Safety features for medicinal products for human use

Questions & Answers

This document sets out frequently-asked 'questions and answers' regarding the implementation of the rules on the safety features for medicinal products for human use, that received Czech Medicines Verification Organization (Národní organizace pro ověřování pravosti léčiv – NOOL).

Document history	
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Changes vs. previous version	Added article 5.7 Reviewed answers 3.4 and 4.5

Important notice: The views expressed in this questions and answers document are not legally binding. Ultimately, only the European Court of Justice can give an authoritative interpretation of Union law.

These rules are enshrined in Articles 47a, 54(o) a 54a od Directive 2001/83/EC, and in the Commission Delegated Regulation No 2016/161. [1]

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[1] Commission Delegated Regulation (EU) No 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.

1. System technical requirements

1.1. Required HW and SW (serialization) is expensive for small quantities (e.g. 1,500 pc/month); the medicinal product is in demand – necessary – and we are not considering to terminate its production. Is it possible to use a third party (manufacturer<- -->third party - --> EU repository), e.g. another manufacturer that, due to its production volume, has acquired SW and HW, or a company that, due to small quantities of products of other manufacturers, could become a guarantor for the relevant communication with the EU repository?

Every medicinal product (hereinafter referred to as MP) has a registered production chain, including the point of release. Pursuant to Section 66 (1,c) of Act No. 378/2007 of Coll., on pharmaceuticals, a qualified MP manufacturer must furnish MP packaging with safety features. Article 4 of Regulation (EU) 2016/161 (hereinafter referred to as the Regulation) stipulates that the unique identifier must be placed on MP packaging by the manufacturer, i.e. by the manufacturer that has relevant production authorization and is mentioned in the registration documentation of the relevant MP. The MP manufacturer may outsource part of its production activities to another entity, i.e. a third party, based on a contract.

1.2. Is it possible to have a third party print out UIs (database 1), to use the necessary quantity of UIs (Database 2), to liquidate unused UIs (database 3 (D1-D2)) and to let the third party send database 2 to the EU repository?

See the answer in 1.1

2. Product code requirements

2.1. Product Code format and origin: Please clarify local regulations' requirements to the Product Code format and origin? (i.e. How is the Product Code generated? What is the format? NTIN/GTIN/PC etc.?)

GTIN generated by the manufacturer is accepted in the CR as the product code.

According to the State Institute for Drug Control, the product code must be in compliance with the requirements specified in Article 4 (b,i) and Article 5(5) of the Regulation. A marketing authorization holder must upload the MP coding scheme and other data to the repositories system (Article 33 (2,b) before the MP is released by the manufacturer.

2.2. 2D Data-Matrix/GS1 Expiry Date format: Please confirm that regulation requires Data-Matrix/GS1 Expiry data format to follow coding format YYMMDD?

Answer of GS1 ČR: To encode the expiry date in a GS1 DataMatrix, it is necessary to use the application identifier GS1 AI (17), which is in YYMMDD format.

Several options are used to transfer encoded information into human-readable format; HRI = (17)YYMMDD, Non-HRI usually MM YYYY, DD xxx YYYY, where xxx are the first three letters of the month in English.

Answer of the SIDC: The expiry date in 2D code is acceptable in the format shown on MP packaging in compliance with Article 54 (h) of Directive 2001/83/EC, i.e. month/year; however, this format is not in any way specified in Regulation (EU) 2016/161.

2.3. Data matrix Application identifiers: Please confirm that using GS1 Application identifiers are compliant with local regulations?

Yes, they are. To encode data in a GSI DataMatrix, it is necessary to use the following application identifiers:

(01) GTIN (n14)

(21) Serial number (an..20)

(17) Expiry date (YYMMDD)

(10) Lot number (an..20)

2.4. Data matrix/GS1 print sequence: Please state requirements for print sequence inside 2D Data Matrix?

Answer of GS1 ČR: GS1 standard does not define any requirements concerning AI sequence in a GS1DataMatrix (nor in HRI). GS1 DataMatrix must contained required AI (01,21,17,10), and encoded data must also be in HRI format.

2.5. The label of the human-readable data can be printed on the box in several formats. For example the label of the expiration date can be presented in several formats as EXP or EX or 17.

Does SÚKL command in which format these data should be printed? If yes, please specify the format. The possibilities are:

(a)   Usage of letters:

-     *"EMA QRD": Usage of two letters sign:*

PC 01234567890128

SN 10110123456789

NN 1234567

EX 06/2019

BN 3590617

-     *GS1 non-HRI: Usage of several letters sign:*

GTIN 01234567890128

SN   10110123456789

NHRN 1234567

EXP   06/2019

LOT 3590617

(b)   Usage of numbers:

-     *GS1 HRI with label separated by a gap:*

01 01234567890128

21 10110123456789

17 190600

10 3590617

711 1234567

- *GS1 HRI with label separated by a <u>different form</u>:*

01**:**01234567890128 (by a colon)

(01**)**01234567890128 (by brackets)

(01**)** 01234567890128 (by brackets with a gap)

Any sequence of numeric characters identifying product code, serial number and national reimbursement number (if applicable) must be preceded by a QRD-defined abbreviation, which means that the only acceptable option of the above is (a), wherein numeric characters are preceded by PC, SN, NN, respectively.

Expiry date is not part of the human-readable data required by the legislation on safety features. Nevertheless, it is mandatory to indicate expiry date on the packaging as stipulated by Decree No. 228/2008 Coll., on registration of medicinal products. The abbreviation to be printed on packaging to state expiry date is already included in approved texts of the respective medicinal product. The expiry date should be therefore preceded by an abbreviation as per approved texts (Section 8 QRD Template). "EXP" or "Použitelné do:" are acceptable for the Czech Republic (see Appendix IV QRD Template). Expiry date format is stipulated by QRD Template: [The expiry date printed on medicinal products stating only month and year should be taken to mean the last day of that month. Expiry dates should be expressed with the month given as 2 digits or at least 3 characters and the year as 4 digits, e.g.: February 2007, Feb 2007, 02-2007.]. The expiry date does not necessarily have to appear next to 2D code.

Expiry date rules will apply to lot number, accordingly. Thus, lot number does not necessarily have to appear next to 2D code, and the numeric characters identifying the lot will be preceded by an abbreviation approved for packaging texts of the respective medicinal product. "Lot", "č.š." "Č. šarže" are acceptable for the Czech Republic (see Appendix IV QRD Template).

2.6. Please specify whether or not 2D code for expiration YYMMDD can always show DD as 00 (in human-readable form, only month and year are shown and not day).

Based on EMVO's specification, the expiration date can be entered in basic data as year and month only. It is the same in GS1 specifications; therefore, yes, it is possible.

At the same time, it is important to realize that this must also be taken care of in information systems in order to ensure a correct interpretation (190200 actually means 28 February 2019; 200200 means 29 February 2020).

3. Process changes

3.1. We could make the UI - 2D code prior to its printing in off-line mode (database 1 – e.g. 2,500 pcs – based on gross production), then print it out and manually apply it to packaging. The UIs used during the last production operation – packaging (database 2 – e.g. 2,300 pcs – net packaged production sent to quarantine) would be sent to the EU repository upon release to distribution. Database 3 (Databases 1-2) – unused UIs would be liquidated. Is this procedure correct or possible?

4

Every medicinal product (hereinafter referred to as MP) has a registered production chain, including the point of release. Pursuant to Section 66 (1,c) of Act No. 378/2007 of Coll., on pharmaceuticals, a qualified MP manufacturer must furnish MP packaging with safety features that are in compliance with Articles 5 and 6 of the Regulation and include correct information. It is up the manufacturer how it fulfills these obligations; however, the required data must be uploaded to the repositories system before the MP is released by the manufacturer. This procedure as described does not guarantee the fulfillment of the requirements stipulated in Article 5(3) the Regulation, which states that " manufacturers shall print the barcode on the packaging on a smooth, uniform, low-reflective surface."

3.2. How will medicinal products be received in a pharmacy; by pack or by lot and expiration date, which is the current practice? If a delivery bill shows 10 pcs of a specific medicinal product with the same lot and expiration date, it is entered into the system as one line of 10 pcs just like the one line on the delivery bill. However, after the planned changes, each box should have its own identifier. Therefore, a delivery bill (in electronic and paper form) should show 10 lines with different identifiers for 10 pcs of the same medicinal product with the same lot and expiration date. Will distributors take these changes into account?

The requirements concerning the data in a delivery bill do not change in connection with the safety features; they should thus remain the same, the identifiers of every packaging must be printed on MP packaging in human-readable format, but there is no requirement to also show them in a delivery bill. The entering of medicinal products in the pharmacy system does not have to be changed either. Pharmacies must verify the safety features and decommission the unique identifier in compliance with Article 25 of the Regulation, i.e. at the time of supplying medicinal products to the public. The repositories system actually makes it possible to verify the unique identifier repeatedly and thus pharmacies can also verify it at any time before that. MP packaging is verified in the national repository, or in the repositories system, and not in the pharmacy system. When a medicinal product is supplied to the public, a pharmacy will verify the safety features and decommission the unique identifier.

3.3. The UIs will be sent to the EU database at the time of release – is it possible to physically apply pre-printed UIs onto product packaging from the time medicinal products are packed until they are released (medicinal products are in quarantine for 14 days)?

See the answer in 3.1.

3.4. According to Commission Delegated Regulation (EU) 2016/161 manufacturers are required to print the following data elements of the UI on the packaging in human-readable data:
- The product code;
- The serial number;
- The national reimbursement number or other national number identifying the medicinal product, if required by the Member State where the product is intended to be placed on the market and not printed elsewhere on the packaging.

The "product code" and national reimbursement number are data that are identical for each packaging of one product therefore they can be part of the artwork.

Should the "product code" and national reimbursement number (if applicable) be printed as a part of the human-readable data of the UI or can it be part of the artwork (printed next to the UI)? Or is it on the manufacturer decision where to insert these data?

The following data must be given in the 2D code: product code, serial number, batch number and expiration date. Of the data contained in the 2D code, only the product code and serial number must be printed nearby in legible form, provided the package size allows.

During the process of drafting legislation on safety features, it can be expected that the SÚKL code will not be considered the NN number, and therefore the NN number will not be necessary to list on the packaging. According to the current amendment of Act No. 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (the Pharmaceuticals Act), it is not stipulated that the SÚKL code be part of the unique identifier or legible data associated with the UI.

However, the SÚKL code must be printed elsewhere on the packaging. This requirement is set forth in Annex No. 5, let. A, par. 7 of Decree No. 228/2008 Coll., on the Marketing Authorization of Medicinal Products. For easier identification, the Institute recommends placing the introductory phrase "SÚKL code" in front of the SÚKL code. Neither the code nor the introductory phrase are included in the packaging text (in the QRD template).

The specific PC number (possibly NN, if used) is not included in the packaging text approved by the Institute in the QRD template. The text will still only list the PC (possibly NN) (see figure). In the mock-up submitted to the Institute it will suffice to list only the PC: (possibly NN). Submitting a mock-up with particular numbers is also possible but not required.

4. Local regulations

4.1. Serial Number Construction: Please confirm that solution, where Serial Numbers are constructed using either 8 alphanumeric or 13 numeric characters, is compliant with local regulation?

Based on the standard, serial number S AI (21) may contain up to 20 alphanumeric characters (Article 4 of Regulation (EU) 2016/161). Its generation depends on the manufacturer's algorithm.

4.2. Human-readable expiry date format: Please confirm, that preferred expiry date format for Human-readable labelling (MM/YYYY) is compliant with local regulations?

We have no additional national requirements, the expiry date on labelling should be stated in line with QRD template: [The expiry date printed on medicinal products stating only month and year should be taken to mean the last day of that month. Expiry dates should be expressed with the month given as 2 digits or at least 3 characters and the year as 4 digits, e.g.: February 2007, Feb 2007, 02/2007.]

See the answer in 2.2

4.3. Human readable print sequence: Please confirm, that print sequence in format PC - SN - EXP - Lot is compliant with local regulation??)

The sequence should be the same as that in 18 QRD of the template, i.e. PC, SN. It is not required to show other elements (EXP and Lot) right next to the 2D code, but this sequence is acceptable.

See in the answer in 2.4

4.4. Please confirm that prompt name is allowed to be written above the imprint area and that it is sufficient to do so? I.e. PC/SN/EXP/Lot placed above the imprint area on one line with slash using.

It should be in compliance with 18 QRD of the template for the MP code and serial number, with 8 QRD of the template for the expiry data and with 13 QRD of the template for the lot number.

PC: {number}

SN: {number}

Expiry date: the abbreviation based on Annex IV of QRD of the template {number}

Lot number: the abbreviation based on Annex IV of QRD of the template {number}

4.5. Will the reimbursement number (the SIDC code) be required as part of GTIN?

GTIN is a product identification number used as a product code. The national reimbursement number is its attribute and not its part. As agreed with the SIDC, the national reimbursement number will not be encoded in a GS1 DataMatrix but will be shown on MP packaging in human-readable format (Non-HRI).

The current amendment of Act No. 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (the Pharmaceuticals Act), does not stipulate that the SÚKL code should be part of the unique identifier or legible data associated with the UI.

However, the SÚKL code must be printed elsewhere on the packaging. This requirement is set forth in Annex No. 5, let. A, par. 7 of Decree No. 228/2008 Coll., on the Marketing Authorization of Medicinal Products. For easier identification, the Institute recommends placing the introductory phrase "SÚKL code" in front of the SÚKL code. Neither the code nor the introductory phrase is included in the packaging text (in the QRD template).

(see related question no. 3.4)

4.6. If your market uses a GS1 compatible NTIN and is converted to a GTIN for 2D matrix encoding do you require the NTIN to appear as Human Readable rather than the GTIN (or both)

NTIN is not used in the CR and thus it will not appear on the packaging in human-readable format (neither HRI nor NRI). Theoretically, if NTIN was used on some market, It would have to be interpreted in HRI format as well. An internal/national number could be shown in its original format only with respect to Non-HRI information.

4.7. Will the Czech Republic also require the national code to identify medicinal products in EMVS/NMVS? Or which code should it be (I supposed that it would be the SIDC code).

The obligation to show the SIDC code on packaging is laid down in the current version of Section 32 (5) of Act No. 378/2007 of Coll., on pharmaceuticals, as well as in Decree No. 228/2008 of Coll., Annex No. 5, Part A, Item 7.

When amended, the SIDC code will continue to be shown on the packaging, but outside the unique identifier.

5. Other questions/ issues

5.1. What are the obligations of a Czech branch, which is not a manufacturer or distributor but a mere representation of a European MAH on the Czech market, with respect to on-boarding to EUHUB and national HUB?

This depends on the activity of the Czech branch and what the Czech branch actually is. If it is marketing authorization holder, it will have the same obligation as a marketing authorization holder. Based on the

aforesaid, it is not a manufacturer or a distributor, and so it will not have any obligations of a manufacturer or a distributor.

5.2. The EMVO on-boarding portal (a link to the EU repository) concerns only manufacturers / MAHs, i.e. in our case the headquarters, but at the seminar on 2 June, we were informed about the NMVO on-boarding portal (a link to the national system) that will be designated for those authorized to dispense medicinal products – distributors / pharmacies / hospitals. What will be the role of our Czech branch?

See the answer in 5.1.

MAHs, holders of concurrent import/distribution authorization and manufacturers will communicate with the EU HUB (EMVO has already been set up). Distributors and pharmacies, or other persons authorized to dispense medicinal products, will communicate with the national repository for the CR (NMVO has already been set up).

5.3. Would it be acceptable to take a relatively small portion out of a manufactured lot and make it a separate lot of the respective product, attach a 2D code to it and therefore be able to follow it throughout the distribution chain?

We would find that allowable within the pilot project, i.e. until 09/02/2019.

5.4. Would it be acceptable at a certain point in time to attach 2D codes with unique identifiers to one (small) lot of a medicinal product, while any following lot of the same medicinal product would only bear lot number and expiry date as a rule (e.g. we would already use artwork with space provided for the required safety features, but the spaces for 2D code and readable representation of serial number would be left empty)?

We would find that allowable within the pilot project, i.e. until 09/02/2019.

5.5. In the Czech Republic we have a registered medicinal product in the form of a group package 10 x 200 ml. This means that we package 10 sealed glass phials with a label in cardboard packaging, which has protective elements.

The box comes with a label with the name of the product, information about the size of the package 10 x 200 ml and other mandatory information. Such registered group package has its own SIDC code and it is supplied to medical facilities in the aforementioned state. The smallest registered unit is therefore a group package with 10 phials, not an individual phial. From February2019 this product will be subject to serialisation.

In order to comply with the print quality for a two-dimensional bar code, we want to print this unique identifier and other related information on the current labels with a white background and subsequently apply them to boxes for group packages of serialised products. The boxes are made from brown cardboard. Direct printing on these boxes with the products would not comply with requirements for print quality, as stated in Commission Delegated Regulation (EU) 2016/161. This regulation does not prevent the method of printing serialised data on a label. Please provide us with an opinion about whether the printing of serialised data on a label with subsequent application to a secondary package (box) is possible?

In the case of such registered medicinal products that have a registered group size of package that is supplied to the market in cardboard packaging marked with a label with the name and other data, is the proposed procedure of stating a unique identifier and other related data on the package of the medicinal product (i.e. on the box) acceptable.

5.6. Will 2D code data allow to identify the specific type of registered mass-produced medicinal product? Mass-produced medicinal products already available with 2D code had EAN13 in Product Code (01). Is it going to be like this or is it a coincidence?

Indapamid Stada 100X1,5MG

(01)04011548016879

(17)220300

(10)71305

(21)P34JP73PJJLJY3C

2D code will encode the so-called unique identifier, which is product code, serial number, batch number and expiration date. If standard GS1 is used for identification (which is mostly the case), product GTIN will be in the application identifier (01), i.e. the identification number EAN that identifies the type, grammage, strength and form of a medicinal product. In addition to this identification number, the remaining data will also be encoded there.

It means that you can identify a medicinal product based on 2D code. In fact, just like now from the linear code that, however, does not include other data.

5.7. Although Directive 2011/62/EU introduces provisions governing the sale of medicinal products to the public over the Internet and empowers the Commission to introduce screening methods by persons authorized or empowered to dispense medicinal products to the public, the issue of medicines to the public is still largely regulated at the national level. The end of the supplier chain may be organized differently in various member states and may involve various healthcare professionals. Member states should be allowed to exempt certain institutions or persons authorized or empowered to dispense medicinal products to the public from the obligation to verify safety features, to take into account the specific characteristics of the supplier chain in their country and ensure that the impact of verification measures on these subjects is reasonable. What institutions does this pertain to in the CR? Will a specific list be issued?

The situation described in the query is specifically described in Article 23, which allows member states to draft national legislation based on the nature of their supplier chain, but the working of Article 23 significantly restricts this to just the subjects listed therein.

Article 23
Provisions taking into account the particular characteristics of supplier chains of member states
In the event that it is necessary to take into account the particular characteristics of the supplier chain in their country, member states can request that the distributor verify the safety features and eliminate the unique identifier of the medicinal product before dispensing the medicinal product to some of the following persons or institutions:

a) persons authorized or empowered to dispense medicinal products to the public who do not work in a healthcare facility of pharmacy;
b) veterinary doctors or retailers of veterinary medicinal products,
c) dentists;
d) optometrists and opticians

e) emergency medical service personnel;

f) <u>armed forces</u>, police and other government institutions that keep supplies of medicinal products for the purpose of civil protection and managing catastrophes;

g) universities and other higher education institutions that use medicinal products for research and education purposes, with the exception of healthcare facilities.

h) prisons;

i) schools;

j) hospices;

k) care facilities.

This option was worked into the amendment of Act No. 378/2007 Coll., on Pharmaceuticals under item 15, which will amend the current wording of Section 77 of this Act. No list will be issued, but it will be a provision in the Pharmaceuticals Act. According to the draft, this should also apply to supplies of medicinal products to the army and to vets.