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Good Pharmacy Practice in Spanish Community Pharmacy

04 Pharmacovigilance Activities and Prevention of the Entry of Falsified Medicines

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Introduction

An industrially manufactured medicine needs to be approved by the Spanish Medicines and Medical Devices Agency (AEMPS) or, if the centralized authorization procedure was followed, by the European Medicines Agency (EMA), before it can be marketed. In either of these cases, the medicine must be shown to be safe and effective during the clinical trial phase. The safety information obtained during this phase, however, is insufficient, and data must continue to be collected once the medicine is on the market, as it is then that it will be used under typical clinical conditions by a much larger pool of individuals in specific population groups (children, the elderly) for a longer period of time.

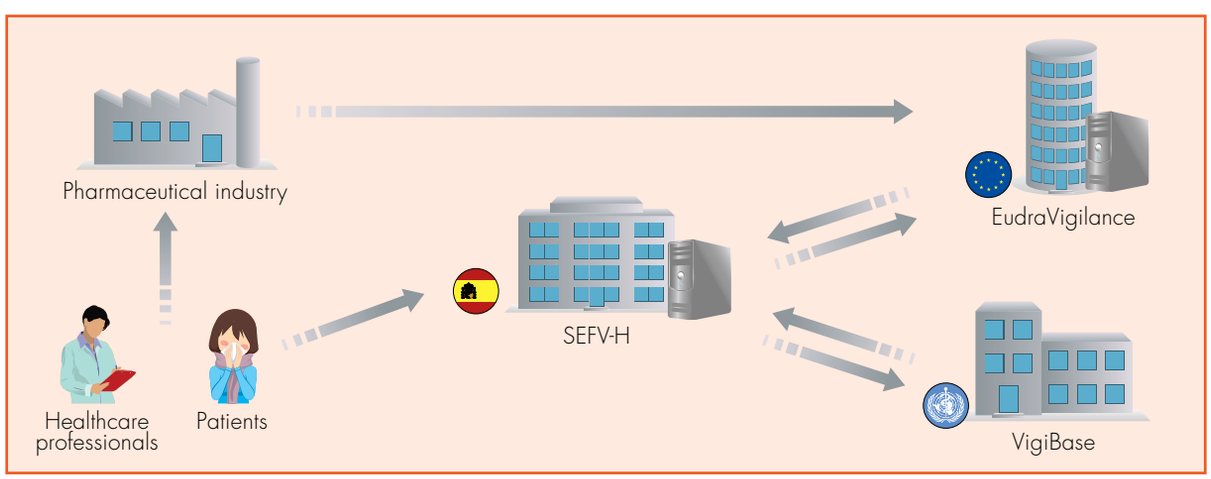
According to the World Health Organization (WHO), pharmacovigilance is *"the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".*

This definition not only refers to what could a priori be the main goal of this discipline, according to the Spanish legislation, namely the adverse effects or reactions to medicines[1], but it expands its area of activity to include other aspects related to the safety and effectiveness of medicines such as low-quality medicines, falsified medicines, medication errors, lack of effectiveness, use for indications not listed on the Summary of Product Characteristics, improper use, the abuse of medicines, interactions, long-term effects, latent effects, environmental impact of the use of medicines, effects on human health of traces of medicines in animals, and so on.

Likewise, pharmacovigilance has expanded in recent years to areas involving medicines of biological origin, those derived from blood, vaccinations, plant-based medicines, traditional medicines, alternative treatments and medical devices. Vigilance of new medicines or of those that require additional monitoring will be more exhaustive.

This trend in pharmacovigilance has led to the development of effective and coordinated national pharmacovigilance systems and to the greater involvement of all healthcare professionals.

The Spanish System of Pharmacovigilance for Medicines for Human Use (SEFV-H) is a decentralized structure formed by the regional pharmacovigilance agencies and the AEMPS. Also involved are the pharmaceutical industry, healthcare professionals and patients themselves through the reporting of suspected adverse reactions to medicines for human use. This information is cataloged in the FEDRA database. Spain is also part of the EU's and WHO's pharmacovigilance programs (EudraVigilance[2] and VigiBase[3], respectively), which compile information from 118 national centers for analysis and subsequent distribution to national medicines agencies.



[1] An adverse reaction is any harmful and unintended response to a medicine. RD 577/2013, of 26th July, which regulates the pharmacovigilance of medicines for human use.
[2] https://eudravigilance.ema.europa.eu/human/index.asp
[3] http://www.who-umc.org

Based on the information received, the AEMPS (in concert with the EMA, if necessary) can determine if the conditions of authorization of a medicine need to be modified and subsequently reflected in its patient information leaflet and Summary of Product Characteristics, or if its authorization should be suspended or revoked.

The main source of information on suspected adverse reactions is the healthcare professionals, though since July 2012 patients have also been able to participate in the spontaneous reporting system for suspected adverse reactions (though they follow a different path than professionals). The inclusion of patients can serve to expand our knowledge and perception of the safety problems involving medicines. Patients can report a reaction using the electronic reporting form available at www.notificaRAM.es, or they can continue to report them to their healthcare professionals.

On the other site, the circulation of falsified medicines[4] continues to grow. The WHO estimates that in developed countries with good detection systems, less than 1% of the medicines available are falsified. This figure is significantly larger and variable in developing countries. Even if the supply chain in Spain is very safe, community pharmacists must be alert in light of the appearance of potentially falsified medicines, especially through online sales.

The community pharmacist is in an ideal position to engage in pharmacovigilance activities and to detect falsified medicines.

This document contains the recommendations needed so that the practice of activities by community pharmacists related to pharmacovigilance and to preventing the entry of falsified medicines into the legal supply chain can be regarded as good professional practices.

[4] A falsified medicine is any medicinal product with a false representation of its identity, source or history. It does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights. Directive 2011/62/EU.

Objectives of the pharmacovigilance activities and activities aimed at preventing the entry of falsified medicines into the legal supply chain

The general objective of this service is to promote the safe, effective and responsible use of medicines.

The specific objectives are:

a) To inform the regional and/or national Pharmacovigilance Services of the safety, suspected adverse reactions related to the use of medicines and public health, including aspects involving quality, falsified medicines, medication errors, improper use/abuse of medicines, long-term effects, latent effects, environmental impact of the use of medicines and effects on human health of traces of veterinary medicines.

b) To prevent harm from adverse reactions associated with the use of medicines, either under the approved conditions of use or under other conditions.

Procedure for reporting suspected adverse reactions to medicines by community pharmacists

When an adverse reaction to a medicine is suspected[5], the community pharmacist must:

1. Know what to report to the SEFV-H: any suspected adverse reaction caused by any kind of medicine (including vaccines, medicines of biological origin, radiopharmaceuticals, non-prescription medicines, homeopathy, herbal medicinal products and compound medicines) must be reported, though priority will be given to suspected adverse reactions from **medicines under additional monitoring**, suspected **serious or unexpected reactions,** suspected **adverse reactions in children** regardless of whether or not the medicine is approved for use in pediatric population, and reactions in **pregnant women and the elderly.**

Any suspected reaction will be reported, regardless of whether or not the medicine was used according to the instructions provided in the summary of product characteristics.

In the EU, **medicines under additional monitoring** are identified with the symbol (▼), which is also shown on the medicine's information leaflet and summary of product characteristics. Medicines subject to additional monitoring are:

– All medicines authorized after 1st January 2011 that contain a new active substance.
– Biological medicines such as vaccines or those derived from plasma, authorized after 1st January 2011.
– Products that required additional post-authorization information or whose authorization is subject to conditions or restrictions based on their safe and effective use.
– Medicines that, in the opinion of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC), should be subject to additional monitoring.

[5] This procedure uses a broad definition of adverse reaction, and includes all those aspects subject to reporting included in the introduction to this document.

These medicines will be monitored for at least an additional five years or for as long as deemed necessary by the PRAC. A list of these medicines is available on the EMA's website and is reviewed monthly by the PRAC.

A **serious adverse reaction** is any reaction that causes death, could endanger life, requires the patient's hospitalization or extending an existing hospital stay, causes a significant or persistent disability or impairment or leads to a congenital disorder or birth defect. For reporting purposes, those suspected adverse reactions considered significant from a medical standpoint shall also be regarded as serious even if they do not fulfill the above criteria.

An **unexpected adverse reaction** is any reaction whose nature, gravity or consequences are inconsistent with the information provided in the medicine's summary of product characteristics.

As for the reporting of suspected **adverse reactions in children and pregnant women,** these are always recommended since clinical trials are not usually performed on these populations, meaning that less information is available on the possible adverse reactions to these medicines. In the case of the **elderly,** they may be more susceptible since they metabolize or excrete medicines less efficiently and may be more sensitive to their effects..

Occasionally it may be difficult to determine the causality between the appearance of an adverse reaction and the use of a medicine. When evaluating this causality, factors such as the timeline, the nature of the reaction, the effect of being re-exposed to the medicine, the dose-response relationship, and the effect of interrupting the use of a suspected medicine and so on should be considered.

Despite this, it is recommended that any type of suspected adverse reaction or event subject to notification, be reported.

In the case of labeling problems that could cause medication errors, everything must be considered that could lead to such errors, such as::

– Medicine brands that could cause confusion due to their similarity (paronymous medicines).
– Names of medicines that are hard to distinguish, either due to the doses or to the route of administration.
– Labeling that includes text that is confusing or hard for the user to see.
– Confusing or limited information for the patient (leaflet) or for the healthcare professional (summary of product characteristics).

If it is desired to involve the scientific community through a publication, it must adhere to generally agreed guidelines for publishing adverse reactions to medicines..

2. Filling out the form for reporting a suspected adverse reaction: there are currently two reporting methods, either using the so-called yellow card (paper format) or the electronic reporting form available at www.notificaRAM.es. These methods are without prejudice to other reporting methods that may be used in the future, such as the electronic prescription system.

The information required to be provided in the report can be divided into five main sections:

a) Patient information:

– First name and at least one surname, or initials.
– Healthcare card or clinical case history number to aid in identifying the patient in the event of duplicate or additional reports (recommended).
– Gender.
– Age (including hours, days, weeks, months, etc. in the case of babies) or age bracket (newborn, breastfeeding, child, adolescent, adult, elderly).
– Approximate weight (kg) and height (cm).

The personal information does not violate patient-pharmacist confidentiality since Law 29/2006 on the rational use of medicines requires healthcare professionals to report any suspected adverse reaction to a medicine.

b) Suspected medicine:

– Trade name of the medicine, or for generic medicines, the name of the active ingredient. For homeopathic or herbal medicines or for compound medicines, provide as much detail on the composition as possible.
– Dose, pharmaceutical form, presentation and brand or manufacturing laboratory.
– Batch number and expiry date.
– Reason for the prescription, that is, the indication of the medicine, if known.
– Daily dose and schedule. For vaccines administered in various doses, indicate which dose produced the suspected adverse reaction.
– Route of administration.
– Measures taken, that is, whether the medicine was discontinued, the dose was decreased or increased, etc.
– Treatment start/end date.

c) Adverse reaction identified:

– Gravity, that is, whether the adverse reaction endangered the patient's life, required hospitalization or extending an existing hospital stay, caused a disability, a congenital disorder or serious defect or the death of the patient.
– Description of the adverse reaction, including signs and symptoms.
– Type of report: whether it is spontaneous or a suspected adverse reaction identified during the course of a study.
– If the reaction identified is related to a medication error[6], it will be indicated and described in this section.
– Treatment applied, if any.
– Start/end date.
– Outcome of the reaction: recovered/treated, in recovery/treatment, not recovered/treated, recovered/treated with consequences, death or unknown.

d) Information on the notifier:

– First and last names.
– Profession.
– Place of work.
– Address of the place of work (town, province, postal code).
– Telephone number.
– E-mail.

e) Additional information: includes any information considered relevant to aid in understanding and evaluating the suspected adverse reaction.

– Medicines used in the months prior to the appearance of the adverse reaction or being used at the time of its appearance.
– Information on re-exposure to the suspected medicine, if any.
– Background or information that could be of interest: allergies, relevant biological parameters, etc.
– In the event of congenital disorders, include all medicines that may have been used during the pregnancy, along with approximate dates or trimester. Also provide the approximate date of the last menstruation.
– Foods consumed that may have interacted with the medicine.
– Information on the unauthorized use, overdose, improper use or abuse of the medicine, use of unauthorized medicines, foreign medicines, etc.

A copy of the report sent should be kept for some time to enable completion or continuation of the monitoring if necessary.

[6] A medication error is an unintentional mistake in the prescription, dispensation or administration process of a medicine under the control of a healthcare professional or of the individual taking the medicine. Medication errors that cause harm to the patient are regarded as adverse reactions, except those stemming from therapeutic faults due to the omission of a treatment (RD 577/2013 of 26th July, which regulates the pharmacovigilance of medicines for human use).

3. Submitting the form for reporting a suspected adverse reaction: depending on the reporting method chosen, the notification will either be sent through the post to the relevant regional pharmacovigilance center or, if sent via e-mail, the region in which the notification is being sent will be indicated, and the computer system will redirect it to the regional center.

The suspected adverse reaction report will be sent as soon as possible.

The regional pharmacovigilance center will send back an acknowledgment that will include a reference number. This reference number must be indicated when modifying or adding to information that has already been sent.

The information is analyzed at the center to determine if there are new risks or if the gravity or frequency of known risks has changed.

Each regional center is connected to FEDRA, the SEFV-H database, which stores all of the information on suspected adverse reactions to medicines.

FEDRA then sends its information to international databases: Eurovigilance (EVPM module for post-authorization notifications) and VigiBase (WHO - Uppsala Monitoring Center).

Notifications involving the labeling and/or packaging of a medicine will include all those aspects that may lead to medication errors and contain as much information as possible to allow for an assessment of the case and for the relevant decisions to be made. The notification may be sent by any interested party (patient, professional, etc.).

The e-mail address to which to send notifications is: etiquetado@aemps.es

4. Follow-up: the community pharmacist should offer the patient affected by the suspected adverse reaction the Medicine Review with Follow-up Service so as to evaluate his/her condition.

Procedure for detecting and reporting the suspected entry of falsified medicines into the legal supply chain

When a falsified medicine is suspected of entering the legal supply chain, the community pharmacist must:

1. Check the origin of the medicine: community pharmacists must always ensure that the suppliers, industry and distributors they work with adhere to all of the legal requirements applicable to the supply and distribution of medicines. They may do so by checking the public register of pharmaceutical[7] industry and the catalog of distribution companies[8] available on the AEMPS website.

In the case of suspected medicines handed in by a patient that were purchased online or through some illegal means of distribution, the pharmacist will attempt to obtain as much information as possible.

In Spain the sale by post or online of prescription medicines is prohibited. Non-prescription medicines shall be dispensed through a legally authorized community pharmacy after the pharmacist advises the patient. The online dispensing of non-prescription medicines for human use must rely on the same professional principles as the dispensing that may take place at a community pharmacy.

[7] https://labofar.aemps.es/labofar/registro/entidadesDistribucion/consulta.do?metodo=detalleBusqueda
[8] https://labofar.aemps.es/labofar/registro/farmaceutico/consulta.do?metodo=detalleBusqueda

Community pharmacies that are legally authorized to sell non-prescription medicines for human use through the internet must report this activity to the government and display a logo that is common to the entire European Union. The logo will be linked to the AEMPS website, where users can verify that the pharmacy is in fact authorized to engage in this activity.

When the buyer is in another EU member State, the online sale must take place in accordance with the requirements laid out in RD 870/2013 of 8th November, which regulates the online sale to the public of non-prescription medicines for human use, as well as with the requirements for the country of destination, in terms of both the medicines (including their labeling, leaflet and classification) and the dispensing conditions.

If a certain website is suspected of selling illegal or falsified medicines, or of selling medicines without the proper authorization, the pharmacist should report this activity through the relevant pharmacy chamber.

Pharmacists must help raise public awareness of the risks of purchasing medicines from unauthorized outlets or online.

2. Check the condition of the outer packaging and the presence and condition of any safety features on the packaging: some medicines now include safety elements such as seals, holograms, tamper-resistant devices (pop-up tabs, seals, etc.), and so on. These components will become increasingly commonplace, as will the addition of a unique identification number that can be used to identify each unit of packaging legally put on the market.

When an order is received, the pharmacy will ensure that the safety features that a medicine may have are intact and, when available, the package will be authenticated prior to dispensation using the established methods and procedures.

3. Reporting a suspected falsified medicine: the community pharmacist will immediately inform the AEMPS of any suspected falsified medicine detected. The notification will be made through the e-mail address made available for this purpose: medicamentos.falsificados@aemps.es

The notification may be made by pharmacists, other healthcare professionals, the holders of the marketing authorization, manufacturing laboratories, importers and the distribution.

This email address can be used to report the suspected presence of falsified medicines in the legal supply chain.

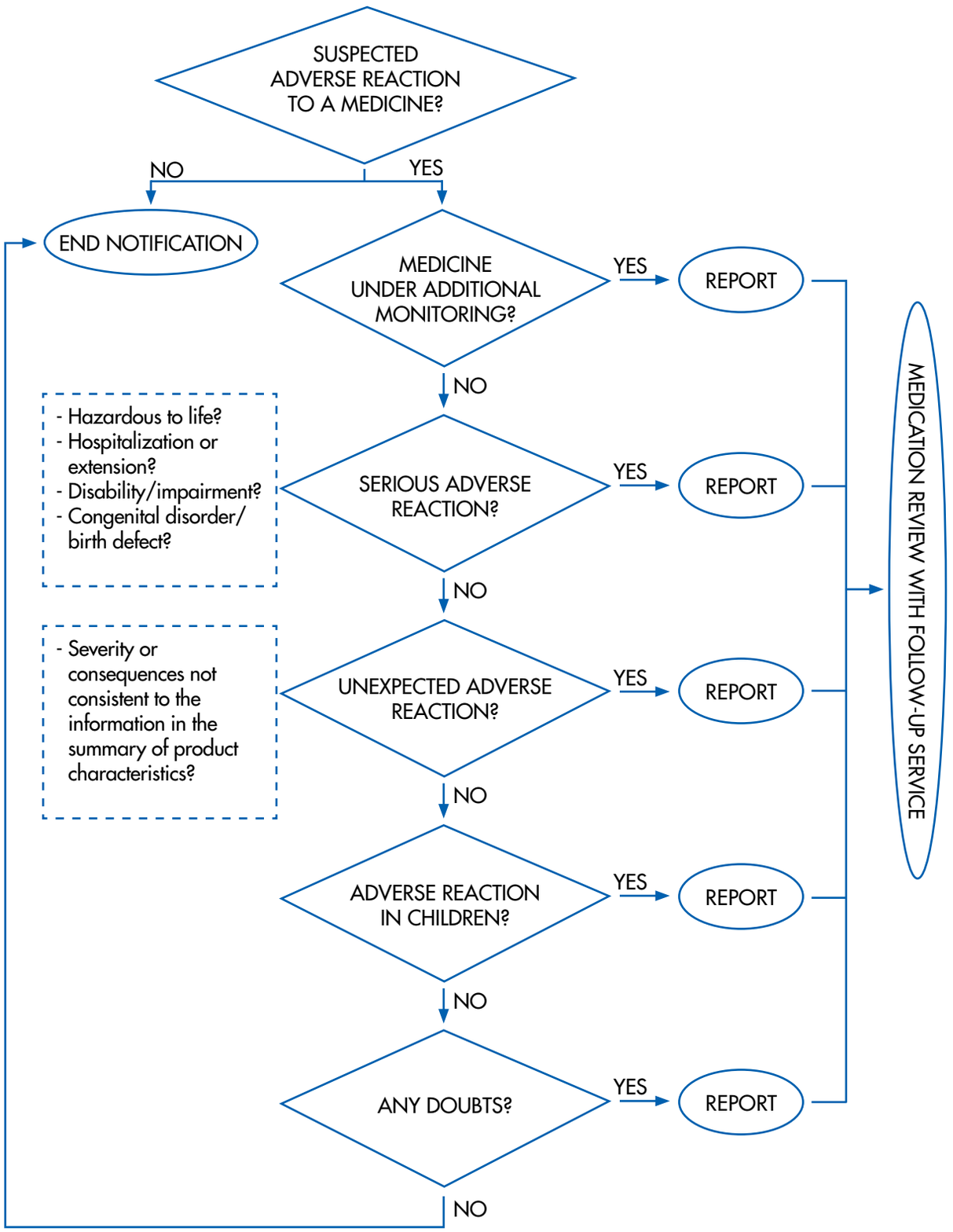
The notification will include the following information:

– Name of the medicine, pharmaceutical form and National Code.
– Batch number and expiry date.
– Place where the suspected falsified medicine was detected or purchased.
– Basis for the suspicion and differences noted between falsified and original medicines.
– Other data of interest, photographs.
– First and last names, phone number and e-mail of the person reporting.

The community pharmacist will preserve the suspected medicine for possible tests and investigations by the AEMPS.

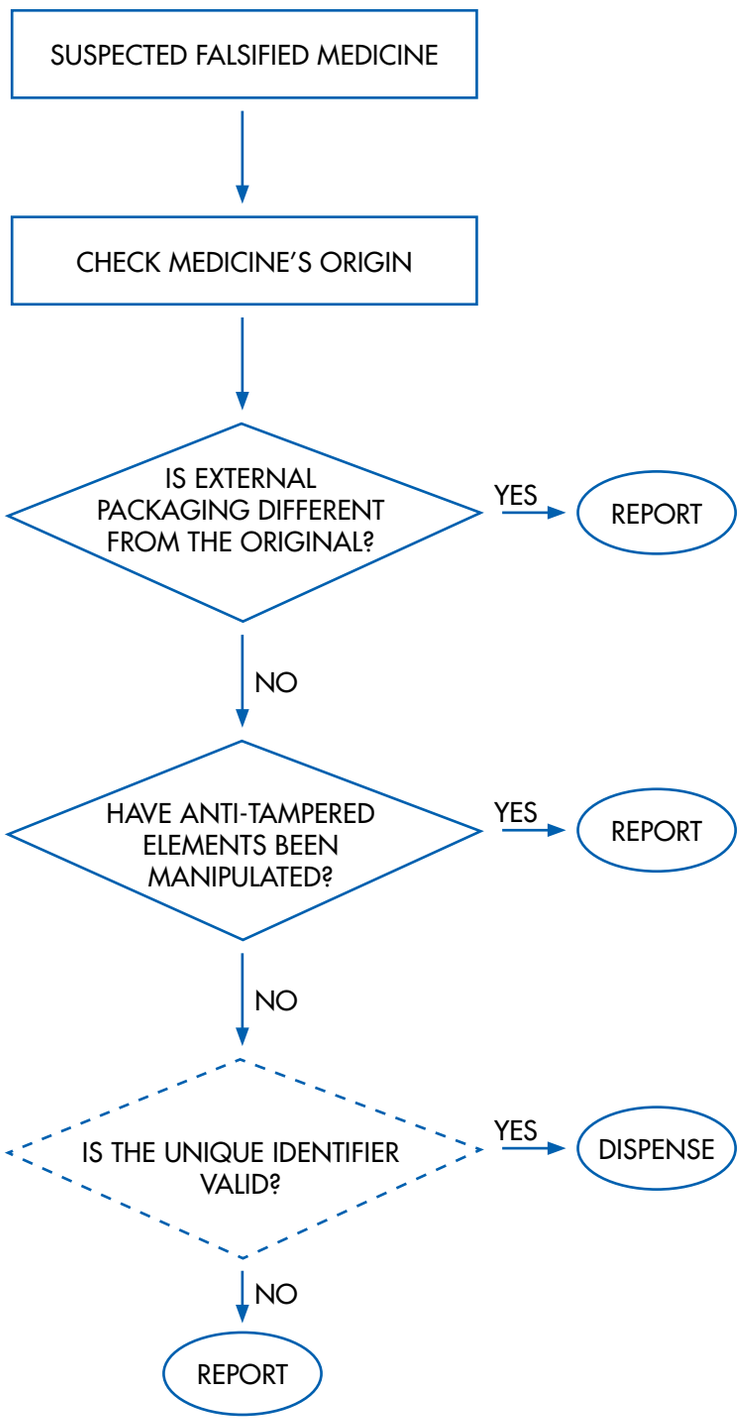
The AEMPS will notify the Autonomous Communities, professional organizations, wholesaler associations and other parties involved in the medicines supply chain of any alert concerning any falsified medicines detected.

Flowchart of the procedure for reporting[9] suspected adverse reactions to medicines by community pharmacists



[9] www.notificaRAM.es

Flowchart of the procedure for detecting and reporting[10] the suspected entry of falsified medicines into the legal supply chain



[10] medicamentos.falsificados@aemps.es

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