EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems and products
Medicinal products – authorisations, European Medicines Agency

PHARM 682

PHARMACEUTICAL COMMITTEE
17 March 2015

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

- **Transposition**
- **Notifications under Article 117a**
- **Delegated act on the safety features – update**
- **APIs – update on listing applications**
- **Delegated Regulation on GMP for APIs**
- **Guidelines on "principles of good distribution practices for active substances" and on "formalised risk assessment for verification of the appropriate good manufacturing practice for excipients".**

Agenda item 2 d

---

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:

- Importation of active substances (application date 2 July 2013);
- Rules in relation to Article 85c of Directive 2001/83/EC (application date one year after publication of the implementing act); and
- Rules in relation to the safety feature (unique identifier and anti-tampering device) (application date three years after publication of the delegated act).

2. TRANSPOSITION BY MEMBER STATES

As of March 2015, most Member States have notified the transposing national laws to the Commission, according to Article 2(1) of Directive 2011/62/EU.

Only the infringement procedure against Poland is still open. Poland however notified its transposing national laws to the Commission on 20 February 2015. The Commission will assess whether the Polish transposition is complete and take a decision on the infringement procedure accordingly.

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

Article 117a of Directive 2001/83/EC obliged 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.

The Commission has received only 19 notifications (17 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, Finland, France, Greece, Hungary, Lithuania, Luxembourg, The Netherlands, Poland, Portugal 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.

4. IMPLEMENTATION MEASURES BY THE COMMISSION

Directive 2011/62/EU contains no less than 14 implementation measures (delegated acts, implementing acts, guidelines, 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 work on the Guidelines on “principles of good distribution practices for active substances”;
- The work on the Guidelines on “formalised risk assessment for verification of the appropriate good manufacturing practice for excipients”.

5. WORK ON THE PREPARATION OF A DELEGATED ACT ON THE DETAILED RULES FOR THE SAFETY FEATURES OF MEDICINAL PRODUCTS FOR HUMAN USE.

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.

The Commission is now finalising 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.

It is expected that the delegated act will be adopted – together with the relative impact assessment - by Q2 2015 and published in Q4 2015.

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

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

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

obligation for a "written confirmation" in case the active substance is accompanied by a 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 and Denmark.

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.
Currently, there are 4 equivalence assessments ongoing.

South Korea has applied for listing in January 2015 but did not yet submit all necessary documents. The Commission will start the assessment once it receives the additional documents requested.

Brazil has applied for listing in April 2013. The Commission, in collaboration with inspectors from the United Kingdom and Portugal, carried out a second on-site audit of Brazil's system for the control and enforcement of GMP applicable to the production of APIs on 17-27 November 2014. The outcome of the audit was not fully positive. The auditors addressed additional recommendations to Brazilian authorities. The Commission is now waiting for Brazil's replies before taking a decision on whether to list Brazil.

Israel has re-applied for listing in September 2014, after being initially denied listing due to the lack of "*de jure*" supervision over API sites producing for export only. The Commission has performed a preliminary assessment of the revised Israeli legislation. Several questions were put forward to the Israeli authorities. The Commission is now waiting for their replies.

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 outcome of the assessment was positive. However, in order to finalise the equivalence assessment without an on-site audit, it is necessary to clarify 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.

7. DELEGATED REGULATION ON GMP FOR APIS

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.

After consultations with an *ad hoc* Member State expert group[3], 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[4].

[2] Article 46b(4) of Directive 2001/83/EC.
[3] Expert group on the preparation of delegated acts relating to manufacturing, import and introduction of medicinal products for human use and their active substances.
[4] 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

Member States are invited to verify the accuracy of their language version of the above Delegated Regulation. Should they find factual mistakes, Member States are invited to communicate such mistakes, together with the respective corrections, to sante-pharmaceuticals-d6@ec.europa.eu.

DG SANTE will forward Member States' corrections to the translation services so that an amendment can be issued, where necessary.

8. GUIDELINES ON "PRINCIPLES OF GOOD DISTRIBUTION PRACTICES FOR ACTIVE SUBSTANCES" AND ON "FORMALISED RISK ASSESSMENT FOR VERIFICATION OF THE APPROPRIATE GOOD MANUFACTURING PRACTICE FOR EXCIPIENTS".

The fourth and fifth paragraphs of Article 47 of Directive 2001/83/EU places the Commission under the obligation to adopt guidelines setting out (1) principles of good distribution practices for active substances; and (2) formalised risk assessment for verification of the appropriate good manufacturing practice for excipients.

Both Guidelines have been drafted in cooperation with EMA's GMDP inspector working group and are now in the final stages before adoption. It is expected that they will be adopted by the Commission and published in the Official Journal by end of March 2015.

9. 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 3 and 7)
For information (all other points)

good manufacturing practice for active substances for medicinal products for human use. OJ L 337, 25.11.2014, p. 1.

Annex 2: 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**	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**	2015	Public consultation closed. Strong collaboration with Good Distribution and Manufacturing Practices Inspector's Working Group[5] (GMDP IWG). Adoption by Commission anticipated by Q1 2015

5 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000161.jsp&mid=WC0b01ac05800296c9&jsenabled=true

	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
6.	47	**Guideline**	Formalised risk assessment for verification of the appropriate **good manufacturing practice for excipients**	2015	Public consultation closed. Strong collaboration with GMDP IWG. Adoption by Commission anticipated by Q1 2015
7.	85b	**Guideline**	Specific provisions for **brokering** in the **guidelines** on good distribution practices		**Adopted and published** (OJ C68, 8.3.2013, p. 1): http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:068:0001:0014:EN:PDF A revised version of the guidelines, correcting small mistakes in chapters 5.5 and 6.3, was published in November 2013 (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**	-	GMDP IWG.
9.	54a(4) of Directive 2001/83/EC and Article 2b of Directive 2011/62/EU	**Delegated act**	(a) the **characteristics and technical specifications** of the safety features (SF) (b) the **lists** of **prescription medicines that should not bear** the SF and the list of **non-prescription medicines that should bear the SF** (c) **procedures for the notification** of medicinal products at risk of falsification and **a rapid system for evaluation** and decision on these notifications (d) the **modalities of verifications** of the SF by the manufacturers, wholesalers, pharmacists (e) provisions on the **establishment, management and accessibility of the repositories** system	2015	In cooperation with Good Manufacturing and Distribution Practices Inspectors' Working Group (GMDP IWG). Public stakeholder consultation closed. Consultation of Member States Expert group ongoing.[6] Impact assessment finalised. Adoption expected in Q2 2015 Publication in the OJ expected in Q4 2015

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

	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
10	85c(2)	**Implementing act**	**Design of the common logo for legally-operating online-websites, including the technical, electronic, cryptographic requirements**		**Adopted** on 24 June 2014 (Commission Implementing Regulation (EU) No 699/2014) 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
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	June 2015	Covers all delegated powers given in Directive 2001/83/EC. Internal adoption procedure launched.

Annex 3:

New rules on API quality in the EU – state of play of exporting third countries (top 18 API exporters to the EU, plus South Africa and Ukraine)[7]

Third country	Number of API manufacturing sites supplying EU[8]	Option 1 (written confirmation) or option 2 (listing)	State of play
India	496	Option 1	**Situation under control.** IND issued 274 written confirmations to date (published at: http://www.cdsco.nic.in/writereaddata/WC_scanned_copies.htm).
China	438	Option 1	**Situation under control.** CHN set up a database containing all issued written confirmations. The database can be accessed at the following address: http://125.35.6.41/eucdwan/ApplyServlet?method=doLogin#. The database currently contains 424 written confirmations.
U.S.	186	Option 2	**Situation under control.** Listed.
Japan	108	Option 2	**Situation under control.** Listed
Switzerland	67	Option 2	**Situation under control.** Listed.
Korea	37	Option 1; then 2	**Situation under control.** Korea has applied for listing in January 2015. KOR issues written confirmation (54 issued to date, covering 105 API).
Israel	36	Option 1; then 2	**Situation under control.** Israel has revised its legislation in order to be reconsidered for listing. The reassessment is ongoing. Israel has issued 160 written confirmations to date.
Mexico	35	Option 1, then 2	**Situation under control.** MEX has issued written confirmation (9 issued to date) and later will apply for listing.
Brazil	23	Option 1, then 2	**Situation under control.** BRA has applied for listing. Assessment ongoing. On-site audits took place on 23 September – 1 October 2013 and 17-28 November 2014. BRA has issued 11 written confirmations covering 56 APIs.
Canada	17	Option 1	**Situation under control.** CAN has issued written confirmations (13 issued to date, out of 13 applications).
Taiwan	16	Option 1	**Situation under control.** TWN has issued 76 written confirmations to 18 APIs manufacturers. A total of 138 active substances were covered.
Argentina	12	Option 1, then 2	**Situation under control.** ARG has issued written confirmation (16 issued to date, covering 36 API.
Turkey	12	Option 1	**Situation under control.** TUR has issued 12 'written confirmations', covering 212 API.
Malaysia	7	Option 1, then 2	**Situation under control.** MYS has issued 4written confirmations to date (out of 4 applications).
Singapore	7	Option 1, then 2	**Situation under control.** SGP has issued 9 written confirmations to date. Listing had to be refused for the time being but SGP is revising its legislation to be reconsidered.
Thailand	6		**More work needed – in particular by industry stakeholders.** THA has informed COM that they are going to issue written confirmation. No further information available.

[7] These 20 countries account for 97% of all non-EU API manufacturing sites supplying the EU.

[8] Survey of the 'Heads of Medicines Agencies' amongst medicines manufacturers in the EU. Duplicates have been removed by MHRA. However, this figure does not take account of the possibility of manufacturers to substitute one API source by another one.

Australia	5	Option 2	**Situation under control.** Listed
Russia	5	Option 1	**More work needed – in particular by industry stakeholders.** RUS has informed COM in a meeting that they are going to issue written confirmation. No further information available.
Ukraine	4	Option 1	**Situation under control.** UKR has issued written confirmation.
South Africa	2	Option 1	**Situation under control.** ZAF has issued written confirmation.

Annex 4: 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.
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 185 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	Information on falsified medicines is available on the Agency's website (http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000186.jsp&mid=WC0b01ac058002d4e8). Work is underway to expand this section. In addition, work in cooperation with the European Commission and Member States is ongoing, in order to create the new EMA webpages requested by the FMD as regards on-line sales of medicines.