

SAFETY ELEMENTS FOR MEDICINAL PRODUCTS FOR HUMAN USE

FREQUENTLY ASKED QUESTIONS AND ANSWERS

This document includes a set of frequently asked „Questions and Answers” related to the implementation of the safety elements requirements’ on the packaging of the medicinal products for human use.

The document represents the common current view of the National Agency for Medicines and Medical Devices (ANMDM) and of the Romanian Organisation for Serializing Medicines (OSMR) regarding specific aspects of the implementation of the Directive’s 2011/62 and the Delegated Regulation’s 2016/161 provisions and has as purpose facilitating the understanding of these provisions by all stakeholders. The opinions are also in line with the answers formulated by the European Commission in the Questions and Answers document (https://ec.europa.eu/health/sites/health/files/files/falsified_medicines/qa_safetyfeature_en.pdf) in order to facilitate the consistent implementation of the new requirements related to the safety elements in Europe. The document will be updated whenever necessary.

I. DEFINITIONS AND LEGISLATION

1. What are falsified medicinal products?

Answer: The definition of the falsified medicinal product is included in Law 95/2006 republished – Title XVIII, the Medicinal Product

“Falsified medicinal product – any medicinal product with a false representation of:

- a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients, including excipients and the strength of those ingredients;
- b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorization holder; or
- c) its history, including the records and documents relating to the distribution channels used.

This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual “property rights”. Such products usually contain sub-standard or falsified ingredients, or no ingredients or ingredients, including active substances, in the wrong dosage thus posing an important threat to public health.

Medicinal products with unintentional quality defects resulting from manufacturing or distribution errors should not be confused with falsified medicinal products

2. Are actions taken against falsified medicinal products?

Answer: The European Union (EU) has stipulated a catalogue of measures in Directive 2011/62/EU (named also the Falsified Medicines Directive – FMD) to prevent falsified medicines from entering the legal supply chain. The EU Commission has published additional technical details for defining the safety features in the Delegated Regulation (EU) 2016/161 in the Official Journal of the European Union.

Starting with February 9, 2019 only prescription medicines (with very few exceptions) which bear the new safety features may be put into circulation.

In Romania, the provisions of the Falsified Medicines Directive have been transposed into the national legislation in Law 95/2006 republished Title XVIII the Medicinal Product and starting with 09.02.2019 the provisions of the Delegated Regulation 2016/161 come into force also on Romanian territory.

3. Do the rules apply to all medicinal products?

Answer: No. The rules are only for prescription medicinal products. However, there are exceptions to this in Annex I of the Delegated Regulation (EU) 2016/161.

The rules do not apply to non-prescription medicinal products. However, there are exceptions to this in Annex II of the Delegated Regulation (EU) 2016/161.

The above annexes can be found

here: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2016_161/reg_2016_161_en.pdf

4. In the context of the Go-live of the system on February the 9th, 2019, what will happen to the medicinal products in place at that time? Will they be released for sale? Will there be a transition period?

Answer: According to the Delegated Regulation (EU) 2016/161, Article 48, the medicinal products available on the market on February 9th, 2019 may be distributed to the public until their expiry date.

The medicinal products without safety elements, that have been certified and released for distribution by February 9th, 2019 by a qualified person according to the provisions of Art. 769 of Law 95/2006, may be placed on the market, distributed and provided to the public until their expiry date.

5. The EU Directive's provisions are applicable also to medicinal products for veterinary use?

Answer: No, the rules apply only to medicinal products for human use.

- 6. What are the states referred to in Article 2 second paragraph letter (b) of the EU Directive 2011/62 (Member States which, on July 21st, 2011, already had safety systems in place and which will apply the provisions of the Delegated Regulation starting with 9.02.2021)?**

Answer: Greece and Italy.

II. SAFETY FEATURES

- 7. What are the safety features which will be placed on the medicinal products?**

Answer: The safety features consist of a unique identifier that enables the authenticity of the medicinal product to be verified and each individual pack to be identified and an anti-tempering device that allows the verification of whether the packaging of the medicinal product has been tampered with.

- 8. Does an obligation to bear „the safety features” imply an obligation to bear both a unique identifier and an anti-tempering device?**

Answer: Yes.

- 9. What is a unique identifier?**

Answer: Unique identifier means the safety feature enabling the verification of the authenticity and the identification of an individual pack of a medicinal product. The unique identifier frame, meaning the graphic representation used for the automated data collection is the two-dimensional Data Matrix barcode. The code shall be scanned and compared with the unique identifiers stored in the repository system, in order to identify and verify the authenticity of medicinal products.

- The unique identifier - a sequence of numeric or alphanumeric characters to a given pack of a medicinal product;
- The unique identifier shall consist of the following data elements:
 - a. a code allowing the identification of at least the name, the common name, the pharmaceutical form, the strength, the pack size and the pack type of the medicinal product bearing the unique identifier;
 - b. batch number;
 - c. the expiry date;
 - d. serial number – a numeric or alphanumeric sequence of maximum 20 characters, generated by a deterministic or a non-deterministic randomisation algorithm;

- the probability that the serial number can be guessed shall be negligible and in any case lower than one in ten thousand;
- the character sequence shall be unique to a given pack of a medicinal product until at least one year after the expiry date of the pack or five years after the pack has been released for sale or distribution.

10. Is it necessary in Romania to include in the Unique Identifier a national reimbursement number or other national identification number of the medicinal product, as stated in art. 4 (b) (iii) of the Delegated Regulation 2016/161?

Answer: No.

11. How will a medicine pack that is subject to the provisions of the Delegated Regulation, manufactured after 09.02.2019, look like?

Answer: You can find below a two-dimensional barcode example and information which appears in human-readable format printed on a medicine pack.



In the example above, the product information represents:

Product code (PC): 05940010999992

Batch number (Lot): AMDC14263

Expiry date (EXP): 9 februarie 2019

Serial number (SN): BRF7XHN6GV6KI

12. How does the verification of the Unique Identifier work?

Answer: The verification of the authenticity of a unique identifier is performed by scanning the barcode and comparing that unique identifier, by interrogating the NMVS, with the legitimate unique identifiers introduced in the repositories system by the marketing authorization holder.

13. Where on the packaging should the Unique Identifier be placed?

Answer: The Delegated Regulation does not specify where on the outer packaging the safety features should be placed. The placement of the safety features is therefore to be supervised by competent authorities in accordance with current practice for labelling requirements.

14. Is it acceptable to print the Unique Identifier (UI) on self-adhesive labels on the secondary packaging?

Answer: The manufacturer must print the UI directly on the secondary packaging in accordance with art. 5 par. (3) of the Delegated Regulation.

Printing of the UI on adhesive labels stuck to the secondary packaging is allowed by NAMMD under the following conditions:

- a) there is no legal and/or technical alternative (e.g.: because of the protection of brand rights or because the medicine is authorized without secondary packaging and the primary packaging is a glass/plastic bottle);
- b) to be necessary for the protection of public health and the provision of continuous medicines' stocks.

The self-adhesive label on which the UI is printed has to be stuck on the packaging by an authorized producer so that the detachment leaves visible traces or, it is not possible to take it off without destroying the packaging; the packaging on which the label is fixed has to be inscribed in accordance with the legal requirements on labelling.

Applying a self-adhesive label that has a UI printed is not allowed when it prevents the readability of the information printed on the packaging or when it is placed on another self-adhesive label.

15. After the implementation of the Delegated Regulation 2016/161, can manufacturers apply the safety features on a voluntary basis on medicinal products which are not in the scope of the Regulation?

Answer: It is forbidden for manufacturers to apply UIs on medicines which are not in the scope of the Delegated Regulation.

16. What are the requirements related to the printing on the medicinal packaging in human-readable format of the data elements stored in the UI?

Answer: It is possible to place the data elements in different positions on the packaging, depending on the data elements and the size of the packaging. Whenever possible, the product code and serial number must be placed on the same side of the packaging. Any element of the unique identifier printed in human-readable format is represented on one line and is preceded by the following acronyms: "PC" for product code, "SN" for serial number, "Lot" for batch number and "EXP" for the expiration date. The acronyms („PC", „SN", „Lot" and „EXP") can be placed in any position that allows the unequivocal identification of the element represented in human-readable format. It is not mandatory that they are placed next to or on the same line as the respective element.

17. Is the distribution of a medicinal product whose bidimensional bar code is destroyed or cannot be read by a scanner allowed?

Answer: It depends. If the verification of the authenticity of the Unique Identifier and the decommissioning can be done using the printed elements in human-readable format, by using the graphical interface NMVS PROD WEB GUI, the medicinal product can be distributed (please see also question 29).

18. Are there any mandatory specifications for the anti-tampering device?

Answer: In accordance with Article 3(2)(b) of the Delegated Regulation (EU) No. 2016/161, an anti-tampering device has to allow the verification of whether the packaging of the medicinal product has been tampered with. There are no other mandatory specifications.

However, the anti-tampering device has to be placed on the packaging in such a way that, after tearing it, the information related to the batch number and expiry date remain visible. The anti-tampering device can be a transparent label, which can be stuck over the two-dimensional bar code, provided that there is no impact in the bi-dimensional bar code reading and that the information contained in the bi-dimensional bar code is not necessary to the patient. If the packaging containing an anti-tampering device is open according to the legislation by a manufacturer performing repackaging, this must be replaced with an equivalent protection device.

According to the European Commission's recommendations related to the anti-tampering device, the following standard should be taken into consideration by the manufacturers: CEN EN 16679:2014 "Tamper verification features for medicinal product packaging"

III. EMVO, OSMR

19. What is EMVO?

Answer: The European Medicines Verification Organization (EMVO) has been created at the joint initiative of EU stakeholders, represented by medicines manufacturers (Medicines for Europe, European Federation of Pharmaceutical Industries and Associations -EFPIA, European Association of Euro-Pharmaceutical Companies -EAEPC), wholesalers (European Healthcare Distribution Association -GIRP) and community pharmacists (Pharmaceutical Group of the European Union -PGEU), as a result of the infiltration of the falsified medicines in the European supply chain – a major and continuous threat to the patients' health and safety.

EMVO took on the responsibility of creating the **European Medicines Verification System (EMVS)** according with FMD and DR.

EMVO has to ensure the implementation of a functional, secure, interoperable and efficient system throughout the entire Europe.

20. What is OSMR?

Answer: **The Romanian Organization for Serializing Medicines (OSMR)** is a non-governmental, autonomous, independent, apolitical and non-profit organization, established for the implementation of the European Directive no. 2011/62/EU on falsified medicines and the Delegated Regulation 2016/161.

OSMR is also responsible for implementing and managing **the National Medicines Verification System (NMVS)**, a verification platform through which pharmacies or other stakeholders, such as wholesalers in Romania, can verify the authenticity of a product.

21. What is an OBP?

Answer: An OBP (Onboarding Partner) is a legal entity that has a contract with EMVO, it is part of a Corporation or a Group and is empowered to send data to the EU Hub on behalf of Marketing Authorisation Holders that are also part of that corporation. The group of MAHs represented by the OBP either consists of Original Pack Manufacturers (MAH without Parallel Distribution Activities) or Parallel Distributors (MAH with Parallel Distribution Activities).

The OBP is the contracting party of EMVO and concludes the Participation Agreement. The OBP is legally authorised to sign on behalf of a MAH/a group of MAHs. The OBP has to be affiliated to a MAH/a group of MAHs.

For smaller companies the MAH and OBP could be the same.

22. What is the procedure to establish a connection to the EU Hub? How to upload data to the European database?

Answer: The European Medicines Verification Organisation (EMVO) has described the procedure to register and connect to the EU Hub on the EMVO-<https://emvo-medicines.eu> website in the section On-boarding. It also posted an 'Onboarding' video on their website. The video explains the requirements imposed on manufacturer/parallel importers and the steps they need to take to be able to upload data to the European database/hub. Click here: <https://emvo-medicines.eu/knowledge-database/>

23. How is the connection between the EU Hub and the Romanian national system? Do the codes need to be loaded in both systems?

Answer: The OBP uploads in EMVS both the products' Master Data and the specific data per pack, after it has been produced (batch number and serial number). The onboarding and loading procedures are documented on the <https://emvo-medicines.eu> site.

Loading Master Data is done initially and occasionally if required, whilst the loading of specific data belonging to each pack is a frequently performed operation. The data referred to in art. 33 of the Delegated Regulation will then be automatically transferred to the NMVS. It is important to

be aware that the data can only be loaded when the connection between the Hub and the national system is active (in Romania: after August 30th , see announcement: <https://osmr.ro/sistemul-roman-de-verificare-al-medicamentelor-devine-operational/?lang=en>). The files with unique pack codes are only kept active for 24 hours on the EU Hub. If the connection to the national system is not ready, the file with the codes will be deleted after 24 hours and the codes will have to be reloaded at a later stage.

24. What happens if we upload the same information more than once?

Answer: Nothing.

The EU Hub detects that the information has already been loaded and does not allow duplication to occur. If you upload information a second time, for a product that is only intended for a specific country, you will receive an error message indicating that this has already been loaded. If during the transition period until February 2019 information is loaded for a multi-market pack and not all the relevant NMVS's are up and running then, only the information for the market with a functioning NMVS is accepted. For the other markets, the information must be reloaded retrospectively, when their NMVS system is up and running. This could lead to upload of the same information several times. However, this does not create any problems for the EU Hub.

25. What is a GLN?

Answer: A GLN (Global Location Number) identifies each legal entity (organization) or organization part, physical or functional, with a unique number, according to semantic and allocation rules accredited by ISO 6523 - *Information technology – Structure for the identification of organizations and organization parts*.

By establishing the minimum technical and procedural requirements applicable to the End Users for NMVS access registration (<https://osmr.ro/english-cerinte-minimale-tehnice-si-procedurale-necesare-pentru-utilizatorii-finali/?lang=en>) and by the technical documentation for users, the EAN Location Code (GLN) coding scheme is used for the unique identification of organizations and organization parts.

Unique global codes are obtained from any non-profit entity authorized and affiliated to the GS1 AISBL international non-profit association, registered in Belgium, Avenue Louise 326, box 10, 1050 Brussels (Enterprise number: 419.640.608).

More information at international level: <https://www.gs1.org/standards/id-keys/gln>

More information in Romania: <https://www.gs1.ro/programe-sectoriale/serializarea-medicamentelor/>

26. What is a repository or medicines verification system?

Answer: The repository system stores information about the safety features of medicinal products and it enables their verification, it consists of the following electronic repositories:

- The Hub – central information and data router;
- The national repository – servicing the territory of one Member State, connected with the Hub;

The repositories system shall not include the physical scanning equipment used for reading the unique identifier.

27. How will the identity, role and legitimacy of the users of the repository system be verified?

Answer: In Romania it is the responsibility of OSMR to put in place appropriate security procedures, ensuring access to the repository system only to the users whose identity, role and legitimacy have been verified, according to the quality assurance and work documentation procedures validated by EMVO.

28. Do the records referred to in Article 15 of the Delegated Regulation (EU) 2016/161 have to be stored in the repositories system?

Answer: No.

The manufacturers can decide how and where to keep the records of each operation they perform with or on the unique identifier.

29. How should the expressions "Application Programming Interface" or "Graphical User Interface" referred to in Articles 32(4) and 35(1) of Regulation (EU) No 2016/161 be interpreted?

Answer: The expression “application programming interface” refers to a software/software interface consisting of a set of programming instructions and standards used by a piece of software to ask another piece of software to perform a task. The programming instructions and standards are set by the software being called upon. In the context of Regulation (EU) No 2016/161, the expression refers to the programming instructions and standards allowing the software of pharmacies, wholesalers and national competent authorities to query the repository system.

The expression “graphical user interface” (GUI) refers to a human/computer interface that allows users to interact with software or a database through graphical icons and visual indicators without the need of using complex programming language.

Article 35(1)(i) limits the use of the GUI by wholesalers and persons authorised/entitled to supply medicines to the public to the very specific case of failure of their own software. The use of GUI in other circumstances is not forbidden but can only be done with OSMR approval.

30. How can an open circuit pharmacy, a wholesaler or a hospital (with or without closed-circuit pharmacy) connect to the NMVS?

Answer: General information related to the pharmacy readiness activity can be found in the dedicated section: <https://osmr.ro/farmacii/?lang=en>

The registration process, briefly described, and the minimum technical and procedural requirements are published here: <https://osmr.ro/english-cerinte-minimale-tehnice-si-procedurale-necesare-pentru-utilizatorii-finali/?lang=en>

The registration process can be initiated by the software company that has applications installed in that pharmacy (this is the preferred and recommended procedure), by notifying the OSMR SIMI - Register and Incident Management System, or directly by the pharmacy that will become an End User (see public communication here: <https://osmr.ro/acces-direct-al-utilizatorilor-finali-la-snm/?lang=en> and by completing the participation form – NMVS access: <https://tinyurl.com/y8ycxp58>)

The registration process is a collaborative process between the future End User and OSMR in which guidance notifications are received, validated access to OSMR SIMI and technical documentation are received, documents are uploaded, LUF and PTC are defined, followed by testing in the NMVS IQE environment, the End User account is created in NMVS PROD, account which will be used also after February 9th, 2019.

Authorized wholesalers register in NMVS and perform the operations stipulated by the Delegated Regulation (UE) 2016/161 on their behalf, for the products in their portfolio. For those operations performed by third parties on behalf of the authorized wholesaler, based on a contractual relationship, the End User Locations of the wholesaler are used, hosted by the third party and Technical Connection Point (PTC) and software application belonging to the third party.

The software company working for the third party, having the connecting software applications to the NMVS on its TCPs, who will perform the operations on behalf of the wholesaler (with the authorized wholesaler's credentials) has the obligation to register wholesaler, respectively, the End User in the OSMR Register and Incident Management System.

IV. MICELLANEOUS

31. When should Free Samples be decommissioned?

Answer: Article 41 of the Delegated Regulation states that medicinal products to be supplied as free samples, need to be indicated as free samples in the repository system and the decommissioning must be done before providing them to the persons qualified to prescribe them.

32. Does the system support scanning of aggregated codes on pallets by wholesalers or hospitals?

Answer: The European Medicines Verification System (EMVS) does not currently support scanning of aggregated codes.

33. Members States may hold stocks of certain medicinal products in order to protect public health. How should these medicinal products be decommissioned?

Answer: Any entity providing and holding stocks for the mobilization reserve for medicinal products in accordance with the provisions of Law no. 477/2003 on the readiness of the national economy and of the territory, for defense purposes, republished, decommissions according to the provisions of the Order of the Ministry of Health no. 131/2016, as amended.

34. Is it possible that a patient who purchased from a pharmacy a medicinal product bearing the Datamatrix bidimensional bar code use a smartphone application to read the bidimensional bar code and to verify the authenticity of the respective medicinal product?

Answer: The Delegated Regulation does not stipulate that the authenticity of the medicinal product be verified by the patient. The verification performed by a pharmacy or by a person entitled to provide medicinal products to the population is enough to ensure that the medicinal product provided to the patient is not falsified. These data are not public, therefore such applications cannot exist, at least not at this point and not in the current legislative context.
