Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Text with EEA relevance)

CHAPTER III

AUTHORISATION PROCEDURE FOR A SUBSTANTIAL MODIFICATION OF A CLINICAL TRIAL

Article 15

General principles

A substantial modification, including the addition of a clinical trial site or the change of a principal investigator in the clinical trial site, may only be implemented if it has been approved in accordance with the procedure set out in this Chapter.

Article 16

Submission of application

In order to obtain an authorisation, the sponsor shall submit an application dossier to the Member States concerned through the EU portal.

Article 17

Validation of an application for the authorisation of a substantial modification of an aspect covered by Part I of the assessment report

1 The reporting Member State for the authorisation of a substantial modification shall be the reporting Member State for the initial authorisation procedure.

Member States concerned may communicate to the reporting Member State any considerations relevant to the validation of the application of a substantial modification within five days from the submission of the application dossier.

2 Within six days from the submission of the application dossier, the reporting Member State shall validate the application taking into account considerations expressed by the other Member States concerned and notify the sponsor through the EU portal as to whether:

a the substantial modification concerns an aspect covered by Part I of the assessment report; and

b the application dossier is complete in accordance with Annex II.

3 Where the reporting Member State has not notified the sponsor within the period referred to in paragraph 2, the substantial modification applied for shall be deemed to concern an aspect covered by Part I of the assessment report and the application dossier shall be deemed to be complete.

4 Where the reporting Member State, taking into account considerations expressed by the other Member States concerned, finds that the application does not concern an aspect

covered by Part I of the assessment report or that the application dossier is not complete, it shall inform the sponsor thereof through the EU portal and shall set a maximum of 10 days for the sponsor to comment on the application or to complete the application dossier through the EU portal.

Within five days from receipt of the comments or the completed application dossier, the reporting Member State shall notify the sponsor as to whether or not the application complies with the requirements set out in points (a) and (b) of paragraph 2.

Where the reporting Member State has not notified the sponsor within the period referred to in the second subparagraph, the substantial modification applied for shall be deemed to concern an aspect covered by Part I of the assessment report and the application dossier shall be deemed to be complete.

Where the sponsor has not provided comments or completed the application dossier within the period referred to in the first subparagraph, the application shall be deemed to have lapsed in all Member States concerned.

5 For the purposes of Articles 18, 19 and 22, the date on which the sponsor is notified in accordance with paragraph 2 or 4 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the respective periods referred to in paragraphs 2 and 4.

Article 18

Assessment of a substantial modification of an aspect covered by Part I of the assessment report

1 The reporting Member State shall assess the application with regard to an aspect covered by Part I of the assessment report, including whether the clinical trial will remain a low-intervention clinical trial after its substantial modification, and draw up an assessment report.

2 The assessment report shall contain one of the following conclusions concerning the aspects addressed in Part I of the assessment report:

a the substantial modification is acceptable in view of the requirements set out in this Regulation;

b the substantial modification is acceptable in view of the requirements set out in this Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion; or

c the substantial modification is not acceptable in view of the requirements set out in this Regulation.

3 The reporting Member State shall submit, through the EU portal, the final assessment report including its conclusion, to the sponsor and to the other Member States concerned within 38 days from the validation date.

For the purposes of this Article and Articles 19 and 23, the reporting date shall be the date on which the final assessment report is submitted to the sponsor and to the other Member States concerned.

4 For clinical trials involving more than one Member State the assessment process of substantial modification shall include three phases:

a an initial assessment phase performed by the reporting Member State within 19 days from the validation date;

b a coordinated review phase performed within 12 days from the end of the initial assessment phase involving all Member States concerned; and

c a consolidation phase performed by the reporting Member State within seven days from the end of coordinated review phase.

During the initial assessment phase, the reporting Member State shall develop a draft assessment report and circulate it to all Member States concerned.

During the coordinated review phase, all Member States concerned shall jointly review the application based on the draft assessment report and shall share any considerations relevant to the application.

During the consolidation phase, the reporting Member State shall take due account of the considerations of the other Member States concerned when finalising the assessment report and shall record how all such considerations have been dealt with. The reporting Member State shall submit the final assessment report to the sponsor and all other Member States concerned by the reporting date.

5 The reporting Member State may extend the period referred to in paragraph 3 by a further 50 days for clinical trials involving an advanced therapy investigational medicinal product or a medicinal product as set out in point 1 of the Annex to Regulation (EC) No 726/2004, for the purpose of consulting with experts. In such case, the periods referred to in paragraphs 4 and 6 of this Article shall apply *mutatis mutandis*.

6 Between the validation date and the reporting date, only the reporting Member State may request additional information from the sponsor, taking into account the considerations referred to in paragraph 4.

For the purpose of obtaining and reviewing this additional information from the sponsor in accordance with the third and fourth subparagraph, the reporting Member State may extend the period referred to in the first subparagraph of paragraph 3 by a maximum of 31 days.

The sponsor shall submit the requested additional information within the period set by the reporting Member State which shall not exceed 12 days from receipt of the request.

Upon receipt of the additional information, the Member States concerned shall jointly review any additional information provided by the sponsor together with the original application and shall share any considerations relevant to the application. The coordinated review shall be performed within a maximum of 12 days from receipt of the additional information and the further consolidation shall be performed within a maximum of seven days from the end of the coordinated review. When finalising the assessment report, the reporting Member State shall take due account of the considerations of the other Member States concerned and shall record how all such considerations have been dealt with.

Where the sponsor does not provide additional information within the period determined by the reporting Member State in accordance with the third subparagraph, the application shall be deemed to have lapsed in all Member States concerned.

The request for additional information and the additional information shall be submitted through the EU portal.

Article 19

Decision on the substantial modification of an aspect covered by Part I of the assessment report

1 Each Member State concerned shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of a single decision within five days from the reporting date.

An authorisation of a substantial modification subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.

2 Where the conclusion of the reporting Member State is that the substantial modification is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the Member State concerned.

Notwithstanding the first subparagraph, a Member State concerned may disagree with that conclusion of the reporting Member State only on the following grounds:

a when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;

b infringement of its national law as referred to in Article 90;

c considerations as regards subject safety and data reliability and robustness submitted under paragraph 4 or 6 of Article 18.

Where the Member State concerned disagrees with the conclusion on the basis of the second subparagraph, it shall communicate its disagreement, together with a detailed justification, through the EU portal, to the Commission, to all Member States and to the sponsor.

A Member State concerned shall refuse to authorise a substantial modification if it disagrees with the conclusion of the reporting Member State as regards Part I of the assessment report on any of the grounds referred to in the second subparagraph, or where an ethics committee has issued a negative opinion which, in accordance with the law of that Member State concerned, is valid for that entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.

3 Where the conclusion of the reporting Member State, as regards the substantial modification of aspects covered by Part I of the assessment report, is that the substantial modification is not acceptable, that conclusion shall be deemed to be the conclusion of all Member States concerned.

4 Where the Member State concerned has not notified the sponsor of its decision within the period referred to in paragraph 1, the conclusion of the assessment report shall be deemed to be the decision of the Member State concerned on the application for authorisation of the substantial modification.

Article 20

Validation, assessment and decision regarding a substantial modification of an aspect covered by Part II of the assessment report

1 Within six days from the submission of the application dossier, the Member State concerned shall notify the sponsor through the EU portal of the following:

a whether the substantial modification concerns an aspect covered by Part II of the assessment report; and

b whether the application dossier is complete in accordance with Annex II.

2 Where the Member State concerned has not notified the sponsor within the period referred to in paragraph 1, the substantial modification applied for shall be deemed to concern an aspect covered by Part II of the assessment report and the application dossier shall be deemed to be complete.

3 Where the Member State concerned finds that the substantial modification does not concern an aspect covered by Part II of the assessment report or that the application dossier is not complete, it shall inform the sponsor thereof through the EU portal and shall set a maximum of 10 days for the sponsor to comment on the application or to complete the application dossier through the EU portal.

Within five days from receipt of the comments or the completed application dossier, the reporting Member State shall notify the sponsor as to whether or not the application complies with the requirements set out in points (a) and (b) of paragraph 1.

Where the Member State concerned has not notified the sponsor within the period referred to in the second subparagraph, the substantial modification shall be deemed to concern an aspect covered by Part II of the assessment report and the application dossier shall be deemed to be complete.

Where the sponsor has not provided comments nor completed the application dossier within the period referred to in the first subparagraph, the application shall be deemed to have lapsed in the Member State concerned.

4 For the purpose of this Article, the date on which the sponsor is notified in accordance with paragraph 1 or 3 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the respective periods referred to in paragraphs 1 and 3.

5 The Member State concerned shall assess the application and shall submit to the sponsor, through the EU portal, Part II of the assessment report, including its conclusion, and the decision as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of a single decision within 38 days from the validation date.

An authorisation of a substantial modification subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.

6 During the period referred to in the second subparagraph of paragraph 5, the Member State concerned may request, with justified reasons, additional information from the sponsor regarding the substantial modification as far as its territory is concerned.

For the purpose of obtaining and reviewing this additional information from the sponsor, the Member State concerned may extend the period referred to in the second subparagraph of paragraph 5 by a maximum of 31 days.

The sponsor shall submit the requested additional information within the period set by the Member State concerned which shall not exceed 12 days from receipt of the request.

Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of 19 days.

Where the sponsor does not provide additional information within the period set by the Member State concerned in accordance with the third subparagraph, the application shall be deemed to have lapsed in that Member State.

The request for additional information and the additional information shall be submitted through the EU portal.

7 A Member State concerned shall refuse to authorise a substantial modification if it finds, on duly justified grounds, that the aspects covered by Part II of the assessment report are not complied with or where an ethics committee has issued a negative opinion which, in accordance with the law of that Member State concerned, is valid for that entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.

8 Where the Member State concerned has not notified the sponsor of its decision within the periods set out in paragraphs 5 and 6, the substantial modification shall be deemed to be authorised in that Member State.

Article 21

Substantial modification of aspects covered by Parts I and II of the assessment report

1 Where a substantial modification relates to aspects covered by Parts I and II of the assessment report, the application for authorisation of that substantial modification shall be validated in accordance with Article 17.

2 The aspects covered by Part I of the assessment report shall be assessed in accordance with Article 18 and the aspects covered by Part II of the assessment report shall be assessed in accordance with Article 22.

Article 22

Assessment of a substantial modification of aspects covered by Parts I and II of the assessment report — Assessment of the aspects covered by Part II of the assessment report

1 Each Member State concerned shall assess, for its own territory, the aspects of the substantial modification which are covered by Part II of the assessment report and submit, through the EU portal, that report, including its conclusion, to the sponsor within 38 days from the validation date.

2 During the period referred to in paragraph 1, the Member State concerned may request, with justified reasons, additional information from the sponsor regarding this substantial modification as far as its territory is concerned.

3 For the purpose of obtaining and reviewing the additional information referred to in paragraph 2 from the sponsor in accordance with the third and fourth subparagraph, the Member State concerned may extend the period referred to paragraph 1 by a maximum of 31 days.

The sponsor shall submit the requested additional information within the period set by the Member State concerned which shall not exceed 12 days from the receipt of the request.

Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of 19 days.

Where the sponsor does not provide the requested additional information within the period set by the Member State concerned in accordance with the second subparagraph, the application shall be deemed to have lapsed in that Member State.

The request for additional information and the additional information shall be submitted through the EU portal.

Article 23

Decision on the substantial modification of aspects covered by Parts I and II of the assessment report

1 Each Member State concerned shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of a single decision within five days from the reporting date or from the last day of the assessment period referred to in Article 22, whichever is later.

An authorisation of a substantial modification subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.

2 Where the conclusion of the reporting Member State is that the substantial modification of aspects covered by Part I of the assessment report is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the Member State concerned.

Notwithstanding the first subparagraph, a Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds:

a when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;

b infringement of its national law as referred to in Article 90;

c considerations as regards suject safety and data reliability and robustness submitted under paragraph 4 or 6 of Article 18.

Where the Member State concerned disagrees with the conclusion regarding the substantial modification of aspects covered by Part I of the assessment report on the basis of the second subparagraph, it shall communicate its disagreement, together with a detailed justification through the EU portal to the Commission, to all Member States, and to the sponsor.

3 Where, regarding the substantial modification of aspects covered by Part I of the assessment report, the substantial modification is acceptable or acceptable subject to compliance

with specific conditions, the Member State concerned shall include in its decision its conclusion on the substantial modification of aspects covered by Part II of the assessment report.

4 A Member State concerned shall refuse to authorise a substantial modification if it disagrees with the conclusion of the reporting Member State as regards the substantial modification of aspects covered by Part I of the assessment report on any of the grounds referred to in second subparagraph of paragraph 2, or if it finds, on duly justified grounds, that the aspects covered by Part II of the assessment report are not complied with, or where an ethics committee has issued a negative opinion which in accordance with the law of the Member State concerned, is valid for that entire Member State. That Member State concerned shall provide for an appeal procedure in respect of such refusal.

5 **[**[X1]Where the conclusion of the reporting Member State as regards the substantial modification of aspects covered by Part I of the assessment report is that the substantial modification is not acceptable, that conclusion shall be deemed to be the conclusion of all Member States concerned.**]**

6 Where the Member State concerned has not notified the sponsor of its decision within the periods referred to in paragraph 1, the conclusion on the substantial modification of aspects covered by Part I of the assessment report shall be deemed to be the decision of the Member State concerned on the application for authorisation of the substantial modification.

Editorial Information

X1 Substituted by Corrigendum to Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Official Journal of the European Union L 158 of 27 May 2014).

Article 24

Persons assessing the application for a substantial modification

Article 9 applies to assessments made under this Chapter.

Changes to legislation:
There are currently no known outstanding effects for the Regulation (EU) No 536/2014 of the European Parliament and of the Council, CHAPTER III.