STATUTORY INSTRUMENTS.

S.I. No. 163 of 2013

MEDICINAL PRODUCTS (CONTROL OF MANUFACTURE) (AMENDMENT) REGULATIONS 2013

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I, JAMES REILLY, Minister for Health, in exercise of the powers conferred on me by section 32 (as amended by section 16 of the Irish Medicines Board (Miscellaneous Provisions) Act 2006 (No. 3 of 2006)) of the Irish Medicines Board Act 1995 (No. 29 of 1995) and for the purpose of giving effect to Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011[1], and for the purpose of giving further effect to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001[2], hereby make the following regulations:

1. (1) These Regulations may be cited as the Medicinal Products (Control of Manufacture) (Amendment) Regulations 2013.

(2) These Regulations shall be construed as one with the Medicinal Products (Control of Manufacture) Regulations 2007 to 2010 and the Medicinal Products (Control of Manufacture) (Amendment) Regulations 2012 (S.I. 273 of 2012), and may be cited together with those Regulations as the Medicinal Products (Control of Manufacture) Regulations 2007 to 2013.

2. In these Regulations "Principal Regulations" means the Medicinal Products (Control of Manufacture) Regulations 2007 (S.I. No. 539 of 2007).

3. Regulation 3(1) (as amended by the Medicinal Products (Control of Manufacture) (Amendment) Regulations 2012 (S.I. No. 273 of 2012)) of the Principal Regulations is amended—

(*a*) by inserting after the definition of "Act" the following definitions:

"'active substance' means any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis;

'active substances register' means the register of importers, manufacturers and distributors of active substances maintained by the Board in pursuance of Regulation 14D;",

(*b*) by inserting after the definition of "Community" the following definitions:

[1]OJ No. L 174, 1.7.2011, p. 74.
[2]OJ No. L 311, 28.11.2001, p. 67.

Notice of the making of this Statutory Instrument was published in "Iris Oifigiúil" of 28*th May*, 2013.

"'Community marketing authorisation' means a marketing authorisation granted by the Commission under Regulation (EEC) No. 2309/93[3] or Regulation (EC) No. 726/2004;

'Community Regulation on medicinal products for paediatric use' means Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006[4], as amended by Regulation (EC) No. 1902/2006 of the European Parliament and of the Council of 20 December 2006[5];";

(*c*) by substituting for the definition of "2001 Directive" the following definition:

"'2001 Directive' means Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001[2], as amended by Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003[6], Commission Directive 2003/63/EC of 25 June 2003[7], Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004[8], Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004[9], the Community Regulation on medicinal products for paediatric use, the advanced therapy regulation, Directive 2008/29/EC of the European Parliament and of the Council of 11 March 2008[10], Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009[11], Commission Directive 2009/120/EC of 14 September 2009[12], Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010[13] and Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011[1];",

(*d*) by substituting for the definition of "EudraGMP Database" the following definition:

"'EudraGMDP database' means the Union database referred to in Article 111(6) of the 2001 Directive;",

(*e*) by inserting after the definition of "European Economic Area" the following definition:

"'excipient' means any constituent of a medicinal product other than the active substance and the packaging material;",

[3]OJ No. L 214, 24.8.1993, p. 1.
[4]OJ No. L 378, 27.12.2006, p. 1.
[5]OJ No. L 378, 27.12.2006, p. 20.
[6]OJ No. L 33, 8.2.2003, p. 30.
[7]OJ No. L 159, 27.6.2003, p. 46.
[8]OJ No. L 136, 30.4.2004, p. 85.
[9]OJ No. L 136, 30.4.2004, p. 34.
[10]OJ No. L 81, 20.3.2008, p. 51.
[11]OJ No. L 168, 30.6.2009, p. 33.
[12]OJ No. L 242, 15.9.2009, p. 3.
[13]OJ No. L 348, 31.12.2010, p. 74. As affected by Corrigendum to Directive 2010/84/EU, OJ No. L 21, 25.1.2011, p. 8.

(*f*) by inserting after the definition of "export" the following definition:

"'falsified medicinal product' means any medicinal product with a false representation of—

(*a*) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients,

(*b*) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder, or

(*c*) its history, including the records and documents relating to the distribution channels used,

but does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights;", and

(*g*) by inserting after the definition of "registered medical practitioner" the following definitions:

"'Regulation (EC) No. 726/2004' means Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004[14], as amended by Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006[15], the advanced therapy regulation, Regulation (EC) No. 219/2009 of the European Parliament and of the Council of 11 March 2009[16], Regulation (EC) No. 470/2009 of the European Parliament and of the Council of 6 May 2009[17] and Regulation (EU) No. 1235/2010 of the European Parliament and of the Council of 15 December 2010[18];

'relevant date' means—

(*a*) in the case of a medicinal product placed on the market in the State, the date 3 years after the date of publication of the delegated acts adopted by the Commission pursuant to Article 54a(2) of the 2001 Directive, or

(*b*) in the case of a medicinal product placed on the market of an EEA State which, on 21 July 2011, had in place a system of safety features, the date 6 years after the date of publication of the delegated acts adopted by the Commission pursuant to Article 54a(2) of the 2001 Directive;

'safety features' means safety features affixed on the packaging of a medicinal product pursuant to Regulation 17 (inserted by Regulation

[14]OJ No. L 136, 30.4.2004, p. 1.
[15]OJ No. L 378, 27.12.2006, p.1.
[16]OJ No. L 87, 31.3.2009, p. 109.
[17]OJ No. L 152, 16.6.2009, p. 11.
[18]OJ No. L 348, 31.12.2010, p. 1.

5 of the Medicinal Products (Control of Placing on the Market) (Amendment) Regulations 2013 (S.I. 162 of 2013)) of the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007);".

4. Regulation 8 of the Principal Regulations is amended by inserting after paragraph (5) the following paragraph:

"(6) The Board shall enter information in the EudraGMDP database in relation to all manufacturer's authorisations granted."

5. Regulation 13(3) of the Principal Regulations is amended by substituting for subparagraphs (*a*) and (*b*) the following:

"(*a*) in the case of medicinal products, other than investigational medicinal products and products to which sub-paragraph (*b*) refers, to ensure that every batch of a medicinal product to which the authorisation relates has been manufactured and checked in compliance with—

(i) the laws in force in the State in respect of such product,

(ii) the provisions of the manufacturer's authorisation, and

(iii) the provisions of the marketing authorisation, certificate of registration, certificate of traditional-use registration or other standard which relates to the said product,

and, from the relevant date, that safety features, where required, have been affixed on the packaging of any such products;

(*b*) in the case of medicinal products that have been imported by the authorisation holder, other than investigational medicinal products, to ensure that every batch of such products has undergone—

(i) a full qualitative analysis,

(ii) a quantitative analysis of at least all of the active ingredients, and

(iii) all other tests or checks necessary to ensure that the quality of the medicinal products is in accordance with the requirements of the relevant marketing authorisation, certificate of registration or certificate of traditional-use registration,

and, from the relevant date, that safety features, where required, have been affixed on the packaging of any such products;".

6. Regulation 14A (inserted by the Medicinal Products (Control of Manufacture) (Amendment) Regulations 2012 (S.I. No. 273 of 2012)) of the Principal Regulations is amended—

(*a*) in paragraph (1), by inserting "repeated" after " by means of",

(*b*) in paragraph (5), by substituting "EudraGMDP database" for "EudraGMP database",

(*c*) by substituting for paragraphs (6) and (7) the following paragraphs:

"(6) If the outcome of an inspection referred to in paragraph (1) is that the inspected entity does not comply with—

(*a*) the legal requirements governing medicinal products,

(*b*) the principles and guidelines of good manufacturing practice,

(*c*) the principles and guidelines of good manufacturing practice for active substances,

(*d*) the guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients,

(*e*) the principles and guidelines of good distribution practice, or

(*f*) the principles and guidelines of good distribution practices for active substances,

the Board shall enter the information in the EudraGMDP database.

(7) If the outcome of an inspection referred to in paragraph (1) is that the inspected entity complies with the principles and guidelines of good manufacturing practice, the Board shall, when applicable, within 90 days of the inspection, issue to the inspected entity a certificate of good manufacturing practice.

(8) Where an inspection is performed as part of the certification procedure for the monographs of the European Pharmacopoeia, pursuant to Article 111(1e) of the 2001 Directive, the Board shall issue a certificate to that effect.

(9) In this Regulation the principles and guidelines referred to are those adopted or published by the Commission pursuant to Articles 47 and 84 of the 2001 Directive, including the GMP Directive.".

7. The Principal Regulations are amended by inserting after Regulation 14A (inserted by the Medicinal Products (Control of Manufacture) (Amendment) Regulations 2012 (S.I. No. 273 of 2012)) the following Regulations:

"Falsified medicinal products and excipients

14B. (1) A person shall not manufacture, import or export a medicinal product if he or she knows, or there are sufficient grounds to suspect, that it is a falsified medicinal product.

(2) Subject to paragraph (3), a person shall not use an excipient in a medicinal product, or in the manufacture of a medicinal product, other than in accordance with these Regulations and the 2001 Directive.

(3) Paragraph (2) shall not apply in respect of investigational medicinal products, or the manufacture of such medicinal products.

Prohibitions in relation to active substances

14C. (1) A person shall not manufacture, import or export an active substance other than in accordance with these Regulations and the 2001 Directive.

(2) A person shall not manufacture active substances, including active substances intended for export, that do not comply with—

(*a*) the principles and guidelines of good manufacturing practice for active substances, and

(*b*) the principles and guidelines of good distribution practice for active substances.

(3) A person shall not distribute active substances, including active substances intended for export, that do not comply with the principles and guidelines of good distribution practice for active substances.

(4) Subject to paragraphs (5) and (6), and without prejudice to the obligations set out in Schedule 1 and paragraph 16 of Schedule 2, a person shall not import active substances from outside the European Economic Area unless—

(*a*) the active substances have been manufactured in accordance with standards at least equivalent to the principles and guidelines of good manufacturing practice for active substances, and

(*b*) the active substances are accompanied by a written confirmation from the competent authority of the exporting third country that—

(i) the standards of good manufacturing practice applicable to the plant manufacturing the exported active substance are at least equivalent to the principles and guidelines of good manufacturing practice;

(ii) the manufacturing plant concerned is subject to regular, strict and transparent controls and to the effective enforcement of good manufacturing practice, including repeated and unannounced inspections, so as to ensure a protection of public health at least equivalent to that in the European Economic Area; and

(iii) in the event of findings relating to non-compliance, information on such findings is supplied by the exporting third country to the European Economic Area without any delay.

(5) The requirement set out in paragraph (4)(*b*) shall not apply if the exporting country is included in the list adopted by the Commission pursuant to Article 111b of the 2001 Directive.

(6) The requirement set out in paragraph (4)(*b*) may be waived by the Board in accordance with Article 46b(4) of the 2001 Directive.

(7) This Regulation shall not apply in the case of active substances used in the manufacture of investigational medicinal products.

(8) In this Regulation the principles and guidelines referred to are those adopted by the Commission pursuant to Articles 47 of the 2001 Directive, including the GMP Directive.

Active substances register

14D. (1) The Board shall maintain a register of importers, manufacturers and distributors of active substances, known as the active substances register.

(2) A person shall not import, manufacture or distribute active substances in or from the State unless he or she is on the active substances register.

(3) An application for entry on to the active substances register shall—

(*a*) be made in writing to the Board,

(*b*) be signed by or on behalf of the applicant, whether in ink or by means of electronic signature, and

(*c*) be submitted at least 60 days prior to the intended commencement of the activity.

(4) Every application for entry on to the active substances register shall contain at least the information specified in Article 52a(2) of the 2001 Directive and be accompanied by any fee which may be payable in connection with that application.

(5) Following the receipt of an application under this Regulation, the Board may, based on a risk assessment, decide to carry out an inspection of the applicant.

(6) Where the Board decides to carry out an inspection under paragraph (5) it shall notify the applicant of same within 60 days of the receipt of the application and the applicant may not commence the activity in relation to the active substances until the Board has notified him or her that he or she may do so.

(7) Where the Board does not notify the applicant within 60 days of his or her application that it has decided to carry out an inspection, the applicant may commence the activity in relation to the active substances.

(8) Subject to paragraph (9), a person on the active substances register shall communicate annually to the Board an inventory of the changes which have taken place as regards the information provided in his or her application form for entry on to the register.

(9) A person on the active substances register shall immediately notify the Board of any changes which may have an impact on the quality or safety of the active substances.

(10) The Board shall enter information regarding registrations under this Regulation in the EudraGMDP database.

(11) The Board may remove a person from the active substances register where—

(*a*) he or she fails to comply with these Regulations or a condition of entry on to the register,

(*b*) he or she requests the removal, or

(*c*) the information submitted pursuant to paragraphs (4) and (9) is false or materially inaccurate.

Inspections in relation to active substances

14E. (1) The Board shall operate a system of supervision in relation to active substances, including by inspection at an appropriate frequency based on risk, at the premises of the manufacturers, importers and distributors of active substances located in the State, and effective follow up thereof.

(2) Where it considers that there are grounds for suspecting non-compliance with the legal requirements laid down in these Regulations and the 2001 Directive, including the principles and guidelines of good manufacturing practice adopted by the Commission pursuant to Article 47 of the 2001 Directive and the principles and guidelines of good distribution practice published by the Commission pursuant to Article 84 and Article 85b(3) of the 2001 Directive, the Board may carry out inspections at the premises of—

(*a*) manufacturers or distributors of active substances located in countries outside of the European Economic Area, and

(*b*) manufacturers or importers of excipients.

Safety features

14F. (1) Subject to paragraph (4), safety features shall not be removed or covered, either fully or partially, unless—

(*a*) the replacement of the safety features is conducted by an authorisation holder,

(*b*) the authorisation holder verifies, prior to partly or fully removing or covering those safety features, that the medicinal product concerned is authentic and that it has not been tampered with,

(*c*) the authorisation holder, without opening the container or other form of packaging immediately in contact with the medicinal product, replaces those safety features with safety features which are equivalent as regards the possibility to verify the authenticity, identification and to provide evidence of tampering of the medicinal product,

(*d*) the replacement of the safety features is conducted in accordance with applicable good manufacturing practice for medicinal products, and

(*e*) the replacement of the safety features is subject to supervision by the Board.

(2) Safety features shall be considered equivalent for the purposes of paragraph (1)(*c*) if they—

(*a*) comply with the requirements adopted by the Commission pursuant to Article 54a(2) of the 2001 Directive, and

(*b*) are equally effective in enabling the verification of authenticity and identification of medicinal products and in providing evidence of tampering with medicinal products.

(3) Authorisation holders shall be regarded as producers under s. 2 of the Liability for Defective Products Act 1991 and therefore may be held liable for damages in the cases and under the conditions set forth in that Act.

(4) Paragraph (1) shall not apply to the preparation, dividing up, changing of packaging or presentation of a medicinal product, where such process is carried out—

(i) in a dispensing pharmacy by or under the personal supervision of a pharmacist, for supply in or from such pharmacy, or

(ii) by a registered medical practitioner or registered dentist for supply to a patient under his or her care.".

8. Regulation 15 of the Principal Regulations is amended by inserting after paragraph (3) the following paragraphs:

"(4) Regulation 14C(3)(*b*), (4) and (5) shall not apply to the import of active substances from outside the European Economic Area until after 2 July 2013.

(5) Notwithstanding Regulation 14D(2), a person who commenced importing, manufacturing or distributing active substances in or from the State before 2 January 2013 may continue such activity, without being on the active substances register, provided that he or she applies for entry on to the register by 14 June 2013.".

9. Schedule 2 (as amended by the Medicinal Products (Control of Manufacture) Regulations 2007 (Amendment) Regulations 2009 (S.I. No. 4 of 2009)) to the Principal Regulations is amended—

(*a*) by substituting for paragraph 16 the following paragraph:

"16. Except in the case of investigational medicinal products or exempt medicinal products, the authorisation holder shall—

(*a*) only use active substances manufactured in accordance with the principles and guidelines of good manufacturing practice for active substances, as adopted by the Commission pursuant to Article 47 of the 2001 Directive,

(*b*) only use active substances distributed in accordance with the principles and guidelines of good distribution practices for active substances, as adopted by the Commission pursuant to Article 47 of the 2001 Directive,

(*c*) conduct audits, personally or through an entity acting on his or her behalf under a contract, of manufacturing and distribution sites to ensure compliance with subparagraphs (*a*) and (*b*),

(*d*) verify that all manufacturers, importers and distributors from whom he or she obtains active substances are registered with the competent authority of the EEA State in which they are established, and

(*e*) verify the authenticity and quality of the active substances he or she uses.", and

(*b*) by inserting after paragraph 33 the following paragraphs:

"34. Except in the case of investigational medicinal products and exempt medicinal products, the authorisation holder shall—

(*a*) ensure that excipients he or she uses are suitable for use in medicinal products by applying the appropriate good manufacturing practice ascertained following a formalised risk assessment in compliance with the requirements of the second paragraph of Article 46(*f*) of the 2001 Directive,

(*b*) document the measures taken under subparagraph (*a*), and

(*c*) verify the authenticity and quality of the excipients he or she uses.

35. The authorisation holder shall immediately inform the Board, and the holder of the relevant Community marketing authorisation, marketing authorisation, certificate of registration or certificate of traditional-use registration, if he or she obtains information that medicinal products which come under the scope of his or her manufacturer's authorisation are, or are suspected of being, falsified, irrespective of whether those medicinal products were distributed within the legal supply chain or by illegal means, including legal and illegal sale by means of information society services."

L.S.

GIVEN under my Official Seal,
22 May 2013.

JAMES REILLY,
Minister for Health.

EXPLANATORY NOTE

(This note is not part of the Instrument and does not purport to be a legal interpretation.)

These Regulations amend the Medicinal Products (Control of Manufacture) Regulations 2007 (S.I. No. 539 of 2007).

These Regulations give effect to Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 and give further effect to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001.

These Regulations may be cited as the Medicinal Products (Control of Manufacture) (Amendment) Regulations 2013.

BAILE ÁTHA CLIATH
ARNA FHOILSIÚ AG OIFIG AN tSOLÁTHAIR
Le ceannach díreach ó
FOILSEACHÁIN RIALTAIS,
52 FAICHE STIABHNA, BAILE ÁTHA CLIATH 2
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