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Recommendations for health authorities on criteria for risk assessment and prioritization of cases of unregistered/unlicensed, substandard and falsified medical products

Activity A of the WHO Member State mechanism November 2017

INTRODUCTION

1. The existence of unregistered/unlicensed, substandard and falsified medical products on the market and their consequences for public health cause national and/or regional regulatory authorities (NRRAs) to face the need for structuring and improving their processes for an effective response.

2. The document "Recommendations for health authorities to detect and deal with actions, activities and behaviours that result in substandard/spurious/falsely-labelled/falsified/counterfeit medical products",[1] reviewed by the Member State mechanism at its third meeting, refers to the need for a risk assessment approach in the evaluation of alerts, notifications and reports received by NRRAs. The present document was developed with the aim of presenting information on this matter for the consideration of NRRAs, given the mandate of the Member State mechanism prioritized activity A (drafting recommendations on criteria for risk classification and assessment prioritization of cases of unregistered/unlicensed, substandard and falsified medical products),[2] and taking into consideration the fact that there are no references approved by WHO in this area.

3. The risk assessment is a process of assessing the potential severity of each risk event, based on the premise that not all of them are equally important. The results of a risk assessment should be used to establish an importance ranking, based on the identification of cases with greater potential to cause serious damage to public health, in relation to which the NRRA must take immediate action. Ranking the events based on their significance provides references for the decision-makers of NRRAs to better understand where resources may be most needed in order to protect patients' health and safety. Also, the ranking allows the adoption of other strategies in cases identified as lower risk.

[1] The term "substandard/spurious/falsely-labelled/falsified/counterfeit medical products" was replaced with "substandard and falsified medical products" at the request of the Seventieth World Health Assembly in May 2017 (decision WHA70(21)).

[2] See A/MSM/3/3, Annex 3 (Available at http://apps.who.int/gb/sf/pdf_files/MSM3/A_MSM3_3-en.pdf, accessed 7 November 2018).

4. This risk assessment is intended to provide NRRAs with a simple tool, so that regulators can quickly assess information presented in the alerts, notifications and reports received and take proportionate action, as appropriate.

5. The use of a well-defined procedure/tool to perform a risk assessment is desirable. The possibility of multiple interpretations or evaluations of the same event by different personnel involved in this activity within a given NRRA often results in different prioritization of cases. The difficulty inherent in this kind of evaluation arises from the existence of several factors involved in defining the severity of an event, and different factors influence the final analysis differently. In this scenario, a systematic procedure/tool would allow the NRRA to obtain standardized and reliable results.

6. Besides helping the identification of potentially serious cases, the risk assessment of the alerts, notifications and reports received by an NRRA allows the adoption of broader strategies for regulatory action in the face of the detected problems and risks, considering the regional and national circumstances and the NRRA's technical capacities. All alerts, notifications and reports, when considered as a whole, can provide input to various regulatory actions, such as the establishment of inspection programmes, the definition of the scope and focus of specific inspections, the content of a specific regulation and the scope of capacity-building activities, as well as educational and information programmes targeting the public in general, health professionals, etc.

OBJECTIVE

7. The objective of the present document is to describe elements and criteria that might be considered in the risk assessment and prioritization of events involving unregistered/unlicensed, substandard and falsified medical products. It should serve as a reference for NRRAs to customize or create their own risk analysis and management procedure/tool, promoting better application of their existing resources.

8. This document does not aim to define mandatory or stringent procedures to be adopted by NRRAs or to exhaust the discussions related to the theme. The application of the present document by NRRAs should consider the regional/national reality, as well as the infrastructure of the NRRA itself.

SUGGESTED RISK ASSESSMENT

9. There are many different risk analysis and management tools ready for use that may need to be customized, based on the regional/national needs and realities. The NRRA can also develop its own procedure/tool. In both cases, the selection must consider, initially, the support required for the analysis that the organization is trying to accomplish, as well as the subsequent decisions, providing the necessary information with the required amount of detail. The availability of the required data should also be considered. If the NRRA has in place systems to collect and treat notifications of unregistered/unlicensed, substandard and falsified medical products, the integration of the tool with these systems is desirable.

10. The ultimate goal of risk analysis and management tools should be to evaluate the potential impact of the alerts, notifications and reports received by NRRAs on patients' health and safety, and several factors contribute to this overall risk.

11. **Falsified products should always be considered by NRRAs as high-risk cases.** The level of uncertainty (and hence the level of potential risk) is usually higher for falsified products when compared with substandard products. Because of this, **any case of falsification or suspicion regarding a falsification must be investigated immediately**. Some elements of the risk assessment might be

considered to assist when prioritizing confirmed or suspected cases of falsified products, in order to assist the NRRA in the decision on where to act first when faced with multiple cases of falsified medical products and limited resources. Each NRRA may adapt the risk assessment tool to fit these purposes.

12. **A similar rationale applies to unregistered/unlicensed medical products whose origin is unknown**, meaning that manufacturers and other agents act without due authorization from the NRRA in a specific territory. Nonetheless, **the evaluation of unregistered/unlicensed medical products may consider other factors**, as the contact with other NRRAs may reveal that products are properly registered/licensed and in good standing elsewhere, which might minimize their potential risk.

13. Since falsified products should always be considered by NRRAs as high-risk cases, the risk assessment tool to indicate priority levels will be especially useful for the analysis of unregistered/unlicensed and substandard medical products, and mainly for the latter.

14. Assessment of the potential risk of unregistered/unlicensed and substandard medical products on patients' health and safety requires the evaluation of a combination of many factors, some of which are presented below. Each NRRA should identify and select, based on its experience and the data available, factors to be considered in the evaluation. Some data may not be important to define the immediate impact of the product on patients' health and safety, but are a relevant part of the assessment carried out by NRRAs, since they might impact the time frame for the initiation of action, the extension of action and the decision itself.

15. The examples are provided for illustrative purposes only; they are not exhaustive and should not be used as sole guidance for risk classification.

- **Severity of defect/non-compliance:** non-compliant[1] medical products can present problems of various kinds, as they result from distinctive actions, activities and behaviours. These cases of non-compliance offer different levels of risk to public health. The NRRAs must evaluate the consequences of each deviation for the health and safety of patients.

- A defective package can constitute a minor case of non-compliance if it does not affect the quality of the product; or it can be a major or even a critical case of non-compliance if it affects the quality of the product or its integrity. The absence of registration or licence for a product or company should also be considered a type of event, and its severity should be taken into account. Examples are listed in Annex 1.

- **Potential clinical consequences, taking therapeutic indication into account:** the intended use of a medical product should be considered by NRRAs alongside the severity of defect/non-compliance to estimate the consequences for the health and safety of patients.

- Depending on the deviation, non-compliant medical products used in the control of severe diseases can lead to death or to permanent impairment or loss of quality of life, having usually a higher impact on the patient's health than products used for the treatment of symptoms or for prevention. Both acute and long-term risk (cumulative risk) should be considered.

[1] For the purposes of the present document, the expression "non-compliant" will be used when collectively referring to "unregistered/unlicensed and substandard medical products", for reasons of simplicity.

- **High-potency or low-therapeutic-index medical product:** among medical products of system-wide action, those with high potency or a low therapeutic index normally represent even higher risks.

- **Patient population:** the public for which the medical product is intended may increase the risk posed by a deviation for the patient's health and safety. This evaluation should consider the vulnerability of the patients who may take the medicine and the ability to recover based on their health condition.

- Cases involving products employed by patients who are more vulnerable tend to present a higher level of priority when compared with cases involving products with a different targeted public. Paediatric or geriatric patients, pregnant women, neonates and immunocompromised patients usually have higher vulnerability.

- **Route of administration and place of action:** the route of administration of the medical product and its place of action in the body can give information about its extent of action, as well as about the possibility of interrupting its use. Medical products with local action usually present a lower potential to cause damage to the patient's health when compared with products with systemic action.

16. **It is desirable that the risk assessment should include, as a minimum, the subjects listed above.**

17. The subjects listed below might not have a direct impact on risk categorization, but may be relevant in the action plan developed by a given NRRA to define the next steps for a specific case.

- **Probable place of the deviation occurrence:** probability that the defect has occurred in the medical product as supplied by the manufacturer or importer, or is caused by inadequate transport or storage, or is introduced at the time of dispensing.

- **Exposed population:** the potential number of patients exposed to a non-compliant medical product can define the extension of the action – local, regional, national or global – and also the time frame to initiate the actions.

- Inevitably, this evaluation must consider the clinical relevance of the medical product. It is sometimes impossible to determine the number of patients exposed, and in this case the exposed population might be calculated considering the amount of product manufactured and distributed, when applicable.

- **Frequency of occurrence:** the frequency of occurrence of a deviation (related to a product or company) can indicate to NRRAs if the actions should be restricted to the product or lot/batch involved, or if a broader approach may be required. However, determining frequency may be difficult in some cases, because product defects are not always readily detected and data may therefore be incomplete.

- **Market turnover and expiration date:** this information might help NRRAs to decide which action should be taken, based on the probability of having the non-compliant medical products still on the market and also the possibility of collecting samples for official analysis.

- **Single medical product on the market or medical product used in national/international health-care programmes (e.g. WHO prequalified medicines, public vaccination campaigns):** this information must be considered before the decision to withdraw a medically critical product from the market or ban a company, taking into account the possibility that a shortage/lack of a specific product might cause more damage than the presence of a marginally substandard product. This risk–benefit analysis will depend on the level of criticality of the deviation.

- **Detectability of defect/non-compliance:** for the purposes of analysis as a risk factor, if a defect or case of non-compliance is easily detectable by the consumer or health care professional, the risk can be considered as lower, because its use will be usually less likely. However, it is important to note that patients might decide to consume the medical product regardless of their suspicions of non-compliance. This may arise due to patient vulnerability or patient belief that no real harm will occur or that harm has not occurred in the past in similar situations.

18. Apart from the above-mentioned issues, other elements may be aggregated to the analysis, such as: the relevance of the investigated case of non-compliance in the local community; the history of the manufacturer and of the product involved; the frequency with which the alerts, notifications and reports of a certain kind of problem are received; the severity of risk to patients who may be exposed to the product; the existence of elements related to the toxicity or microbiological risk of the products; the existence of analytical reports or other scientific evidence of non-compliance.

19. As mentioned, each factor affects the "final risk" with a different weight, meaning that some of them are more relevant than others to the final conclusion. With this in mind, it is desirable that NRRAs define the importance level of each factor.

PRIORITIZATION

20. The risk assessment is an important tool to evaluate each event individually, allowing NRRAs to define the associated risk. The results of this assessment should be used to identify the cases with the greatest impacts on the health and safety of patients, allowing the NRRA to reduce the time frame to initiate actions and also to establish a protocol of actions according to the severity of the case. This kind of evaluation is especially important where the number of alerts, notifications and reports received by NRRAs, including those from patients, are larger than the NRRAs' capacity to act immediately in all cases. A prioritization evaluation is based on the premise that not all events are equally important.

RISK CLASSIFICATION AND PRIORITIZATION MATRIX

21. As mentioned, it is desirable that NRRAs establish a procedure or develop/customize a tool to perform a risk assessment, in order to obtain standardized and reliable results during the evaluation of alerts, notifications and reports related to unregistered/unlicensed, substandard and falsified medical products, avoiding multiple interpretations and evaluations of the same event by the different personnel involved in this activity.

22. There are several different prioritization matrices, each of them using unique criteria to define priorities. The selection of the criteria is a decision to be taken by each NRRA.

23. One possible approach is the internal development of a matrix to help an NRRA to perform this assessment. A suggested methodology and matrix are described below, provided for illustrative purposes only.

24. The proposed matrix has two main principles. The first is that the risk factors that compound the evaluation have different importance for the final result, which means some are more relevant than others. Relevance levels and rates (expressed as numbers) must be established by NRRAs individually, taking into consideration national/regional circumstances, as specific guidance is not provided by the present document.

25. The second principle is that the evaluation can be performed individually for each risk factor; this strategy facilitates the analysis, which involves many factors. The combination of the values will provide a final result, which indicates the severity and, consequently, the prioritization level for the case. The results obtained with the matrix should not be used strictly, being a reference for the NRRA.

26. Based on this, four steps are recommended.

- Step 1: the identification of the main elements involved in the risk assessment, considered "risk factors". Examples are detailed in section 3 of the present document.

- Step 2: the establishment of the "importance level" or, in other words, rating the "weight" of each risk factor.

- Step 3: the definition of different categories inside each risk factor, taking into consideration criteria related to the severity of the case and to the possible impact on patients' health and safety. Three categories are suggested: low risk (rated as 1); medium risk (rated as 2); and high risk (rated as 3) (see Fig. 1).

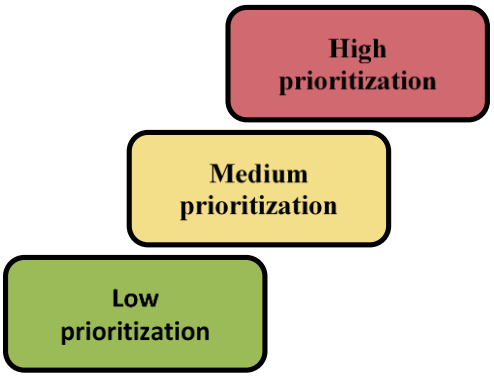
Fig. 1. Suggested matrix

Risk factor	Importance level	Categories	Rate	Rate per factor
		Low risk	1	
		Medium risk	2	
		High risk	3	

27. The result using the matrix is obtained by multiplying the importance level of each risk factor by the rate of the selected categories, and then adding up the rates per factor.

- Step 4: the establishment of groups of prioritization, based on the sums obtained from the matrix. Suggested groups are: low prioritization, medium prioritization and high prioritization (see Fig. 2).

Fig. 2. Groups of prioritization



28. The results should also be reviewed in the light of risk factors that are not included in the matrix, so as to guarantee that the case is correctly placed in one group of prioritization.

29. The final result should come into one of the three groups of prioritization, and represents an index to be employed as the indicator for prioritization against other assessed cases. The higher the index, the higher the severity and importance of the case for public health. See Annex 2 for an illustrative example.

30. After the development of the matrix, it is desirable that the NRRA proceeds with its validation within a specified period of time or number of notifications, in order to confirm the results obtained with its use before its full implementation.

FINAL COMMENTS

31. All alerts, notifications and reports regarding falsified, unlicensed/unregistered and substandard medical products should be assessed by NRRAs as soon as possible, aiming at identifying the cases with greater potential to cause serious damage to public health, in relation to which the NRRA must take immediate action. Each NRRA should establish a target time frame for the speedy assessment of alerts, notifications and reports to be referred, based on the resources available for analysis. The assessment should be performed by experienced personnel, qualified within the necessary field of expertise, and may require a multidisciplinary team to accurately assess public health risks.

32. Bearing in mind the need to provide the necessary regulatory answers for the complaints received, it is important to establish, for each group of prioritization, a procedure that states a maximum time frame to initiate action, and also the tasks and activities that might be performed for each prioritization group (e.g. inspection of a company, product recall, issuing of public alerts, etc.).

33. The NRRAs can also include, in their risk assessment and prioritization procedure/tool, the evaluation of non-compliance related to good practice requirements, considering that the actions adopted by the NRRAs may differ based on the evaluation of each case of non-compliance as minor, major or critical, according to its impact on the final product.

ANNEX 1

EXAMPLES OF QUALITY DEFECTS IN PRODUCTS

1. The examples listed below are provided for illustrative purposes only, and they are not exhaustive. It is important to bear in mind that the same defect might be categorized in more than one risk category, depending on the potential clinical consequences, taking therapeutic indications into account, and the exposed population.

	Type of defect
Related to the secondary packaging	Absent, illegible or incorrect mandatory labelling information
	Absence of anti-tampering devices
	Defects on the packaging (crushed, wet, partially open, ripped)
	Different packaging than that approved by the NRRA (colour, size, information, font, etc.)
	Absent or incorrect leaflet
	Absent or incorrect accessories (dropper, dosing cup, syringe, applicator, etc.)
	Lower quantity of units of the product (missing ampoules, blisters, etc.)
Related to the primary packaging	Absent, illegible or incorrect mandatory labelling information
	Inconsistency between information contained in primary and secondary packaging
	Different packing than approved by the NRRA (material, colour, size, information, font, etc.)
	Lack of information about pharmaceutical form, volume
	Defects in the packaging (deformed or punctured stopper, broken or cracked glass, vial leakage, punctured or open blister, etc.)
	Absent label or wrong label (due to mix-up)
	Label not properly fixed or damaged
	Inoperable or malfunctioning devices (filled syringe, inhaler, etc.)
Related to the product itself	Unexpected modification of organoleptic or appearance properties
	Contaminants or unexpected physical–chemical modifications
	Products manufactured in non-compliance with the marketing authorization specifications
	Out-of-specification status confirmed by analysis (assay, disintegration time, dissolution, sterility, endotoxin, friability, viscosity, hardness, etc.)
	Presence of foreign material on the surface or inside the product
	Difficulty of resuspension, material compacted in the bottom or adhering to the inner surfaces of the bottle
	Microbiological contamination
Others	Unregistered/unlicensed products
	Products manufactured by unauthorized manufacturer
	Products with altered expiration date
	Product illegally packaged reusing the original package of a legal product

ANNEX 2

PRACTICAL EXAMPLES OF THE USE OF THE MATRIX

1. The examples presented below are provided for illustrative purposes only, in order to demonstrate the application of the matrix to fictional cases in a fictional national reality (Country X). Relevance levels and rates might vary in different jurisdictions.

2. Situation: the NRRA in Country X receives three notifications, according to the description below, and it needs to identify the prioritization to be given to each of them.

3. First, the NRRA in Country X selected the risk assessment factors to be considered in the evaluation, and defined the relevance level of each factor in the final result. In this case, the NRRA considered that the potential clinical consequences (taking therapeutic indications into account) are more relevant than severity of defect/non-compliance and the recommended patient population. Less relevant are the route of administration and place of action.

4. The prioritization categories defined by the NRRA in Country X are: low prioritization 8–13, medium prioritization 14–18, high prioritization 19–24.

5. Based on the sums of the matrix, situation 1 received 23 points, situation 2 received 12 points and situation 3 received 17 points. The analysis of this scenario indicated that situation 1 has a higher risk than situation 3, and situation 2 has the lowest risk. This information might suggest when and how an NRRA should act in each described situation.

Situation 1: Medicine (tablet) used as the main treatment for breast cancer was tested, and the official laboratory detected an assay 40% below the specification.

Risk assessment factor	Importance level	Categories	Rate	Rate per factor
Severity of defect/ non-compliance	2	~~Low risk~~	~~1~~	2 x 3 = 6
		~~Medium risk~~	~~2~~	
		High risk: assay below the specification	3	
Potential clinical consequences	3	~~Low risk~~	~~1~~	3 x 3 = 9
		~~Medium risk~~	~~2~~	
		High risk: medicine used in breast cancer	3	
Recommended patient population	2	~~Low risk~~	~~1~~	2 x 3 = 6
		~~Medium risk~~	~~2~~	
		High risk: immunocompromised patients	3	
Route of administration and place of action	1	~~Low risk~~	~~1~~	1 x 2 = 2
		Medium risk: internal use, oral use	2	
		~~High risk~~	~~3~~	
			TOTAL (6 + 9 + 6 + 2)	**23**

Situation 2: Medicine (tablet) used for flatulence was tested, and the official laboratory detected an assay 40% below the specification.

Risk assessment factor	Importance level	Categories	Rate	Rate per factor
Severity of defect/ non-compliance	2	~~Low risk~~	~~1~~	2 x 3 = 6
		~~Medium risk~~	~~2~~	
		High risk: assay below the specification	3	
Potential clinical consequences	3	**Low risk: symptom treatment**	1	3 x 1 = 3
		~~Medium risk~~	~~2~~	
		~~High risk~~	~~3~~	
Recommended patient population	2	**Low risk**	1	2 x 1 = 2
		~~Medium risk~~	~~2~~	
		~~High risk~~	~~3~~	
Route of administration and place of action	1	**Low risk: oral use, not absorbed**	1	1 x 1 = 1
		~~Medium risk~~	~~2~~	
		~~High risk~~	~~3~~	
			TOTAL (6 + 3 + 2 + 1)	**12**

Situation 3: Medicine (solution) used for fever in babies was tested, and the official laboratory detected an assay 40% below the specification.

Risk assessment factor	Importance level	Categories	Rate	Rate per factor
Severity of defect/non-compliance	2	~~Low risk~~	~~1~~	2 x 3 = 6
		~~Medium risk~~	~~2~~	
		High risk: assay below the specification	3	
Potential clinical consequences	3	**Low risk: symptom treatment**	1	3 x 1 = 3
		~~Medium risk~~	~~2~~	
		~~High risk~~	~~3~~	
Recommended patient population	2	~~Low risk~~	~~1~~	2 x 3 = 6
		~~Medium risk~~	~~2~~	
		High risk: medicine used in children	3	
Route of administration and place of action	1	~~Low risk~~	~~1~~	1 x 2 = 2
		Medium risk: internal use, oral use	2	
		~~High risk~~	~~3~~	
			TOTAL (6 + 3 + 6 + 2)	**17**

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