



PHARM 695

**PHARMACEUTICAL COMMITTEE**  
**21 October 2015**

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**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**
- **Delegated Regulation on GMP for APIs**
- **Common logo**

**Agenda item 2f**

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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 1<sup>st</sup> 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 only 25 notifications (23 Member States and 2 EEA States).

**The following Member States not having yet notified are requested to comply with the requirement of the Directive:**

## **Bulgaria, France, Greece, Luxembourg and Slovenia.**

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-d6@ec.europa.eu](mailto:sante-pharmaceuticals-d6@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. WORK ON THE PREPARATION OF A DELEGATED ACT ON THE DETAILED RULES FOR THE SAFETY FEATURES OF MEDICINAL PRODUCTS FOR HUMAN USE.**

#### ***Updates***

The Commission has now finalised the drafting of the delegated act, on the basis of the outcome of the impact assessment, and following extensive consultation of the Member State expert group on the delegated act on the safety features.

The delegated act was adopted – together with the relative impact assessment – on 2 October 2015 and is expected published early February 2016, after scrutiny by the European Parliament and the Council.

The Commission plans to continue working in close collaboration with the Member State expert group 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<sup>1</sup> 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;

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<sup>1</sup> Art. 54a(2) of Directive 2001/83/EC.

- (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**  
Brazil and Israel were listed in July 2015, bringing to 6 the number of third countries listed as equivalent to the EU (CH, AUS, JP, US, BRA, IL).

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 tentatively planned for Q1 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. The assessment procedure is currently on hold, waiting for the clarification that the existing Mutual Recognition Agreement between New Zealand and the EU includes active substances in its scope. The Commission has proposed to New Zealand authorities to proceed with a formal exchange of letters to this regard and we are waiting for New Zealand's feedback.

- **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"), Finland 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 to be used in the manufacture of authorised medicinal products intended for research and development trials.

The revised text of the answer to Question n 3 of the Q&A document is provided in Annex 2. Member States should submit their comments to [sante-pharmaceuticals-d6@ec.europa.eu](mailto:sante-pharmaceuticals-d6@ec.europa.eu) **by 15 November 2015**.

We plan to publish the updated Q&A document by the end of November.

### ***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<sup>2</sup> 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. DELEGATED REGULATION ON GMP FOR APIs**

### ***Updates***

At the last meeting in March 2015, the Commission invited Member States to verify the accuracy of their language version of the Delegated Regulation and communicate factual mistakes to the Commission. We received feedback from PL, FR and DE.

To this date, a corrigendum of the PL version was finalised and published. Corrigenda for the FR and DE linguistic versions are expected to be published in the course of the autumn 2015.

### ***Background***

The third paragraph of Article 47 of Directive 2001/83/EU places the Commission under the obligation to adopt delegated acts setting out the principles and guidelines of good manufacturing practices for active substances.

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<sup>2</sup> Article 46b(4) of Directive 2001/83/EC.

After consultations with an *ad hoc* Member State expert group<sup>3</sup>, a Commission Delegated Regulation was adopted to this effect on 28 May 2014 and published, after the European Parliament and Council scrutiny, on 25 November 2014<sup>4</sup>.

## **7. 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 1<sup>st</sup> July 2015 and the use of the logo is mandatory for all legally operating on-line retailers of medicinal products established in the EU.

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 invites 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-D6@ec.europa.eu](mailto:SANTE-PHARMACEUTICALS-D6@ec.europa.eu).

We would like also to highlight 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 invite the Member States which have not yet done so to **inform us about the national information campaigns they are conducting or they plan to conduct.**

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<sup>3</sup> Expert group on the preparation of delegated acts relating to manufacturing, import and introduction of medicinal products for human use and their active substances.

<sup>4</sup> Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use. OJ L 337, 25.11.2014, p. 1.

## **8. IMPLEMENTATION MEASURES BY THE EUROPEAN MEDICINES AGENCY**

Annex 3 contains the overview of the implementation measures to be taken by the European Medicines Agency (EMA), together with a state of play.

### **Action to be taken:**

For follow-up (points 1 and 5)

For information (all other points)

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

	<b>Article in Directive 2001/83/EC</b>	<b>Type of Commission measure</b>	<b>Topic</b>	<b>Target date for adoption/publication</b>	<b>State of play Involvement of Member States/experts from Member States, Other comments</b>
1.	47	<b>Delegated act</b>	<b>Good manufacturing practice for active substances</b>		<b>Adopted and published</b> (OJ L 337, 25.11.2014, p. 1) <a href="http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2014_337_R_0001&amp;from=EN">http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2014_337_R_0001&amp;from=EN</a>
2.	52b	<b>Delegated act</b>	<b>Criteria to be considered and verifications to be made</b> when assessing the potential falsified character of <b>medicinal products introduced into the EU</b> 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	<b>Implementing act</b>	Implementing measure on the <b>requirements for the assessment of a third country in terms of API manufacturing</b>		<b>Adopted and published</b> (OJ L 21, 24.1.2013, p. 36): <a href="http://ec.europa.eu/health/files/eudralex/vol-1/dec_2013_51/dec_2013_51_en.pdf">http://ec.europa.eu/health/files/eudralex/vol-1/dec_2013_51/dec_2013_51_en.pdf</a>
4.	111b	<b>Decisions ('Autonomous Decisions')</b> (at the request of a third country)	Inclusion of a <b>third country on a list</b>	Continuously ongoing	<b>Adopted and published</b> (OJ L 325, 23.11.2012, p. 15): <a href="http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:325:0015:0016:EN:PDF">http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:325:0015:0016:EN:PDF</a>  Finalised and ongoing assessments: <a href="http://ec.europa.eu/health/human-use/quality/index_en.htm#ias">http://ec.europa.eu/health/human-use/quality/index_en.htm#ias</a>
5.	47	<b>Guidelines</b>	Principles of <b>good distribution practices for active substances</b>		<b>Adopted and published</b> (OJ C 95, 21.3.2015, p. 1–9): <a href="http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.C_.2015.095.01.0001.01.ENG">http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.C_.2015.095.01.0001.01.ENG</a>
6.	47	<b>Guideline</b>	Formalised risk assessment for verification of the appropriate <b>good manufacturing practice for excipients</b>		<b>Adopted and published</b> (OJ C 95, 21.3.2015, p. 10–13): <a href="http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.C_.2015.095.01.0010.01.ENG">http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.C_.2015.095.01.0010.01.ENG</a>

	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	<b>Guideline</b>	Specific provisions for <b>brokering</b> in the <b>guidelines</b> on good distribution practices		<b>Adopted and published</b> (OJ C343, 23.11.2013, p. 1) <a href="http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:343:0001:0014:EN:PDF">http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:343:0001:0014:EN:PDF</a>
8.	111a	<b>Guideline</b>	<b>Principles for inspections</b>		Compilation of Community Procedures on Inspections and Exchange of Information exists: <a href="http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf">http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf</a>
9.	54a(4) of Directive 2001/83/EC and Article 2b of Directive 2011/62/EU	<b>Delegated act</b>	(a) the <b>characteristics and technical specifications</b> of the safety features (SF) (b) the <b>lists of prescription medicines that should not bear</b> the SF and the list of <b>non-prescription medicines that should bear the SF</b> (c) <b>procedures for the notification</b> of medicinal products at risk of falsification and <b>a rapid system for evaluation</b> and decision on these notifications (d) the <b>modalities of verifications</b> of the SF by the manufacturers, wholesalers, pharmacists (e) provisions on the <b>establishment, management and accessibility of the repositories</b> system	2015	<b>Adopted</b> on 2 October 2015 and communicated to the European Parliament and the Council for scrutiny. Publication in the OJ expected in Q1 2016.
10.	85c(2)	<b>Implementing act</b>	<b>Design of the common logo for legally-operating online-websites, including the technical, electronic, cryptographic requirements</b>		<b>Adopted</b> on 24 June 2014 (Commission Implementing Regulation (EU) No 699/2014) and published (OJ L185, 25.6.2014, p.5): <a href="http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2014_184_R_0004&amp;from=EN">http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2014_184_R_0004&amp;from=EN</a> Applies as of 1 July 2015.
11.	85d	<b>Awareness raising</b>	Conducting or promoting information campaigns on the dangers of falsified medicinal products	Continuously ongoing	In cooperation with the European Medicines Agency and Member States <a href="http://ec.europa.eu/health/human-use/videos/index_en.htm">http://ec.europa.eu/health/human-use/videos/index_en.htm</a>
12.	118a	Report to the	Overview of transposition measures on the rules on	By 2 January	-

	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
		Council and the European Parliament	<b>penalties</b> applicable to infringements of the national provisions adopted pursuant to the Directive	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		<b>Adopted</b> (30 March 2015) <b>and communicated to the EP and the Council</b> <a href="http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2015:138:FIN">http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2015:138:FIN</a>

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

### **QUESTION 3:**

**DO THE RULES ON THE WRITTEN CONFIRMATION APPLY TO ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS INTENDED FOR RESEARCH AND DEVELOPMENT TRIALS?**

Answer: Active substances imported to be used in the manufacture of non-authorised medicinal products intended for research and development trials are excluded from the rules.

Active substances imported to be used in the manufacture of authorised medicinal products intended for research and development trials are expected to fulfil the requirements of Directive 2001/83/EC and be accompanied by a written confirmation, unless there is reasonable proof that the full amount of the imported API will be used for the manufacture of batches/units of an authorised medicinal product exclusively intended for research and development trials. In the latter case, those batches/units of an authorised medicinal product fall outside the scope of Directive 2001/83/EC and the API used in their manufacture is exempted from the rules on the written confirmation.

### **Annex 3: Deliverables EMA – Overview and state of play**

<b>Topic</b>	<b>Relevant provision in Directive 2001/83/EC</b>	<b>Output</b>	<b>State of play, Comments</b>
EU database for API, distributors, GMDP non-compliance certificates,	111(6),(7), 52a(7), 77(4), 40(4); 111a, 2 <sup>nd</sup> paragraph.	Extension of existing EudraGMP database	<p>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.  <a href="http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf">http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf</a></p> <p>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:</p> <ul style="list-style-type: none"> <li>• WDA module: over 6600 wholesale distribution authorisations have been uploaded by Member States to date.</li> <li>• GDP module: over 4000 GDP certificates have been uploaded by Member States to date.</li> <li>• API registration module: over 1000 registrations have been uploaded by Member States to date.</li> </ul>
MS to share information with EMA on inspections.	111(1), 2 <sup>nd</sup> 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), 3 <sup>rd</sup> sentence	Planning module for EudraGMP application	<p>Planning module launched in December 2012 provides a tool for this purpose. Over 300 planned inspections have been uploaded by Member States to date.</p> <p>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.</p>
Online information on legislation on falsified medicines	85c(5)	Amendments on the website of the Agency	<p>A new webpage on falsified medicines, developed in collaboration with the European Commission and the Member States has been launched on 1 July 2015.</p> <p>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:</p>

			<a href="http://ema-wip.emea.eu.int/ema/index.jsp?curl=/pages/regulation/general/general_content_000630.jsp">http://ema-wip.emea.eu.int/ema/index.jsp?curl=/pages/regulation/general/general_content_000630.jsp</a>
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