MEDISAFE P-66

MEDISAFE NATIONAL PHARMACEUTICAL SUPPLY CHAIN SECURITY GUIDE

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Foreword

The Supply Chain Security for medicines poses a highly complex challenge in normal times and is seriously exacerbated during crisis, conflicts, natural disasters and emergencies. The European Union/Expertise France Medisafe Project has recognized the difficulties this challenge represents to the safety and integrity of supply chains endangering public health and public safety.

The National Pharmaceutical Supply Chain Security Guide describes supply chain organisation and offers recommendations for its establishment from a risk management approach recognizing that countries have different capacities and resources to secure national supply chains. It analyses the whole spectrum of security measures encompassing storage transportation, storage, distribution and stock management.

The Guide lays a strong emphasis on traceability systems, market surveillance, vigilance and control including reporting systems. It identifies the main actors in national supply chain and their authorisation and supervision within legal and regulatory provisions required for them.

It contains a number of recommendations for customs/borders controls and the legal responsibilities to ensure that proper documentation checks are performed. It highlights the salient features of online sales of medical products, its legal aspects, proposes a strategy to control them and formulates recommendations for cybercrime teams to address this growing phenomenon.

Finally, the Guide proposes a communication strategy which needs to be in place when a substandard and falsified product is suspected or detected.

We sincerely hope that this Guide will be a useful complement to countries toolbox to comprehensively address the enormous challenge that supply chain security constitutes and that it will provide critical and practical guidance to regional and national authorities for effective control.

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INTRODUCTION

MEDISAFE is a project funded by the European Commission that is managed by Expertise France.

The overall objective of MEDISAFE is to support the fight against the production and trafficking of Substandard and Falsified Medical Products (SFMP) for better public health outcomes in eleven countries (Burundi, Ethiopia, Democratic Republic of Congo, Ghana, Kenya, Malawi, Rwanda, Seychelles, Tanzania, Uganda, and Zambia) supported by the European Union Chemical Biological Radiological and Nuclear (CoE CBRN) Regional Secretariat for Eastern and Central Africa.

Specifically, the project is contributing to the fight against organised crime and to achieve better health outcomes, based on two strategies:

1. **Contribute to strengthening partner countries' capacities** in the definition, identification, and control of SFMP, and in the fight against their production, trafficking and use in Eastern and Central Africa

2. **Develop or strengthen the legal framework and promote regional cooperation** and harmonization in terms of approaches, procedures, and joint operations to combat the production and trafficking of SFMP.

The presence of SFMP is a problem that appears to be growing as global supply chains become more complex and e-commerce spreads. Driven by globalisation of trade and the increasing complexity of supply chains, involving several actors (manufacturers, importers, distributors, pur chasers, retailers, regulators, health workers, patients) in a variety of countries and frequent transfer of product responsibilities in global and national supply chains, it is likely to increase unless serious, well-resourced efforts are undertaken to tackle the issue.

SFMP are more likely to be present in national supply chains (SC) when corruption or bad practices exist, but also due to poor infrastructure, lack of human resources, lack of proper control, lack of awareness and information and in the long term a decrease in vigilance at different levels. The presence of SFMP in formal supply chains can harm patients/consumers, is reducing trust in health systems, but could also lead to an increase in drug resistance and resources being wasted.

The MEDISAFE project, in line with the World Health Organization strategy to prevent, detect and respond to substandard and falsified medical products, is supporting countries to strengthen pharmaceutical systems and legal frameworks. This guide looks at different activities that are necessary to strengthen supply chain security (from the arrival of products in country, to procurement from local manufacturers to delivery to health facilities or private pharmacies/outlets) to prevent the presence of SFMP in formal supply chains but also to guide national supply chain actors to detect SFMP in national supply chains and to deal with suspected cases. This guide does not cover direct measures necessary to reduce the informal sector in a country. However, one of the best ways to combat the informal market is to provide assurance that the legal market is controlled and guarantees the quality of the medicines available.

This guide has been developed based on international guidelines, experiences shared by Medisafe country representatives during a regional workshop in Nairobi, Kenya in April 2022, and experiences from international experts from organisations that are part of the Medisafe consortium (APROPHISP and CHMP). In each chapter, a risk management approach is suggested, which takes account of the fact that countries may have different capacities and resources to secure national supply chains.

A first draft of this guide was piloted in three countries (Burundi, Malawi, and Zambia) with the support of national experts and the guide was then amended to include the lessons learned from the first assessments undertaken.

This guide will be useful for all actors involved in supply chain activities in the public and private sector for medical products (including medicines and other medical products, such as medical devices).

OBJECTIVE OF THIS GUIDE

The objective of this guide is to describe the main measures that need to be in place in a country to secure national supply chains (public and private). It includes regulatory aspects, good practices, points for vigilance and guidance for developing reporting systems, for investigations or to manage incidents. It is also a tool to assess national supply chain security, and when gaps are identified, to guide policymakers and national actors on how to further strengthen their system to reduce the presence of SFMP and to manage suspected cases in line with the national resources available.

This guide does not cover the upstream (manufacturing) and downstream (prescribing and dispensing) activities and assumes that institutions responsible for procurement have put in place strong quality assurance systems to ensure products entering in the national supply chains are of appropriate quality, safety, and efficacy. It is also does not focus on potential measures to combat the presence of SFMP in the informal sector.

NATIONAL PHARMACEUTICAL SUPPLY CHAINE SECURITY GUIDE

HOW TO USE THIS GUIDE?

This guide can be used to assess the current situation in each country and to identify gaps/weaknesses in supply chain security. It can also help to identify good practices to secure the formal supply chain.

In each chapter, a list of key points for attention is provided to help make an assessment and there are some suggested questions in Annex 1 for assessing the context.

To carry out this assessment, it is strongly recommended that key national actors in the fight against SFMP work together. Critical points should be identified, and assessors should keep in mind gaps or weaknesses identified that will help to identify improvements needed to limit the introduction of SFMP into the national supply chain and to strengthen supply chain security.

The improvements needed should be converted in a work plan with concrete interventions/activities listed for consideration by the government and the National Regulatory Authority (NRA). These activities should be prioritised and then a responsible entity and a reasonable timeline for each activity should be identified. The assessment and the plan may help to mobilise resources with the government and partners to move the agenda forward.

Given that each chapter includes concrete recommendations, the SC security guide could also be used by national actors to look at specific activities when designing or reviewing an existing system to ensure all critical elements are in place to strengthen SC security. It can also be used to support training activities of national SC actors.

The reference documents listed at the end of this guide are classified as general references or are linked to a specific chapter and could also help the reader to find additional references to further strengthen national supply chain security. They complement the initial recommendations provided in this guide.

ACRONYMS

AMA	African Medicine Agency
APROPHISP	Association professionnelle des pharmaciens inspecteurs de santé publique
B2B	Business to Business
CAPA	Corrective Action Preventive Action
CHMP	Centre Humanitaire des Métiers de la Pharmacie
COE CBRN	Centre of Excellence for chemical, biological, radiological, and nuclear defence
COVID-19	Coronavirus
EDQM	European Directorate for the Quality of Medicines
FEFO	First Expired First Out
GDISPP	Good Dispensing Practices
GMP	Good Manufacturing Practices
GPS	Global Positioning System
GSDP	Good Storage and Distribution Practices
ICH	International Council for Harmonisation
INN	International Non-Proprietary Name
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
LMIC	Low- and Middle-Income Countries
LMIS	Logistic Management Information System
MOH	Ministry of Health
MOU	Memorandum of Understanding
MRA	Mutual Recognition Agreement
NGO	Non-governmental Organization
NQCL	National Quality Control Laboratory
NRA	National Regulatory Authority
PMS	Post Marketing Surveillance
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality Control
QCL	Quality Control Laboratory
QR	Quick Response
QRM	Quality Review Management
REC	Regional Economic Community
SFMP	Substandard and Falsified Medical Products
SC	Supply Chain
SMS	Short Message Service
SOP	Standard Operating Procedure
TV	Television
UMC	Uppsala Monitoring Centre
WHO	World Health Organization
WHO TRS	World Health Organization Technical Report Series
WMS	Warehouse Management System

1. SUPPLY CHAIN ORGANISATION

1.1 Brief description

In order to strengthen medical product supply chain security in a country, it is critical to have a clear overview of the SC actors in the public and private supply chains. This mapping is needed to check who are the actors in the supply chains and to identify the regulatory body (or bodies) that should control these entities. The National Medicine Policy should clarify who has the responsibility to control the SC actors and the national regulations should set out the responsibilities of regulatory bodies and empower them to act.

This mapping exercise is critical to identify where SFMP could enter the formal supply chain. The more actors there are in national supply chains, the more frequent the transfer of responsibilities for products is and the higher the risk of introducing SFMP.

WHY IS THIS ACTIVITY IMPORTANT IN THE FIGHT AGAINST SFMP?

Having a clear mapping of SC actors in a country will help the regulatory bodies to control them and to reduce SFMP entering the supply chain. It will also help to identify actors in the informal sector and to take measures to ensure they comply or to stop their activities.

Supervision of SC security is based on four building blocks:

1. National capacity with adequate resources
2. Availability of clear regulations for all SC activities
3. Licensing and limiting the number of the SC actors while ensuring they respect the national guidelines for their interventions
4. Checks by the regulatory bodies of the capacity of SC actors to implement regulations

The main regulator that controls supply chain actors in a country is the National Regulatory Authority (NRA). Without a functional NRA, the country is not able to ensure the regulatory oversight of medical products and to have a regulatory system able to prevent, detect and respond to SFHMP. The WHO Global Benchmarking Tool for assessing NRAs has identified several SFMP related indicators (11 directly measuring SF medical products and 80 sub-indicators indirectly measuring SF products) among different regulatory functions that should be in place: National Regulatory System, Market Surveillance and Control, Vigilance, Laboratory Testing, Regulatory Inspection.

1.2 Recommendations for supply chain organisation

OBJECTIVE: A MAPPING OF THE SUPPLY CHAIN ACTORS IN THE PUBLIC AND THE PRIVATE SECTOR IS AVAILABLE

The existence of an updated mapping of supply chain actors is the responsibility of the pharmaceutical department in the Ministry of Health or the NRA.

A mapping of the national supply chain should confirm the type and number of SC actors existing in a country and check that they have authorisation to operate. This mapping should also show how these actors interact with the others in relation to the flow of products. It is also necessary to update this mapping on a regular basis.

It is always good practice in a country to have a graph showing this mapping when presenting the national supply chain to external parties. It may also help stakeholders to have a good understanding of their environment.

SC actors to be considered:

- **Public sector:** National Procurement Centre, Central Medical Store, Regional/Provincial warehouses, District warehouses, Pharmacies in Hospitals/Health Centres.
- **Private sector for profit:** Wholesalers, Distributors, Importers, Private pharmacies, Private Outlets, Pharmacies in private clinics, other pharmaceutical retailers.
- **Private sector non for profit:** Faith based procurement organisations, NGOs, pharmacies in faith-based hospitals and health facilities, community-based organisations.

OBJECTIVE: REGULATORY BODIES/ENTITIES CONTROLLING SC ACTORS ARE IDENTIFIED AND EMPOWERED TO ACT

The control of SC actors is the responsibility of different administrative entities in the country. It will depend on how the health and pharmaceutical systems are organised.

In addition to the National Regulatory Authorities, in many countries professional associations or councils may play a role in controlling retailers, particularly in the private sector. Roles and responsibilities of each entity should be clearly defined in national regulations.

Potential conflict of interests of staff, experts or board members of regulatory entities including NRAs should be properly managed to strengthen public confidence in the control done by the authority.

OBJECTIVE: THE FIGHT AGAINST SFMP IS BASED ON ACTIVE SYNERGY BETWEEN ALL STAKEHOLDERS

The fight against SFMP is the responsibility of many actors at national level and also needs to interact with other countries to exchange information or work on joint operations.

Therefore, SC actors and NRA should work closely with revenue authorities/customs, law enforcement (police, enforcement officers), ministry of justice (prosecutors/magis-

trates) and other health authorities to secure supply chains. A national coordination mechanism/task force/commission should be in place to bring these actors together to prevent and manage suspected/confirmed cases. It will be important to identify who should lead this coordination mechanism/task force/commission to drive this agenda. It is often the National Regulatory Authority, but it may sometimes require the involvement of a higher level to facilitate work among different sectors. Active synergy will require continuous communication with regular meetings, defined processes, and a shared action plan. Greater formalisation of relations and collaborations maybe also be needed between two actors through signing a Memorandum of Understanding (MoU).

It is also important within NRA that people leading the work on different regulatory functions (licensing, inspection, market surveillance and control, vigilance, and quality control) interact with others and that processes for that are defined.

1.3 Risk management approach

All investigative departments or stakeholders should implement a risk approach for assigning resources, prioritising tasks, and activities to carry out its obligations and conduct investigations. This approach is specifically intended for national competent authorities to assist them in their investigation and other risk mitigation actions. The methodology should be based on the principles and concepts of Quality Risk Management (QRM) as outlined in ICH Q9 or WHO TRS 981 Annex 2 for risk assessment, risk control, risk review and risk communication. It is necessary to develop a systematic and risk-based approach to make the best use of surveillance and enforcement resources.

The risk management approach is fundamental and should be applied in a cross-cutting way for the supervision of security by the different actors and for products and activities. This relates to all regulatory activities: market surveillance and control, vigilance, quality control, inspection, and management of suspected cases.

For instance, a model for risk-based planning for supervision should be based upon the concept of rating operators on the basis of an estimated risk that they may pose to patients or consumers. The methodology also considers the risk to product quality. The risk-based approach will enable the frequency, depth, and breadth of supervision. This will allow a flexible approach and supervision whilst maintaining a high level of safety. However, the risk-based approach should not mean that monitoring of activities considered low-risk does not happen.

2. REGIONAL AND GLOBAL COORDINATION

2.1 Brief description

Given that supply chains are more complex today, the fight against SFMP will be successful only through collaborations between governments and entities responsible for tackling this issue in these countries.

Effective global coordination mechanisms like the Member State mechanism now exist and are growing ever stronger. Global institutions, including WHO, are working in broad partnerships on many fronts to support the development of the systems, workforce, tools, and skills that are needed. The world has never been better equipped to tackle the issue of substandard and falsified medical products. If governments and other decision-makers sustain these efforts and resource them appropriately, it will be possible to turn back the rising tide of falsification, increase quality standards globally, and ensure that people all around the world have reliable access to medical products that work in the way they are supposed to.

WHY IS THIS ACTIVITY IMPORTANT IN THE FIGHT AGAINST SFMP?

Effective collaborations between countries and various sectors at regional, continental, and global level is the only way to fight against substandard and falsified medical products.

Another important global project is the program coordinated by WHO through its collaborating centre in Uppsala, Sweden (UMC: Uppsala Monitoring Centre). UMC receives and analyses the notifications that arrive in its database (VIGIFLOW database). The existence of an international adverse events monitoring network provides valuable information on the safety of use of medical products that can form the basis for detecting substandard/falsified products.

Coordination should start at the regional level and often Regional Economic Communities are a smart place to start. Through ongoing regulatory harmonization initiatives and by having stronger NRAs, a lot could be done to align regulations much more, establish stronger regulatory systems, exchange information more easily, and share good practices in the fight against SFMP. Joint post-marketing surveillance programs could also be a way to detect SF products circulating in a particular region. This could also be reinforced by reporting and sharing information

between other authorities, such as the customs, police, and judiciary bodies.

Joint operations could also be organised between countries, such as Interpol operations targeting specific supply chains, particularly online sales of medical products.

Interaction between similar actors in neighbouring countries or at international level will also facilitate sharing of expertise and information exchange and could also lead to mutual recognition/reliance and avoid duplicating efforts.

2.2 Recommendations for regional and global cooperation

OBJECTIVE: COUNTRIES SHOULD BE ACTIVE IN REGIONAL AND GLOBAL COOPERATION AGAINST SF PRODUCTS

- Countries should be part of the Member State Mechanism and participate in working groups according to national priorities and an NRA focal point should be identified.
- An NRA representative should be appointed as the focal point for the WHO Global Surveillance and Monitoring System and should report suspected/confirmed cases, when relevant.
- The NRA should adhere to regional/continental regulatory harmonization initiatives and should contribute to joint activities in the fight against SF products (e.g., post-marketing surveys). Some critical aspects of the fight against SF products can be considered at regional level when solutions at country level are difficult to find (e.g., maintenance of laboratory equipment, access to pharmacopoeias…).
- The NRA vigilance team should ensure that its national PV database is linked to the Vigibase.
- Country representatives of customs, police, and judiciary should be active in regional networks to share information.
- Countries could consider being part of joint operations under Interpol.

3. SECURITY MEASURES DURING TRANSPORTATION AND STORAGE

3.1 Brief description

To ensure the quality and the security of products transported, received, stored, and distributed, it is essential to respect several conditions and obligations throughout the supply chain. Good storage and distribution practices (GSDPs) for wholesalers/distributors have been developed for this purpose, to propose common rules to pharmaceutical actors, whatever their status (private, NGOs, faith-based, public).

The GSDPs cover all the key points in managing wholesale, distribution, and transportation of medical products and maintaining product quality.

WHY IS THIS ACTIVITY IMPORTANT IN THE FIGHT AGAINST SFMP?

In national supply chains, conditions during storage and distribution of medical products can affect the quality of products if not appropriate, leading to substandard products being supplied to patients and consumers. At the same time, security measures during storage and distribution, if not appropriate, could lead to the introduction of SF products into the legitimate supply chain or to the leakage of products to the informal supply chain.

One of the major risks is an increase in the number of intermediaries. At all levels, from central to local level in a country, during storage and transportation, non-adapted conditions could lead to substandard products, the introduction of falsified medical products or stolen medicines ending up in the illegal circuit. Distribution should be as short and direct as possible, storage and distribution conditions should be appropriate and security measures should be taken at all steps in the various storage places and during transportation in the supply chain.

4 CRITICAL RISKS TO BE MASTERED AND CONTROLLED

during the storage and distribution process, to avoid the introduction of substandard and falsified products into the legal supply chain and the feeding of the illegal market

1. Non-compliance with GSDPs, lack of quality assurance system, and lack of controls and inspection
2. Repackaging and distribution to non-authorized health facilities and/or supply to non-pharmaceutical customers
3. Storage in poor and unsecured conditions
4. Unsecured transport

3.2 Recommendations on what should be in place to secure storage and distribution

OBJECTIVE: TO ENSURE THE SECURITY OF MEDICAL PRODUCTS DURING STORAGE AND TRANSPORTATION

- Maintain the quality of medicines and medical products.
- Limit storage and transportation under temperatures and hygiene conditions that are detrimental to the integrity of the products.
- Prevent theft.
- Prevent the introduction of falsified medicines into the supply chain.

To achieve these objectives, the following points must be in place and require focused attention.

3.2.1. CONTROLS WHEN PRODUCTS ARE RECEIVED

When goods are received in a warehouse, this is a high potential point of entry for falsified products and risk of introducing them into the legal supply chain. Particular vigilance is needed at this point. It should include checks of documentation, visual inspections, and testing. As receiving good is a pharmaceutical intervention, it must be carried out by trained staff under the supervision of trained pharmacists available at each site. Controls must be carried out systematically upon receipt of goods in the following areas:

- Integrity of the medicines received (good condition of pallets, boxes, and primary packaging) with vigilance when the product is subject to special transport conditions: cold chain items, narcotics, etc.
- Conformity of the goods received with the purchase order initially placed (delivery note, invoice, transport documentation, nature of the products, identification, dosage form, strength, number of boxes).
- Visual inspection of goods received done based on an internal SOP and a checklist and any quality concerns identified must be reported to the Quality Assurance department (QA manager).
- Products received are promptly moved to an appropriate storage area after conformity checks are carried out and they should be recorded as incoming products in the warehouse management system (WMS).
- In case of doubt, the products should be quarantined, and samples of the products should be taken and sent to a quality control laboratory for analysis.
- The national regulatory authorities should be informed at this stage if a suspected product is detected, as they may have other information that could confirm the suspicion about the quality and nature of the product received.

3.2.2. PREMISES AND EQUIPMENT

The premises and equipment must be designed and maintained to provide the following:

1. Effective security and control of access to warehouses

- A security system must be put in place, with fences, an alarm system, entrance control, security guards, and permanent video surveillance.
- Only authorised staff should be allowed to enter the premises. Some premises require specific authorisation: storage rooms for narcotic medicines, expensive medicines, and computer rooms. Staff must be easily identifiable (uniform, wearing a company badge).

2. Good conditions and adequate storage capacity

- The capacity should be adapted to the volume of stocks to be kept.
- Adapted storage areas should be available, with separate marked off areas (floor markings, barriers, etc).
- The lighting, cleanliness, and temperature/humidity conditions should be controlled to avoid any impact of the local climate.
- Storage conditions should be adapted to the storage recommendations for specific products (air conditioning, cold rooms, ambient temperature rooms).
- There should be a way of separating medicines/medical products awaiting a decision (withdrawal, returns, destruction) in an identified area or under an identified validated computerised status.
- For wholesaler-distributors and national procurement centres/central medical stores: a restricted pick-up area (for collection of orders directly from the pharmacists at the wholesaler's premises) will avoid any people being able to enter the premises.
- Premises should protect the products from weather conditions and rodents: protected reception area, fire alarms, protection against pests and extreme temperatures.
- Regular checks, or preferably continuous monitoring of the temperature/humidity conditions in the facilities and freezers are in place. Records of temperature/humidity should be regularly assessed by the QA manager and adequate solutions should be taken immediately if temperature excursions are observed, in line with an SOP.

3. Special attention should be given to computerised systems (WMS)

- A detailed written description of the WMS should be available - objectives to be achieved - safeguards, scope.
- A description of the authorisation levels should exist (administrators, users).
- Protection against accidental and malicious modifications should be in place.
- The system should be designed in a way that rejected goods cannot be released.

- Regular data backups within the company and backups outside the company (data recovery in in the event of equipment being destroyed) should be carried out. Where data storage and archiving sit with a third party, a contract must be put in place and the conditions for securing data storage assessed and audited.
- The computer system must have the functionality to set levels of authorisation (user, administrator, etc.) and to describe the methods used to guarantee the protection of data against loss and modifications.
- The measures in place in the event of a system failure occurring must be detailed in an SOP for degraded operations. These procedures should be evaluated, applied, and tested.
- A dedicated data room, protected from weather conditions, that is ventilated with ambient temperature conditions compatible with IT equipment and with secure access should be available (and not used for other purposes, such as a cleaning room!), with a fire alarm, protected from rodents (risk of cable damage).

3.2.3. STOCK MANAGEMENT

Stock management should be adapted to detect, quarantine, and remove substandard and falsified products:

- Stock rotation: first expired - first out (FEFO).
- Regular stocktaking, to remove expired stock as it occurs.
- Physical and/or IT quarantine of the products, before their control, in case of doubt or in case of return.
- Traceability of all incoming and outgoing products, with purchase orders, invoices, and delivery notes. A reconciliation between incoming and outgoing products must be possible.
- Coherence of the logistic flows according to the principle of "forward motion" (reception, control, storage, preparation of orders, pick-up area for delivery).
- When samples are taken for analysis by an accredited quality control laboratory, before the release of the consignment as per national legislation, the consignment should be placed in quarantine at approved sites.
- Products suspected of being substandard, falsified, or not authorised should be kept under quarantine pending the analysis of samples and forensic investigation.

Particular attention should be paid to the **management of** clients/customers' r**eturned goods**, to avoid the resale of medical products that have lost their quality or the introduction of falsified products into the legal supply chain through this route. Returns should only be authorised if the integrity of the packaging is confirmed and is in good condition, and with a long expiry date. This requires:

- An SOP to be in place based on risk analysis: nature of the products, expiry dates, storage conditions, contractual conditions.
- Clarification of the shortest possible time acceptable between delivery and return (e.g., 10-15 days).
- Respecting the logistics chain. This must be proven, by ensuring that the customer has indeed purchased the product from the distributor. The return of cold products is possible but under certain conditions and with the assurance of respect for the cold chain.
- The evaluation of returns is carried out by a trained and authorised person.
- Finally, the decision can only be taken by the QA manager or a qualified person.

Recalled medical products need always to be managed quickly. They must be identified and stored separately in a secure area pending a decision. The status of all recalled products must be formally decided and documented. Several actions need to be taken:

- A recall procedure should be available and tested at least once a year, assessing the time taken to retrieve goods, reconciling the quantities already sold and retrieved. Results should be obtained for each customer.
- Development of a communication strategy and information channels (telephone number available 24/7, information through newspapers, TV, radio, social networks ...).
- These products must be removed and placed in a destruction area existing for this purpose.
- A record of recall operations should be available: customers impacted, batch numbers, quantities, etc.

Falsified medical products should be given special attention, through:

- Systematically informing the competent authority and the marketing authorisation holder of the presence of a SFMP, including in suspected cases.
- Developing a dedicated SOP.
- Immediate separation of detected falsified products from other medical products.
- Training staff to detect the risk of introducing a falsified health product.

3.2.4. DISPOSAL OF EXPIRED, SUBSTANDARD, FALSIFIED, AND REJECTED PRODUCTS

The disposal of expired, substandard, falsified, and rejected products must be carried out in good conditions. National regulations should exist defining how medical products should be disposed.

- Products available in the area for rejected products should be disposed of on a regular basis and should not be easily accessible.
- Disposal of medical products should be carried according to national regulations in high temperature incinerators or through other methods recommended by the regulator to limit the impact on the environment. In countries where high temperature incinerators don't exist, cement kilns can be used.
- Transportation of products to be disposed of should be carried out with caution to avoid the risk that these products

end up on the illegal market (paying particular attention to reverse logistics, particularly during transportation if they are being destroyed in a different location).

- Traceability of disposed products, in compliance with national regulations, should be in place (often a certificate of disposal is issued by the authorities).

3.2.5. TRANSPORTATION CONDITIONS

Transportation conditions are a particularly sensitive issue. The following must be respected:

- Boxes used to transport medical products should be in a packaging material that does no not interact with the content of the box to ensure the quality of the medicines and to protect them from potential contamination.
- For cold chain products or temperature-sensitive products, it is important to estimate the maximum transport time (be aware of bonded stocks), validate the container to be used and avoid any contact between ice packs and medicines/medical products.
- For temperature sensitive products, dataloggers should be placed in the shipment and data should be checked after transportation and any temperature excursion should be reported to the QA manager.
- Labelling of boxes should be clear to inform the transport agent: identification, fragility, dangerous products, cold chain, etc.
- Trucks or vehicles used should be dedicated to medicines and other medical products and should not include foodstuffs and other non-pharmaceuticals goods.They should be closed and sealed, ideally with traceability of the seal.
- If transportation is carried out by a sub-contractor, a contract should be put in place stating the conditions and security measures to transport medical products.
- Monitoring of the fleet of trucks, when possible, should be done using GPS.

3.2.6. REGULAR SELF-INSPECTIONS OR INTERNAL AUDITS

Pharmaceutical establishments should carry out regular self-inspections or internal audits in addition to NRA inspections. The process of self-inspections or internal audits should involve:

- A comprehensive self-inspection programme checking key aspects of good storage and distribution practices.
- Impartial and competent auditors (trained, accredited).
- A record of the findings observed and follow-up on corrective actions.

4. TRACEABILITY SYSTEMS

4.1 *Brief description*

Traceability is the ability to identify the origin and various stages of consumer goods production and distribution processes. It is the ability to track where a product is at any given time within a distribution system.

WHY IS THIS ACTIVITY IMPORTANT IN THE FIGHT AGAINST SFMP?

Medical products traceability systems and mechanisms are useful tools to fight against SF products. It should help to ensure only genuine products are in the supply chain and could help to track SF products where they are suspected or detected and to protect the population.

For medical products, traceability systems are crucial to track batch numbers and expiry dates, to ensure only authorised products circulate in legal SC, and prevent stolen or smuggled products entering or circulating.

Traceability systems are also extremely important to facilitate recalls when alerts are received by the country or where there is a confirmed case at national level.

Traceability systems require the availability of strong inventory systems in the national SC including batch traceability. Therefore, entities managing stocks should use Warehouse Management Systems (WMS) and countries should ensure a Logistic Management Information System (LMIS) is in place from the central to local level. These systems should systematically record the movements of products with their batch number and expiry date.

More sophisticated systems are also progressively appearing in countries called “Track and Trace systems” with authentication processes of medical products throughout the SC. This requires the implementation of barcodes and data matrix reading systems affixed by manufacturers to primary packaging to facilitate registration, stock management and order preparation. Countries could also consider as part of their regulations on traceability to ask manufacturers to include tamper-proof systems on products supplied to countries (such as stickers to seal boxes).

When implemented, the evidence provided by track and trace systems should be linked to the reporting system in NRAs and if necessary, with WHO Global surveillance and monitoring system. However, such sophisticated systems require countries to define regulations, to inform manufacturers supplying the countries about the new requirements and then to have the necessary tools to use these codes at different levels.

4.2. Recommendations for a traceability system

OBJECTIVE: AN ANALYSIS OF TRACEABILITY SYSTEMS AVAILABLE IN THE DIFFERENT SECTORS SHOULD BE CARRIED OUT TO ENSURE THAT AT A MINIMUM BATCH NUMBERS AND EXPIRY DATES ARE RECORDED

It is important to ensure that all SC actors managing medical products when recording movement of goods record batch numbers and expiry dates.

This should be checked when inspecting/supervising SC actors.

It is also important to ensure pharmaceutical actors are regularly testing their capacity to handle recalls through mock recalls at least once a year and to have a clear communication strategy in case of a recall (with a ready to use list of contacts). This will help to ensure when a suspected/confirmed case occurs that the identification of products can be done quickly to quarantine or to recall them.

OBJECTIVE: IN COUNTRIES PLANNING TO IMPLEMENT A TRACK AND TRACE SYSTEM, A ROADMAP SHOULD BE DEVELOPED SETTING OUT THE MAIN ACTIVITIES AND REALISTIC TIMELINES

- Countries should not underestimate the investments needed to implement a Track and Trace System.
- Implementing such a system requires resources at national level but also at the manufacturer level and will also mean ensuring the codes put on the product can be used by all SC actors from the central to the local level.
- Set out the traceability model to be used (point of dispensing check or full track and trace) and define what products/steps should be identified in the SC and how they should be identified.
- Products will have to be identified at a minimum by their INN, formulation, strength, batch number, and expiry dates but some countries may decide to also use serialisation, so that each unit produced can be clearly identified.
- Develop regulations and define regulatory requirements that should be communicated to manufacturers/suppliers supplying products to the country (from abroad or locally).
- Define if they will use global or local identification standards (bar code/QR code).
- Timelines for the implementation of the codes on products should be defined clearly and realistic as it requires investments from manufacturers on packaging lines and to maintain a database of codes.
- A national database holding this information should be put in place and accessible to all SC actors.
- SC actors will also need to consider having the capacity to check these codes each time a product or a parcel is moved. This will require resources and reading tools to be available in the SC.
- Countries may also consider starting with some categories of products to test the new system before expanding it to more products.

Considering the complexity of establishing a Track and Trace system and the significant investments and high costs associated, a phased approach to implementation is strongly recommended.

5. OVERSIGHT OF THE MAIN ACTORS IN NATIONAL SUPPLY CHAIN (SC)

5.1 Brief description

The main actors in the national supply chain (SC) are manufacturers, wholesalers and distributors, retailers, such as private pharmacies and outlets, national procurement centres, central medical stores, and health facilities from regional/provincial, district and local levels.

To improve oversight of the private and public supply chains, an important aspect is to authorise and control these actors.

Comprehensive allocation of resources and capacity to enforce regulations is required for authorisation and inspection activities and assessing their performance is essential to ensure that SC oversight achieve its objectives and targets.

This chapter aims to guide countries in assessing measures to be put in place to better control SC actors to ensure they work in line with national guidelines set out for their area of activity.

WHY IS THIS ACTIVITY IMPORTANT IN THE FIGHT AGAINST SFMP?

Ensuring that all actors in the SC are respecting regulations is fundamental to prevent SFMP from entering in the national supply chains in all sectors (public and private).

1. The risks associated with SC activities that could lead to supplying SFMP and applicable regulations, including good practices.
2. The role of the NRA and applicable sanctions.

5.2 Recommendations for the authorisation and supervision of the supply chain actors

5.2.1. LEGAL AND REGULATORY PROVISIONS FOR SC ACTORS

OBJECTIVE: A CLEAR REGULATORY FRAMEWORK BASED ON THE RISK ASSOCIATED WITH SC ACTIVITIES IS ESSENTIAL TO GUIDE SC ACTORS AND FOR THE NRA AND OTHER ADMINISTRATIVE ENTITIES TO CARRY OUT THEIR WORK EFFECTIVELY.

- Responsibilities of administrative entities in charge of authorising and supervising SC actors are clearly defined and there is no overlapping of responsibilities between them (e.g., NRAs and pharmaceutical council having a consultative role).
- All SC actors in public and private sectors should possess a license/an authorisation to operate (manufacturers, distributors, wholesalers, importers, exporters, retailers, national procurement centres/central medical stores, including non-for-profit actors).
- The NRA and/or other entities are empowered to issue, suspend, or revoke licenses for premises and establishments and their activities.
- Legal provisions, regulations, and guidelines applicable to SC activities are available and known, notably good practices.
- Measures exist to limit the number of wholesalers and retail pharmacies based on regional mapping and the needs of the population, to ensure the NRA can have effective oversight of them.
- Competencies required for each type of SC actor is clarified including streamlining regulatory requirements in terms of diplomas for pharmaceutical practice (e.g., recognition of foreign diplomas, roles that can be carried by pharmacy technicians) to ensure consistency between the level of competence of the various players and the responsibilities undertaken.
- Submission by SC actors of a site master file / annual activity report may be requested by the NRA to improve their knowledge of SC activities.

Legislation should also enable the NRA/administrative entity to issue sanctions and penalties, and to propose prosecutions when necessary (please refer to chapter 11 of this guide for further information on the regulatory enforcement and compliance activities).

5.2.2. LICENSING

OBJECTIVE: AN EFFECTIVE STRUCTURE IS IN PLACE AT THE NRA FOR LICENSING ESTABLISHMENTS THAT INCLUDES A CLEAR DEFINITION OF THE PROCESSES AND RESPONSIBILITIES

- Process of issuing or renewing licenses should be based on implementation and compliance with good practices at least equivalent to WHO standards (good manufacturing practices – GMP, good storage and distribution practices – GSDP and good dispensing practices-GDispP).
- NRAs or the relevant authority should have a clear process in place to grant licenses to SC actors and for licensing inspections and this process should be well communicated to SC actors.
- An inspection for confirmation of compliance with GMP/GSDP/GDispP is required, when necessary, to grant or re-grant a license or approval of a substantial modification, and regular inspections should be carried out to maintain licenses.
- An updated list of all licensed establishments in a country should be made publicly available on the NRA website using an electronic tool (database).
- Importers or wholesalers/distributors in the public and private sectors are responsible for ensuring that the product supplied is coming from a manufacturer compliant with good manufacturing practices and is registered in the country or authorised for importation for non-registered products.

5.2.3. INSPECTIONS

OBJECTIVE: A STRUCTURED INSPECTION STRATEGY IS ESSENTIAL TO ENSURE QUALITY PRACTICES OF SC ACTORS

- NRA or other administrative entities are the only ones responsible for inspecting pharmaceutical establishments located within their countries.
- NRA can inspect pharmaceutical establishments outside the country from which the products are imported unless a mutual recognition agreement (MRA) is in place with the country, or the NRA can rely on other NRA's inspections.
- Inspection strategy should be carried out taking a risk-based approach and continuous assessment of risk. Risk ratings are based on an assessment of intrinsic risk and compliance risk.
- Reference guidelines for inspections of the different pharmaceutical establishments should be available on regulators' website and known by SC actors:
  - Good manufacturing practices for manufacturers
  - Good distribution and storage practices and model quality assurance system for procurement agencies for wholesalers/distributors/national procurement centres/central medical stores/hospital pharmacies
  - Good dispensing practices for hospital pharmacies/retail pharmacies/private outlets
- Following an inspection, a report including findings should be systematically sent to the pharmaceutical establishment by the NRA.
- Submission of a Corrective Action/Preventive Action (CAPA) plan by the inspected establishment should be mandatory.

- The effectiveness of the CAPA plan is, at least, checked during the next inspection.
- A minimum timeframe for re-inspection of pharmaceutical establishments should be set out according to the type of activity.
- An efficient Quality Management System for inspections should be implemented for a consistent and continuous improvement approach to supply chain supervision.
- Competence and regular training of bodies carrying out inspections and their impartiality and consistency in inspection activities is critical.

3 types of inspections, each with specific objectives, can be carried out:

	Global Compliance of GSDP – GMP - GDispP	Inspection campaign	For cause inspection
Background	Inspection to grant an initial license and routine inspection	Compliance strategy	After a SFMP signal
The general objective of the inspection	Ensure that good practice requirements are implemented	Strengthen a specific activity or step in the supply chain	Identify trafficking or bad practices
Scope	GSDP/GMP/GDispP	Targeted inspection	Targeted inspection
Proposed objectives of an associated communication	Explain the NRA's work (e.g., publication of the NRA inspection strategy)	Raise awareness of a particular aspect of good practice or a reference document (e.g., communication strategy before, during, and after the inspection campaign)	Highlight the role of the NRA in the fight for SFMP and deter potential offenders (e.g., publication of sanctions after the inspection)

Scope of a global compliance inspection will focus on:

- Compliance with all public service obligations to avoid disruptions to supply.
- Control of the legal distribution chain to avoid any risk of placing falsified and illegal medicines on the market.
- Securitisation of facilities.
- Qualification of suppliers and recipients.
- Traceability of batches received and supplied.
- Validation of computerised systems.
- Existence of possible illegal channels, with possible national or regional market releases, return management, export activities.

An inspection campaign may focus on one of the following topics:

- Integration of the concept of falsified medicines into the wholesaler's quality assurance system.
- Cold chain (entry in the national supply chain and after).
- Computerised systems and management of returned/unsuitable goods.
- Management of imports (e.g., quality assurance system for qualification of sources supplied by wholesalers).

5.2.4. APPLYING A RISK-BASED APPROACH FOR SC INSPECTIONS

The use of risk-based approaches for SC oversight is described in the introduction section of this guide. This approach can be applied to the routine inspection programme by assigning a risk rating to companies and/or sites which is a combination of intrinsic and compliance-related risk.[1]

	Intrinsic risk	Compliance-related risk
Principle	Based on the complexities and critical nature of the site's activities	Based on historical inspection data
Examples of criteria that can be used	- Use of data from licensing of establishments, imports authorisation, annual activity reports - Type and number of activities: imports, exports, distribution, transportation, manufacturing, pharmacies, retail, internet sales, etc. - Volume and type of medicines: e.g., categories more prone to be SFMP, cold products - Country of origins of the medicines: e.g., mutual recognition - Criteria to be adapted to the mapping of the supply chain	- Number of critical/major deficiencies detected - Number of reiterations from the previous inspection - Importance of the follow-up of actions

1. The full methodology is presented in chapter "A model for risk-based planning for inspections of pharmaceutical manufacturers" in the EU "compilation of Union procedures on inspections and exchange of information" (please see Reference documents chapter).

5.2.5. DUE DILIGENCE BY NRAS AND SC ACTORS WHEN USING INFORMATION

OBJECTIVE: ENABLE THE USE OF RELIABLE INFORMATION BY NRA FOR SC OVERSIGHT FROM A RISK-ORIENTED AND RESOURCE-SAVING PERSPECTIVE (WHEN USING RELIANCE MECHANISMS OR ASSESSING AN IMPORT REQUEST OR VERIFYING DATA) OR BY PURCHASERS TO ENSURE PRODUCTS SUPPLIED ARE COMING FROM AN AUTHORISED SUPPLIER

Recommendations:

- Access to the Internet and relevant databases , including databases[2] on licensed establishments and authorised medicinal products.
- Information systems should allow for checking the authenticity of documents at the national (licenses, authorisations, and diplomas) and international levels (GMP/GSDP certificates, marketing authorisations, any other authorisation of pharmaceutical activities).
- Access to all templates and documents relating to applications in a document management system / shared network.

6. CONTROL OF IMPORT ACTIVITIES AT CUSTOMS/BORDERS

6.1 *Brief description*

Importation of medical products is one of the most significant areas to be considered in the fight against SFMP, particularly in countries that primarily import medical products to meet their health needs. Indeed, the control of medical products when entering countries at the customs/borders level is crucial to ensure quality-assured medical products are made available to the population and to avoid market penetration by substandard and falsified medical products.

This chapter aims to guide countries around assessing measures to be put in place to better control importation and the roles to be played by NRAs and customs/revenue authorities at the ports of entry.

WHY IS THIS ACTIVITY IMPORTANT IN THE FIGHT AGAINST SFMP?

Given that the medical products market is global, many products will arrive in countries through importation. This requires continuous improvement in border control. The objective being mainly to detect through import control the presence of non-authorised, substandard, and falsified products. This requires close collaboration between the NRA and the custom officers. This includes a change from the traditional reactive control system to a risk-based and proactive approach. A risk-based approach can improve the cost-benefit ratio with existing or reduced resources, through more effective and efficient controls.

6.2. *Recommendations for customs/borders controls*

The key requisites around the control of import activities are:

- Ensuring that regulations and SOPs exist to control import activities as part of the NRA's Market Surveillance and Control activities and compliance when goods arrive in country.
- Ensuring the delivery of the import permits/authorisations by NRAs with a clear and accessible process and SOPs (documents required, SOPs for registered and non-registered products).
- Defining designated ports for imports and exports of medical products and ensuring a regulatory presence at those ports.
- Ensuring the control of medical products at the defined entry ports is carried out by trained custom officers and/or pharmaceutical inspectors.

This requires close collaboration (with identified focal points) between NRA and revenue authorities/customs, and formalised collaboration and exchange of information through an MoU.

6.2.1. LEGAL RESPONSIBILITIES

OBJECTIVE: REGULATIONS CLARIFYING THE STAKEHOLDERS' RESPONSIBILITIES AND THE PROCESS TO BE FOLLOWED IN THE CONTROL OF MEDICAL PRODUCTS AT CUSTOMS/BORDERS ARE AVAILABLE

- There is national legislation that is enforced by the NRA and customs and other relevant actors describing the responsibilities concerning the importation of medical products.
- The list of specific ports of entry designated for the importation of all medical products (port, airport, land custom points…) is officially published.

2. Please see examples of databases in the reference documents chapter and data obtained from other NRAs (websites, information exchange) to consider.

- The regular entry points for products being imported following Internet sales are identified if they exist.

- The NRA as part of its Market Surveillance and Control function has clear SOPs and tools to deliver import permits/authorisations of importation.

- Only medical products authorised (registered or not registered) by appropriate documentation (duly registered or authorised) are cleared by customs authorities based on the import permit issued by the NRA.

- Import permits issued by the NRA and, if possible, photos of goods to be received should be uploaded by the NRA to the Asycuda database (Automated System for Customs Data) available at borders to allow custom officers to confirm the authenticity of the document presented by the importer and allow quantitative monitoring of imported products.

6.2.2. REQUIRED DOCUMENTATION

OBJECTIVE: GUIDELINES DESCRIBING THE DOCUMENTATION REQUIRED TO IMPORT MEDICAL PRODUCTS ARE AVAILABLE

- Importers should have access to the list of documents to be presented when importing medical products and this list should be available on the NRA and revenue/custom authority websites. This includes documents showing:
  - The importer is duly authorised to import medical products.
  - The product is duly authorised to be marketed or authorised (if not yet registered) in the country.

HOW TO VERIFY THE AUTHENTICITY AND COHERENCE OF THE DOCUMENTS RECEIVED WITH THE NATURE OF THE CONSIGNMENT?

It is always important when checking the documents received with a consignment to check their validity, as documents can also be falsified or may no longer be valid. This means custom officers should be trained on potential sources of information to control this. Samples of expected documents, as with any official source of information, should be made available.

  - Binding documents with the consignment: packing list, invoice, bill of lading, certificate of analysis.
  - Any other documentation required by national legislation that should be issued by the competent authority of the exporting country, as applicable.

6.2.3. IMPLEMENTATION OF BORDER CONTROLS

OBJECTIVE: BORDER CONTROLS ARE EFFECTIVE AND ALLOW FOR THE DETECTION OF FALSIFIED PRODUCTS THROUGH GOOD COLLABORATION BETWEEN CUSTOM OFFICERS AND PHARMACEUTICAL INSPECTORS

- Customs officers are aware of the documents to be checked for medical products (invoice, packing list, import permit/authorisation of importation) and are regularly trained on the detection of importation of SFMP, on the importance of monitoring quantities received versus quantities in the import permit, on the risk of having additional products in same shipments and on how to detect SFMP entering with other goods.

- Custom authorities have access to the NRA website where they can find a database with authorised importers and registered products.

- Pharmaceutical inspectors are stationed at the authorised ports of entry or can be easily reached by custom officers when a suspected consignment is detected.

- The NRA has developed an efficient and confidential channel for communicating information on SFMP and other illicit activities with revenue/custom authorities.

- If pharmaceutical inspectors are not present at all borders where medical products will enter, in-land physical inspections can be considered for medical product shipments in addition to inspections at the importers' place.

- Screening tools are available and custom officers/pharma inspectors have been trained to use them and to interpret results.

- Document checks and visual inspections of consignments at customs are documented and attention is given to the nature and conditions of the packaging and labelling. The external package should be compared with a standard one, where possible.

- A list of potential products subject to falsification should be provided by NRAs to customs authorities.

- When a suspected product is detected through documentation check or screening techniques, the consignment should be placed under quarantine at approved sites pending the analysis and forensic investigation.

- Customs and inspectors should have a clear SOP to take samples of suspected products at borders and they should be sent to an accredited quality control laboratory for confirmation of the results.

7. CONTROL OF ONLINE SALES

7.1 Brief description

As technological advances have facilitated the widespread use of the Internet, advertising, selling, and supplying medical products by unauthorised and unregulated websites has become a global threat. It is a continually expanding problem, particularly where online sales are developed due to the availability of good internet connections, online secured payment systems and reliable transport systems to deliver the products to patients. Online sales of medical products are generally done through online pharmacies, e-commerce sites, social networks, or virtual commercial platforms.

Networks are difficult to break due to the ease with which new websites can be developed; the use of different company owners, names, and addresses; and the low-risk factor involved. Networks often use similar names to genuine online pharmacies of pharmaceutical companies.

This chapter will guide countries in the measures to be put in place to better control the online sale of medicines and other medical products. There is no single strategy for fighting against falsified medical products sold on the Internet. The most important is cooperation between NRAs, police, customs, and judiciary authorities. It requires a multidisciplinary and multisectoral approach around detection, communication, investigation, and prosecution. There are countless illegal sites selling medicines on the Internet, many of which are falsified. The WHO estimates[3] that for over 50% of medicines purchased online, the physical address of the sites are falsified. Furthemore, there has been an observed increase in the online distribution of medical products during the COVID-19 pandemic. All countries are vulnerable, particularly where there are weak regulatory systems.

WHY IS THIS ACTIVITY IMPORTANT IN THE FIGHT AGAINST SFMP?

The sources of supply, as well as the distribution channels of medical products sold online are unknown and escape the controls of national regulatory authorities.

The development of electronic commerce of medical products represents a danger for public health because of the risk of misuse of these products purchased outside of medical and pharmaceutical control. The patient is exposed to receiving falsified or substandard medicines that may have expired or been altered by inadequate storage or transport conditions.

7.2 Things to be aware of

Some SF cases through online sales of medical products relate to either erectile dysfunction medicines or other lifestyle medicines (products related to physical appearance and well-being, including dietary medicines, health supplements, herbal products, hair loss medicines, and skin tanning). Doping substances, such as steroids are also sold on many websites. Other websites offer a large variety of medical products from different therapeutic categories.

The development of online sales of medical products represents a danger for public health because of the risk of misuse of these products purchased outside of medical and pharmaceutical control. The sources of supply, as well as the distribution channels of medicines sold online are unknown and escape the controls of regulatory authorities.

The main direct or indirect sources of supply of falsified or substandard medical products online are:

- Online pharmacies and direct shipment (medical products delivered in an envelope from overseas directly to the user)
- B2B portals (commercial exchanges between professionals)
- Sites that connect manufacturers and wholesalers
- Advertisements or sites claiming to provide information on online pharmacies when in fact they only offer advertising links to online sales sites. Often the ads lead to illegal or fraudulent sites
- Social networks and spam.

Various criteria should be considered to detect on illegal online activity and a potentially dangerous online pharmacy:

- They are not licensed or authorised by a national regulatory authority.
- The checks carried out on the domain name led to anonymous information.
- The site includes online consultations or questionnaires.
- No prescription is required for medicines that should be sold only under prescription.
- They are difficult to locate.

7.3. Recommendations for the control of online sales of medical products

7.3.1. LEGAL ASPECTS

OBJECTIVE: IN CLOSE COORDINATION WITH RELEVANT AUTHORITIES, DEVELOP LAWS AND REGULATIONS FOR INTERNET SALES OF MEDICAL PRODUCTS

Internet law covers all the legal rules applicable to the Internet network. There is no international regulation for the online sale of medical products, but rather an application of common law alongside adjustments to certain national legislations with a special liability regime. This overall di-

3. WHO-Key facts, Substandard and falsified medical products, 31 January 2018.

versity complicates cooperation, which is a key element in the fight against illegal online trade of medical products.

The application of the law on the internet is made difficult for two main reasons:

- The internet is an international network, yet the laws are generally national.
- Under cover of the Internet, it is often difficult to identify operators and therefore those responsible for infringements.

Relevant authorities (including communication authorities and NRAs) should develop regulations to control the online sale of medicines and other medical products.

HOW TO ASSESS THE ONLINE SALE OF MEDICAL PRODUCTS IN YOUR COUNTRY?

7 MAJOR QUESTIONS

When assessing the situation in a country for online sales of medicines and other medical products, the questions below should be asked:

1. Is the selling of medical products for human use through the Internet allowed in your country? For Prescription only medicines (POM) or Over the Counter medicines (OTC)?
2. Are there any legal provisions/regulations for Internet sale of medicines and other medical products in your country (e.g., good internet practices applicable)?
3. Is it mandatory to get an authorisation from the NRA to sell medicines/medical products through websites? And do you have a list of registered websites available online?
4. Can the NRA in your country take criminal and administrative actions against websites offering illegal medical products?
5. Do you conduct public awareness raising campaigns on the danger of illegal websites selling medicines or other medical products?
6. Are there any surveillance or monitoring systems of postal parcels or courier services in your country?
7. Are postal parcels or couriers containing non-authorised medical products seized?

7.3.2. STRATEGY PROPOSED TO CONTROL THE ONLINE SALE OF MEDICINES AND OTHER MEDICAL PRODUCTS

OBJECTIVE: SAFEGUARDING PUBLIC HEALTH EVEN IF MEDICINES AND OTHER MEDICAL PRODUCTS ARE SOLD ONLINE

The strategy to control online sale of medicines and other medical products is to:

- Develop regulations to control the online sale of medicines and other medical products and implement them based on these fundamental principles.
  - The creation and operation of an internet site for the sale of medicines is under the responsibility of pharmacists.
  - The site must be attached to a physical pharmacy in the country.
  - Only over the counter medicines (not subject to mandatory prescription) can be sold on the Internet.
- Raise public awareness on the risk of buying medical products from fraudulent websites (develop concepts for public awareness campaigns, press releases, and assess their effectiveness).
- Ensure falsified and illicit medical products will be seized by customs officers to remove them from the market.
- Identify the producers and suppliers of falsified and illicit medical products and the criminal networks supporting them and establish contact with the NRA of the exporting country.

AN EXAMPLE OF REGULATION

A common logo has been introduced for legally operating online pharmacies/retailers in EU countries as one of the measures to fight against falsified medicines.

This logo vouches for the authenticity of the websites and guarantees the safety of the products.

- Consider putting in place a system to help consumers to identify unauthorised websites.
- Close fraudulent websites (research and identify the key pharmaceutical websites to which others are affiliated and assess suitability for targeting).
- Prosecute those responsible, where appropriate, and seize their assets.
- Enhance cooperation amongst national and international services by developing a cybercrime team.
- Organise a dedicated training for law enforcers and pharmacist inspectors on the legal and illegal online sale of medicines.

This strategy requires cooperation and collaboration between NRAs and enforcement officers in different countries (particularly with the exporting countries).

A legal basis is necessary to develop a common logo for authorised online pharmacies that can be checked by customers as well as the technical electronic and cryptographic requirements for verification of its authenticity.

7.3.3. GENERAL RECOMMENDATIONS FOR CYBERCRIME TEAMS

Within the framework of its investigation mission, the cybercrime team should identify the legal and physical persons involved in fraudulent networks, in the country and abroad and gather the necessary evidence of their involvement, to track financial flows linked to these activities, and to identify customs offenses.

The guidelines below include recommendations when the cybercrime team is conducting internet searches using available free internet resources as part of enforcement actions against illegal online sale of medical products:

- Encourage countries to join international operations as the online sale of medical products is not a national problem only.
- Develop or implement existing good internet practices.
- Identify a Single Point of Contact to receive information about suspected or verified cases, to facilitate the exchange of information between national authorities, and for the operational management of cases.
- Facilitate regular meetings or briefings with all key national partners, including communication authorities, and develop and implement a flowchart that will improve the level of national coordination.
- Make support from forensic police a requirement to confirm the quality and authenticity of the results coming from investigations.
- Develop indicators to measure the impact of the interventions on public awareness.
- Publish the list of the authorised online pharmacies on the NRA website.

8. MARKET SURVEILLANCE AND CONTROL INCLUDING REPORTING SYSTEMS

8.1 Brief description

Market surveillance and control plays a crucial role in assuring patient safety since its objective is to ensure compliance of the products placed on the market with pre-set criteria for quality, safety, and efficacy (i.e., verify compliance with marketing authorisation and good practice guidelines). As per the WHO definition, NRA Market Surveillance and Control functions should include the control of import activities (covered in chapter 6), prevention, detection, and response to SF products (covered throughout the guide), market surveillance program for monitoring the quality of medical products throughout the supply chain, and control of promotional, marketing and advertising activities (not covered in this guide).

WHY IS THIS ACTIVITY IMPORTANT IN THE FIGHT AGAINST SFMP?

Strong national market surveillance and control programmes capable of monitoring the overall quality and safety of medical products (e.g., medicines, vaccines, devices, and diagnostic kits) can help protect citizens from the threats posed by substandard and falsified medical products and to detect SFMP available on the market. Having a reporting system to notify suspected cases that is well known by all actors in the health sector, the supply chain actors and the population is critical to ensure potential cases are investigated quickly, and products, if confirmed as substandard or falsified, will be withdrawn from the market and will not harm the population.

This chapter will mainly focus on reporting systems (vigilance and quality complaint systems) and on market surveillance programs, which consist of monitoring the safety of medicinal products or medical devices after they have been released on the market throughout the supply chain. It is a systematic process to collect and analyse experience gained from products that have been placed on the market.

The process can further refine, or confirm or deny, the safety of the product after it is used in the general population. It uses several approaches to monitor medicinal products or medical devices' safety, including spontaneous reporting databases, signal detection, event monitoring, electronic health records, patient registries, and record linkage.

8.2. Recommendations for reporting systems

OBJECTIVE: REPORTING SYSTEMS SHOULD BE PUT IN PLACE BY THE NRA AND SHOULD ALLOW SC ACTORS, HEALTH PROFESSIONALS, AND CONSUMERS/PATIENTS TO REPORT SUSPECTED CASES WITH A MINIMUM OF INFORMATION NEEDED

8.2.1. REPORTING ACTORS

Users or patients, healthcare professionals, manufacturers, and suppliers can observe or detect issues. Reports should be sent directly to NRAs and to manufacturers/suppliers. Reported incidents can be linked to an issue with appearance, labelling, manufacturing, packaging, shipping, or storage conditions.

All reports should be assessed by the NRA and manufacturers/suppliers to examine options for preventing or reducing risks and, if necessary, to take appropriate measures. The NRA is responsible for monitoring and analysing adverse effects and quality complaints of registered medical products, as well as for the recall and withdrawal of substandard/falsified products.

NRAs are also part of a network under the WHO Global Surveillance and Monitoring System. Their objective is to

work with Member States to improve the quantity, quality, and analysis of accurate data concerning SF medical products, and to use that data to improve prevention, detection, and response to those products, to protect public health.

Under the Global Surveillance and Monitoring System countries can get:

- Immediate technical and operational support to investigate cases.
- Information on cases through a Rapid Alert System and a global database.
- Support for capacity building of NRAs.
- Improve current knowledge to influence policy and investment.

8.2.2. QUALITY COMPLAINT SYSTEMS

8.2.2.1. FOR SUPPLIERS

A quality complaint management system should be in place in all pharmaceutical establishments licensed, as part of the quality management system, and roles and responsibilities should be defined and implemented throughout the organisation.

To protect public health, a system and appropriate SOP must be in place to record, evaluate, investigate, and review complaints about suspected medical products and, where appropriate, to remove them from the distribution system in an efficient and timely manner. Quality Risk Management principles should be applied in the investigation and evaluation of quality defects. An annual test of the recall procedure should be carried out by each SC actor.

In addition, suppliers should also regularly monitor alerts coming from manufacturers, NRAs or WHO and check if these products are part of their portfolio and act appropriately.

8.2.2.2. AT THE NRA LEVEL

Cases should also be reported through the existing NRA notification system. When necessary, they will be further investigated. The law should require it from the manufacturer/supplier or health professionals and encourage patients to report to the NRA any suspected case.

- Reporting systems considered as passive surveillance systems, should be adapted to the actors who will make notifications and include the collection of information on the case. It should use various communication tools to ensure reports will reach the NRAs as quickly as possible.
- An SOP regarding how recall and risk reduction measures will be organised must be developed, regularly reviewed, and updated as necessary.
- A mock recall should be implemented regularly, to test the capacity of the supply chain actors to quickly perform a recall when SFMP are detected.
- After a product is marketed, any withdrawal due to a quality defect must be considered and managed as a recall.
- Recalls should be initiated promptly and at any time, with full collaboration, and financial and technical support from the supplier.
- The processing, evaluation, and review of complaints and quality defects, the investigation carried out, as well as the implementation of risk reduction measures, require the provision of sufficient resources and qualified staff.
- An appropriate level of root cause analysis must be for the investigation of quality defects.
- All relevant authorities must be informed of any intended product recall. When a recall proposal involves more than one country, the specific consequences for each country must be taken into consideration.
- In addition to recall decisions, other measures to reduce the risks associated with quality defects may be considered, such as the distribution of alerts to healthcare professionals related to the use of a potentially defective batch.
- An alert system should also be in place at the NRA level to communicate specific cases raised by manufacturers/suppliers or through the WHO alert system to SC actors, health professionals or the population, depending on the severity of the case.

8.2.3. VIGILANCE SYSTEMS

A vigilance system is defined as a system used by an organisation (manufacturers/suppliers or NRA) to fulfil its legal tasks and responsibilities related to vigilance and is designed to monitor the safety of the authorised product. Sufficient competent and appropriately qualified and trained personnel must be available to facilitate vigilance activities.

The NRA ensures the safe use of medicinal products and medical devices. They oversee implementation of the national pharmacovigilance (PV) system to carry out a scientific assessment of all information, and to examine options for preventing or reducing risks. The NRA collects and centralises information on adverse reactions suspected of being due to a product.

An updated written document detailing the PV system must also be available at the manufacturer/supplier level.

A vigilance system at the NRA level, or in an entity working under the authority of the NRA, should include:

- The identity, qualification, and contact information of the person responsible for vigilance.
- The organogram for the department in charge of vigilance.
- A description of how the vigilance system is structured.
- A list of SOPs related to vigilance.
- A national vigilance database linked to the Global Vigilance Database (Vigibase) in Upsala.
- A description of PV training for the operator's staff.
- A vigilance advisory committee to provide technical assistance on causality assessment, risk management case investigation, and crisis management.

8.2.4. REPORTING TOOLS

NRAs should put in place reporting tools to support the documentation of suspected cases by supply chain actors,

health professionals or patients/consumers.

- These tools should be available on the NRA website, and the existence and objectives of such reporting tools should be well communicated. For example, they should be widely shared with health professionals and supply chain actors when pharmacovigilance trainings are organised for health professionals.
- These tools should help supply chain actors/health professionals/patients/consumers to provide a minimum set of information when a suspected case is identified. It will also help the NRA to make a quick analysis of the information received and detect if a serious alert should be further investigated.
- Reporting tools for adverse events or quality complaints can be paper or electronic forms.
- For reporting from patients/consumers, the information required should be simplified and mobile applications used to facilitate reporting.
- Electronic tools can facilitate the analysis of cases from the NRAs and can facilitate communication with SC actors or patients/consumers. More streamlined tools, such as those for vigilance reporting, will facilitate the exchange of information between countries.

It is also critical for NRAs to provide feedback on cases notified or identified through PMS or to present a regular analysis of cases identified to encourage SC actors, health professionals and patients/consumers to continue notifying.

8.3. Recommendations for Market Surveillance Programmes

OBJECTIVE: STRONG ACTIVE MARKET SURVEILLANCE PROGRAMMES ARE IN PLACE AND REGULARLY IMPLEMENTED AND RESULTS ARE PUBLISHED

In addition to reporting carried out by health professionals, SC actors or patients, the market surveillance programme is a crucial tool to ensure that products continue to be safe and well-performing. Post-marketing surveillance is conducted by manufacturers (Marketing Authorisation Holder for pharmaceuticals or authorised representatives for medical devices) and regulators (NRAs) under the marketing surveillance and control function. Stakeholders are encouraged to take a risk-based approach to expand market surveillance.

In order to carry out active market surveillance, the following things need to be in place:

- The NRA has a well-developed Market Surveillance and Control function and can carry out post-marketing surveys.
- A national plan for Post Marketing Surveillance (PMS) surveys is available and results are made available publicly on the NRA website.
- Adverse or unusual effects reported through the PMS are systematically registered, analysed, and an appropriate decision made.
- Surveys have been carried out for specific categories of products and the selection of products covered has been done using a risk-based approach (sampling and analysis process).
- Screening technics are used in PMS activities to reduce the number of full tests performed by a QC laboratory and reduce the cost.
- Frequency of inspections has been adapted to risks identified.
- Based on results obtained from PMS surveys, regulatory actions have been implemented and communicated to relevant stakeholders.
- Results of PMS are shared with neighbouring countries and within Regional Economic Communities (RECs).
- Alerts received by the country could further guide PMS activities.
- Joint PMS activities are organised between countries (under RECs), and MC regulations are streamlined.

9. QUALITY CONTROL STRATEGIES

9.1 Brief description

When a suspected product is detected at the national level through inspections, reporting systems, or from customs, the NRA and the National Quality control laboratory (NQCL), in collaboration with relevant national stakeholders, are responsible for checking if the product is substandard or falsified or not registered, and for removing them from the market, if confirmed. Quality control could also be used as part of post-marketing surveillance for categories of products most at risk of being SFMP.

Given the public health and economic impact of a recall of a substandard and falsified product, it is important to use quality control testing to confirm the status of a suspected product and to make sure results from the laboratory are reliable to inform regulatory and public health decisions.

Therefore, it is important for the NRA to have a clear strategy on how to handle sampling and testing of samples but also to use a reliable QC laboratory and test products using

the correct validated methods and specifications. As testing is costly, it is important to apply a risk-based testing strategy and it may be necessary to consider less costly screening testing to scan products before going to full testing.

Depending on the objectives of each sampling and testing activity, implementing a tiered approach to testing can drastically reduce the number of samples to be collected and the types of tests to be performed without affecting market surveillance. Controlling the quality of all medicines registered is extremely difficult and often unfeasible everywhere, particularly in low and middle-income countries (LMICs), so applying risk-based approaches to select medicines for sampling and testing as part of a market surveillance strategy is imperative.

WHY IS THIS ACTIVITY IMPORTANT IN THE FIGHT AGAINST SFMP?

Medicine quality testing allows for early detection of SFMP when performed through a reliable and accurate analytical testing process. It should be carried out by qualified and authorised QC laboratories (ISO 17025 certified and/or WHO prequalified). Based on the capability to accurately detect SF products, the regulatory and/or public health authorities will take appropriate decisions to ensure the safety of end users, such as removing the SF product from the market. This process needs to be adjusted to the available resources while ensuring the accuracy of test results (by visual inspection at the field level or using testing tools).

9.2. Recommendations for a Quality Control strategy

The NRA should have a mature Laboratory Testing function and should be able to perform quality control testing in a reliable laboratory (internal or through a contract with an external laboratory).

9.2.1. CAPACITY OF THE LABORATORY TO CARRY OUT RELIABLE TESTING

OBJECTIVE: TO ENSURE THE QUALITY CONTROL LABORATORY (QCL) USED CAN IMPLEMENT GOOD LABORATORY PRACTICES TO GUARANTEE THE RELIABILITY OF TESTS CARRIED OUT AND THE RESULTS

- The laboratory used for QC testing should operate according to WHO Good Laboratory Practices
- Laboratories WHO Prequalified or ISO/IEC 17025 should be used where possible (and are often required when donor funding is used for testing)
- Necessary resources (premises, human resources, equipment, reference substances and pharmacopoeias, access to databases…) should be available at the QC laboratory level to perform the relevant tests (appearance, identification, related substances, water content, assay, disintegration, and or dissolution tests, uniformity of weight, pH and microbial limits for solutions, sterility, and bacterial endo-toxins test for injectables) as specified in the monograph or as per the in-house specifications.
- Some tests can be subcontracted to an external laboratory based on a contract established between the NRA and the laboratory.
- Equipment should be regularly qualified and maintenance contracts should be put in place as well as regular procurement of reagents.

9.2.2. RISK-BASED SAMPLING & TESTING

OBJECTIVE: TO APPLY A RISK-BASED APPROACH TO SELECT MEDICINES TO BE SAMPLED AND FOR TESTING TO CONFIRM THE QUALITY OF A SUSPECTED PRODUCT OR AS PART OF A POST-MARKETING SURVEILLANCE PROGRAM

- Map the actors, the subcategories of medical products, and locations where samples can be collected and where screening/testing (NRA, customs) should be performed (with a view of optimising synergies and pooling).
- A clear QC strategy should be developed to reduce the cost associated with testing and where possible, visual/physical controls should be carried out by checking the incoming delivery against the relevant purchase order, physically checking the products, examining the packaging, checking the manufacturer and expiry dates, checking that the medicine looks right, comparing the secondary packaging received with a standard, where possible.
- An efficient QC strategy should promote the use of external resources (databases) to check if a product is registered or not and is manufacturer approved. As well as screening techniques (mobile and handheld devices) to identify the chemical fingerprint (spectrum) of the active ingredient and to identify products requiring further investigation.
- A clear QC strategy should detect products requiring further investigation through advanced analytical techniques by identifying active ingredients with precision, measuring the quantity (content) of active ingredients, detecting related substances, impurities, and toxic compounds.
- An established SOP the follows a risk-based approach should be available and implemented by the NRA and the NQCL, for the sampling and subsequent selection of the tests to be applied for the targeted medical products.
- Sampling of suspected products is typically performed by pharmaceutical inspectors or by enforcement officers (such as police or customs officers) or other competent personnel, for example, laboratory personnel.
- Care should be taken to ensure that the samples taken or seized are representative of the suspected medical pro-

duct, and that sufficient samples are taken to allow subsequent checks (at least the quantity necessary to do two full tests).

- An information form should be filled out and sent with the samples to the NQCL as well as a copy of the Certificate of Analysis received with the product (and the analytical method, if available).
- NRAs, based on historical information, can share with customs a list of products most at risk of being substandard and falsified to guide their work and alert the NQCL to have reference substances to be able to test these products.

9.2.3. USE TEST RESULTS TO DEFINE REGULATORY ACTION

OBJECTIVE: TO USE NON CONFORMED TEST RESULTS TO DEFINE REGULATORY ACTION TO PROTECT PUBLIC HEALTH

- The NQCL has an SOP describing the process to report the results to the stakeholders, including the NRA (if it is an external laboratory).
- When results confirm a substandard or falsified product, they are quickly shared with the head of the NRA.
- The NRA has an SOP setting out further potential actions (e.g., further testing, additional information required or clarifications from market authorisation holders, other appropriate regulatory actions, such as recall).
- The NRA should then perform a risk assessment to determine what further action is required to protect public health based on the results received.
- Results from post-marketing surveillance are captured and collated in online publicly available databases, such as the Medicines Quality Database.
- The NRA must share QC results with WHO Global Monitoring System or Interpol and other NRAs.
- Data from sampling and testing activities within post-marketing surveillance programs are used to strengthen the programmes themselves and are used to continuously shape, fine-tune, and improve future activities and national post-marketing surveillance priorities.

10. INVESTIGATIONS AND REGULATORY MEASURES

10.1 Brief description

In the fight against SFMPs, the implementation of efficient measures by the NRA involves a defined process to assess and investigate serious notifications received by the NRA, strengthened by appropriate NRA sanctioning capacity.

This chapter aims to guide countries around the investigation of notifications, and decision-making processes for intervention and presents different levels of measures to be taken.

WHY IS THIS ACTIVITY IMPORTANT IN THE FIGHT AGAINST SFMP?

Public awareness and predictability of follow-up measures that can be taken by the NRA against SFMPs act as an important dissuasive tool. For comprehensive action against SFMPs, the NRA's investigation and decision-making processes must be well-defined, and a varied arsenal of measures should be implemented.

10.2. Recommendations for regulatory and disciplinary measures

10.2.1. INVESTIGATION BY THE NRA

OBJECTIVE: A FORMALISED INVESTIGATION AND DECISION-MAKING PROCESS, INCORPORATING ETHICS MANAGEMENT PRINCIPLES IS FUNDAMENTAL TO ACT AND TAKE APPROPRIATE DECISIONS IN THE PUBLIC INTEREST

10.2.1.1. DOCUMENTATION FOR INVESTIGATING A SUSPECTED CASE

An SOP should be available that covers:

- Reception and assessment of notifications and alerts coming from international organisations, such as WHO, EDQM or other sources.
- Resources needed and responsibilities.
- Risk analysis.

- Decision criteria for actions to be taken.
- Cooperation to be sought.
- Crisis management, including a communications plan.
- Handling of records regarding the case at the NRA:
  - Chronological documentation of the event and the decisions taken.
  - This is fundamental when the event is suspected of being the cause of a particularly serious act affecting people and/or involving judiciary bodies.

What? Description of the problem, activity, or task concerned	- What is the criticality/gravity, credibility (source), and accuracy of the alert? - What is the product? Is it medicine, a medical device, a food supplement, or a cosmetic product? Language? - What happened? What is the risk for public health? - What political and media considerations should be anticipated?
Who? Description of the stakeholders concerned	- Who is the person that reported the alert? - Who has the suspected products? - Who is the supplier? Who was it delivered to? - Who are the victims?
Where? Description of places	- Where are the suspected products currently located? - Where does the suspected product come from? Is the suspected product manufactured/stored in an authorised entity? Import authorisation/permit? - Where is the provider located and is it a legal/illegal channel? - Where were the products going? Is the product intended for an authorised entity in the country (in case of seizures in customs)?
When? Description of timing, duration, frequency	- When was the problem discovered and/or started? - When was the suspected product sold/purchased? - When was the first notification filed?
How? Description of methods, operating modes	- How to obtain several samples of the suspected product? - How many samples should be taken for testing? - How is the suspected product distributed? - Distribution at national level (of the batch/product concerned) or at regional level? Need to communicate/cooperate with other NRAs? - Limited to sales on the Internet? - Extent of risk that these products are present on the national market (batch number already used, identical expiry date…)? - Possibility that the product arrives in the country via another channel?

10.2.2. NRA DECISION-MAKING PROCESS

• Decision criteria for intervention

The decision criteria for actions may include, but are not limited to:

- Assessment of the NRA's capacity to act through inspection.
- Need to seek help from other authorities/experts.
- Risk of the destruction of evidence resulting from the mode of action.
- Need to take urgent administrative measures.
- Identification of persons to be informed immediately.

• Decision of intervention

Methods of intervention should be defined through a collegial decision by a follow-up committee at the NRA level with assessors of the notification and management team:

- Action plan, including communications.
- Type of intervention (inspection, evaluation, health policy action, or enforcement action…).
- Timing of intervention.
- Make-up of the multidisciplinary team/soliciting experts

Coordination required with:

- Enforcement officers.
- Market authorisation and surveillance teams.
- Quality control team.
- Other agencies or relevant services, when relevant.
- Customs/tax departments.

Coordination with other entities to provide:

- Technical support during the investigations.
- Autonomous decision-making capacity.
- Strategic support and taking over for follow-up actions

- **Ethics in decision-making**

✓ **Objectivity**

- NRA decisions are based exclusively on non-compliances raised during inspections and related procedures (e.g., instructions, hearings, or investigations).
- Decisions are taken in compliance with legally binding guidelines.

✓ **Transparency of NRA actions: publication of binding decisions on the NRA website**

- Demonstrate the coherence of NRA decisions.
- Contribute to ensuring the best possible clarity and predictability of the NRA policy in terms of follow-up actions.
- Act as a preventive tool for dissuasion.
- Inform all SC actors, the population and other NRAs.

✓ **Impartiality**

- Retain the same binding decision to similar findings from different inspections.
- Absence of conflict of interests with the operator(s) concerned.
- Inspections raising findings with a pre-defined severity criteria (e.g., number of critical or major deficiencies) are subject to a peer/collegial review.

✓ **Proportionality principles for binding decisions:**

- Taken in the interest of patient protection.
- Proportionate to the seriousness of the deficiencies identified.
- Taken with due consideration of the risk of shortage of healthcare products.
- Considering any precautionary measures adopted and implemented by the operator to reduce the risks identified.

10.2.3. RECOMMENDATIONS FOR MEASURES TO BE TAKEN REGARDING SFMP

OBJECTIVE: A VARIED ARSENAL OF MEASURES IS NEEDED TO DEAL WITH THE DIVERSITY OF SFMP SITUATIONS

After the on-site and/or document findings (recorded as deviations and remarks in an inspection report or as findings in an official report), several types of measures can be taken.

10.2.3.1. VARIOUS ADMINISTRATIVE MEASURES

- **Warning administrative measures**

- Non-binding compliance measure used for the lower level of a risk situation (e.g., a letter sent with the inspection report).

- **Binding administrative measures**

- Decisions based on a contradictory procedure
  - Defined by national regulation.
  - Binding decisions adopted by the NRA should be made following a contradictory procedure during which the operator can submit responses to:
    - Propose measures to restore the compliance of their activities.
    - Mitigate the effects of non-compliance (implementing conservative measures in particular) to restore compliance.
    - Express their point of view regarding evidence held by inspectors if it appears to be inadequate.

In some cases that can be stipulated by law, and when required by the urgency of the situation, for the protection of patients/consumers, decisions may be taken without a contradictory procedure.

- Three levels of action can be considered:
  - Warning administrative measure
  - Injunction / warning letters
  - Health policy decision

- **Batch recalls and product withdrawals**

- On a case-by-case basis, depending on the scope of non-compliance.
- In cooperation with the manufacturer/wholesaler/distributor and/or through health policy decisions.

	Warning administrative measure	Injunction/warning letter	Health policy decision
Risk for public health	acceptable	moderate	high
Context	Need for specific actions to be taken by the operator to restore a satisfactory level of compliance with current standards.	Significant deficiencies which are not likely to cause direct or immediate risk to the quality or safety of the product or the patient.	- Manipulation of data and/or serious findings that can affect the quality, safety, or efficacy of a health product or the safety of the patient. - Violations of the ethical rules. - Reiterated observations from other inspections. - Evidence of fraudulent practices.
Risk for public health	acceptable	moderate	high

	Warning administrative measure	Injunction/warning letter	Health policy decision
Objectives	Draw the attention of the operator to specific points.	Instruct the operator to reinstate their compliance within a specific timeframe.	Imposing any measure necessary to ensure patient safety.
Outcome / Follow-up	Considered when determining the monitoring conditions of the operator (e.g., inspection planning based on risk management principles).	The situation is considered to be regularised where compliance has been verified by the NRA (on-site).	Suspension or revocation of the license or suspension of the marketing authorisation of the product in question
Communication	Limited to the operator	NRA website	- NRA website. - Information on all stakeholders by the NRA. - Information on neighbouring NRAs or regional/continental RA (e.g., AMA).
Sanctions	Draw the attention of the operator to specific points.	When applicable, the case may be referred for possible disciplinary action to a professional body and financial penalties may be considered.	- The case should be referred for possible disciplinary action to a professional body. - Referral to the courts if the inspection was not carried out in a judicial context from the outset.

10.2.3.2. FINANCIAL PENALTIES

- Financial penalties can be considered when:
  - Findings result from deliberate intention of the operator to avoid an obligation.
  - Findings show a reoccurrence or continuation over time of non-compliance.
- Penalties may include a daily fine until the situation has been regularised.
- The law should clarify in which cases the Director General of the NRA could apply a financial sanction.
- Rules for determining the amount of these financial penalties should be defined in guidelines and published (e.g., published on the NRA website) to minimise ligations.

10.2.3.3. DISCIPLINARY MEASURES

These measures will be taken by a pharmacist council or a professional council when pharmacists infringe their code of deontology such as:

- Exposing patients or subjects participating in a clinical trial to an abnormal risk.
- Having exercised pharmaceutical duties in an inappropriate manner.
- Having not prevented non-compliant practices of a particular severity.

The case can be investigated by the relevant Council's chamber or equivalent and disciplinary measures taken will be proportionate to the infringement (warning, suspension, or revocation of the license of the professional).

10.2.3.4. LEGAL PROSECUTION

• Prerogatives of inspectors

Inspectors can be empowered by law for the investigation and report of infringements concerning medical products:

- To access to all documents and data (access to storage/archives, communication and/or copy of the documents) including electronic system (access to software and data stored and clear restitution of information) and medical and pharmaceutical data from physician and pharmacist inspectors.
- To sample products.
- To quarantine consignment of suspicious products.
- To seize products with judicial authorisation.
- To buy products on the Internet.
- To establish judicial minutes of visits, findings, declaration, sampling, consignment, seizure, etc.

THE ROLE OF THE JUDICIARY BODIES

1. To conduct/finalise/validate investigations.
2. To judge/determine the responsibilities of actors for cases presented to Court.
3. To pass sentences.

The transmission of a well-documented dossier concerning the infringements to the Prosecutor is particularly crucial where findings show:

- Practices aimed at deliberately infringing a regulatory obligation to the quality, safety, and efficacy of medical products.
- Endangerment of the life or health of patients, consumers, or subjects participating in a clinical trial.
- A manifest major breach of ethical rules.
- A violation of a health policy decision taken by the NRA.
- Evidence of fraudulent practices.

• Examples of infractions and fraudulent practices

- Falsification of medicinal substances.
- Marketing or distribution of medicines without marketing authorisation.
- Deception as to the nature, substantial-quality, origin, or the quantity of a merchandise.
- Opening of a pharmaceutical establishment without permission.
- Illegally operating as a pharmacist.

11. CONTROL OF ONLINE SALES

11.1 Brief description

Care should be taken by the NRA to convey clear and appropriate messages when communicating information about a suspected or confirmed substandard or falsified medical products to stakeholders (name, batch numbers, table, photos, details…). Dissemination of information should be well planned, to reach all relevant stakeholders while ensuring confidentiality as appropriate.

WHY IS THIS ACTIVIT IMPORTANT IN THE FIGHT AGAINST SFMP?

When a case is suspected or detected, a clear communication plan will help SC actors and the population to understand the seriousness of the situation and that the NRA is handling it professionally to protect public health.

The communication approach will be different during an investigation and will target specific stakeholders to give them clear instructions. When a case is confirmed, communications can also include instructions on how to handle the stock available and guidance for health workers and patients/consumers on what to do if products have been used.

WHO and other regulatory authorities should also be informed as appropriate.

It will also require identifying the person(s) who could speak about the suspected/confirmed case, particularly communications with the media, as this needs to be informative and provide clear instructions to the population that demonstrate protecting the public is the authority's primary objective without creating anxiety.

11.2 Recommendations for a communication strategy

OBJECTIVE: THE NRA SHOULD HAVE A SYSTEM IN PLACE TO COMMUNICATE ALERTS THROUGHOUT THE SUPPLY CHAIN

In addition to cases identified at national level, alerts on confirmed SF cases can be received by NRAs from manufacturers or through the WHO alert system.

An information system should be in place to share alerts received from WHO or manufacturers to all SC actors. This system can use different tools to communicate the alerts (e-mails, official letters, SMS, NRA or MoH website, WhatsApp/Telegram/SMS/etc. groups).

These alerts should include clear instructions for SC actors or health workers and patients/consumers and a focal point person with contact details that can be reached for further questions.

OBJECTIVE: A COMMUNICATION PLAN IS AVAILABLE AT NRA AND IMPLEMENTED WHEN A CASE IS SUSPECTED OR CONFIRMED

This plan should include:

- A list of the communication targets depending on the case.
- Communication channels to be used: NRA website, official letters (MoH/Health facilities/private sector), media (radio/TV/newsletters), social media, WhatsApp/Telegram/SMS/etc. groups, religious and traditional leaders.
- Critical aspects when communicating on a suspected or confirmed case.
- Key/standard messages to reach SC actors and the population using media:
  - Patients who might be affected by falsified medical products should be advised to consult their health professional.
  - Health professionals and procurement agencies, wholesalers, and importers should be instructed on the action(s) to be taken to enable a continued supply and treatment while ensuring patient safety.
- The plan should identify a focal point for further communication and include their contact details.
- The plan can also consider briefing the media on a specific case when necessary to guide their messaging and explain the NRA's role in such a case.
- In all communications the manufacturer whose name is printed on the packaging of the products should be described as the "Stated manufacturer", making it clear that the falsified medical product may not have originated from the stated manufacturer.
- Miscommunication can lead to false accusations against the legitimate manufacturer of falsifying a product, which would be grounds for legal action by that manufacturer.
- Description of the management of specific cases can also be used by the NRA to strengthen awareness of professionals and population.

NRAs should keep a record of the date, recipients, and content of information disseminated.

ANNEX 1: LIST OF POINTS TO BE CONSIDERED WHEN ASSESSING SUPPLY CHAIN SECURITY AT NATIONAL LEVEL (BY NATIONAL ENTITY)

When assessing supply chain security in a country, if the assessment is carried out by external stakeholders, it is important to inform the high-level authorities, such as the ministry in charge of international relations or foreign affairs and the Ministry of Health or the Permanent Secretary of the MoH.

Pharmaceutical Department at the MoH

- Mapping of the national supply chain
- Authorities responsible to control the actors in the national supply chain (NRA, Pharma Council...)
- National Pharmaceutical Policy
- National Coordination Platform for pharmaceutical systems
- National Coordination for the fight against SFMP
- National Action Plan for the fight against SFMP
- Relations with other Ministries on SFMP
- Support received from international partners for the fight against SFMP

National Regulatory Authority (NRA)

- Role and mission
- Structure and Legal status
- Relation with Ministry of Health
- Human resources
- Organogram
- Budget
- Regulatory functions that exist and resources available and feedback from the most recent benchmarking carried out using the WHO Global Benchmarking Tool
- Website and information available to the public
- SFMP: what measures are in place?
- Reporting system available at national level (procedure, tools)
- Management of suspected products detected (investigation, inspection, samples, QC, follow-up actions)
- Import control (regulation, documents necessary, import authorisation/permit, inspectors at borders, screening devices used by NRA inspectors/customs, communication customs/NRA inspectors)
- Authorisation of pharmaceutical establishments (regulation, documents, inspection, list on website)
- Inspection
- Vigilance system
- Internet sales of medical products (regulation)
- Traceability regulation
- Good practices available (GMP, GDSP, any certificate issued?)
- Post marketing surveillance (any study recently carried out?)
- Collaboration with other countries at regional level
- Reporting and collaboration with WHO Global Surveillance and Monitoring System
- National coordination for SF actions

National Quality Control Laboratory (NQCL)

- General presentation including human resources, equipment (existing and maintenance), documents available.
- Tests performed.
- Do they sub-contract some tests? If yes, where?
- WHO Prequalification status or progress/ISO 17025 certification
- Management of out-of-specification results
- Management of samples
- Selection of tests to be performed in case of a suspected product
- % of non-conformed samples in a year
- Role in qualification of screening devices used at borders
- Relation with other departments in the NRA
- Regional collaboration
- Statistical data on substandard and falsified medicines detected in the last 3 years

National Procurement Centre or Central Medical Store

- Role and mission
- Facilities supplied
- Stock availability and management of stock out situations
- Structure and organigram (QA role)
- Frequency of inspection for GSDP
- Description on how procurement and importation is done
- Selection of suppliers and sources
- Selection of clients
- Controls carried out upon receipt
- Quality control policy
- Warehouse: storage conditions, security measures
- Transport being used including conditions and security measures
- Traceability system (Warehouse Management System, management of expiry dates, barre coding or QR coding system)
- Management of complaints and procedure if a SFMP is detected
- Communication with the NRA
- Management of returned goods, expired products, and substandard/falsified products
- Disposal of rejected products

Private wholesaler

- Main customers and how they check customers are authorised
- Structure and organogram (QA role)

- Frequency of inspection for GDSP
- Describe how procurement and importation is done
- Selection of suppliers and sources
- Selection of clients
- Controls carried out upon receipt
- Management of stock out situations
- Quality control policy
- Warehouse: storage conditions, security measures
- Transport being used including conditions and security measures
- Traceability system (Warehouse Management System, management of expiry dates, barre coding or QR coding system)
- Management of complaints and procedure if a SFMP is detected
- Communication with the NRA
- Management of returned goods, expired products, and substandard/falsified products
- Disposal of rejected products
- History of detection of SFMP

Large Hospital

- How the pharmacy is organised in the hospital (central level, outpatients, and supply to wards)
- Procurement channel to supply the hospital
- Does the hospital have the option to import medicines?
- Is it possible for patients to bring their medicines from outside?
- Any possibility for staff to bring products from outside?
- Controls on medical products upon receipt
- Pharmacovigilance activities
- How they deal with suspected products (internal management, notification)
- Security measures in storage areas
- Supply of wards, storage in wards
- Management of returned products or expired products from services
- Disposal of rejected products
- Prevention of theft
- How alerts from the NRA are received and managed internally
- Any example of SF products recently detected?

Retail pharmacy

- Description of the team
- Frequency of inspection for Good Pharmaceutical Practices
- Selection of suppliers
- Can they import? If yes, in what cases?
- Selection of sources
- Controls carried out upon receipt
- Management of stock out situations
- Storage and security measures
- Procedure if a SF product is detected
- Management of SFMP
- Relation with the NRA

Pharma council or pharmaceutical association

- Role and mission
- Are they involved in the regulation of retail pharmacies or medicines outlets?
- Are they consulted before an authorisation is given to a pharmaceutical establishment?
- Do they have rules for opening a new retail pharmacy (according to population size)?
- If a pharmacist is involved in trafficking SF products, what would be the sanctions?
- Any concrete example to share?
- What are they doing to sensitise pharmacists on the presence of SF medical products?
- Relation with the NRA
- Are they forwarding any information received from the NRA to their network?
- Training activities proposed

Revenue/Custom authorities

- Do they have a specific list of ports of entry for medical products?
- Description of custom clearance procedure for medical products?
- Specific training on SF heath products provided to custom officers
- Collaboration and communication with the NRA
- Presence of pharmaceutical inspectors at the borders. If not, how collaboration is organised with them
- Screening tools used by custom officers at the borders
- Collaborations with the custom officers of neighbouring countries?
- Regional communication platform
- Collaboration with NRA
- List of medical products for specific attention at borders given by the NRA?
- Experience with medical devices

Police – Interpol

- Recent operations conducted in country
- Analysis of the pharmaceutical market and main ports of entry for SFMP
- Collaboration with NRA and judiciary bodies
- Collaboration with other countries
- Participation in regional and international operations against SFMP (Pangea..)
- Awareness of officers on SFMP issues

World Health Organization (WHO)

- Support provided by WHO to the country on pharmaceutical systems
- Specific support related to the fight against SF health products
- Participation of the country in the Global Surveillance Mechanism and the Member State Mechanism (working groups)

ANNEX 2: REFERENCE DOCUMENTS

a. General references

1. WHO Global Surveillance and Monitoring System for substandard and falsified medical products **WHO Global Surveillance and Monitoring System**
2. A study on the public health and socioeconomic impact of substandard and falsified medical products **A study on the public health and socioeconomic impact of substandard and falsified medical products (who. int)**
3. WHO Global Benchmarking Tool **Global Benchmarking Tools (who. int)**
4. Model Quality Assurance System for Procurement Agencies **trs986-annex3-who-model-quality-assurance-system-for-procurement-agencies.pdf**
5. Supply chain security toolkit for medical products – Good Distribution Practices. Asia-Pacific Economic Cooperation **APEC Supply Chain Security Toolkit (needs.go.KR)**
6. **WHO Member State Mechanism** – Technical guidance

b. Specific references for supply chain organisation

1. MDS-3: Managing Access to Medicines and Health Technologies, **MDS-3: Managing Access to Medicines and Health Technologies - Management Sciences for Health (msh.org)**
2. WHO guidelines on quality risk management **TRS981.pdf (who.int)**
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2. **BPDG-EU-2013**
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6. Building security and fire protection **trs961-annex9-supp 4.pdf (who.int)**

d. Specific references for Traceability systems

1- Policy paper on traceability of medical products, March 2021 **Policy paper on traceability of medical products (who.int)**

e. Specific references for oversight of the main actors in the national Supply Chain

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1. WHO databases:
   Prequalified product lists: **https://extranet.who.int/pqweb/medicines/prequalified-lists**
   WHO Public Inspection Reports (WHO PIRs): **https://extranet.who.int/pqweb/inspection-services/whopirs**
2. FDA firm compliance and enforcement information database (public access): **https://www.accessdata.fda.gov/scripts/inspsearch/**
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4. List of EU mutual recognition agreements: **https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra**
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6. PIC/S website (Pharmaceutical Inspection Co-operation Scheme): **https://picscheme.org/en/picscheme**
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8. ISO/IEC 17020:2012 "Requirements for the operation of various types of bodies performing inspection" **ISO-17020-2012.pdf (qic-eg.com)**

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3. Building Capacity at Borders to Help Protect Medicine Quality: **https://www.usp-pqm.org/results/building-capacity-borders-help-protect-medicine-quality**

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1. **Problem statement identifying the range of issues that facilitate the sale and supply of substandard and falsified medical products through the internet both nationally and across borders (who.int)**
2. Identify experiences, best practices and/or regulation of the distribution or supply of medical products via the internet to prevent and reduce the risk of substandard and falsified medical products reaching consumers EB Document Format (who.int) **EB Document Format (who.int)**
3. Develop guidance on strategies to enable national/regional regulatory authorities to address the distribution or supply of substandard and falsified medical products via the internet EB Document (who.int) **EB Document (who.int)**
4. Council of Europe - Convention on Cybercrime - Budapest Convention and Its Protocols - Budapest, 23.XI.2001 **Budapest Convention - Cybercrime (coe.int)**
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6. Tenth meeting of the Member State Mechanism – A/MSM /10/16 – 7 October 2021 **Report of the tenth meeting of the Member State mechanism on substandard and falsified medical products (who.int)**

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1. VigiGrade: A tool to identify Well-documented Individual Case Reports and Highlight Systematic Data Quality Issues, Drug Safety 37 65-77 (2014) vigiGrade: a tool to identify well-documented individual case reports and highlight systematic data quality issues - PubMed (nih.gov)
2. EU Good Vigilance Practices modules I to XVI covering major pharmacovigilance processes - **https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices**
3. Patient safety incident reporting and learning systems: technical report and guidance, WHO 2020. Patient safety incident reporting and learning systems: technical report and guidance (who.int)
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2. WHO guidelines for sampling of pharmaceutical products and related materials **ECP PR (who.int)**

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1. ISO/IEC 17020:2012 "Requirements for the operation of various types of bodies performing inspection" **ISO-17020-2012.pdf (qic-eg.com)**
2. ICH guideline Q9 on quality risk management **draft-international-conference-harmonisation-technical-requirements-registration-pharmaceuticals_en-1.pdf (europa.eu)**
3. ANSM guidelines of follow-up actions after an inspection, May 2018, available on **https://ansm.sante.fr**
4. PIC/S website (Pharmaceutical Inspection Co-operation Scheme): **https://picscheme.org/en/picscheme**
5. EMA Compilation of Union procedures on inspections and exchange of information: **https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/eudragmdp-database**

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