STATUTORY INSTRUMENTS

2006 No. 1928

MEDICINES

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006

Made - - - -	*13th July 2006*
Laid before Parliament	*20th July 2006*
Coming into force - -	*29th August 2006*

The Secretary of State makes the following Regulations in exercise of the powers conferred upon her by section 2(2) of the European Communities Act 1972(**a**). She has been designated for the purposes of that section in relation to medicinal products(**b**).

Citation, commencement and interpretation

1.—(1) These Regulations may be cited as the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 and shall come into force on 29th August 2006.

(2) In these Regulations, the "principal Regulations" means the Medicines for Human Use (Clinical Trials) Regulations 2004(**c**).

Amendment of regulation 2 of the principal Regulations

2. In regulation 2 of the principal Regulations (interpretation), in paragraph (1)—

(a) in the definition of "chief investigator", in sub-paragraph (b), omit "care";

(b) for the definition of "EEA State" substitute the following definition—

""EEA State" means a Member State, Norway, Iceland or Liechtenstein;";

(c) omit the definition of "EEA Agreement"; and

(d) after the definition of "export", insert the following definition—

""the GCP Directive" means Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products(**d**);".

Amendment of regulation 3 of the principal Regulations

3. In regulation 3 of the principal Regulations (sponsor of a clinical trial)—

(**a**) 1972 c.68.
(**b**) S.I. 1972/1811.
(**c**) S.I. 2004/1031; as amended by S.I. 2005/2754 and 2759.
(**d**) OJ No. L91, 9.4.2005, p.13.

(a) in paragraph (11), in sub-paragraph (a), for "the European Community" substitute "an EEA State"; and

(b) after paragraph (11), insert the following paragraph—

"(12) A person who is a sponsor of a clinical trial in accordance with this regulation may delegate any or all of his functions under these Regulations to any person but any such arrangement shall not affect the responsibility of the sponsor.".

Insertion of regulation 3A of the principal Regulations

4. After regulation 3 of the principal Regulations (sponsor of a clinical trial) insert the following regulation—

"Sponsor's responsibility for the investigator's brochure

3A. The sponsor of a clinical trial shall—

(a) ensure that the investigator's brochure for that trial, and any update of that brochure, presents the information it contains in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial; and

(b) validate and update the investigator's brochure at least once a year.".

Amendment of regulation 4 of the principal Regulations

5. In regulation 4 of the principal Regulations (responsibility for functions under the Directive), in paragraphs (1) and (2), after "the Directive", in both places those words appear, insert " and the GCP Directive".

Amendment of regulation 7 of the principal Regulations

6. In regulation 7 of the principal Regulations (recognition of ethics committees), in paragraph (5), in sub-paragraph (c), for "(5)" substitute "(4)".

Amendment of regulation 12 of the principal Regulations

7. In regulation 12 of the principal Regulations (requirement for authorisation and ethics committee opinion), in paragraph (3), in sub-paragraph (a), after "ethics committee" insert "to which an application in relation to the trial may be made in accordance with regulation 14".

Amendment of regulation 13 of the principal Regulations

8. In regulation 13 of the principal Regulations (supply of investigational medicinal products for the purpose of clinical trials), in paragraph (2), in sub-paragraph (b), for head (i) substitute—

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

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

(bb) in accordance with the terms of an authorisation referred to in Article 13 of the Directive granted by a competent authority of an EEA State other than the United Kingdom, or

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

Amendment of regulation 15 of the principal Regulations

9. In regulation 15 of the principal Regulations (ethics committee opinion), in paragraph (5)—

(a) in sub-paragraph (b), for "paragraph 2" substitute "paragraph 10";

(b) in sub-paragraph (e), after "investigator's brochure" insert " or, where the investigational medicinal product has a marketing authorization and the product is to be used in accordance with the terms of that authorization, the summary of product characteristics relating to that product"; and

(c) in sub-paragraph (h)—

(i) after "include" insert " minors or", and

(ii) for "Part 5" substitute "Part 4 or Part 5 respectively".

Amendment of regulation 16 of the principal Regulations

10. In regulation 16 of the principal Regulations (review and appeal relating to ethics committee opinion), in paragraph (1), for "13" substitute "14".

Amendment of regulation 17 of the principal Regulations

11. In regulation 17 of the principal Regulations (request for authorisation to conduct a clinical trial)—

(a) in paragraph (2), for "A" substitute "Subject to paragraph (2A), a"; and

(b) after paragraph (2), insert the following paragraph—

"(2A) No fee need accompany a request where arrangements have been made with the licensing authority for payment of the fee referred to in paragraph (2)(b)(ii) other than at the time of request.".

Amendment of regulation 23 of the principal Regulations

12. In regulation 23 of the principal Regulations (amendments by the licensing authority), in paragraph (1), for "(1) and (2)" substitute "(2) and (3)".

Amendment of regulation 24 of the principal Regulations

13. In regulation 24 of the principal Regulations (amendments by the sponsor), in paragraph (10)—

(a) before the definition of "valid notice of amendment", insert the following definition—

""any relevant fee" means, in relation to a notice of amendment, any fee which may be payable in connection with that notice under the Medicines (Products for Human Use—Fees) Regulations 1995(**a**); and"; and

(b) in the definition of "valid notice of amendment", in paragraph (b), for sub-paragraph (ii) substitute the following sub-paragraph—

"(ii) unless arrangements have been made with the licensing authority for the payment of any relevant fee other than at the time of the request, any such fee.".

Insertion of regulation 27A of the principal Regulations

14. After regulation 27 of the principal Regulations (conclusion of trial) insert the following regulation—

"Information sharing

27A. The licensing authority and an ethics committee may disclose to each other any information acquired in carrying out their respective functions under these Regulations where disclosing such information may assist the other body in carrying out its functions under these Regulations.".

(**a**) S.I. 1995/1116; relevant amending instruments are S.I. 2004/1157 and 2006/494.

Amendment of regulation 29 of the principal Regulations

15. In regulation 29 of the principal Regulations (conduct of trial in accordance with clinical trial authorisation etc.), in paragraph (c), for "24(4)" substitute "24(5)".

Insertion of regulation 29A of the principal Regulations

16. After regulation 29 of the principal Regulations (conduct of trial in accordance with clinical trial authorisation etc.), insert the following regulation—

"Notification of serious breaches

29A.—(1) The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of—

(a) the conditions and principles of good clinical practice in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25,

within 7 days of becoming aware of that breach.

(2) For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree—

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.".

Amendment of regulation 31 of the principal Regulations

17. In regulation 31 of the principal Regulations (suspension or termination of clinical trial), in paragraph (1), in paragraph (a), in head (ii), for "24(4)" substitute "24(5)".

Insertion of regulation 31A of the principal Regulations

18. After regulation 31 of the principal Regulations (suspension or termination of clinical trial), insert the following regulation—

"Trial master file and archiving

31A.—(1) The sponsor shall keep a trial master file for a clinical trial.

(2) The sponsor shall ensure that the trial master file is readily available at all reasonable times for inspection by the licensing authority or any person appointed by the sponsor to audit the arrangements for the trial.

(3) The master file shall at all times contain the essential documents relating to that clinical trial.

(4) The essential documents relating to a clinical trial are those which—

(a) enable both the conduct of the clinical trial and the quality of the data produced to be evaluated; and

(b) show whether the trial is, or has been, conducted in accordance with the applicable requirements of Directive 2001/83/EC, the Directive, the GCP Directive and Commission Directive 2003/94/EC.

(5) The essential documents shall contain information specific to each phase of the trial.

(6) The sponsor shall ensure that any alteration to a document contained, or which has been contained, in the trial master file shall be traceable.

(7) The sponsor and the chief investigator shall ensure that the documents contained, or which have been contained, in the trial master file are retained for at least 5 years after the conclusion of the trial and that during that period are—

(a) readily available to the licensing authority on request; and

(b) complete and legible.

(8) The sponsor and chief investigator shall ensure that the medical files of trial subjects are retained for at least 5 years after the conclusion of the trial.

(9) The sponsor shall appoint named individuals within his organisation to be responsible for archiving the documents which are, or have been, contained in the trial master file and, subject to paragraph (2), access to those documents shall be restricted to those appointed individuals.

(10) If there is transfer of ownership of data or documents connected with the clinical trial—

(a) the sponsor shall record the transfer; and

(b) the new owner shall be responsible for data retention and archiving in accordance with paragraphs (2), (7) and (8).

(11) For the purposes of this regulation, an individual is an individual within the sponsor's organisation where—

(a) he is employed or engaged by the sponsor;

(b) he is acting under arrangements made with the sponsor for the purposes of managing or conducting the clinical trial;

(c) where the sponsor is an individual, he is the sponsor; or

(d) where the sponsor is a body of persons, he is—

(i) a member of the body, or

(ii) employed or engaged by such a member.".

Amendment of regulation 38 of the principal Regulations

19. In regulation 38 of the principal Regulations (application for manufacturing authorisation)—

(a) in paragraph (3), for "Every" substitute "Subject to paragraph (3A), every"; and

(b) after paragraph (3), insert the following paragraph—

"(3A) No fee need accompany an application for the grant of a manufacturing authorisation where arrangements have been made with the licensing authority for the payment of the fee referred to in paragraph (3)(b) other than at the time of the application.".

Amendment of regulation 40 of the principal Regulations

20. In regulation 40 of the principal Regulations (grant or refusal of manufacturing authorisation), in paragraph (1), in sub-paragraph (a), for head (ii) substitute—

"(ii) has at his disposal—

(aa) the services of staff, and

(bb) suitable and sufficient premises, technical equipment and control facilities,

complying with the requirements of Commission Directive 2003/94/EC, as regards the manufacture or import, and control, of the products to which the authorisation relates and the storage of such products,".

Amendment of regulation 41 of the principal Regulations

21. In regulation 41 of the principal Regulations (application and effect of manufacturing authorisation)—

(a) in paragraph (b), omit "and"; and

(b) after paragraph (b), insert the following paragraph—

"(bb) in the case of an authorisation relating to the inactivation of viral or non-conventional agents, the manufacturing process; and".

Amendment of regulation 42 of the principal Regulations

22. For regulation 42 of the principal Regulations (obligations of manufacturing authorisation holder), substitute—

"42. The holder of a manufacturing authorisation shall—

(a) comply with the principles and guidelines of good manufacturing practice;

(b) comply with the provisions referred to in regulation 40(3);

(c) allow the licensing authority access to his premises at any reasonable time; and

(d) put and keep in place arrangements which enable the qualified person to carry out his duties, including placing at his disposal all the necessary facilities.".

Amendment of regulation 44 of the principal Regulations

23. In regulation 44 of the principal Regulations (variation of manufacturing authorisation)—

(a) in paragraph (2), in sub-paragraph (a)—

(i) substitute "change—" for "change the—"

(ii) after head (ii), insert the following head—

"(iia) the manufacturing process,",

(iii) in head (iv), after "facilities,", insert "or", and

(iv) after head (iv), insert the following head—

"(v) the staff, including the qualified person,"; and

(b) for paragraph (8), substitute the following paragraph—

"(8) In this regulation—

"any relevant fee" means, in relation to an application to vary a manufacturing authorisation, any fee which may be payable in connection with that application under the Medicines (Products for Human Use—Fees) Regulations 1995(**a**); and

"valid application" means an application—

(a) made to the licensing authority,

(b) in writing and signed by or on behalf of the applicants,

(c) specifying the variation requested by the applicant,

(d) accompanied by—

(i) such particulars as are necessary to enable the licensing authority to consider the application, and

(ii) unless arrangements have been made with the licensing authority for the payment of any relevant fee other than at the time of the application, any such fee, and

(e) where the application, and any accompanying material, is in the English language.".

Amendment of regulation 46 of the principal Regulations

24. In regulation 46 of the principal Regulations (labelling), in paragraph (2), in sub-paragraph (b), for "an authorised" substitute "a".

Amendment of regulation 48 of the principal Regulations

25. In regulation 48 of the principal Regulations (infringement notices), in paragraph (4)—

(a) after "regulations", insert " 3A, 12(1),";

(**a**) S.I. 1995/1116; relevant amending instruments are S.I. 2004/1157 and 2006/494.

(b) after “29,”, insert “ 29A,”; and

(c) after “30(2)”, insert “, 31A”.

Amendment to regulation 49 of the principal Regulations

26. In regulation 49 of the principal Regulations (offences), in paragraph (1)—

(a) re-number sub-paragraph (a) as sub-paragraph (aa);

(b) before sub-paragraph (aa), insert the following sub-paragraph—

“(a) regulation 3A;”;

(c) after sub-paragraph (e), insert the following sub-paragraph—

“(ee) regulation 29A;”; and

(d) after sub-paragraph (f), insert the following sub-paragraph—

“(ff) regulation 31A(1) to (3) and (5) to (10);”.

Amendment of Schedule 1 to the principal Regulations

27. Schedule 1 to the principal Regulations (conditions and principles of good clinical practice and for the protection of clinical trial subjects) shall be amended as follows.

(1) In Part 1 (application and interpretation), in paragraph 2—

(i) in the definition of “legal representative”, in paragraph (a)—

(aa) in sub-paragraph (i), for “involved in” substitute “connected with”, and

(bb) in sub-paragraph (ii), in head (aa), after “adult” insert “or that minor”; and

(ii) in the definition of “parental responsibility”, in paragraph (b), for “1985” substitute “1995”.

(2) For Part 2 (conditions and principles which apply to all clinical trials), substitute the following—

“PART 2

CONDITIONS AND PRINCIPLES WHICH APPLY TO ALL CLINICAL TRIALS

Principles based on Articles 2 to 5 of the GCP Directive

1. The rights, safety and well-being of the trial subjects shall prevail over the interests of science and society.

2. Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks.

3. Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects.

4. The necessary procedures to secure the quality of every aspect of the trial shall be complied with.

5. The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.

6. Clinical trials shall be conducted in accordance with the principles of the Declaration of Helsinki.

7. The protocol shall provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy.

8. The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.

9. All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.

Conditions based on Article 3 of the Directive

10. Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A trial should be initiated and continued only if the anticipated benefits justify the risks.

11. The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist.

12. A trial shall be initiated only if an ethics committee and the licensing authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.

13. The rights of each subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with the Data Protection Act 1998 are safeguarded.

14. Provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor which may arise in relation to the clinical trial.".

(3) In Part 4 (conditions and principles which apply in relation a minor), in paragraph 1, for "Subject to paragraph 6, a" substitute "A".

Amendment of Schedule 2 to the principal Regulations

28. In Schedule 2 to the principal Regulations (additional provisions relating to ethics committees)—

(a) in paragraph 1 (interpretation), in the definition of "appointing authority"—

(i) in sub-paragraph (b), omit "or",

(ii) in sub-paragraph (c), for "the Authority;" substitute "the Authority, or",

(iii) after sub-paragraph (c), insert the following sub-paragraph—

"(d) in relation to the Gene Therapy Advisory Committee, the Secretary of State;";

(b) in paragraph 6 (committees, meetings and proceedings), after sub-paragraph (4), insert—

"(5) An ethics committee shall retain all the documents relating to a clinical trial on which it gives an opinion for—

(a) where the trial proceeds, at least three years from the conclusion of the trial; or

(b) where the trial does not proceed, at least three years from the date of the opinion."; and

(c) in paragraph 8 (deputies and co-opted members), in sub-paragraph (6), for "(4)" substitute "(5)".

Amendment of Schedule 3 to the principal Regulations

29. In Schedule 3 to the principal Regulations (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)—

(a) in Part 2 (request for authorisation), in paragraph 1, in sub-paragraph (b), for "the European Community" substitute "an EEA State";

(b) in Part 3 (notice of amendment)—

(i) in paragraph 1, in sub-paragraph (b), for "the European Community" substitute "an EEA State", and

(ii) in paragraph 2, in sub-paragraph (b), for "the number" substitute "any number"; and

(c) in Part 4 (notification of conclusion of a clinical trial)—

(i) in paragraph 1, in sub-paragraph (b), for "the European Community" substitute "an EEA State", and

(ii) in paragraph 2, in sub-paragraph (b), for "the number" substitute "any number".

Amendment of Schedule 4 to the principal Regulations

30. In Schedule 4 to the principal Regulations (appeal against unfavourable ethics committee opinion)—

(a) in paragraph 1, in sub-paragraph 1, after "regulation 16(3)", insert ", (4)(b)";

(b) in paragraph 4, in sub-paragraph (2)—

(i) in head (d), for "(6)" substitute "(5)", and

(ii) in head (f)—

(aa) omit "on a review", and

(bb) for "(5)" substitute "(6)"; and

(c) in paragraph 5, for "11" substitute "12".

Amendment of Schedule 6 to the principal Regulations

31. In Schedule 6 to the principal Regulations (particulars that must accompany an application for a manufacturing authorisation)—

(a) for paragraph 2 substitute—

"**2.** A statement describing the types of investigational medicinal product in respect of which the authorisation is required, including their pharmaceutical forms."; and

(b) after paragraph 3, insert the following paragraph—

"3A. Where the application relates to the inactivation of viral or non-conventional agents, a statement of the manufacturing process to which the authorisation is to relate.".

Amendment of Schedule 9 to the principal Regulations

32. In Schedule 9 to the principal Regulations (modifications of the enforcement provisions of the Act subject to which those provisions are applied for the purposes of these Regulations), in paragraph 5 for "England and Wales" substitute "Northern Ireland".

Amendment of Schedule 12 to the principal Regulations

33. In Schedule 12 to the principal Regulations (transitional provisions)—

(a) in paragraph 1—

(i) in sub-paragraph (2), in head (b), for "(3)" substitute "(4)",

(ii) in sub-paragraph (6), after "opinion in relation" insert " to", and

(iii) in sub-paragraph (7), for "(a)" substitute "(b)"; and

(b) in paragraph 6, in sub-paragraph (1), in head (a), after "conducted" insert "after".

Signed by authority of the Secretary of State for Health

Andrew Burnham
Minister of State
Department of Health

13th July 2006

EXPLANATORY NOTE

(This note is not part of the Regulations)

These Regulations amend the Medicines for Human Use (Clinical Trials) Regulations 2004 (the principal Regulations) which implement Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products in human use(**a**). In particular, they implement Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (the GCP Directive)(**b**) and make other miscellaneous amendments.

Regulations 2(d), 3(b), 4, 5, 9(a) and (b), 14, 18, 20 to 22, 23(a), 25(a) and (c), 26(b) and (d), 27(3), 28(b) and 31 implement the GCP Directive. In particular they amend the principal Regulations so as to make provision for the following matters:

(a) delegation of functions by the sponsor (regulation 3(b));

(b) imposition of new requirements on sponsors/investigators in relation to the investigator's brochure and trial documentation (regulation 4, 18, 25(a) and (c) and 26(b) and (d));

(c) functions of the Member State and the competent authority under the GCP Directive to be exercised by the licensing authority, unless the functions fall to be performed by the exercise of powers and duties conferred on another person or body under or by virtue of the principal Regulations (regulation 2(d) and 5);

(d) changes to the obligations of ethics committees (regulation 9(b) and 28(b));

(e) the sharing of information between ethics committees and the licensing authority (regulation 14);

(f) amendment of the provisions on the scope of, and procedures for, manufacturing authorisations and the obligations of the holders of such authorisations (regulations 20 to 22, 23(a) and 31); and

(g) a revision of the conditions and principles of good clinical practice which apply to all trials (regulations 9(a) and 27(3)).

Regulations 11, 13, 19 and 23(b) remove the requirement that the appropriate fee must accompany applications for clinical trial authorisations, applications to amend clinical trial authorisations, applications for manufacturing authorisations and applications to amend manufacturing authorisations, where the applicant has made arrangements with the licensing authority for the payment of the fee at a different time.

Regulation 16 makes provision for a new requirement that serious breaches of good clinical practice or the trial protocol must be notified to the licensing authority.

Regulation 25 extends the application of the infringement notices regime in the principal Regulations to a) breaches of the sponsor's responsibilities for the investigator's brochure; b) the requirement not to start or conduct a clinical trial without a clinical trial authorisation or a favourable opinion from an ethics committee; c) the requirement of the sponsor to report serious breaches of good clinical practice or the trial protocol; and d) the requirements relating to the trial master file and archiving.

Regulation 26 makes the following a criminal offence: a) breach of the sponsor's responsibility for the investigator's brochure; b) breach of the requirement on a sponsor to report serious breaches of good clinical practice or the trial protocol; and c) breach of the trial master file and archiving requirements.

Regulations 2(a) to (c), 3(a), 6 to 8, 9(c), 10, 12, 15, 17, 24, 27(2) and (4), 28(a) and (c), 29, 30, 32 and 33 correct various errors in the principal Regulations.

A full regulatory impact assessment of the effect that this instrument will have on the costs of business and a Transposition Note is available from the Medicines and Healthcare products Regulatory Agency,

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(**a**) OJ No. L121, 1.5.2001, p.34.
(**b**) OJ No. L91, 9.4.2005, p.13.

Market Towers, 1 Nine Elms Lane, London, SW8 5NQ and copies have been placed in the library of both Houses of Parliament.

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