EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL
Health systems, medical products and innovation

Unit "Medicines: policy, authorisation and monitoring"

PHARM 706 Rev1

PHARMACEUTICAL COMMITTEE
28 April 2016

Subject: **Implementation of the 'Falsified Medicines Directive' 2011/62/EU**

- **Notifications under Article 117a**
- **Delegated act on the safety features – update**
- **APIs – update on listing applications**
- **Common logo**

Agenda item 2iv

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1. BACKGROUND

The 'Falsified Medicines Directive' 2011/62/EU has been adopted in June 2011 and published on 1 July 2011.

It had to be transposed by Member States by 2 January 2013 and applied as of this date. However, the application date is extended for the rules on:

- the importation of active substances (application date 2 July 2013);
- the online sale of medicines (application date 1st July 2015); and
- the safety features (a unique identifier and an anti-tampering device) (application date three years after publication of the delegated act).

2. NOTIFICATION BY MEMBER STATES IN ACCORDANCE OF ARTICLE 117A OF DIRECTIVE 2001/83/EC

Article 117a of Directive 2001/83/EC obliges Member States to notify the Commission, by 22 July 2013, of the details of their respective national systems for the receipt and handling of notifications of suspected falsified medicinal products, suspected quality defects of medicinal products, recalls of medicinal products by marketing authorisation holders, and withdrawals of medicinal products from the market.

To date, the Commission has received 28 notifications (26 Member States and 2 EEA States). **The following Member States not having yet notified are requested to comply with the requirement of the Directive:**

France and Luxembourg.

As previously explained, there is no specific template for the notification. Member States should simply outline the system they have in place and how does it work. **Notifications should be sent as soon as possible to** sante-pharmaceuticals-b4@ec.europa.eu.

3. IMPLEMENTATION MEASURES BY THE COMMISSION

Directive 2011/62/EU contains several implementation measures (delegated acts, implementing acts, guidelines and reports) to be taken by the Commission.

Annex 1 contains the overview of these implementation measures, together with a state of play.

Detailed feedback is provided below on:

- The work on the delegated act on the detailed rules for the safety features of medicinal products for human use, and their verification;
- The implementation of the new rules on the importation of active substances from third countries and the state of play of the current listing applications;
- The common logo for online pharmacies.

4. DELEGATED REGULATION ON THE DETAILED RULES FOR THE SAFETY FEATURES OF MEDICINAL PRODUCTS FOR HUMAN USE

Updates

The delegated Regulation on the safety features was published in the Official Journal on 9th February 2016, after scrutiny by the European Parliament and the Council. It will apply as of 9 February 2019 in all Member States. BE, EL and IT have the possibility of deferring the application of part of the Regulation for up to 6 years.

To facilitate the implementation of the delegated Regulation and the new rules on medicine verification, the Commission has published a "Questions and Answers" document on its public health website:
http://ec.europa.eu/health/files/falsified_medicines/qa_safetyfeature.pdf.

In addition, 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:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/02/WC500201413.pdf

The regulatory requirements for nationally authorised products have been made available by the CMDh on its website:
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Falsified_Medicines/CMDh_345_2016_Rev00_02_2016_1.pdf

The Commission will continue working in close collaboration with the Member State expert group on the safety features to ensure a smooth implementation of the new rules.

Background

Directive 2011/62/EU introduces obligatory 'safety features' (a unique identifier and an anti-tampering device) as part of the outer packaging of medicinal products for human use subject to prescription (while medicinal products not subject to prescription shall not bear the safety features).

In particular, Directive 2011/62/EU places the Commission[1] under the obligation to adopt delegated acts setting out, *inter alia*:

(a) the characteristics and technical specifications of the unique identifier;

(b) the modalities for the verification of the safety features;

(c) the establishment and management of the repository system containing the unique identifiers.

Before adopting these delegated acts, Article 4 of Directive 2011/62/EC requires the Commission to perform a study assessing benefits, costs and cost-effectiveness of the different technical options for the unique identifier, for the verification of the authenticity of the medicinal product bearing the safety features and for establishing and managing the repository system storing the unique identifiers. This study, conducted in the form of an impact assessment, identified the options presented below as the most cost-effective:

1. **The composition, format and carrier of the unique identifier should be fully harmonised** across the EU. The unique identifier should be placed in a 2D barcode and contain the product code, a serialisation number, a national reimbursement number (if requested by Member States), the batch number and the expiry date.

2. Medicine authenticity should be guaranteed by an **end-to-end verification system supplemented by risk-based verifications by wholesale distributors**. Medicines should be systematically verified before being dispensed to patients (e.g. at pharmacy level). Medicines at higher risk of falsification (returns or medicines not being distributed directly by manufacturers or marketing authorisation holders or wholesalers distributing on their behalf) should additionally be checked at wholesaler level.

3. **The repository** containing the unique identifiers **should be set up and managed by stakeholders** (stakeholder's model). National competent authorities should be able to access and supervise the database.

5. IMPLEMENTATION OF THE NEW RULES ON IMPORTATION OF ACTIVE SUBSTANCES

Updates

- ***Listing***

  Currently, there are still 2 equivalence assessments ongoing.

  South Korea has applied for listing in January 2015. The desk assessment is ongoing. The onsite audit is planned for December 2016.

  New Zealand has applied for listing in June 2013. The Commission completed the desk assessment of the New Zealand regulatory framework for APIs in April 2014. New Zealand has now agreed to a formal exchange of letters to clarify that the existing Mutual Recognition Agreement between New Zealand and the EU

[1] Art. 54a(2) of Directive 2001/83/EC.

includes active substances in its scope. The text of the joint statement that will be formalised through an exchange of letters is provided in Annex 2 for your information.

- ***Use of waiver 2***
  With regard to the use of the waiver referred to in Article 46b(5) of Directive 2001/83/EC ("presence of a EU GMP certificate"), Poland communicated to the Commission its intention to use that waiver.

- ***Q&A revision***
  The Q&A on the importation of active substances needs to be clarified with regard to the requirements in case of importation of active substances accompanied by an expired written confirmation but released for sale before the expiration date of that written confirmation.
  The revised text of the answer to Question n°35 of the Q&A document is provided in Annex 2. Member States should submit their comments to sante-pharmaceuticals-b4@ec.europa.eu **by 20 May 2016**.
  We plan to publish the updated Q&A document by the end of May.

Background
The 'Falsified Medicines Directive' 2011/62/EU introduced EU-wide rules for the importation of active substances for medicines for human use. As of 2 January 2013, all active substances have to be manufactured in accordance with good manufacturing practice (GMP) for active substances or, where imported, with equivalent rules.

In case of active substances imported from outside the EU, the compliance with GMP rules for active substances equivalent to those of the EU has to be certified by a "written confirmation" accompanying the active substance. Member States can waive the obligation for a "written confirmation" in case the active substance is accompanied by an EU GMP certificate. However, Directive 2001/83/EC[2] requires Member States wishing to use this waiver to communicate this to the Commission. To date, the following Member States have communicated to the Commission their intention to use this waiver: *Spain, Italy, United Kingdom, Ireland, Germany, Romania, Malta, France, Latvia, Croatia, Netherlands, Cyprus, Lithuania, Greece, Denmark and Finland*.

The requirement for a "written confirmation" can also be waived in case the active substance originates from a third country that has been assessed by the Commission as having a regulatory framework for active substances equivalent to that of the EU, in accordance with Article 111b of Directive 2001/83/EC.

6. THE COMMON LOGO FOR ONLINE PHARMACIES

The Commission Implementing Regulation (EU) 699/2014 *on the design of the common logo to identify persons offering medicinal products for sale at a distance to the public and the technical, electronic and cryptographic requirements for verification of its authenticity* is applicable as of 1st July 2015 and the use of the logo is mandatory for all legally operating on-line retailers of medicinal products established in the EU.

[2] Article 46b(4) of Directive 2001/83/EC.

The European Commission has obtained trademark protection for the logo in the name and on behalf of the European Union. Therefore, Member States authorities responsible in each Member State for the application of the Implementing Regulation were invited to sign a licence agreement on the use of the logo with the European Commission prior to the date of entry into application of the Regulation. The signature of the licence agreement will facilitate the enforcement by Member States of possible unlawful use of the logo also on the basis of the trademark legislation.

The following Member States have not yet signed a license agreement: Greece and Romania. The Commission urges these Member States to proceed with the signature of the licence agreement as soon as possible.

For more information or in order to arrange the signature of the agreement please contact: SANTE-PHARMACEUTICALS-B4@ec.europa.eu.

We would like also to reiterate that in accordance with Regulation (EU) 669/2014 on the design of the common logo to identify persons offering medicinal products for sale at a distance to the public and the technical, electronic and cryptographic requirements for verification of its authenticity, the hyperlinks between the online logo and the national list of the persons offering the medicinal products for sale at a distance to the public by means of information society services, have to be permanent and secured. Furthermore the websites hosting those national lists have to be secured and hosted on trusted domains. **We strongly encourage Member States to ensure that these provisions are fulfilled when granting operators the right to use the common logo.**

Finally, the European Commission would like to gather more information on how the provisions of Title VIIA of Directive 2001/83/EC have been implemented in the Member States.

Therefore the European Commission would like to:

(a) repeat the request to the Member States which have not yet done so to **inform us about the national information campaigns,** as required by Article 85d, they are conducting or they plan to conduct;

b) invite Member states to **inform us on the national law implementing Article 85c** by filing in a table enclosed in Annex 4 to this note.

7. IMPLEMENTATION MEASURES BY THE EUROPEAN MEDICINES AGENCY

Annex 5 contains the overview of the implementation measures taken by the European Medicines Agency (EMA), together with a state of play.

Annex 1: Implementation measures of the Commission in the context of Directive 2011/62/EU – overview and state of play

	Article in Directive 2001/83/EC	Type of Commission measure	Topic	Target date for adoption/ publication	State of play Involvement of Member States/experts from Member States, Other comments
1	47	**Delegated act**	**Good manufacturing practice for active substances**		**Adopted and published** (OJ L 337, 25.11.2014, p. 1) http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2014_337_R_0001&from=EN
2	52b	**Delegated act**	**Criteria to be considered and verifications to be made** when assessing the potential falsified character of **medicinal products introduced into the EU** but not intended to be placed on the market		Public stakeholder consultation closed. Member States expert group consulted once. Following consultation by Commission with stakeholders and Member States, adoption is not going to be pursued for the time being (NB: adoption is not mandatory - "may provision").
3	111b	**Implementing act**	Implementing measure on the **requirements for the assessment of a third country in terms of API manufacturing**		**Adopted and published** (OJ L 21, 24.1.2013, p. 36): http://ec.europa.eu/health/files/eudralex/vol-1/dec_2013_51/dec_2013_51_en.pdf
4	111b	**Decisions ('Autonomous Decisions')** (at the request of a third country)	Inclusion of a **third country on a list**	Continuously ongoing	**Adopted and published** (OJ L 325, 23.11.2012, p. 15): http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:325:0015:0016:EN:PDF Finalised and ongoing assessments: http://ec.europa.eu/health/human-use/quality/index_en.htm#ias
5	47	**Guidelines**	Principles of **good distribution practices for active substances**		**Adopted and published** (OJ C 95, 21.3.2015, p. 1–9): http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.C_.2015.095.01.0001.01.ENG
6	47	**Guideline**	Formalised risk assessment for verification of the appropriate **good manufacturing practice for excipients**		**Adopted and published** (OJ C 95, 21.3.2015, p. 10–13): http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.C_.2015.095.01.0010.01.ENG

	Article in Directive 2001/83/EC	Type of Commission measure	Topic	Target date for adoption/ publication	State of play Involvement of Member States/experts from Member States, Other comments
7	85b	**Guideline**	Specific provisions for **brokering** in the **guidelines** on good distribution practices		**Adopted and published** (OJ C343, 23.11.2013, p1) http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:343:0001:0014:EN:PDF
8	111a	**Guideline**	**Principles for inspections**		Compilation of Community Procedures on Inspections and Exchange of Information exists: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf
9	54a(4) of Directive 2001/83/EC and Article 2b of Directive 2011/62/EU	**Delegated act**	Detailed rules for the **safety features** appearing on the packaging of medicinal products for human use In particular: (a) the **characteristics and technical specifications** of the safety features (SF) (b) the **modalities of verifications** of the SF by the manufacturers, wholesalers, pharmacists (c) provisions on the **establishment, management and accessibility of the repositories** system (d) the **lists** of **prescription medicines that should not bear** the SF and the list of **non-prescription medicines that should bear the SF** (e) **procedures for the notification** of medicinal products at risk of falsification and **a rapid system for evaluation** and decision on these notifications		**Adopted and published** (OJ L 32, 9.2.2016, p. 1-27) http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2016_032_R_0001&from=EN All linguistic versions: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2016.032.01.0001.01.ENG
10	85c(2)	**Implementing act**	**Design of the common logo for legally-operating online-websites, including the technical, electronic, cryptographic requirements**		**Adopted and published** (OJ L185, 25.6.2014, p.5): http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2014_184_R_0004&from=EN Applies as of 1 July 2015

	Article in Directive 2001/83/EC	Type of Commission measure	Topic	Target date for adoption/ publication	State of play Involvement of Member States/experts from Member States, Other comments
11	85d	**Awareness raising**	Conducting or promoting information campaigns on the dangers of falsified medicinal products	Continuously ongoing	In cooperation with the European Medicines Agency and Member States http://ec.europa.eu/health/human-use/videos/index_en.htm
12	118a	Report to the Council and the European Parliament	Overview of transposition measures on the rules on **penalties** applicable to infringements of the national provisions adopted pursuant to the Directive	By 2 January 2018	-
13	3 of Directive 2011/62/EU	Report to the Council and the European Parliament	Trends of falsifications	See Article 3 of Directive 2011/62/EU	-
14	121a	Report	In respect of the delegated powers conferred to the Commission		**Adopted** (30 March 2015) **and communicated to the EP and the Council** http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2015:138:FIN

Annex 2: Revised Q&A on the importation of active substances

QUESTION 35 (NEW):

CAN AN API BATCH MANUFACTURED DURING THE PERIOD OF VALIDITY OF A WRITTEN CONFIRMATION BE IMPORTED INTO THE EU ONCE THE WRITTEN CONFIRMATION IS EXPIRED?

Answer: Article 46(b)(2)(b) sets out that active substances can only be imported if manufactured in accordance with EU GMP or equivalent, and accompanied by a written confirmation from the competent authority of the exporting third country certifying, inter alia, that (1) the GMP standards applicable to the manufacturing plant are equivalent to those of the EU, and (2) the supervision of the plant compliance with GMP ensures a protection of public health equivalent to that of the EU.

It is legitimate to consider that the guarantees of equivalence provided by the written confirmation apply to any API batch in the scope of the written confirmation which was released for sale within the period of validity of the written confirmation, even if not exported in that time period.

Against this background, it can therefore be considered that the importation into the EU of an API accompanied by an expired WC is acceptable provided that the paperwork accompanying the consignment (1) unequivocally proves that the whole consignment has been manufactured and released for sale by the quality unit before the expiry date of the written confirmation; and (2) provides a solid justification of why a valid written confirmation is not available.

Annex 3: Joint statement to be formalised through an exchange of letter between New Zealand and the Commission

EU – New Zealand MRA
Sectoral Annex on medicinal products, GMP inspection and batch certification

Operation of the Annex with respect to active pharmaceutical ingredients for medicinal products for human use

Joint Statement

The Sectoral Annex on medicinal products (the Annex)[3] of the Mutual Recognition Agreement (MRA) between the European Union (EU) and New Zealand[4] covers "*all medicinal products which are industrially manufactured in New Zealand and in the European Union, and to which Good Manufacturing Practice (GMP) requirements apply*."[5]

According to the Annex, "'*Medicinal products' means all products regulated by the pharmaceutical legislation in the European Union and New Zealand referred to in Section I.*"[6]

Section 1 of the Annex lists Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, New Zealand's Medicines Act 1981 and the New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods.

While at the time of implementing the Sectorial Annex only New Zealand had legal requirements for GMP for Active Pharmaceutical Ingredients (API) in place[7], with the adoption of Directives 2004/27/EC[8] and 2011/62/EU[9] amending Directive 2001/83/EC as regards GMP for API the EU explicitly included

3 Sectoral Annex on medicinal product GMP inspections and batch certification to the European Community-New Zealand Agreement on mutual recognition in relation to conformity assessment, certificates and markings.

4 Agreement on mutual recognition in relation to conformity assessment between the European Community and New Zealand (OJ L 229, 17.8.1998, p. 62) as amended (OJ L356, 22.11.2012, p. 2).

5 "Scope and Coverage", first paragraph.

6 "Scope and Coverage", fourth paragraph.

7 Medicines Act 1981and the New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods, Part 1

8 Directive 2004/7/EC of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (OJ L 136, 30.4.2004, p. 34)

API in the scope of Directive 2001/83/EC.[10]

The 'equivalence assessment' which was conducted by the European Commission in the context of Article 111b of Directive 2001/83/EC has confirmed that the New Zealand legislation has equivalent legal requirements for GMP for API in place. The scope of the 'equivalence assessment' did not include radioactive API, as these substances are outside the scope of the pharmaceutical legislation in New Zealand.

It is therefore jointly understood that all operative provisions of the Sectoral Annex of the MRA between New Zealand and the EU apply to non-radioactive API for medicinal products for human use.

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9 Directive 2011/62/EU of 8 June 2011 amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of falsified medicinal products (OJ L 174, 1.7.2011, p. 74).

10 See in particular Articles 2(3), 46(f) and 46b(1) of Directive 2001/83/EC.

Annex 4: table on the implementation by the Member States of Article 85c of Directive 200/83/EC

Member State	Reference to the national law implementing Article 85c of Directive 2001/83/EC	Does the national law allow for sale on line of prescription medicinal products?	Does the national law provides for conditions of retail supply on their territory of the medicinal products for sale at the distance to the public by means of information society services, in line with Article 85c(2) of Directive 2001/83/EC?

Annex 5: Deliverables EMA – Overview and state of play

Topic	Relevant provision in Directive 2001/83/EC	Output	State of play, Comments
EU database for API, distributors, GMDP certificates, non-compliance	111(6),(7), 52a(7), 77(4), 40(4); 111a, 2nd paragraph.	Extension of existing EudraGMP database	A common format for 5 new documents connected to the new content of the database has been agreed and published as part of the Compilation of Community Procedures in May 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf The extension of the database to accommodate new information required by the FMD (GDP certificates, Wholesale authorisations and active substance manufacturers, importers and distributor registration) was launched in April 2013 and Member States are now populating these modules accordingly: • WDA module: Over 7400 Wholesale Distribution Authorisations have been uploaded by Member States to date. • GDP module: Over 5000 GDP certificates have been uploaded by Member States to date. • API registration module: Over 1400 registrations have been uploaded by Member States to date.
MS to share information with EMA on inspections.	111(1), 2nd sentence		Information on conducted GMP inspections is already shared through EudraGMDP. The database now extends this to GDP inspections. For planned GMP inspections see below.
MS and EMA to cooperate in the coordination of inspections in third countries	111(1), 3rd sentence	Planning module for EudraGMP application	Planning module launched in December 2012 provides a tool for this purpose. Over 380 planned inspections have been uploaded by Member States to date. In addition, an inspection programme in cooperation with MS in the context of Article 46b(4) of Directive 2001/83/EC has been ongoing from July 2013.
Online information on legislation on falsified medicines	85c(5)	Amendments on the website of the Agency	A new webpage on falsified medicines, developed in collaboration with the European Commission and the Member States has been launched on 1 July 2015.

			The new page introduces the EU common logo to be displayed on the websites of authorised on-line medicine retailers and provides a list with the links to the Member States' dedicated websites: http://ema-wip.emea.eu.int/ema/index.jsp?curl=/pages/regulation/general/general_content_000630.jsp

Action to be taken:

For follow-up (points 2, 5 and 6)

For information (all other points)