



**PHARMACEUTICAL COMMITTEE
26 March 2014**

**Subject: Implementation of the 'Falsified Medicines Directive' 2011/62/EU
Transposition
Notifications under Article 117a
API
Impact assessment on the safety features
EU logo for online pharmacies**

Agenda item 2e

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

More than a year after the entry into force of Directive 2011/62/EU, a few Member States have yet to notify the transposing national laws to the Commission, according to Article 2(1) of Directive 2011/62/EU.

The Commission has launched infringement procedures against the Member States not complying with Article 2(1) of Directive 2011/62/EU. As of March 2014, there are 4 infringement procedures still open.

The Commission is preparing to refer the infringing Member States to the Court of Justice with proposals for penalties.

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 13 notifications.

Member States not having yet notified are requested to comply with the requirement of the Directive.

4. APPLICATION OF THE FMD BY MEMBER STATES

In the context of the actual application, Member States have requested the Commission to clarify some aspects.

The documents "PHARM 602, PHARM 623 and PHARM 633, submitted for the meeting of the Pharmaceutical committee on 28 March 2012, 27 March and 23 October 2013 respectively, list in their Annexes some "questions and answers" as regards the application of various aspects of Directive 2011/62/EU.

Annex 1 to this document gives an answer in response to a question raised by a Member State.

Should Member States have other questions they want to raise with the Commission as regards the application of the Directive 2011/62/EU, they are invited to submit them in writing.

5. 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 2 contains the overview of these implementation measures, together with a state of play.

Detailed feedback is provided below on:

- The implementation of the new rules on the importation of active substances from third countries;

- The finalisation of the impact assessment exercise in view of the preparation of a delegated act on the detailed rules for the safety features of medicinal products for human use, and their verification.
- EU logo for online pharmacies/retailers of medicinal products.

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

The 'Falsified Medicines Directive' 2011/62/EU has been adopted in June 2011 and published on 1 July 2011. It introduces (for the first time) 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), or (if imported) with equivalent rules.

As of 2 July 2013, the import of these substances is only possible if:

- **Option 1:** the consignment is accompanied by a 'written confirmation' by the authority of the third country that the plant manufacturing active substances operates in compliance with EU GMP, or with equivalent rules, and is subject to equivalence rules for control and inspections; or
- **Option 2:** the third country has been listed by the Commission as a country with an equivalent system of supervision and inspection as in the EU; or
- **Option 3:** exceptionally, and where necessary to ensure the availability of medicinal products, the need for the written confirmation can be waived by a Member State if a Member State has inspected the specific plant.

Article 46b(4) requires Member States wishing to use Option 3 to communicate this to the Commission. To date, the following Member States have communicated to the Commission the intention to use this waiver:

- Spain
- Italy
- United Kingdom
- Ireland
- Germany
- Romania
- Malta
- France
- Latvia
- Croatia
- Netherlands
- Cyprus
- Lithuania

The new rules on API imports entered into force smoothly, without the feared trade disruptions, due to the combined effort of all players involved - regulators, Member States and industry. Currently, most of the top exporters of API into the EU are either "listed" (U.S, Japan, Switzerland and Australia) or issuing written confirmations. Annex 3 contains an update of the state of play for information.

The Commission is now following up with third countries the non-compliance with EU manufacturing standards of certain active substance manufacturing sites covered by written confirmations. The names of non-compliant active substance manufacturing sites are publicly accessible through the European database called EudraGMDP¹.

The Commission has updated its website² and the Q&A document on the new rules on active substances to clarify that, in case an active substance manufacturing site covered by a written confirmation is found GMP non-compliant following inspection by an EU Member State, and a statement of GMP non-compliance (NCS) is issued, the NCS supersedes the corresponding written confirmation.

7. THE IMPACT ASSESSMENT IN VIEW OF THE PREPARATION OF A DELEGATED ACT ON THE DETAILED RULES FOR THE SAFETY FEATURES OF MEDICINAL PRODUCTS FOR HUMAN USE, AND THEIR VERIFICATION.

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 Commission³ 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:

- (a) the technical options for the unique identifier (i.e.: what will be the composition of the unique identifier or the format of the barcode holding it?);
- (b) the options for the extent of verification of the authenticity of the medicinal product bearing the safety features and the practical arrangements for such verification (i.e.: who will check the barcode? Wholesale distributors, pharmacies?);
- (c) the technical options for establishing and managing the repository system (i.e.: who will establish and manage the database?)

This study was conducted in the form of an impact assessment and was recently finalised. The most cost-effective options, as identified by the impact assessment, are presented below:

- 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

¹ <http://eudragmdp.eudra.org/inspections/displayWelcome.do>

² http://ec.europa.eu/health/human-use/quality/index_en.htm#ias

³ Art. 54a(2) of Directive 2001/83/EC

barcode and contain the manufacturer code, a serialisation number, a national reimbursement number (if present), 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) 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 will now proceed with the drafting of the delegated act taking into account the outcome of the impact assessment, in consultation with the Member State expert group on the delegated act on the safety features.

8. EU LOGO FOR AUTHORISED ON-LINE PHARMACIES/RETAILERS

Directive 2011/62/EU introduced new requirements concerning the on-line sale of medicinal products.

Article 85c of Directive 2001/83/EC, introduced by Directive 2011/62/EU, obliges the on-line pharmacies and retailers legally operating in the EU to display on each page of their websites a common EU logo. Furthermore it provides for Member States to set up a website with a list of persons offering the medicinal products for sale a distance to the public by means of information society services. The common logo shall be hyperlinked to the entry of the pharmacy/retailer on the national lists mentioned above. It shall enable any person wishing to buy medicines on-line to verify, by clicking on the logo, whether the pharmacy/retailer is authorised/entitled to sell medicines online. The Directive empowers the Commission to adopt an implementing act on the design for a common logo for EU as well as the technical, electronic and cryptographic requirements for verification of its authenticity. In addition, the Directive provides for the Commission and the Member States and the EMA to run the information campaigns on the functioning of the common logo and on the risks of buying on-line from illegal sources.

The Commission, on the basis of the contributions received from stakeholders during the public consultation closed in 2013, selected a design for the logo and prepared the text of Commission Implementing Regulation. As already indicated in the previous meeting, in the Implementing Regulation the Commission will set only high level requirements concerning the verification of the authenticity of the common logo, in order not to conflict with solutions already in place in a number of Member States. The Implementing Act is being finalised and will be transmitted to the Standing Committee for opinion in the coming months.

The Commission is also preparing a toolkit with communication material which could be used by Member States when running the national information campaigns. The information toolkit will be at the Member states disposal once the Implementing regulation is adopted.

Member States will have one year from the day of the publication of the Implementing Regulation to comply with the requirements of Article 85c of the Directive.

9. IMPLEMENTATION MEASURES BY THE EUROPEAN MEDICINES AGENCY

Annex 4 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 information.

Annex 1: Questions relating to application of Directive 2011/62/EU

1. Question: Should wholesale distributors acting in free trade zones or from free warehouses have a wholesale distribution authorisation? And are Member States obliged to periodically verify GDP compliance by means of inspections?

Answer: A wholesale distributor acting in a free trade zone or from a free warehouse distributing medicinal products intended to be placed on the market in EU needs a wholesale distribution authorisation. Member States are thus obliged to verify GDP compliance by means of inspections.

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	2014	Public stakeholder consultation closed. Member States expert group consulted twice. ⁴ The procedure for adoption of a Delegated Regulation has been launched. Adoption by Commission is foreseen for Q2 2014, publication in the OJ for second half of 2014
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	2013	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	2014	Public consultation closed. Analysis of replies ongoing.

⁴ <http://ec.europa.eu/transparency/regexpert/index.cfm?do=groupDetail.groupDetail&groupID=2752>

	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
					Strong collaboration with Good Distribution and Manufacturing Practices Inspector's Working Group ⁵ (GMDP IWG). Adoption by Commission foreseen by Q2 2014
6.	47	Guideline	Formalised risk assessment for verification of the appropriate good manufacturing practice for excipients	2014	Public consultation closed. Analysis of replies ongoing. Strong collaboration with GMDP IWG. Adoption by Commission foreseen by Q2 2014
7.	85b	Guideline	Specific provisions for brokering in the guidelines on good distribution practices	2013	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	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	2014	Public stakeholder consultation closed . Consultation of Member States Expert group ongoing. ⁶ Impact assessment finalised.

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

⁶ <http://ec.europa.eu/transparency/regexpert/detailGroup.cfm?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
	2011/62/EU		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		
10	85c(2)	Implementing act	Design of the common logo for legally-operating online-websites, including the technical, electronic, cryptographic requirements	First semester of 2014	Finalisation of the act. Transmission to the Standing Committee for opinion in the coming months.
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	By June 2015.	Covers all delegated powers given in Directive 2001/83/EC.

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 265 written confirmations to date (published at: http://www.cdsc0.nic.in/writereaddata/WC_scanned_copies.htm).
China	438	Option 1	Situation under control. CHN is issuing written confirmations. At the end of October 2013, 378 written confirmations were issued, concerning 210 manufacturers and 657 APIs (source: CFDA).
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	Situation under control. Korea has issued written confirmation (54 issued to date, covering 105 API).
Israel	36	Option 1; then 2	Situation under control. Israel has issued 114 written confirmations to date. Listing had to be refused for the time being but Israel is revising its legislation to be reconsidered.
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 audit took place on 23 September – 1 October 2013.
Canada	17	Option 1	Situation under control. CAN has issued written confirmation (8 issued to date, out of 13 applications).
Taiwan	16	Option 1	Situation under control. TWN has issued 59 written confirmations to 15 APIs manufacturers. A total of 124 active substances were covered.
Argentina	12	Option 1, then 2	Situation under control. ARG has issued written confirmation (12 issued to date, covering 46 API). It is in the process of translating the required documentation into English to request "listing" later this year.
Turkey	12	Option 1	Situation under control. TUR has issued 8 'written confirmations', covering 88 API.
Malaysia	7	Option 1, then 2	Situation under control. MYS has issued written confirmation (2 issued to date) and confirmed that it intends to request "listing" later this year.
Singapore	7	Option 1, then 2	Situation under control. SGP has issued 8 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.
Australia	5	Option 2	Situation under control. Listed

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.

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.
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, 2 nd 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. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf</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 (on-line version) and May 2013 (XML version). Member States have started to populate these new modules.</p>
MS to share information with EMA on inspections.	111(1), 2 nd sentence		Information on conducted GMP inspections is already shared through EudraGMP. 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 rd sentence	Planning module for EudraGMP application	<p>Planning module launched in December 2012 provides a tool for this purpose. Over 80 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	Some information on falsified medicines is already 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 has started, in order to create the new EMA webpages requested by the FMD as regards on-line sales of medicines.