources, however, exist within national, regional and sectoral systems which could, with appropriate safeguards, be used to enrich our understanding of the magnitude, distribution and impact of substandard and falsified medical products. Data routinely recorded by national regulatory authorities could, if shared within appropriate partnerships, help identify patterns and trends regionally and globally. Postmarket surveillance systems maintained by regulatory and health authorities, global health bodies and the pharmaceutical industry could contribute information that would increase understanding about prevalence. Customs seizures provide a potential entry point for risk-based surveillance that has a public health focus. Pharmacovigilance systems may also provide useful information in terms of health impact of substandard and falsified medical products.

In this study, the exclusion of studies that tested samples acquired only over the Internet may also have reduced representation for those countries where Internet purchases are widespread. For example, in high income countries, this may under-represent prevalence and costs in the large United States market, where consumers bear a higher burden of out-of-pocket spending on medicines than their counterparts in most European Union countries, and where the use of Internet pharmacies that can introduce vulnerabilities to the supply chain is well-developed *(5, 40)*. The public health concern with online pharmacies is clear, particularly as many have been found to sell medicines that are unapproved, contain the wrong concentration or no API, and sometimes have toxic ingredients *(40)*. The absence of advice from a health practitioner, such as a physician or pharmacist, leading to patient self‐diagnosis and self‐medication, introduces additional risks of adverse events. These include overdosing, drug interactions and administration of the wrong medication and/or dose. Despite efforts to regulate online pharmacies, they pose unique challenges, ranging from jurisdictional concerns to the difficulty in tracking physical locations *(40, 41)*. The full spectrum of e-commerce of medical products, ranging from Internet pharmacies to smartphone applicationsthrough to social media and business to business platforms, requires detailed understanding which can only be achieved by targeted research. These sources may contribute to national and global estimations over time, but it is clear that more primary data collection will be necessary.

Box 7 lists areas in which it would be useful to gather data to enable a more complete, accurate and representative picture to be built up of the health and economic impact of substandard and falsified medical products.

**Box 7: Data to better understand health and economic impact**

**To construct estimates of the health impact of substandard and falsified medical products the following data would be useful:**

* reliable estimates of the prevalence of substandard and falsified medical products, by product type, geographical distribution and level of active ingredient;
* reliable estimates of the burden of disease and health service utilization, by geographical distribution;
* estimates of the effect of subtherapeutic dosing on morbidity, mortality and (for anti-infectives) antimicrobial resistance, for each drug/disease pairing.

**Estimates of the economic impact of substandard and falsified medical products will be based largely on these health impact estimates, but will require additional information, including:**

* publicly available estimates of out-of-pocket and health system spending on health care, appropriately disaggregated by disease and geographical region;
* estimates of income lost to death or increased morbidity;
* estimates of the economic impact of increased antimicrobial resistance on health systems;
* estimates of the costs to regulators and industry of product recalls and other expenses associated with substandard production or falsification of medical products.

It is well recognized that investing in public health generates cost-effective health outcomes and contributes to wider sustainability, with economic, social and environmental benefits *(42).* Taken in conjunction with the report on the *WHO*

*Global Surveillance and Monitoring System for substandard and falsified medical products*, it is hoped that these two studieswill provide the impetus to make a compelling case for mainstreaming the prevention, detection and response to substandard and falsified medical products as a “good buy” for health.