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SAFETY FEATURES FOR MEDICINAL PRODUCTS FOR HUMAN USE

QUESTIONS AND ANSWERS - VERSION 22

(Submitted for discussion to the Member State expert group on the safety features[1])

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Important disclaimer: The views expressed in this questions and answers document are not a formal interpretation of Union law, nor are legally binding. Ultimately, only the European Court of Justice can give an authoritative interpretation of Union law. This document aims at informing on the technical aspects of Commission Delegated Regulation (EU) 2016/161 with a view to facilitating its implementation.

This documents sets out frequently-asked 'questions and answers' regarding the implementation of the rules on the safety features for medicinal products for human use.

These rules are enshrined in Articles 47a, 54(o) and 54a of Directive 2001/83/EC, and in Commission Delegated Regulation (EU) 2016/161[2].

This document is only available in English.

[1] http://ec.europa.eu/transparency/regexpert/index.cfm?do=groupDetail.groupDetail&groupID=2719

[2] Commission Delegated Regulation (EU) 2016/161 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use. OJ L 32, 9.2.2016, p. 1-27.

TABLE OF CONTENTS

1. GENERAL

1.1. Question: What are the safety features?

Answer: The safety features consist of two elements placed on the packaging of a medicinal product:

(1) a unique identifier, a unique sequence carried by a two-dimensional barcode allowing the identification and authentication of the individual pack on which it is placed; and

(2) a device allowing the verification of whether the packaging of the medicinal product has been tampered with (anti-tampering device).

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1.3. Question: Do the safety features need to be applied on all medicinal products for human use?

Answer: No. The safety features should only be applied on the packaging of the following medicinal products for human use:

(1) medicinal products subject to prescription which are not included in the list set out in Annex I to of Commission Delegated Regulation (EU) 2016/161;

(2) medicinal products not subject to prescription included in the list set out in Annex II of Commission Delegated Regulation (EU) 2016/161.

(3) medicinal products to which Member States have extended the scope of the unique identifier or the anti-tampering device to in accordance with Article 54a(5) of Directive 2001/83/EC.

1.4. Question: Are there exceptions from the requirements for certain medicinal products to bear or not the safety features?

Answer: Yes. The list of categories of medicinal products subject to prescription which shall not bear the safety features are set out in Annex I of Commission Delegated Regulation (EU) 2016/161, while the list of medicinal products not subject to prescription which shall bear the safety features are set out in Annex II of the same Regulation.

1.5. Question: Do the rules on the safety features also apply to veterinary medicinal products?

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

1.6. Question: Do the rules on the safety features apply to medicinal products intended for research and development trials?

Answer: Medicinal products intended for research and development trials and not yet granted a marketing authorisation are excluded from the rules on the safety features.

Authorised medicinal products have to fulfil the requirements of Directive 2001/83/EC and Commission Delegated Regulation (EU) 2016/161 up to the moment it becomes

known which batch/unit will be used for research and development trials. In practice, there are two possible situations:

1. The product is manufactured for known use in a clinical trial

An investigational medicinal product (IMP) that is manufactured in accordance with the marketing authorisation but is packaged for a clinical trial (not in the commercial presentation) is excluded from the rules on the safety features as it is solely manufactured and packed for the use in the clinical trial. The manufacturer would be required to hold a manufacturing and importation authorisation covering IMPs and the IMP certified under that authorisation in accordance with the clinical trial application noting that the clinical trial application must reflect these arrangements.

Authorised auxiliary medicinal products cannot be manufactured under a manufacturing and importation authorisation covering IMPs and must fulfil the requirements of a marketed pack bearing safety features and decommissioned appropriately (see below).

2. The product is authorised and sourced from the regulated supply chain

Medicines in their commercial presentations bearing safety features should be decommissioned in accordance with Articles 16 and 25(4)(c) of Commission Delegated Regulation (EU) 2016/161 before use as investigational medicinal products or authorised auxiliary medicinal products.

1.7. Question: Are the safety features required where the medicinal product manufactured in the EU is destined for exportation only?

Answer: No.

1.8. Question: In the case of a medicinal product bearing the safety features is brought into the territory of a Member State in accordance with Article 5(1) of Directive 2001/83/EC, do the rules on the safety features apply?

Answer: When a medicinal product is brought into the territory of a Member State in accordance with Article 5(1) of Directive 2001/83/EC, the rules on the safety features in principle do not apply, unless there is applicable national legislation requiring otherwise.

Member States can, however, use national legislation to regulate which provisions of Directive 2001/83/EC or of Commission Delegated Regulation (EU) 2016/161 apply to Article 5(1) products brought into their territory. Member States can, for example, require the mandatory verification/decommissioning of Article 5(1) products in accordance with Commission Delegated Regulation (EU) 2016/161.

In the absence of national legislation requiring otherwise, the rules on the safety features do not apply. The "importer" of a medicinal product brought into the territory of a Member State in accordance with Article 5(1) is not required, for example, to (re)place the safety features on its packaging (e.g. through labelling/relabelling operations) or to upload the unique identifiers, if present, into the national repository of the new Member State of destination. The verification of the safety features and decommissioning of the unique identifiers of Article 5(1) products already bearing the safety features are also not mandatory.

Pharmacies, healthcare institutions and other relevant stakeholders in that Member State are nevertheless strongly encouraged to verify the authenticity of and decommission the medicinal product before supplying it to the public.

1.9. Question: Does an obligation to bear "the safety features" imply an obligation to bear both a unique identifier and an anti-tampering device?

Answer: Yes.

1.10. Question: Once Commission Delegated Regulation (EU) 2016/161 applies, can manufacturers place the safety features, on a voluntary basis, on medicinal products not required to bear the safety features?

Answer: No. Once Commission Delegated Regulation (EU) 2016/161 applies, manufacturers cannot place the safety features on medicinal products not required to bear the safety features, unless the Member States have extended the scope of application of the unique identifier or of the anti-tampering device to those medicinal products in accordance with Article 54a(5) of Directive 2001/83/EC.

1.11. Question: Are medicinal products allowed to bear the anti-tampering device, if they are not required to bear the safety features?

Answer: Under Commission Delegated Regulation (EU) 2016/161, medicinal products can only bear an anti-tampering device if they are in the scope of Article 54a(1) of Directive 2001/83/EC (i.e. if they are medicinal products subject to prescription or medicinal products listed in Annex II of Commission Delegated Regulation (EU) 2016/161) or if the Member State(s) where they are placed on the market extended the scope of the anti-tampering device to those medicinal products.

1.12. Deleted

1.13. Question: Will the mandatory changes to the packaging due to the placing of the unique identifier and of the anti-tampering device require the submission of variations to marketing authorisations?

Answer: The regulatory requirements to be followed to notify the EMA of the placing of the unique identifier and/or the anti-tampering device on centrally authorised products are detailed in an implementation plan developed by the EMA and the European Commission and published in the "product information templates" section of the EMA website:
https://www.ema.europa.eu/en/documents/other/implementation-plan-introduction-safety-features-packaging-centrally-authorised-medicinal-products-human-use_en.pdf

The regulatory requirements for nationally authorised products are available on the HMA/CMDh website:
https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Falsified_Medicines/CMDh_345_2016_Rev00_02_2016_1.pdf

1.14. Question: Are there any mandatory specifications for the anti-tampering device?

Answer: In accordance with Article 54(o) of Directive 2001/83/EC and Article 3(2)(b) of Commission Delegated Regulation (EU) 2016/161, an anti-tampering device has to allow the verification of whether the packaging of the medicinal product has been tampered with.

The integrity of the antitampering device should indicate whether the packaging has been opened or altered since it left the manufacturer, thereby ensuring that the content of the packaging is authentic. It should be possible to demonstrate that if the ATD is removed or broken, this is evident visually from the pack. The tamper evident nature should also be proven throughout the shelf life of the medicinal product.

In particular, the ATD should not break under normal conditions of handling in the supply chain without using e.g. source of heat or external tool. The quantity and quality of the materials used for the ATD and the packaging should be appropriate to ensure the effectiveness of the anti-tampering feature.

The standard EN ISO 21976:2020 "Packaging – Tamper verification features for medicinal product packaging" is available for manufacturers to consider.

1.15. Question: Will the pharmaceutical companies receive any financial support (EU or national) for acquiring the instrumentation for applying the safety features on individual packages?

Answer: No, it is not currently foreseen that pharmaceutical companies will receive any financial support (EU or national) for acquiring the instrumentation for applying the safety features on individual packages.

1.16. Question: Who shall bear the financial responsibility for the covering the expenses of establishment and implementation of the repository system?

Answer: In accordance with Article 31(1) of Commission Delegated Regulation (EU) 2016/161, the repositories system shall be set up and managed by a non-profit legal entity or non-profit legal entities in the Union by manufacturers and marketing authorisation holders. The costs of the system shall be borne by the manufacturers of medicinal products bearing the safety features in accordance with Article 54a(2)(e) of Directive 2001/83/EC.

1.17. Question: Are radiopharmaceuticals required to bear the safety features?

Answer: No. All pharmaceutical forms and strengths of radiopharmaceuticals (as defined by Article 1(6) of Directive 2001/83/EC), radionuclide generators (as defined by Article 1(7) of Directive 2001/83/EC), radionuclide precursors (as defined by Article 1(9) of Directive 2001/83/EC) and kits (as defined by Article 1(8) of Directive 2001/83/EC) shall not bear safety features.

The wording of Article 54(o) of Directive 2001/83/EC ("medicinal products other than radiopharmaceuticals") excludes radiopharmaceuticals, as defined by Article 1.6 of the said Directive, from the scope of the safety features. Consequently, any medicinal product fulfilling the definition of radiopharmaceutical shall not bear the safety feature. Since

radiopharmaceuticals are outside of the scope of the safety features, their addition to Annex I of Commission Delegated Regulation (EU) 2016/161 is unnecessary.

1.18. Question: Concerning pandemic-influenza vaccines, the EMA mock-up procedure allows a vaccine to be developed and authorized in advance of a pandemic, containing a strain of flu virus that few people have been exposed to but that could potentially cause a pandemic. These can be modified into pandemic-influenza vaccines in a future pandemic case. After a pandemic has been declared there is an emergency procedure for the final vaccine. Are there exceptions from the requirements for pandemic-influenza vaccines to bear or not the safety features?

Answer: No, as pandemic influenza vaccines are not included in Annex I of Commission Delegated Regulation (EU) 2016/161. Pandemic–influenza vaccines authorised via the mock-up procedure should bear the safety features in accordance with the said Regulation.

1.19. Question: In case of a bundle of several single packs sold as one unit, should the anti-tampering device and unique identifier be placed on the bundle packaging or on each single pack?

Answer: Whether a manufacturer needs to place the safety features on the bundle packaging or on each single pack within the bundle depends on how the medicinal product is described in its marketing authorisation dossier – regardless of what is the commercial sellable unit.

If, in the marketing authorisation dossier, the product presentation is described as a "multi-pack", the outer packaging as that of the bundle and the single packs as not for individual sale (the text 'can't be sold separately' or equivalent is present on the packs), then both the UI and the ATD need to be placed on the bundle packaging. The outer packaging must include, in addition to the unique identifier and ATD, all applicable labelling requirements as laid down in Article 54 of Directive 2001/83/EC.

If, however, the marketing authorisation dossier of the medicinal product describes the product presentation as a single pack and the text 'can't be sold separately' or equivalent is not present on the packs, then each pack within the bundle needs to be serialised and have an anti-tampering device. In this case, the bundle packaging should not bear a unique identifier, but it may bear an aggregated code containing the information on all unique identifiers within the bundle.

1.20. Question: If a pack bearing the safety features is lawfully opened (e.g. by parallel traders/manufacturers replacing the leaflet under the supervision of national competent authorities), can it be resealed (e.g. by applying a new ATD on top of the old, broken ATD)?

Answer: Yes, such package can be resealed (e.g. by applying a new ATD on top of the original, broken ATD) provided the requirements in Article 47a (1) of Directive 2001/83/EC are fulfilled.

This implies that:

(a) the authenticity of the unique identifier and the integrity of the ATD on the original pack were verified as authentic before breaking the original ATD/pack.

(b) the replacement of the ATD is conducted in accordance with applicable Good Manufacturing Practice principles and is subject to supervision by the competent authority.

c) the replacement ATD must make it possible to verify, with the same effectiveness as an original ATD, that the outer packaging of a medicinal product has not been unlawfully opened - tampered with - between the time at which that medicinal product is repackaged and that at which it is supplied to the public. This assumes that it is evident for everybody that a new ATD has been placed and by whom. The latter implies that the repackager of the medicinal product must be clearly stated on the outer packaging.

1.21. Question: Is it possible for manufacturers/wholesales/parallel traders to market/supply medicinal products with a packaging showing visible signs of opening/intrusion, but where the ATD has been replaced by a new ATD in accordance with Article 47a of Directive 2001/83/EC?

Answer: Yes, this is possible if the presence of visible signs of opening on the packaging are consistent with legal repackaging of that medicinal product by a parallel importer or by a parallel distributor.

It should be noted that Articles 24 and 30 of Commission Delegated Regulation (EU) 2016/161 prohibit wholesalers and persons authorised or entitled to supply medicinal products to the public who receive a medicinal product having a packaging showing signs of tampering from supplying that product. So they must be free of doubt that traces of opening are attributable to the repackaging of that medicinal product by an authorised parallel importer or by a parallel distributor.

1.22. Question: In case of parallel-traded packs, can parallel traders cover or remove the safety features of the original pack?

Answer: Parallel traders covering or removing the existing safety features are required to place equivalent safety features in accordance with Article 47a of Directive 2001/83/EC (see also Q&A 1.20).

The new unique identifier should comply with the requirements of the Member State where the medicine is intended to be placed on the market (Article 17 of Commission Delegated Regulation (EU) 2016/161).

Furthermore, if the product code and/or batch number of the parallel-traded product change compared to the original product, parallel traders must place a new unique identifier after first decommissioning the original one. For further details on the requirements for batch numbers appearing on the packaging of medicinal products subject to parallel trade, see

Q&A 4 under 'EU GMP guide part I: Basic requirements for medicinal products: Chapter 5: Production' on the EMA website.[3]

When placing an equivalent unique identifier, parallel traders are required to fulfil, inter alia, the obligations laid down in Articles 33, 40 and 42 of Commission Delegated Regulation (EU) 2016/161 concerning the uploading and keeping up to date of the information on the new unique identifier into the repositories system.

In all cases, traceability must be maintained in the repository system in accordance with Article 35(4).

1.23. Question: Is it possible to place a transparent sticker used as an ATD over the human readable codes or the 2D Data Matrix, even if opening the pack might lead to the human-readable data and/or 2D barcode being damaged and unreadable?

Answer: It is acceptable to place a transparent sticker, used as an ATD, over the 2D Data Matrix, provided that it does not impact its readability (for example if the sticker is reflective), and the Data Matrix does not contain information intended for the patient or included in accordance with the recommendation in Q&A 2.12 (e.g. content previously included in a QR code).

Concerning the human-readable code, the human-readable batch number and expiry date are relevant information for the patient and should remain readable after the pack is opened. Hence, it is not acceptable to place a transparent sticker, used as an ATD, over the human-readable batch number and expiry date if it risks damaging this information when the pack is opened.

1.24. Question: In some cases a medicinal product may carry more than one batch number, typically when the product consists of an active component and a solvent. Which batch number(s) should be encoded in the medicines verification system in that case?

Answer: Only the batch number of the active substance needs to be encoded in the medicines verification system.

1.25. Question: When repackaging or re-labelling a pack for the purpose of using it as authorised investigational medicinal product or authorised auxiliary medicinal product according to Article 16(2) of Commission Delegated Regulation (EU) 2016/161, the unique identifier should be decommissioned. What status of decommissioning should the pack have?

Answer: Until there is a specific status for these medicines in the EMVS system, the pack should be decommissioned as "SUPPLIED" when repackaging or re-labelling for use as an authorised investigational medicinal product or authorised auxiliary medicinal product.

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[3] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers#eu-gmp-guide-part-i:-basic-requirements-for-medicinal-products:-chapter-5:-production-section

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1.27. Deleted

1.28. Question: Is there an obligation for direct suppliers to healthcare institutions to offer aggregation services?

Answer: No. The Delegated Regulation does not require hospital suppliers to provide aggregation services. Direct suppliers may however offer the service on a voluntary basis, providing the safeguards outlined in the *Expert Group paper on implementation of the Falsified Medicines Directive in the hospital setting*[4] are met.

1.29. Question: Do the unique identifiers of reference and retention samples taken from stock in compliance with Annex 19 of the EU GMP Guidelines[5] and uploaded to the EMVS have to be decommissioned? If yes, to what status?

Answer: Yes. In case a pack is taken from a batch and stored as a reference and retention sample after upload to the EMVS it should be decommissioned as "SAMPLE". In general, however, the serial numbers of packs that are taken from a batch and stored as reference and retention samples in order to comply with Annex 19 of the EU GMP Guidelines should not be uploaded in the EMVS. Samples taken voluntarily from a batch by a wholesaler that fall outside of the scope of Annex 19 should be decommissioned as "DESTROYED".

2. TECHNICAL SPECIFICATIONS OF THE UNIQUE IDENTIFIER

2.1. Question: Does Commission Delegated Regulation (EU) 2016/161 limit the length of the unique identifier to 50 characters?

Answer: No. Only the length of the product code, one of the data elements of the unique identifier, is limited to 50 characters.

2.2. Question: Would it be possible to include, on a voluntary basis, a two-dimensional barcode on the packaging of medicinal products for human use not having to bear the safety features if the information carried by the barcode does not serve the purposes of identification and authentication of the medicinal product and does not include a unique identifier?

Answer: Yes, provided that the relevant labelling provisions of Title V of Directive 2001/83/EC are complied with.

Examples may include two-dimensional barcodes encoding price indications, reimbursement conditions, etc.

[4]https://ec.europa.eu/health/sites/health/files/files/falsified_medicines/2018_hospitalsetting_en.pdf
[5] https://ec.europa.eu/health/documents/eudralex/vol-4_en

2.3. Is it possible to keep one-dimensional barcodes on the packaging of medicinal products for human use having to bear the safety features, when adding the two-dimensional barcode carrying the unique identifier?

Answer: Yes, provided that the presence of both barcodes does not negatively impact the legibility of the outer packaging. In order to avoid incorrect scanning by end-users, if possible, the barcodes should not be placed in proximity to each other, preferably on different sides of the packaging.

2.4. Question: Is a printing quality of 1.5 according to ISO/IEC 15415 mandatory?

Answer: No. Manufacturers are required to use a printing quality which ensures the accurate readability of the Data Matrix throughout the supply chain 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 in accordance with Article 51(3) of Directive 2001/83/EC, whichever is the longer period.

The use of a printing quality of 1.5 or higher gives a presumption of conformity, i.e. manufactures using a printing quality of 1.5 or higher will be presumed to have fulfilled the requirement mentioned in the first paragraph without need to prove that it is actually the case.

If a printing quality lower than 1.5 is used, manufacturers may be asked to prove that requirements mentioned in the first paragraph are met.

2.5. Can manufacturers, on a voluntary basis, place the human readable code on medicinal products with packaging having the sum of the two longest dimensions equal or less than 10 centimetres?

Answer: Yes.

2.6. Are medicinal products with packaging having the sum of the two longest dimensions equal or less than 10 centimetres exempted from bearing the two-dimensional barcode carrying the unique identifier?

Answer: No, Article 7(2) only provides for an exemption from bearing the unique identifier in human readable format. The unique identifier in machine-readable format – the 2D barcode – is still required.

2.7. Question: Is it compulsory to print the national reimbursement number in human-readable format?

Answer: The national reimbursement number or other national number should be printed in human readable format only if required by the national competent authorities of the relevant Member State and not printed elsewhere on the packaging. It should be printed adjacent to the two-dimensional barcode if the dimensions of the packaging allow it, unless national legislation provides otherwise.

2.8. Question: Is it compulsory for the human-readable data elements of the unique identifier to be placed adjacent to the two-dimensional barcode?

Answer: Yes, whenever the dimensions of the packaging allow it.

2.9. Question: What is the smallest font size that can be used to print the unique identifier in human-readable format?

Answer: The font size of the unique identifier should be in accordance with the "Guideline on the readability of the labelling and package leaflet of medicinal products for human use" published in Eudralex – Notice to Applicants - Volume 2C.
https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf.

2.10. Question: When encoded in the 2D Data Matrix or printed on the packaging in human-readable format, should the data elements of the unique identifier follow the order laid down in Articles 4(b) or 7(1), respectively, of Commission Delegated Regulation (EU) 2016/161?

Answer: No. Manufacturers can choose the order of the data elements provided that all data elements required by national legislation and Article 4(b) (for the 2D Data Matrix) or Article 7 (for the human-readable format) are present.

2.11. Question: Commission Delegated Regulation (EU) 2016/161 does not mention batch number and expiry date as mandatory components of the human readable code. Is it mandatory to print the batch number and the expiry date in a human-readable format and adjacent to the two dimensional barcode?

Answer: Batch number and expiry date are mandatory components of the labelling of all medicinal products – regardless of whether they bear the safety features – and should be printed on the packaging in accordance with Article 54(h) and (m) of Directive 2001/83/EC. There is no obligation to place batch number and expiry date adjacent to the two dimensional barcode.

2.12. Question: Is it allowed to place a QR code on the packaging of a medicinal product bearing the safety features?

Answer: Commission Delegated Regulation (EU) 2016/161 does not prohibit the placing of a QR code as far as it is not used for the purposes of identification and authentication of medicinal products.

Marketing authorisation holders are however encouraged, wherever technically feasible, to exploit the residual storage capacity of the Data Matrix to include the information they would otherwise include in the QR code (see also Q&A 2.16). This would minimise the number of visible barcodes on the packaging and reduce the risk of confusion as regard the barcode to be scanned for verifying the authenticity of the medicinal product.

Furthermore, in order to avoid incorrect scanning by end-users, if possible, the QR code should not be placed in proximity of the Data Matrix, preferably on a different side of the packaging.

2.13. Question: 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.

2.14. Question: Can the graphics on the containers of the medicinal products be printed separately and the Data Matrix added at the final packaging stage - or are there digital printing technologies where all packaging graphics and the UI can be printed in one step?

Answer: The Delegated Regulation does not specify how the safety features should be applied to the outer packaging. The placement of the safety features is therefore to be supervised by competent authorities in accordance with current practice for labelling requirements. The specifics of the technologies used to apply the UI will be for the individual manufacturer to decide and for them to select the most appropriate model suitable for their needs.

According to Annex 16 of the EU GMP Guidelines paragraph 1.7.21, affixing the UI to the packaging of a medicinal product is the responsibility of the Qualified Person. Any outsourcing of this activity to a third party by the manufacturer of the finished medicinal product must be in accordance with the principles described in Chapter 7 of Part I of the EU GMP Guidelines.

2.15. Question: Upon the medicinal product being supplied to the public, the UI is decommissioned and the package is no longer active in the repository. However, the 2D Data Matrix can still be read-out, for example by a consumer using a smartphone application. Will the possibility to verify the authenticity of the product via the Data Matrix be extended to the end-user (patient)?

Answer: The Delegated Regulation does not provide for verification of the authenticity of the product by the end user. In fact, the verification conducted by the person authorised to supply to the public guarantees that the product is not falsified.

2.16. Question: After the UI data has been encoded, can any residual storage capacity in the Data Matrix be used to store other information?

Answer: The Delegated Regulation states in Article 8 that manufacturers may include information additional to the information contained within the unique identifier in the two-dimensional barcode, where permitted by the competent authority in accordance with article 62 of Title V of the Directive 2001/83/EC. That information should be consistent with the summary of product characteristics, useful for the patient and may not contain promotional elements.

The amount of residual storage capacity of the Data Matrix after the UI data has been encoded will depend upon the size of the Data Matrix as selected by the individual manufacturers responsible for the placing of the UI on the packaging.

2.17. Question: Do human-readable headers (PC, SN, Lot, EXP, NN) have to be placed adjacent to the respective data elements, on the same line, or is some flexibility possible?

Answer: Human-readable headers are not required to be placed adjacent/on the same line as the respective data element. Headers can be placed in any position which allows the unequivocal identification of the human-readable data element.

2.18. Question: For products bearing the human-readable code, is it acceptable to place data elements in multiple locations across the packaging?

Answer: It depends on the data elements and dimensions of the packaging. The product code and serial number should be placed on the same surface, where space allows, so to facilitate manual decommissioning of the unique identifier. Concerning the other data elements, an effort should be made to place them on the same surface as the product code and serial number. Should the packaging dimensions not allow it, however, it is acceptable to place the other data elements as close to the product code and serial number as possible (e.g. adjacent sides).

2.19. Question: Is it acceptable to use a 2D Data Matrix which is rectangular (rather than square) or printed white on black (rather than black on white)?

Answer: Yes. Manufactures can chose to encode the unique identifier in a 2D Data Matrix which is rectangular and/or printed white on black, provided that it fulfils the technical requirement laid down in Article 5 of Commission Delegated Regulation (EU) 2016/161.

2.20. Question: Is it mandatory to include Application/Data Identifiers as part of the human-readable headers or data elements?

Answer: No. Manufacturers can choose whether to include the Application/Data Identifiers as part of the human-readable headers/data elements.

2.21. Question: Is it acceptable to use stickers to place the unique identifier on the outer/immediate packaging?

Answer: As a rule the unique identifier must be printed on the packaging (Article 5(3) of Commission Delegated Regulation (EU) 2016/161).

For medicinal products subject to parallel import and parallel distribution it is possible to use a sticker (adhesive label) provided that the sticker cannot be removed without being damaged and that the sticker fulfils the quality of the printing requirements set out in Article 6 of the Commission Delegated Regulation (EU) 2016/161 (case C-147/20, Novartis Pharma GmbH v Abacus Medicine A/S).

In addition, for medicinal products other than those subject to parallel import and parallel distribution, placing the unique identifier by means of stickers can be accepted in the following circumstances:

- No legal and/or technically feasible alternative exists (e.g. safeguard of trademark rights; glass/plastic immediate packaging without outer packaging; etc.); or

- Competent authorities authorise it due to the marketing authorisation to safeguard public health and ensure continued supply.

The placing/replacement of the unique identifier using stickers must be conducted in accordance with applicable Good Manufacturing Practice principles. Moreover all applicable labelling requirements in Directive 2001/83/EC must be met and the sticker must not impair the readability of other required labelling elements. The sticker should be tamper-evident, i.e. it should not be possible to remove it without damaging the packaging or the sticker itself or leaving visible signs. The unique identifier should not be printed on a separate sticker to the other labelling particulars unless agreed with the competent authority.

2.22. Question: Do human-readable headers (PC, SN, Lot, EXP, NN) have to comply with the provisions of the QRD-template?

Answer: Yes, preferably. According to to the current of the QRD-template[6], the product code, serial number and national reimbursement number in the human readable code should be preceded by the letters “PC”, “SN” and “NN”. Batch number and expiry date should follow the abbreviations laid out in Appendix IV of the QRD-template.

2.23. Question: Are there specific requirements for the characters used in batch and serial numbers?

Answer: No. However, in order to reduce the risk of false alerts due to end-user scanner misconfigurations, manufacturers are strongly encouraged to follow the recommendations below.

Serial and batch numbers should preferably:

- Contain only uppercase letters;
- Not include special characters (eg. hyphens, question marks, etc.); and
- Avoid the use of the letters "I", "O", "Y" and "Z".

3. GENERAL PROVISION ON THE VERIFICATION AND DECOMMISSIONING OF THE SAFETY FEATURES

3.1. Question: How should the unique identifier be decommissioned if the two-dimensional barcode is unreadable or deteriorated?

Answer: The unique identifier in human readable format should be recorded by any suitable method allowing the subsequent manual querying of the repository system in order to verify and decommission the unique identifier.

3.2. Question: Where the two-dimensional barcode carrying the unique identifier cannot be read, or in case the verification of the unique

[6] https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/product-information-requirements/product-information-qrd-templates-human

identifier is temporarily impeded, is it possible to supply the medicinal product to the public?

Answer: Article 30 of Commission Delegated Regulation (EU) 2016/161 prohibits supply to the public if there is reason to believe that the packaging of the medicinal product has been tampered with, or the verification of the safety features of the medicinal product indicates that the product may not be authentic.

In all other cases, the supply of medicinal products to the public is regulated by national legislation.

Without prejudice to national legislation, in the case where it is permanently impossible to read the unique identifier and verify the authenticity of the medicinal product, for example because both the Data Matrix and the human readable code are damaged, it is recommended that the medicinal product is not supplied to the public.

3.3. Question: Can a medicinal product which cannot be authenticated be returned, and to whom? Who should pay for the return?

Answer: Commission Delegated Regulation (EU) 2016/161 does not change the national provisions in place regulating returns of medicines from persons authorised or entitled to supply medicinal products to the public (e.g. pharmacies and hospitals). The regulation of returns of medicinal products, including their financial aspects, remains a national competence.

3.4. Question: Is the use of aggregated codes to simultaneously verify the authenticity of or decommission multiple unique identifiers permitted?

Answer: Recital 20 of the Delegated Regulation gives the possibility of giving aggregated codes allowing the simultaneous verification of multiple Unique Identifiers, provided that the requirements of Commission Delegated Regulation (EU) 2016/161 are complied with.

However, since aggregation is not regulated in the Delegated Regulation any action in that sense from manufacturers/wholesalers/parallel traders (or any actor in the supply chain, for the matter) is only voluntary and needs to be agreed upon by the stakeholders.

3.5. Question: Is it possible to reverse the decommissioned status of a medicinal product that has been physically exported to third countries, when such product is brought back into the EU?

Answer: No. When a medicinal product is physically exported outside of the EU, its unique identifier must be decommissioned in accordance with Article 22(a) of Commission Delegated Regulation (EU) 2016/161. If the exported product is subsequently reimported onto the EU territory (e.g. because it is returned), it is considered an "import" and must be imported by a manufacturing import authorisation (MIA) holder (not a wholesaler) and is subject to the import requirements laid down in Article 51 of Directive 2001/83/EC (batch testing, batch release, etc.). The imported medicinal product should also be given a new unique identifier containing a new batch number and expiry date, if applicable, before it is released for sale and distribution in the EU.

3.6. Question: Can a medicine with only one of the safety features (either the UI or ATD) that has been released for sale in Italy or in Greece before 9 February 2025 remain on the market?

Answer: Yes, a medicine with either a UI or ATD that has been released for sale before the entry into application of the Regulation and has not been repackaged or re-labelled may remain on the market until its expiry date.

3.7. Question: Who should verify and decommission medicines with safety features that are to be used in clinical trials as investigational medicinal products or authorised auxiliary medicinal products?

Answer: According to Articles 16, 23 and 25(4)(c) of Commission Delegated Regulation (EU) 2016/161, the unique identifier on medicines in their commercial presentations bearing safety features should be verified and decommissioned either by manufacturers, wholesalers or persons entitled or authorised to supply to the public before use as authorised investigational medicinal products (IMPs) or authorised auxiliary medicinal products.

For medicines repackaged or relabelled for use in clinical trials, the manufacturer holding the manufacturing and importation authorisation covering IMPs should verify and decommission the unique identifier before they repackage or relabel the medicine.

For medicines that are not repackaged or relabelled, the person entitled or authorised to supply to the public who supplies the medicinal product for subsequent use in a clinical trial should verify and decommission the unique identifier.

In some cases, Member States may require wholesalers to verify and decommission unique identifiers on medicines supplied for clinical trials on behalf of certain entitites under Article 23.

4. VERIFICATION OF THE SAFETY FEATURES AND DECOMMISSIONING OF THE UNIQUE IDENTIFIER BY MANUFACTURERS

4.1. Question: Do the records referred to in Article 15 of Commission 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 every operation he performs with or on the unique identifier.

4.2. Question: Article 18 requires that, in case of suspected falsification or tampering, the manufacturer should inform the competent authorities. Should they also inform the holder of the marketing authorization for the medicinal product?

Answer: Yes, Article 46 of Directive 2001/83/EC requires manufacturers to inform the competent authority and the marketing authorisation holder immediately if they obtain information that medicinal products which come under the scope of their manufacturing authorisation are, or are suspected of being, falsified.

4.3. Question: Articles 18, 24 and 30 of Commission Delegated Regulation (EU) 2016/161 require that manufacturers, wholesalers and persons authorised or entitled to supply medicinal products to the public immediately inform national competent authorities in case of suspected falsification of medicinal products. How should this information be notified by manufacturers?

Answer: It is recommended that manufacturers contact national competent authorities, since the procedure to follow for such notification is a national competence. If they exist, national guidelines should be followed.

4.4. Question: Can a manufacturer use outer packaging carrying a unique identifier which has been placed by a packaging materials provider?

Answer: Yes. Art. 14 of Commission Delegated Regulation (EU) 2016/161 requires that the manufacturer responsible for placing the safety features on the medicinal product verifies that the two-dimensional barcode carrying the unique identifier complies with Articles 5 and 6 of the said Regulation, is readable and contains the correct information before releasing the medicinal product for sale and distribution.

Where pre-printed cartons are used, the outsourcing of the pre-printing of the UI to a packaging material provider should be done in accordance with Chapter 7 of Part I of the EU GMP Guidelines, including the signature of a written agreement among the parties establishing the corresponding responsibilities. The packaging materials provider should be audited and qualified.

The manufacturer releasing the product for sale and distribution (see Q&A 7.13) should verify the capacity of the contracted packaging materials provider to perform the task in accordance with the requirements of the Regulation and in compliance with applicable GMP. Upon receipt of the pre-printed packaging materials, the manufacturer of the finished medicinal product is expected to perform appropriate checks on the quantity and quality of the UIs in line with EU-GMP principles.

4.5. Question: Are manufacturers responsible for ensuring unique identifiers are readable and complete?

Answer: Yes. Manufacturers must check that the 2D barcode is readable and contains the correct information (Article 14 of Commission Delegated Regulation (EU) 2016/161).

Furthermore, manufacturers must work closely with marketing authorisation holders to ensure that all relevant information on unique identifiers has been uploaded correctly to the repository system and corresponds to the information encoded in the unique identifier before they release medicines for sale or distribution (Article 33(2) of Commission Delegated Regulation (EU) 2016/161).

4.6. Question: Can a manufacturer outsource the placing of the safety features on a packaged medicinal product to another manufacturer?

Answer: Yes. The outsourcing of the placing of the safety features on a packaged medicinal product can be contracted to another manufacturer in line with Chapter 7 of Part I of the EU GMP Guidelines, as long as they have a manufacturing authorisation (MIA). The

contracting manufacturer must also make a statement confirming compliance with Annex 16 Appendix 1 of the EU GMP Guidelines available to the Qualified Person certifying the final product. The contracted manufacturer must be included in the marketing authorisation.

5. VERIFICATION OF THE SAFETY FEATURES AND DECOMMISSIONING OF THE UNIQUE IDENTIFIER BY WHOLESALERS

5.1. Question: How should the expression "the same legal entity" referred to in Articles 21(b) and 26(3) of Commission Delegated Regulation (EU) 2016/161 be interpreted?

Answer: This expression should be interpreted in accordance with national legislation. As general guidance, and without prejudice to national legislation, a legal entity may be considered the same when, for example, it has the same registration number in the national company registry or, if no national registration is required, the same number for tax purposes (i.e. VAT number).

5.2. Question: Member States may hold stocks of certain medicinal products for the purpose of public health protection. How should the unique identifiers on those products be verified and decommissioned?

Answer: In accordance with Article 23(f) of the Delegated Regulation, Member States may request wholesalers to verify the safety features of and decommission the unique identifier of medicinal products which are supplied to governmental institutions maintaining stocks of medicinal products for the purposes of civil protection and disaster control.

5.3. Question: Articles 18, 24 and 30 of Commission Delegated Regulation (EU) 2016/161 require that manufacturers, wholesalers and persons authorised or entitled to supply medicinal products to the public immediately inform national competent authorities in case of suspected falsification of medicinal products. How should this information be notified by wholesalers?

Answer: It is recommended that wholesalers contact national competent authorities, since the procedure to follow for such notification is a national competence. If they exist, national guidelines should be followed.

5.4. Question: Articles 20, 21 and 22 require wholesalers to verify the authenticity and/or decommission the unique identifier only. Do wholesalers need to verify the integrity of the anti-tampering device when complying with those Articles?

Answer: No, wholesalers do not need to (but can) verify the integrity of the anti-tampering device when complying with Articles 20, 21 and 22.

5.5. Question: Article 22(a) requires a wholesaler to verify the authenticity of and decommission the unique identifier of all medicinal products they intend to distribute outside of the Union. Is it necessary to decommission

the unique identifier if the medicinal product is sold to a party established outside the EU but that product does not physically leave the wholesaler's premises in the EU?

Answer: No. The purpose of Article 22(a) is to ensure the decommissioning of unique identifiers on packs which leave the EU territory, in order to avoid that those active codes may be harvested by traffickers. In case the medicinal product is sold to a party established outside the EU but physically remains in the wholesaler's premises in the EU, the unique identifier on the product should not be decommissioned. If that medicinal product is subsequently imported (while physically remaining in the EU) by a holder of a manufacturing and import authorisation (a wholesaler cannot import medicinal products), no action from the wholesaler physically holding the product is required with regard to the safety features.

5.6. Question: Do wholesalers have the obligation to decommissioning the unique identifier of a medicinal product when they sell the product "business-to-business" to a company which buys it for the purpose of research?

Answer: Article 23(g) allows the decommissioning by wholesalers of medicinal products supplied for the purpose of research, except when supplied to healthcare institutions. Although the Article does not explicitly mention that it applies to the supply of products for the purpose of research to companies which are not universities or other higher education establishments, it is desirable to include such a case in the scope of this Article (provided that those companies are not healthcare institutions) in order to guarantee the decommissioning of the unique identifiers on those products.

5.7. Question: Is wholesale distribution of medicinal products with a damaged/unreadable 2D Data Matrix code allowed, if there is no suspicion of falsification?

Answer: It depends on the human readable code. If the verification of the authenticity of the unique identifier (UI) can be performed using the human readable code, the product can be further distributed.

If the verification of the authenticity of the UI cannot be performed (because the human readable code is damaged or absent), then the wholesaler should not further distribute the product with unreadable codes (Article 24 of Regulation No 2016/161). This requirement is independent of whether the verification was mandatory under Article 20 of Commission Delegated Regulation (EU) 2016/161 or voluntarily performed by wholesalers.

5.8. Question: Can a wholesaler request another wholesaler to verify the authenticity and decommission the unique identifiers for medicinal products they intend to distribute outside the EU on their behalf?

No. According to Article 22(a), the wholesaler who physically holds the medicinal products and intends to distribute these products outside the EU must verify their authenticity and decommission the unique identifiers. This obligation cannot be delegated to another wholesaler, as the audit trail would not reflect the reality of the supply chain, as required by Article 35(1)(g) of the Regulation.

5.9. Deleted

5.10. Question: How can a wholesalers be sure that medicines they receive without safety features have been batch released prior to the entry into application of the safety features (9 February 2019)?

According to Commission Delegated Regulation (EU) 2016/161, marketing authorisation holders and manufacturers may only place medicines released before 9 February 2019 on the EU market without safety features. In principle this means that products on the EU market without safety features must have been released before the entry into application of the safety features.

Wholesalers may request that manufacturers include the batch release date in the delivery note of non-serialised medicines in order to confirm that the medicines were released before the safety features became mandatory.

5.11. Question: Should wholesalers be connected to the national repositories or can they be connected to the European hub?

A wholesaler physically holding products and performing activities related to wholesale outlined in Articles 20-23 Commission Delegated Regulation (EU) 2016/161 (such as the verification of returns or decommissioning for export) should be connected to and perform operations in the national repository where the activities take place. A connection to the national system is necessary to ensure that the the audit trail is accurate and complete.

5.12. Question: Is it possible for a wholesaler with multiple locations to use a single NMVO connection and account to verify and decommission medicines?

Answer: No. In order to ensure compliance with Articles 13 and 35(1)(g) of Commission Delegated Regulation (EU) 2016/161, each physical location of the wholesaler must be uniquely identifiable when connecting to the NMVS and performing operations in the system.

5.13. Question: According to Article 20(b) Commission Delegated Regulation (EU) 2016/161, wholesalers must verify medicinal products they do not receive from the manufacturer, marketing authorisation holder or wholesalers designated by the marketing authorisation holder. Is it necessary to verify the unique identifier of medicinal products sent directly from the manufacturer but purchased from a wholesaler who is neither the manufacturer, marketing authorisation holder or designated by the marketing authorisation holder?

Answer: No. The exemption in Article 20(b) refers to the physical transfer of medicines. Even if they have been purchased from a third party, medicines that have been shipped directly from the manufacturer, marketing authorisation holder or a designated wholesaler do not need to be verified in accordance with Article 20(b).

5.14 Is it allowed to verify the authenticity of the UI when the product is not in physical possession?

Answer: Yes, but only as an additional check to Article 20 of Commission Delegated Regulation (EU) 2016/161.

Article 20 of that Regulation requires wholesalers to verify the authenticity of the Unique Identifier (UI) for *at least* the medicinal products in *his physical possession* the referred to in this Article, i.e.:

> *(a) medicinal products returned to him by persons authorised or entitled to supply medicinal products to the public or by another wholesaler;*
>
> *(b) medicinal products he receives from a wholesaler who is neither the manufacturer nor the wholesaler holding the marketing authorisation nor a wholesaler who is designated by the marketing authorisation holder, by means of a written contract, to store and distribute the products covered by his marketing authorisation on his behalf.*

This obligation is a minimum requirement. Therefore, a wholesaler may verify the authenticity of other products of other origins than those addressed in Article 20 via the UI when the product is not in physical possession. Such practice should be considered an additional check.

It does exempt from the obligation to verify the UI once the product is in physical possession and can thus not replace it.

In this context, it should be stressed that only authorised suppliers located in the EU can put medicinal products on the market in the EU. Verifying the UI of packs located outside the EU does not replace import testing and batch certification after import by authorised manufacturers.

6. VERIFICATION OF THE SAFETY FEATURES AND DECOMMISSIONING OF THE UNIQUE IDENTIFIER BY PERSONS AUTHORISED OR ENTITLED TO SUPPLY MEDICINAL PRODUCTS TO THE PUBLIC.

6.1. Question: In-patients in a hospital may be administered medicinal products during their stay, the costs of which may be charged to their insurer, which constitutes a sale. In this case, would the hospital (or any other healthcare institution) be allowed to verify the safety features and decommission the unique identifier of those products earlier than the time of supply to the public, in accordance with Article 25(2)?

Answer: Yes. In the case described, the charging of the medicinal products costs to the patient's insurer happens as a consequence of the administration of that product to the patient (regardless of whether the sale takes place before or after the actual administration). Consequently, it is considered that the charging of the cost of the medicinal product to the patient's insurer (or to the patient himself, for the matter) does not preclude hospitals from applying the derogation provided for in Article 25(2).

6.2. Question: How should the expression "the same legal entity" referred to in Articles 21(b) and 26(3) of Commission Delegated Regulation (EU) 2016/161 be interpreted?

Answer: See Q&A 5.1.

6.3. Question: Many hospitals and other healthcare institutions supply the contents of packages of a medicinal product to more than one patient. Where only part of a pack of a medicinal product is supplied, when should the decommissioning of the unique identifier be performed?

Answer: The unique identifier should be decommissioned when the packaging is opened for the first time, as required by Article 28 of Commission Delegated Regulation (EU) 2016/161 .

6.4. Question: Does automated dose dispensing require the placing of new safety features on the individual patient doses/packs?

Answer: No. Automated dose dispensing falls in the scope of Article 28 of Commission Delegated Regulation (EU) 2016/161. Consequently, it is not necessary to place new safety features on the individual patient's dose/pack.

6.5. Question: Is it possible for the wholesaler to scan the unique identifiers (UI) in a consignment before shipping the consignment to a hospital, store the UI information and then, once the hospital received the consignment, decommission the UIs using the stored information following an explicit request by the hospital?

Answer: No, the above process is not in line with the provisions of Commission Delegated Regulation (EU) 2016/161:

- Since the decommissioning would happen through the wholesaler's computer using the wholesaler's log-in ID, the decommissioning operation would be recorded in the system and in the audit trail as an operation performed by the wholesaler, and not by the hospital. This is not acceptable as the audit trail would not reflect the reality of the supply chain, as required by Article 35(1)(g) of the Regulation.
- Articles 23 and 26 of Commission Delegated Regulation (EU) 2016/161 are explicit about those cases where wholesalers are entitled to decommission the safety features on behalf of hospitals. Decommissioning on behalf of hospitals under other circumstances is therefore not allowed.

6.6. Question: Is it acceptable for hospitals/hospital pharmacies to subcontract their decommissioning obligations to wholesalers?

Answer: No. However, there are possible scenarios, compatible with Commission Delegated Regulation (EU) 2016/161, where wholesalers (including manufactures supplying their own products by wholesale) could facilitate the decommissioning operation of hospitals (illustrative examples only, list not exhaustive):

- Wholesalers could scan the packs in the hospital consignment to acquire the information on the UIs and encode such information into an aggregated code. Decommissioning would then be performed by the hospital by scanning the aggregated code. The only equipment needed for this operation would be a hand-held scanner and a computer (connected to the national repository).
- Wholesalers could acquire the information on the UIs in the hospital consignment and make this information available to the hospital, by secure

means. The hospital would then use such information to perform the decommissioning (without having to physically scan the packs).

6.7. Question: Articles 18, 24 and 30 of Commission Delegated Regulation (EU) 2016/161 require that manufacturers, wholesalers and persons authorised or entitled to supply medicinal products to the public immediately inform national competent authorities in case of suspected falsification of medicinal products. How should this information be notified by persons authorised or entitled to supply medicinal products to the public?

Answer: It is recommended that persons authorised or entitled to supply medicinal products to the public contact national competent authorities, since the procedure to follow for such notification is a national competence. If they exist, national guidelines should be followed.

6.8. Question: For persons authorised or entitled to supply medicinal products to the public operating within a healthcare institution, must the verification of the integrity of the anti-tampering device be done at the same time as the verification and decommissioning of the unique identifier?

Answer: No. Article 25(2) of Commission Delegated Regulation (EU) 2016/161 outlines that verification of the safety features can be done at any time a medicine is in the physical possession of a healthcare institution as long as no sale takes place between delivery to the healthcare institution and supply to the public. Therefore, decommissioning of the UI and verification of the ATD can be done separately before supply to the public.

6.9. Question: Is it possible for a pharmacy chain with multiple locations to use a single NMVO connection and account to verify and decommission medicines in different branches before dispense?

Answer: No. In order to ensure compliance with Articles 13 and 35(1)(g) of Commission Delegated Regulation (EU) 2016/161, each physical location of a pharmacy chain must be uniquely identifiable when connecting to the NMVS and performing operations in the system.

7. ESTABLISHMENT, MANAGEMENT AND ACCESSIBILITY OF THE REPOSITORIES SYSTEM.

7.1. Question: How should the expression "manufacturers of medicinal products bearing the safety features", as used in Commission Delegated Regulation (EU) 2016/161, be interpreted?

Answer: For the purposes of Commission Delegated Regulation (EU) 2016/161, "manufacturer" means the holder of a manufacturing authorisation in accordance with Article 40 of Directive 2001/83/EC. The expression "manufacturers of medicinal products bearing the safety features" encompasses any holder of the said authorisation performing partial or total manufacture of a medicinal product bearing the safety features.

7.2. Question: Article 31 of Commission Delegated Regulation (EU) 2016/161 allows wholesalers and persons authorised or entitled to supply medicinal products to the public to participate in the legal entity/ies setting up and managing the repositories system, at no costs. Can the terms of such participation be regulated by stakeholders, for examples through the statutes of establishment or incorporation of the legal entity/ies?

Answer: Yes, it is possible, provided that the terms do not contradict what is enshrined in legislation. In case of discrepancy, the provisions of Commission Delegated Regulation (EU) 2016/161 and Directive 2001/83/EC prevail.

7.3. Deleted

7.4. Question: How should the expressions "application programming interface" or "graphical user interface" referred to in Articles 32(4) and 35(1) of Commission Delegated Regulation (EU) 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 Commission Delegated Regulation (EU) 2016/161, the expression refers to the programming instructions and standards allowing the software of persons authorised or entitled to supply medicines to the public, 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.

The purpose of Article 35(1)(i) is to ensure that, in case of software failure, wholesalers and persons authorised/entitled to supply medicines to the public have an alternative way to connect to the national medicine verification system to verify the authenticity of/decommission the unique identifier. However, to avoid that wholesalers and persons authorised/entitled to supply medicines to the public rely routinely on the GUI to verify the authenticity of/decommission the unique identifiers on their products, Article 35(1)(i) limits the circumstances in which they are entitled (i.e. have the legal right) to use the GUI to the case of failure of their own software. The use of the GUI in any other circumstance is not prohibited but is subject to the agreement of the national medicine verification organisation owning the GUI. See also Q&A 7.18.

7.5. Question: Article 33(1), second subparagraph, requires that information referred to in paragraphs 2(a) to 2(d) of that article, with the exception of the serial number, is stored in the hub. Does this mean that the serial number cannot be uploaded to the hub?

Answer: No, the provision only regulates which information is to be stored in the hub.

7.6. Question: Articles 34(4), 35(4) and 36(n) refer to the linking of the information on unique identifiers removed or covered to the information on the equivalent unique identifiers placed for the purposes of complying

with Article 47a of Directive 2001/83/EC. Is the linking required to be at the level of individual unique identifiers? How does the linking work in practice?

Answer: No, it is not necessary to link individual unique identifiers. The link can be made at batch level by linking the list of decommissioned unique identifiers in the "old" batch (the batch to be repacked/relabelled) and the list of new unique identifiers placed on packs in the "new" batch (the repacked batch). The provision does not require the linking to be done at the level of individual unique identifiers, since the number of packs in the batch to be repacked/relabelled (and consequently the number of unique identifiers in that batch) may not correspond to the number of packs (and of unique identifiers) in the new batch – making a one-to-one link between unique identifiers impossible.

7.7. Question: In Article 35(1)(f), does the upper limit of 300 ms for a repository to respond to queries also apply when multiple repositories are implicated in the query, for example in case of cross-border verification?

Answer: 300 ms is the maximum response time of an individual repository. When the verification/decommissioning operation requires the querying of multiple repositories in the repositories system, for example in case of inter-market transactions,, the maximum response time is obtained by multiplying the maximum response time of an individual repository (300 ms) by the number of repositories involved in the query – for example, the maximum response time for a query involving national repository A, the hub, and national repository B would be 900 ms.

It should be noted that the system response time does not include the time needed by the query data to move from one repository to the other (which depends from the speed of the internet connection).

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

Answer: It is the responsibility of the legal entity establishing and managing a repository to put in place appropriate security procedures ensuring that only verified users, i.e. users whose identity, role and legitimacy has been verified, are granted access to that repository.

7.9. Question: In Article 38(1), does the sentence "with the exception of the information referred to in Article 33(2)" refer to data access only, or also to data ownership?

Answer: It refers to data access only.

7.10. Question: In Article 38(1), what is the meaning of "information on the status of the unique identifier"?

Answer: The information on the status of the unique identifier includes whether the unique identifier is active or decommissioned, and in the latter case, the reasons for the decommissioning.

7.11. Question: What is the purpose of the exceptions laid out to in the second sentence of Article 38(1) concerning access to the information referred to in Article 33(2) and the information on the status of a unique identifier?

Answer: Article 38 of Commission Delegated Regulation (EU) 2016/161 regulates the ownership and the access of the data stored in the repositories system. It lays down the general rule and an exception to that rule. Since the purpose of Article 38 is, inter alia, to protect the confidentiality of data in the repositories system, including commercially confidential data, as required by Article 54a(3)(b) and (c) of Directive 2001/83/EC, the exception should be interpreted narrowly. In particular, the use of the exception should be limited to those cases where access to the data is necessary to perform the verification/decommissioning operations required by Commission Delegated Regulation (EU) 2016/161, as explained in recital 38.

7.12. Question: Is it possible to have multiple national repositories, multiple supranational repositories or a combination of national and supranational repositories serving the territory of a given Member State?

Answer: No. In accordance with Article 32, paragraphs 1 and 2, the territory of a given Member State should be served by the hub and either a national or a supranational repository connected to the hub.

7.13. Question: For the purposes of the application of Articles 33 and 48 of Commission Delegated Regulation (EU) 2016/161, what is understood for 'medicinal products that have been released for sale or distribution'?

Answer: The text 'medicinal products that have been released for sale or distribution' refer to products which have been batch released in accordance with Article 51 of Directive 2001/83/EC. According to Annex 16 of the EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use "Certification by a Qualified Person (QP) and Batch Release", the process of batch release comprises of:

i. The checking of the manufacture and testing of the batch in accordance with defined release procedures.
ii. The certification of the finished product batch performed by a QP signifying that the batch is in compliance with GMP and the requirements of its MA. This represents the quality release of the batch.
iii. The transfer to saleable stock, and/or export of the finished batch of product which should take into account the certification performed by the QP. If this transfer is performed at a site other than that where certification takes place, then the arrangement should be documented in a written agreement between the sites.

Therefore, medicinal products that have been certified for release by a QP without including the safety features in their packaging before the entry into application of the Regulation, may be placed on the market, distributed and supplied to the public until their expiry date.

7.14. Question: How should the expression "marketing authorisation holder", as used in Commission Delegated Regulation (EU) 2016/161, be interpreted?

Answer: The term "marketing authorisation holder" is used in Commission Delegated Regulation (EU) 2016/161 to indicate holders of marketing authorisations in the sense of Article 6 of Directive 2001/83/EC.

7.15. Question: Are parallel importers/distributors required to comply with Article 33(1) and upload the information in Article 33(2) into the repository system? Should they also upload a list of designated wholesalers?

Answer: Parallel traders are obliged to comply with Article 33 and upload in the repositories system in the following two cases:

- If they hold a marketing authorisation in the sense of Article 6 of Directive 2001/83/EC, in which case they may also upload the list of wholesalers they have designated in accordance with Article 20(b) of Commission Delegated Regulation (EU) 2016/161; or
- If they repack/relabel and place new safety features or replace safety features in accordance with Article 47a of Directive 2001/83/EC on the medicinal products they supply. In this case, parallel traders who do not hold a marketing authorisation in the sense of Article 6 of Directive 2001/83/EC may not designate their own wholesalers and should not upload a list of wholesalers into the repository system.

Parallel traders who repack/relabel their products and place new safety features or replace safety features in accordance with Article 47a of Directive 2001/83/EC on the medicinal products they supply have to comply with Articles 33, 40 and 42 of Commission Delegated Regulation (EU) 2016/161 as they are considered the "persons responsible for placing those medicinal products on the market" in that Member State.

7.16. Question: In accordance with Article 33(1), the information laid down in Article 33(2) must be uploaded in the repositories system before the product is released for sale and distribution. Does this mean that the upload needs to take place before the Qualified Person (QP) performs the batch certification and thus the safety feature information relative to any manufacturing waste should also be uploaded in the system?

Answer: No. The information laid down in Article 33(2) of Commission Delegated Regulation (EU) 2016/161 needs to be present in the system at the time the batch is released for sale and distribution (see Q&A 7.13 for what is understood for *released for sale or distribution*). It is acceptable to upload that information at such a time that the system is not burdened with information relative to manufacturing waste, i.e. (parts of) manufactured batches that have not been certified, provided that the upload takes place before the medicinal product is transferred to saleable stock.

7.17. Question: Does Article 37(d) require that a national medicine verification organisation (NMVO) directly alerts the relevant national competent

authorities, the EMA and the Commission about a falsification? Is there is a time limit for such alerting?

Answer: The use of the term "provide for" in Article 37(d) of Commission Delegated Regulation (EU) 2016/161 means that an NMVO has to ensure that the national competent authorities, the EMA[7] and the Commission[8] are informed. The NMVO can fulfil this obligation either directly or by ensuring this task is performed by someone else.

The NMVO should ensure authorities are informed as soon as it is clear that the alert triggered in accordance with Article 36(b) cannot be explained by technical issues with the repositories system, the data upload, the person performing the verification or similar technical issues.

7.18. Question: Does Article 35(1)(i) of Commission Delegated Regulation (EU) 2016/161 prohibit wholesalers and persons authorised or entitled to supply medicinal products to the public from using the national medicine verification system's graphical use interface (GUI) to verify/decommission the unique identifiers on their products when their own software is not broken?

Answer: No. The use of the GUI by wholesalers and persons authorised/entitled to supply medicines to the public in circumstances other than the failure of their own software is not prohibited but is subject to the agreement of the national medicine verification organisation owning the GUI (in the absence of entitlement, the agreement of the system owner is necessary). See also Q&A 7.4.

7.19. Question: Can a marketing authorisation holder delegate the uploading of the information laid down in Article 33(2) of Commission Delegated Regulation (EU) 2016/161?

Answer: Yes. Marketing authorisation holders (MAHs) may delegate the uploading of the information laid down in Article 33(2) to third parties (on-boarding partners (OBPs))by means of a written agreement between both parties. The MAH remains legally responsible for these tasks.

In all cases, the MAH must ensure with a high level of confidence the accuracy, confidentiality and integrity of the data uploaded into the system. This includes, but is not limited to: procedures to ensure that uploaded data and actual batch properties correspond (such as, batch number, expiry dates, destination market, batch size), procedures for secure data exchange with the subcontractor and procedures to ascertain that data to be uploaded has not been corrupted in any way. Data uploading performed by means of infrastructures, hardware and software that are physically located outside the EEA is strongly discouraged.

[7] By email to QDEFECT@ema.europa.eu
[8] By email to SANTE-PHARMACEUTICALS-B4@ec.europa.eu

7.20. Question: What is meant by *investigation* of all potential incidents of falsification flagged in the system in Article 37(d) of Commission Delegated Regulation (EU) 2016/161?

Answer: The purpose of the investigation in Article 37(d) is to rule out that alerts triggered in the system have been caused for technical reasons, such as issues with the repository system, data upload, data quality, incorrect end-user scanning or other similar technical issues.

As outlined in Q&A 7.17, national competent authorities, EMA and the European Commission should be informed as soon as it is clear that alert cannot be explained by technical reasons. On the basis of the information received, an investigation into the falsification incident will be launched by the authorities in line with European and national procedures.

7.21 Question: Should NCAs have access to all end-user information in the audit trail, including the names and addresses of end-users in another Member State?

Answer:

Yes, all NCAs shall have full access to all audit trail data upon request. This includes information such as the corporate name and address of wholesalers and persons authorised or entitled to supply medicinal products to the public, who are involved in verifying the authenticity and decommissioning of a unique identifier.

8. OBLIGATIONS OF MARKETING AUTHORISATION HOLDERS, PARALLEL IMPORTERS AND PARALLEL DISTRIBUTORS.

8.1. Question: Can marketing authorization holders delegate the performing of their obligations under Articles 40 and 41 to a third party?

Answer: Marketing authorisation holders can (but are not obliged to) delegate part of their obligations under Articles 40 and 41 to a third party by means of a written agreement between both parties. However, marketing authorisation holders remain legally responsible for those tasks.

In particular, marketing authorisation holders can delegate the performing of their legal obligation under Article 40(a) and 40(b), as well as the decommissioning task in referred to in Article 41.

8.2. Question: Situations arise where, for the same batch of product, competent authorities from different Member States issue different levels of recall, e.g. patient level *vs* wholesaler level, or no recall at all. How will Article 40 of Commission Delegated Regulation (EU) 2016/161 work in this type of scenario?

Answer: Article 40 of Commission Delegated Regulation (EU) 2016/161 would not apply to recalls at patient level as the scope of the Delegated Regulation does not extend beyond

the supply of the medicinal product to the end consumer. Where a medicinal product is recalled at pharmacy level in a Member State and at wholesale level in another, the marketing authorisation holder should customise the information they needs to provide in the relevant national/supranational repositories in accordance with Article 40(c).

8.3. Question: Certain Member States have national systems managing recalls and withdrawals of medicinal products in place. Would it be possible to interface those national systems with the repositories system for the verification of the safety features?

Answer: Commission Delegated Regulation (EU) 2016/161 does not provide for the connection between the national systems for recalls/withdrawal of medicinal product and the repositories system. Such connections may be considered by the legal entities managing the relevant repositories in the repositories system, on a voluntary basis.

8.4. Question: Are parallel importers/distributors required to comply with Articles 40 and 42 of Commssion Delegated Regulation (EU) 2016/161?

Answer: Parallel traders are obliged to comply with Articles 40 and 42 of Commission Delegated Regulation (EU) 2016/161 in the following two cases:

- If they hold a marketing authorisation in the sense of Article 6 of Directive 2001/83/EC.
- If they repack/relabel and place new safety features or replace safety features in accordance with Article 47a of Directive 2001/83/EC on the medicinal products they supply.

Parallel traders who repack/relabel their products and place new safety features or replace safety features in accordance with Article 47a of Directive 2001/83/EC on the medicinal products they supply have to comply with Articles 33, 40 and 42 of Commission Delegated Regulation (EU) 2016/161 as they are considered the "persons responsible for placing those medicinal products on the market" in that Member State.

8.5. Question: In the case of free samples which are obliged by national law to include in their labelling the sentence “Free sample. Not to be sold”, can the obligation to bear the safety features be waived?

Answer: No. Article 41 of Commission Delegated Regulation (EU) 2016/161 requires that marketing authorisation holder intending to supply any of his medicinal products as a free sample shall, where that product bears the safety features, indicate it as a free sample in the repositories system and ensure the decommissioning of its unique identifier before providing it to the persons qualified to prescribe it. Consequently, free samples are in the scope of the Regulation and have to bear the safety features.

8.6. Question: Can marketing authorisation holders upload in the repositories system serial numbers that are never actually used as data elements of unique identifiers?

Answer: No. The purpose of the repository system is to the information on the safety features is contained. Serial numbers that are not actually used as data elements in unique

identifiers should not be uploaded and stored in the repositories system as they represent a security risk for the system.

8.7. Question: What are the obligations of operators who supply medicinal products on the ground of Article 126a (Cyprus clause) with regard to the safety features?

Answer: The term "marketing authorisation holder" is used in Commission Delegated Regulation (EU) 2016/161 and in Directive 2001/83/EC to indicate holders of marketing authorisations in the sense of Article 6 of the said Directive. Hence, the term does not apply to operators who distribute medicinal products on the ground of Article 126a. However, in order to handle medicinal products, those legal entities have to have a manufacturing authorisation and/or a wholesale distribution authorisation and/or a parallel import license. They are therefore subject to the obligations laid down in Commission Delegated Regulation (EU) 2016/161 for manufacturers and/or wholesale distributors and/or parallel importers/distributors.

In addition, should those operators place or replace the safety features in accordance with Article 47a of Directive 2001/83/EC on the medicinal products they supply, they need to comply with Articles 33, 40 and 42 of Commission Delegated Regulation (EU) 2016/161 as they are the "person responsible for placing those medicinal products on the market" in the Member State for which an authorisations in the sense of Article 126a was granted.

8.8. Question: In the case of replacement of the safety features by parallel traders, can the decommissioning of the original unique identifier be carried out by the wholesaler from whom they receive the product?

Answer: No. The decommissioning of the original unique identifier must be performed by the parallel trader holding the manufacturing authorisation and replacing the safety features (Article 16 of Commission Delegated Regulation (EU) 2016/161).

8.9. Question: Should marketing authorisation holders upload the unique identifiers for products with 2D barcodes released for sale or distribution before the date of application of Commission Delegated Regulation (EU) 2016/161?

Answer: Yes. According to Article 48 of Commission Delegated Regulation (EU) 2016/161, medicines released for sale or distribution before the date of application of this Regulation without a unique identifier may remain on the EU market until their expiry date, as long as they are not repackaged or relabelled after that date. If they are repackaged or relabelled after the date of application of the Regulation, the manufacturer must place safety features in accordance with Directive 2001/83/EC and Commission Delegated Regulation (EU) 2016/161.

This transitional measure does not apply for products which were released before the date of application of the Regulation with a unique identifier. The unique identifiers for such products should be uploaded to the system before the entry into application of the new rules. This should help to avoid alerts for genuine products released before the date of application of the Regulation due to lack of data in the repository.

9. LISTS OF DEROGATIONS AND NOTIFICATIONS TO THE COMMISSION.

9.1. Question: Can marketing authorisation holders submit their proposals for amendments to Annex I of Commission Delegated Regulation (EU) 2016/161 to the Commission?

Answer: Only Member States notifications are taken into account for the purpose of establishing Annex I and II of the Delegated Regulation, in accordance with Article 54a(2)(c) of Directive 2001/83/EC. Concerning Annex I, Member States may inform the Commission of medicinal products which they consider not to be at risk of falsification (Article 54a(4) of Directive 2001/83/EC).

10. TRANSITIONAL MEASURES AND ENTRY INTO FORCE [DELETED].

10.1. Deleted

11. ANNEX I

11.1. Question: How should the term "Kits" referred to in Annex I to Commission Delegated Regulation (EU) 2016/161 be interpreted?

Answer: The term "kit" is defined in Article 1(8) of Directive 2001/83/EC. It refers to "any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration".

11.2. Question: Are fat emulsions used for parenteral nutrition and having an ATC code beginning with B05BA exempted from bearing the safety features?

Answer: Yes. Fat emulsions having an ATC code beginning with B05BA are included in the category "solutions for parenteral nutrition" listed in Annex I to Commission Delegated Regulation (EU) 2016/161. Such emulsions are therefore exempted from the obligation to bear the safety features.

12. ANNEX II

12.1. Question: Are over-the-counter omeprazole products formulated as gastro-resistant tablets in the scope of Annex 2 and therefore required to bear the safety features?

Answer: No. Only over-the-counter medicinal products containing omeprazole 20 or 40 mg formulated as hard gastro-resistant capsules have to bear the safety features, as the two reported incidents of falsification that led to certain omeprazole products being added to Annex II concerned that specific pharmaceutical form of omeprazole.

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