STATUTORY INSTRUMENTS

2019 No. 744

EXITING THE EUROPEAN UNION

MEDICINES

The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019

Made - - - - 29th March 2019

Coming into force in accordance with regulation 1

The Secretary of State makes these Regulations in exercise of the powers conferred by section 8(1) of, and paragraph 21 of Schedule 7 to, the European Union (Withdrawal) Act 2018(**a**).

In accordance with paragraph 1(1) of Schedule 7 to that Act, a draft of these Regulations has been laid before and approved by a resolution of each House of Parliament.

Citation and commencement

1. These Regulations may be cited as the Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019 and come into force on exit day.

Amendment of the Medicines for Human Use (Clinical Trials) Regulations 2004

2. The Medicines for Human Use (Clinical Trials) Regulations 2004(**b**) are amended as follows.

Amendment of regulation 2 (interpretation)

3.—(1) Regulation 2(1)(**c**) is amended as follows.

(2) For the definition of "Commission Directive 2003/94/EC" substitute—

""Commission Directive 2003/94/EC" means—

(a) Commission Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice for medicinal products for human use and for investigational medicinal products for human use, as modified by Schedule 2A to the 2012 Regulations(**d**), or

(b) if Regulations have been made under the powers in regulation B17(1) of the 2012 Regulations(**e**), and have come into force, those Regulations;".

(**a**) 2018 c. 16.
(**b**) S.I. 2004/1031.
(**c**) Regulation 2(1) was amended by S.I. 2004/3224, 2005/2759, 2006/562 and 1928, 2007/3101, 2008/941, 2011/2581, 2012/1479, 1641 and 1916, 2013/235 and 2016/696 and S.R. 2008/192.
(**d**) Schedule 2A is inserted by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019.
(**e**) Regulation B17 is inserted by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019.

(3) After the definition of "container" insert—

""country" means a country or territory;".

(4) In the definition of "export", for "a third country from an EEA State" substitute "another country from the United Kingdom".

(5) Omit the definition of "the GCP Directive".

(6) For the definition of "import" substitute—

""import" means import into the United Kingdom, whether by land, sea or air;".

(7) In the definition of "investigational medicinal product", before "marketing authorization" insert "UK".

(8) For the definition of "marketing authorization", substitute—

""marketing authorization" means—

(a) a UK marketing authorization, or

(b) an authorization granted by a regulatory body responsible for licensing medicinal products in a country that is included in the list referred to in regulation 2A(1);".

(9) In the definition of "non-interventional trial", before "marketing authorization", insert "UK".

(10) Omit the definition of "third country".

(11) After the definition of "trial site" insert—

""UK marketing authorization" means—

(a) a marketing authorisation granted by the licensing authority under the 2012 Regulations, or

(b) a product licence granted by the licensing authority for the purposes of section 7 of the Medicines Act 1968;".

(12) In the definition of "unexpected adverse reaction", in paragraph (a), after "summary of product characteristics" insert ", or equivalent document,".

Insertion of regulation 2A (list of countries for the purpose of the definition of "marketing authorization")

4. After regulation 2, insert—

"List of countries for the purpose of the definition of "marketing authorization"

2A.—(1) The licensing authority must publish a list of countries for the purpose of the definition of "marketing authorization".

(2) In order to determine whether a country should be included in the list referred to in paragraph (1), the licensing authority may, in particular, take into account the regulatory equivalence of that country to the United Kingdom in assessing the safety, quality and efficacy of medicinal products.

(3) The licensing authority must—

(a) review the countries it has included in the list referred to in paragraph (1) to determine if it is still satisfied that the country should remain on that list, and if it is not so satisfied, remove that country from the list; and

(b) undertake such a review at least every three years beginning with the date on which that country is included in that list.".

Amendment of regulation 3 (sponsor of a clinical trial)

5.—(1) Regulation 3(**a**) is amended as follows.

(2) In paragraph (11)(a), for "an EEA State", substitute "the United Kingdom or a country that is included in the list referred to in paragraph (11A)".

(3) After paragraph (11), insert—

"(11A) The licensing authority must publish a list of countries where a sponsor of a clinical trial, or their legal representative, may be established for the purpose of paragraph (11).

(11B) In order to determine whether a country should be included in the list referred to in paragraph (11A), the licensing authority may, in particular, take into account—

(a) the mechanisms that the country has in place to assist the licensing authority in contacting, or obtaining information in respect of, a sponsor or legal representative that is established there; and

(b) the country's ability to assist the licensing authority in any action it may need to take in respect of a sponsor or legal representative that is established there.

(11C) The licensing authority must—

(a) review the countries it has included in the list referred to in paragraph (11A) to determine if it is still satisfied that the country should remain on that list, and if it is not so satisfied, remove that country from the list; and

(b) undertake such a review at least every three years beginning on the date on which that country is included in that list.".

Omission of regulation 4 (responsibility for functions under the Directive)

6. Omit regulation 4(**b**).

Amendment of regulation 13 (supply of investigational medicinal products for the purpose of clinical trials)

7.—(1) Regulation 13 is amended as follows.

(2) For paragraph (2)(b)(**c**), substitute—

"(b) the product has been manufactured, assembled or imported—

(i) in accordance with the terms of a manufacturing authorisation, or

(ii) in the case of assembly only, under the exemption in regulation 37.".

(3) After paragraph (2), insert—

"(2A) The condition specified in paragraph (2)(b) does not apply to an investigational medicinal product that has been manufactured or assembled in accordance with the terms of a UK marketing authorization relating to that product.".

(4) Omit paragraph (3).

(5) In paragraph (4)—

(i) for "of a marketing authorisation" substitute "of a UK marketing authorization"; and

(ii) omit the words from ", other than a marketing authorisation" to the end.

(**a**) Regulation 3 was amended by S.I. 2006/1928.
(**b**) Regulation 4 was amended by S.I. 2006/1928 and 2012/1916.
(**c**) Paragraph (2)(b) was amended by S.I. 2006/1928.

Amendment of regulation 15 (ethics committee opinion)

8. In regulation 15(5)(e)(**a**), after "summary of product characteristics" insert ", or equivalent document,".

Amendment of regulation 20 (authorisation procedure for clinical trials involving medicinal products with special characteristics)

9. In regulation 20(1)(a), for paragraph (i) substitute—

"(i) which do not have a marketing authorization and are developed by means of one of the following biotechnological processes—

(aa) recombinant DNA technology,

(bb) controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,

(cc) hybridoma and monoclonal antibody methods, or".

Amendment of regulation 21 (clinical trials conducted in third countries)

10.—(1) Regulation 21 is amended as follows.

(2) In the heading, for "third countries" substitute "countries other than the United Kingdom".

(3) In paragraph (1), for "a third" substitute "another".

Insertion of regulation 27B (publication of information)

11. After regulation 27A (information sharing)(**b**), insert—

"Publication of information

27B.—(1) Subject to paragraph (3), the licensing authority may make accessible to the public information contained in the items listed in paragraph (2) insofar as it relates to a clinical trial carried out, or being carried out, under these Regulations.

(2) The items listed in this paragraph are—

(a) the request for authorisation made under regulation 17;

(b) any amended request for authorisation made under regulation 18, 19 or 20;

(c) any amendment to the protocol made under regulation 23, 24 or 25;

(d) the favourable opinion of the ethics committee given in accordance with regulation 15 or the favourable opinion given by an appeal panel in accordance with paragraph 4 of Schedule 4;

(e) the notification of the end of the clinical trial made under regulation 27.

(3) Prior to making information available to the public under paragraph (1), the licensing authority must, after consulting such persons as the licensing authority considers appropriate, publish a list of the information which may be made accessible to the public under paragraph (1).".

Amendment of regulation 31 (suspension or termination of clinical trial)

12. In regulation 31(4), omit sub-paragraphs (b), (d) and (e).

(**a**) Paragraph (5) was amended by S.I. 2006/1928.
(**b**) Regulation 27A was inserted by S.I. 2006/1928.

Amendment of regulation 31A (trial master file and archiving)

13. In regulation 31A(4)(b)(**a**)—

(a) for "applicable", substitute "relevant"; and

(b) for the words "Directive 2001/83/EC" to the end, substitute "these Regulations".

Amendment of regulation 33 (notification of suspected unexpected serious adverse reactions)

14.—(1) Regulation 33 is amended as follows.

(2) Omit paragraph (1)(b)(ii).

(3) Omit paragraph (3)(b).

(4) Omit paragraph (4).

(5) Omit paragraph (6)(b), and the "and" immediately preceding it.

Amendment of regulation 34 (clinical trials conducted in third countries)

15.—(1) In the heading of regulation 34, for "third countries" substitute "countries other than the United Kingdom".

(2) In regulation 34—

(a) for "a third country" substitute "another country"; and

(b) for the words "entered into" to the end, substitute—

"reported as soon as possible to the licensing authority, and in any event—

(a) in the case of a reaction that is fatal or life-threatening, within 7 days beginning with the day after the sponsor was first aware of the reaction; or

(b) in any other case, within 15 days beginning with the day after the sponsor is first aware of the reaction.".

Amendment of regulation 35 (annual list of suspected serious adverse reactions and safety report)

16.—(1) Regulation 35 is amended as follows.

(2) In paragraph (2)(b), for "EEA State" substitute "any country".

(3) In paragraph (3)—

(a) for "an EEA State" substitute "a country"; and

(b) for sub-paragraphs (a) and (b), substitute—

"(a) the date on which the trial was authorised by a regulatory body responsible for authorising clinical trials in that country; or

(b) where the clinical trial was conducted in a country without a formal authorisation process, a date designated by the sponsor that is linked to the commencement of the first clinical trial.".

Amendment of regulation 36 (requirement for authorisation to manufacture or import investigational medicinal products)

17. In regulation 36(2), before "marketing authorization" insert "UK".

Amendment of regulation 43 (qualified persons)

18. In regulation 43, for paragraph (2) substitute—

(**a**) Regulation 31A was inserted by S.I. 2006/1928.

"(2) Subject to paragraphs (2A) and (2C), the qualified person is responsible for ensuring that—

(a) in the case of an investigational medicinal product manufactured in the United Kingdom, each production batch has been manufactured and checked in compliance with—

(i) the requirements of these Regulations;

(ii) the principles and guidelines of good manufacturing practice;

(iii) the product specification, as defined in Part 1 of Schedule 7; and

(iv) the request, particulars and documents submitted to the licensing authority under regulation 17 in respect of the clinical trial in which the product is to be used;

(b) in the case of an investigational medicinal product manufactured in a country other than the United Kingdom, each production batch has been manufactured and checked in accordance with—

(i) standards of good manufacturing practice at least equivalent to those laid down in Commission Directive 2003/94/EC;

(ii) the product specification, as defined in Part 1 of Schedule 7; and

(iii) the request, particulars and documents submitted to the licensing authority under regulation 17 in respect of the clinical trial in which the product is to be used.

(2A) The qualified person is not responsible for carrying out the controls in paragraph (2) where—

(a) the product is imported from a country that is included on the list referred to in regulation 43A ("approved country for import"); and

(b) the qualified person ensures that there is appropriate evidence to confirm that each production batch has been certified as provided for in Article 13 of the Directive, or such equivalent certification procedure as applies in the approved country for import.

(2B) The licensing authority must publish guidance on the evidence that it considers to be appropriate for the purposes of paragraph (2A)(b).

(2C) The qualified person is not responsible for carrying out the controls in paragraph (2) where—

(a) an investigational medicinal product which has a marketing authorization, or has been approved for marketing in another country, is imported as a comparator product; and

(b) documentation cannot be obtained certifying that each production batch has been manufactured and checked in accordance with standards of good manufacturing practice at least equivalent to those laid down in Commission Directive 2003/94/EC.

(2D) Where paragraph (2) does not apply by virtue of paragraph (2C), the qualified person is responsible for ensuring that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality in accordance with the request, particulars and documents submitted to the licensing authority under to regulation 17.

(2E) The qualified person is responsible for ensuring, in relation to an investigational medicinal product, that documentary evidence is produced that each batch of the product satisfies the provisions of paragraph (2), (2A) or (2D) (as the case may be).

(2F) The documentary evidence referred to in paragraph (2E) must be—

(a) kept up to date as operations are carried out; and

(b) available for inspection by the licensing authority for a period of at least five years beginning with the date on which the documentary evidence is produced.".

Insertion of regulation 43A (approved country for import)

19. After regulation 43 insert—

"**Approved country for import**

43A.—(1) The licensing authority must publish a list of countries which it is satisfied have a regulatory framework applicable to investigational medicinal products exported to the United Kingdom that is equivalent to the regulatory framework in the United Kingdom, in that the respective control and enforcement activities in those countries ensure an equivalent level of protection of public health.

(2) In order to determine whether a country should be included in the list referred to in paragraph (1), the licensing authority may, in particular, take into account—

(a) the country's system for ensuring that each batch of an investigational medicinal product has been manufactured and checked in accordance with the requirements of its legislation and any authorisation in respect of the clinical trial in which the product is to be used;

(b) the country's rules for good manufacturing practice;

(c) the regularity of inspections to verify compliance with good manufacturing practice;

(d) the effectiveness of enforcement of good manufacturing practice;

(e) the regularity and rapidity of information provided by that country relating to non-compliant manufacturers of investigational medicinal products;

(f) any on-site review of that country's regulatory system undertaken by the licensing authority;

(g) any on-site inspection of a manufacturing site in that country observed by the licensing authority; and

(h) any other relevant documentation available to the licensing authority.

(3) The licensing authority must—

(a) review the countries it has included in the list referred to in paragraph (1) to determine if it is still satisfied that the country should remain on that list, and if it is not so satisfied, remove that country from the list; and

(b) undertake such a review at least every three years beginning with the date on which that country is included in that list.".

Amendment of regulation 45 (suspension and revocation of manufacturing authorisation)

20. In regulation 45(1)(f)(i), omit "or any equivalent provisions in any EEA State other than the United Kingdom".

Amendment of regulation 48 (infringement notices)

21. In regulation 48(3)(**a**), omit—

(a) sub-paragraph (a); and

(b) sub-paragraph (c), and the "and" immediately preceding it.

Amendment of regulation 56 (transitional provisions)

22. In regulation 56, for "Schedule 12" substitute "Schedules 12 and 13".

(**a**) Regulation 48 was amended by S.I. 2006/1928 and 2012/1916.

Insertion of regulation 57 (functions in relation to good clinical practice)

23. After regulation 56, insert—

"Functions in relation to good clinical practice

57.—(1) Regulations may—

(a) amend the conditions and principles of good clinical practice to take account of technical and scientific progress;

(b) specify requirements for documentation relating to a clinical trial which constitute the master file on the trial at the time the file is archived;

(c) amend or revoke the requirements of regulation 31A relating to the content of the trial master file; and

(d) require guidance published under regulation 58 to be taken into account when interpreting any enactment or other requirement to which the guidance relates.

(2) Any power to make regulations under paragraph (1)—

(a) is exercisable—

(i) in respect of Northern Ireland only, by the Minister of Health in Northern Ireland by statutory rule for the purposes of the Statutory Rules (Northern Ireland) Order 1979(**a**);

(ii) in respect of any part of the United Kingdom, by the Secretary of State by statutory instrument;

(b) in respect of Northern Ireland may be exercised by—

(i) the Minister of Health acting alone; or

(ii) the Secretary of State acting with the agreement of the Minister of Health;

(c) includes power to make—

(i) different provision for different purposes or different areas;

(ii) consequential, supplementary, incidental, transitional, transitory or saving provisions, including consequential amendments to these Regulations.

(3) Regulations under paragraph (1) are—

(a) in the case of a statutory instrument made by the Secretary of State, subject to annulment in pursuance of a resolution of either House of Parliament;

(b) in the case of statutory rules made by the Minister of Health in Northern Ireland, subject to negative resolution within the meaning of section 41(6) of the Interpretation Act (Northern Ireland) 1954(**b**).

Detailed guidance

58. The licensing authority may publish guidance on—

(a) the application format and documentation to be submitted in an application for an ethics committee opinion, in particular regarding the information that is given to subjects, and on the appropriate safeguards for the protection of personal data;

(b) the format and contents of a request for authorisation of a clinical trial, as well as the documentation to be submitted to support that request, on the quality and manufacture of the investigational medicinal product, any toxicological and pharmacological tests, the protocol and clinical information on the investigational medicinal product including the investigator's brochure;

(**a**) S.I. 1979/1573 (NI 12).
(**b**) 1954 c.33 (NI).

(c) the presentation and content of any proposed substantial amendment to the clinical trial authorisation insofar as it relates to the protocol;

(d) the declaration of the end of the clinical trial;

(e) the collection, verification and presentation of adverse event or adverse reaction reports, together with decoding procedures for unexpected serious adverse reactions;

(f) the content of essential documents forming part of the trial master file;

(g) the elements to be taken into account when evaluating investigational medicinal products for the purpose of regulation 43(2).".

Amendment of Schedule 3 (particulars and documents that must accompany an application for an ethics committee opinion, a request for authorisation, a notice of amendment and a notification of the conclusion of a trial)

24.—(1) Schedule 3 is amended as follows.

(2) In Part 1(**a**), in paragraph 3(b), after "summary of product characteristics" insert ", or equivalent document,".

(3) In Part 2—

(a) in paragraph 1(b), for "an EEA State"(**b**), substitute "the United Kingdom or a country that is included in the list referred to in regulation 3(11A)";

(b) in paragraph 4, for "another", substitute "an";

(c) in paragraph 7—

(i) before "authorisation", insert "manufacturing";

(ii) omit "referred to in Article 13 of the Directive";

(d) in paragraph 8—

(i) in sub-paragraph (1), for "Article 13(3) of the Directive" substitute "regulation 43(2)";

(ii) in sub-paragraph (2)—

(aa) omit "from a third country";

(bb) before "authorisation" insert "manufacturing";

(cc) omit "referred to in Article 13 of the Directive";

(dd) in paragraph (a), for "European Economic Area", substitute "United Kingdom";

(iii) in paragraph 11(4)(a), after "summary of product characteristics" insert "or equivalent document".

(4) In Part 3, in paragraph 1(b), for "an EEA State", substitute "the United Kingdom or a country that is included in the list referred to in regulation 3(11A)".

(5) In Part 4, in paragraph 1(b), for "an EEA State", substitute "the United Kingdom or a country that is included in the list referred to in regulation 3(11A)".

Amendment of Schedule 7 (standard provisions for manufacturing authorisations)

25. In Part 1 of Schedule 7, in the definition of "product specification", omit "or any equivalent provisions in any EEA State other than the United Kingdom".

(**a**) Part 1 was amended by S.I. 2008/941.
(**b**) The words "an EEA State" were substituted by S.I. 2006/1928.

Insertion of Schedule 13 (transitional provisions in relation to EU Exit)

26. After Schedule 12 insert—

"SCHEDULE 13

Regulation 56

Transitional provisions relating to EU Exit

List of countries for the purpose of the definition of "marketing authorization" on exit day (regulation 2A)

1.—(1) For the purpose of regulation 2A, during the transitional period, the licensing authority must include each EEA State in the list referred to in paragraph (1) of that regulation.

(2) Notwithstanding regulation 2A(3), the licensing authority must not, before the end of the transitional period, remove an EEA State from the list referred to in regulation 2A(1).

(3) In this paragraph, "transitional period" is the period of two years beginning with exit day.

List of countries where a sponsor of a clinical trial, or their legal representative, may be established on exit day (regulation 3(11A))

2.—(1) For the purpose of regulation 3, the licensing authority must include each EEA State in the list referred to in paragraph (11A) of that regulation.

(2) Notwithstanding regulation 3(11C), the licensing authority must not, before the end of the transitional period, remove an EEA State from the list referred to in regulation 3(11A).

(3) In this paragraph, "transitional period" is the period of two years beginning with exit day.

Import of investigational medicinal products from EEA States during the transitional period

3.—(1) The condition in regulation 13(2)(b) and the restriction in regulation 36(1) do not apply to an investigational medicinal product that is imported from an EEA State before the end of the transitional period, provided that the production batch of investigational medicinal products of which the product is a part has been checked and certified by a qualified person pursuant to Article 13(3) and (4) of the Directive.

(2) In this paragraph, "transitional period" is the period of one year beginning with exit day.

Approved country for import list on exit day (regulation 43A)

4.—(1) For the purpose of regulation 43A, during the transitional period, the licensing authority must include each EEA State in the list referred to in paragraph (1) of that regulation.

(2) Notwithstanding regulation 43A(3), the licensing authority must not, before the end of the transitional period, remove an EEA State from the list referred to in regulation 43A(1).

(3) In this paragraph, "transitional period" is the period of two years beginning with exit day.".

Signed by authority of the Secretary of State for Health and Social Care.

Jackie Doyle-Price
Parliamentary Under-Secretary of State,
Department of Health and Social Care

29th March 2019

EXPLANATORY NOTE

(This note is not part of the Regulations)

These Regulations are made in exercise of the powers conferred by section 8(1) of the European Union (Withdrawal) Act 2018 (c. 16) and amend the Medicines for Human Use (Clinical Trials) Regulations 2004 in order to address failures of retained EU law to operate effectively and other deficiencies (in particular under section 8(2)(a), (b), (c), (d), (f) and (g) and (6)) arising from the withdrawal of the United Kingdom from the European Union.

An impact assessment of the effect that this instrument will have on the costs of business, the voluntary sector and the public sector is available from the Medicines and Healthcare Products Regulatory Agency, 10 South Colonnade, Canary Wharf, London, E14 4PU and is published alongside this instrument at www.legislation.gov.uk.

Printed and published in the UK by The Stationery Office Limited under the authority and superintendence of Jeff James, Controller of Her Majesty's Stationery Office and Queen's Printer of Acts of Parliament.

£6.90

UK201903291022 04/2019 19585

http://www.legislation.gov.uk/id/uksi/2019/744

ISBN 978-0-11-118543-8