Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (Text with EEA relevance)

CHAPTER VI

CLINICAL EVIDENCE, PERFORMANCE EVALUATION AND PERFORMANCE STUDIES

Article 56

Performance evaluation and clinical evidence

1 Confirmation of conformity with relevant general safety and performance requirements set out in Annex I, in particular those concerning the performance characteristics referred to in Chapter I and Section 9 of Annex I, under the normal conditions of the intended use of the device, and the evaluation of the interference(s) and cross-reaction(s) and of the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 of Annex I, shall be based on scientific validity, analytical and clinical performance data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III.

The manufacturer shall specify and justify the level of the clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose.

To that end, manufacturers shall plan, conduct and document a performance evaluation in accordance with this Article and with Part A of Annex XIII.

2 The clinical evidence shall support the intended purpose of the device as stated by the manufacturer and be based on a continuous process of performance evaluation, following a performance evaluation plan.

3 A performance evaluation shall follow a defined and methodologically sound procedure for the demonstration of the following, in accordance with this Article and with Part A of Annex XIII:

a scientific validity;

b analytical performance;

c clinical performance.

The data and conclusions drawn from the assessment of those elements shall constitute the clinical evidence for the device. The clinical evidence shall be such as to scientifically demonstrate, by reference to the state of the art in medicine, that the intended clinical benefit(s) will be achieved and that the device is safe. The clinical evidence derived from the performance evaluation shall provide scientifically valid assurance, that the relevant general safety and performance requirements set out in Annex I, are fulfilled, under normal conditions of use.

4 Clinical performance studies in accordance with Section 2 of Part A of Annex XIII shall be carried out unless it is duly justified to rely on other sources of clinical performance data.

5 The scientific validity data, the analytical performance data and the clinical performance data, their assessment and the clinical evidence derived therefrom, shall be documented in the performance evaluation report referred to in Section 1.3.2 of Part A of Annex XIII. The performance evaluation report shall be part of the technical documentation, referred to in Annex II, relating to the device concerned.

6 The performance evaluation and its documentation shall be updated throughout the life cycle of the device concerned with data obtained from implementation of the manufacturer's PMPF plan in accordance with Part B of Annex XIII and the post-market surveillance plan referred to in Article 79.

The performance evaluation report for class C and D devices shall be updated when necessary, but at least annually, with the data referred to in the first subparagraph. The summary of safety and performance referred to in Article 29(1) shall be updated as soon as possible, where necessary.

7 Where necessary to ensure the uniform application of Annex XIII, the Commission may, having due regard to technical and scientific progress, adopt implementing acts to the extent necessary to resolve issues of divergent interpretation and of practical application. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 107(3).

Article 57

General requirements regarding performance studies

1 The manufacturer shall ensure that a device for performance study complies with the general safety and performance requirements set out in Annex I apart from the aspects covered by the performance study and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the patient, user and other persons.

2 Where appropriate, performance studies shall be performed in circumstances similar to the normal conditions of use of the device.

3 Performance studies shall be designed and conducted in such a way that the rights, safety, dignity and well-being of the subjects participating in such performance studies are protected and prevail over all other interests and the data generated are scientifically valid, reliable and robust.

Performance studies, including performance studies that use left-over samples, shall be conducted in accordance with applicable law on data protection.

Article 58

Additional requirements for certain performance studies

1 Any performance study:

a in which surgically invasive sample-taking is done only for the purpose of the performance study;

b that is an interventional clinical performance study as defined in point (46) of Article 2; or

c where the conduct of the study involves additional invasive procedures or other risks for the subjects of the studies,

shall, in addition to meeting the requirements set out in Article 57 and Annex XIII, be designed, authorised, conducted, recorded and reported in accordance with this Article and Articles 59 to 77 and Annex XIV.

2 Performance studies involving companion diagnostics shall be subject to the same requirements as the performance studies listed in paragraph 1. This does not apply to performance studies involving companion diagnostics using only left-over samples. Such studies shall however be notified to the competent authority.

3 Performance studies shall be subject to scientific and ethical review. The ethical review shall be performed by an ethics committee in accordance with national law. Member States shall ensure that the procedures for review by ethics committees are compatible with the procedures set out in this Regulation for the assessment of the application for authorisation of a performance study. At least one lay person shall participate in the ethical review.

4 Where the sponsor of a performance study is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative. Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to this Regulation, and shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication with that legal representative shall be deemed to be a communication with the sponsor.

Member States may choose not to apply the first subparagraph to performance studies to be conducted solely on their territory, or on their territory and the territory of a third country, provided that they ensure that the sponsor establishes at least a contact person on their territory in respect of that performance study who shall be the addressee for all communications with the sponsor provided for in this Regulation.

5 A performance study as referred to in paragraph 1 may be conducted only where all of the following conditions are met:

a the performance study is the subject of an authorisation by the Member State(s) in which the performance study is to be conducted, in accordance with this Regulation, unless otherwise stated;

b an ethics committee, set up in accordance with national law, has not issued a negative opinion in relation to the performance study, which is valid for that entire Member State under its national law;

c the sponsor or its legal representative or a contact person pursuant to paragraph 4 is established in the Union;

d vulnerable populations and subjects are appropriately protected in accordance with Articles 59 to 64;

e the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored;

f the subject or, where the subject is not able to give informed consent, his or her legally designated representative has given informed consent, in accordance with Article 59;

g the subject or, where the subject is not able to give informed consent, his or her legally designated representative, has been provided with the contact details of an entity where further information can be received in case of need;

h the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him or her in accordance with Directive 95/46/EC are safeguarded;

i the performance study has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects, and both the risk threshold and the

degree of distress are specifically defined in the performance study plan and constantly monitored;

j the medical care provided to the subjects is the responsibility of an appropriately qualified medical doctor or, where appropriate, any other person entitled by national law to provide the relevant patient care under performance study conditions;

k no undue influence, including that of a financial nature, is exerted on the subject, or, where applicable, on his or her legally designated representatives, to participate in the performance study;

l where appropriate, biological safety testing reflecting the latest scientific knowledge or any other test deemed necessary in the light of the device's intended purpose has been conducted;

m in the case of clinical performance studies, the analytical performance has been demonstrated, taking into consideration the state of the art;

n in the case of interventional clinical performance studies, the analytical performance and scientific validity has been demonstrated, taking into consideration the state of the art. Where, for companion diagnostics, the scientific validity is not established, the scientific rationale for the use of the biomarker shall be provided;

o the technical safety of the device with regard to its use has been proven, taking into consideration the state of the art as well as provisions in the field of occupational safety and accident prevention;

p the requirements of Annex XIV are fulfilled.

6 Any subject, or, where the subject is not able to give informed consent, his or her legally designated representative, may, without any resulting detriment and without having to provide any justification, withdraw from the performance study at any time by revoking his or her informed consent. Without prejudice to Directive 95/46/EC, the withdrawal of the informed consent shall not affect the activities already carried out and the use of data obtained based on informed consent before its withdrawal.

7 The investigator shall be a person exercising a profession which is recognised in the Member State concerned, as qualifying for the role of investigator on account of having the necessary scientific knowledge and experience in patient care or laboratory medicine. Other personnel involved in conducting a performance study shall be suitably qualified, by education, training or experience in the relevant medical field and in clinical research methodology, to perform their tasks.

8 Where appropriate, the facilities where the performance study involving subjects is to be conducted shall be suitable for the performance study and shall be similar to the facilities where the device is intended to be used.

Article 59

Informed consent

1 Informed consent shall be written, dated and signed by the person performing the interview referred to in point (c) of paragraph 2, and by the subject or, where the subject is not able to give informed consent, his or her legally designated representative after having been duly informed in accordance with paragraph 2. Where the subject is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness. In that case, the witness shall sign and date the informed consent document. The subject or, where the subject is not able to give informed consent, his or her legally designated representative shall be provided with a copy of the document or the

record, as appropriate, by which informed consent has been given. The informed consent shall be documented. Adequate time shall be given for the subject or his or her legally designated representative to consider his or her decision to participate in the performance study.

2 Information given to the subject or, where the subject is not able to give informed consent, his or her legally designated representative for the purposes of obtaining his or her informed consent shall:

a enable the subject or his or her legally designated representative to understand:

(i) the nature, objectives, benefits, implications, risks and inconveniences of the performance study;

(ii) the subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate in and the right to withdraw from the performance study at any time without any resulting detriment and without having to provide any justification;

(iii) the conditions under which the performance study is to be conducted, including the expected duration of the subject's participation in the performance study; and

(iv) the possible treatment alternatives, including the follow-up measures if the participation of the subject in the performance study is discontinued;

b be kept comprehensive, concise, clear, relevant, and understandable to the subject or his or her legally designated representative;

c be provided in a prior interview with a member of the investigating team who is appropriately qualified under national law; and

d include information about the applicable damage compensation system referred to in Article 65;

e include the Union-wide unique single identification number for the performance study referred to in Article 66(1) and information about the availability of the performance study results in accordance with paragraph 6 of this Article.

3 The information referred to in paragraph 2 shall be prepared in writing and be available to the subject or, where the subject is not able to give informed consent, his or her legally designated representative.

4 In the interview referred to in point (c) of paragraph 2, special attention shall be paid to the information needs of specific patient populations and of individual subjects, as well as to the methods used to give the information.

5 In the interview referred to in point (c) of paragraph 2, it shall be verified that the subject has understood the information.

6 The subject shall be informed that a report of the performance study and a summary presented in terms understandable to the intended user will be made available pursuant to Article 73(5) in the electronic system on performance studies referred to in Article 69, irrespective of the outcome of the performance study, and shall be informed, to the extent possible, when they have become available.

7 This Regulation is without prejudice to national law requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, shall also assent in order to participate in a performance study.

Article 60

Performance studies on incapacitated subjects

1 In the case of incapacitated subjects who have not given, or have not refused to give, informed consent before the onset of their incapacity, a performance study may be conducted only where, in addition to the conditions set out in Article 58(5), all of the following conditions are met:

a the informed consent of their legally designated representative has been obtained;

b the incapacitated subjects have received the information referred to in Article 59(2) in a way that is adequate in view of their capacity to understand it;

c the explicit wish of an incapacitated subject who is capable of forming an opinion and assessing the information referred to in Article 59(2) to refuse participation in, or to withdraw from, the performance study at any time, is respected by the investigator;

d no incentives or financial inducements are given to subjects or their legally designated representatives, except for compensation for expenses and loss of earnings directly related to the participation in the performance study;

e the performance study is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in performance studies on persons able to give informed consent, or by other research methods;

f the performance study relates directly to a medical condition from which the subject suffers;

g there are scientific grounds for expecting that participation in the performance study will produce:

(i) a direct benefit to the incapacitated subject outweighing the risks and burdens involved; or

(ii) some benefit for the population represented by the incapacitated subject concerned when the performance study will pose only minimal risk to, and will impose minimal burden on, the incapacitated subject concerned in comparison with the standard treatment of the incapacitated subject's condition.

2 The subject shall as far as possible take part in the informed consent procedure.

3 Point (g)(ii) of paragraph 1 shall be without prejudice to more stringent national rules prohibiting the conduct of those performance studies on incapacitated subjects, where there are no scientific grounds to expect that participation in the performance study will produce a direct benefit to the subject outweighing the risks and burdens involved.

Article 61

Performance studies on minors

1 A performance study on minors may be conducted only where, in addition to the conditions set out in Article 58(5), all of the following conditions are met:

a the informed consent of their legally designated representative has been obtained;

b the minors have received the information referred to in Article 59(2) in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;

c the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 59(2) to refuse participation in, or to withdraw from, the performance study at any time, is respected by the investigator;

d no incentives or financial inducements are given to subjects or their legally designated representatives, except for compensation for expenses and loss of earnings directly related to the participation in the performance study;

e the performance study is intended to investigate treatments for a medical condition that only occurs in minors or the performance study is essential with respect to minors to validate data obtained in performance studies on persons able to give informed consent or by other research methods;

f the performance study either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;

g there are scientific grounds for expecting that participation in the performance study will produce:

(i) a direct benefit to the minor subject outweighing the risks and burdens involved; or

(ii) some benefit for the population represented by the minor concerned when the performance study will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition;

h the minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity;

i if during a performance study the minor reaches the age of legal competence to give informed consent as defined in the national law, his or her express informed consent shall be obtained before that subject can continue to participate in the performance study.

2 Point (g)(ii) of paragraph 1 shall be without prejudice to more stringent national rules prohibiting the conduct of those performance studies on minors, where there are no scientific grounds to expect that participation in the performance study will produce a direct benefit to the subject outweighing the risks and burdens involved.

Article 62

Performance studies on pregnant or breastfeeding women

A performance study on pregnant or breastfeeding women may be conducted only where, in addition to the conditions set out in Article 58(5), all of the following conditions are met:

(a) the performance study has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, outweighing the risks and burdens involved;

(b) if such a performance study has no direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, it can be conducted only if:

(i) a performance study of comparable effectiveness cannot be carried out on women who are not pregnant or breastfeeding;

(ii) the performance study contributes to the attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, foetuses or children; and

(iii) the performance study poses a minimal risk to, and imposes a minimal burden on, the pregnant or breastfeeding woman concerned, her embryo, foetus or child after birth;

(c) where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child;

(d) no incentives or financial inducements are given to subjects, except for compensation for expenses and loss of earnings directly related to the participation in the performance study.

Article 63

Additional national measures

Member States may maintain additional measures regarding persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in performance studies, or persons in residential care institutions.

Article 64

Performance studies in emergency situations

1 By way of derogation from point (f) of Article 58(5), from points (a) and (b) of Article 60(1) and from points (a) and (b) of Article 61(1), informed consent to participate in a performance study may be obtained, and information on the performance studies may be given, after the decision to include the subject in the performance study, provided that that decision is taken at the time of the first intervention on the subject, in accordance with the clinical performance study plan for that performance study and that all of the following conditions are fulfilled:

a due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the performance study;

b there are scientific grounds to expect that participation of the subject in the performance study will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition;

c it is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative;

d the investigator certifies that he or she is not aware of any objections to participate in the performance study previously expressed by the subject;

e the performance study relates directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the performance study is of such a nature that it may be conducted exclusively in emergency situations;

f the performance study poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition.

2 Following an intervention pursuant to paragraph 1 of this Article, informed consent in accordance with Article 59 shall be sought to continue the participation of the subject in the performance study, and information on the performance study shall be given, in accordance with the following requirements:

a regarding incapacitated subjects and minors, the informed consent shall be sought by the investigator from his or her legally designated representative without undue delay and the information referred to in Article 59(2) shall be given as soon as possible to the subject and to his or her legally designated representative;

b regarding other subjects, the informed consent shall be sought by the investigator without undue delay from the subject or his or her legally designated representative, whichever can be done sooner, and the information referred to in Article 59(2) shall be given as soon as possible to the subject or his or her legally designated representative, as applicable.

For the purposes of point (b) where informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the performance study shall be obtained from the subject as soon as he or she is capable of giving informed consent.

3 If the subject or, where applicable, his or her legally designated representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the performance study.

Article 65

Damage compensation

1 Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in a performance study conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk.

2 The sponsor and the investigator shall make use of the system referred to in paragraph 1 in the form appropriate for the Member State in which the performance study is conducted.

Article 66

Application for performance studies

1 The sponsor of a performance study referred to in Article 58(1) and (2) shall enter and submit an application to the Member State(s) in which the performance study is to be conducted (referred to for the purposes of this Article as ‘Member State concerned’) accompanied by the documentation referred to in Sections 2 and 3 of Annex XIII and in Annex XIV.

The application shall be submitted by means of the electronic system referred to in Article 69, which shall generate a Union-wide unique single identification number for the performance study which shall be used for all relevant communication in relation to that performance study. Within 10 days of receiving the application, the Member State concerned shall notify the sponsor as to whether the performance study falls within

the scope of this Regulation and as to whether the application dossier is complete in accordance with Chapter I of Annex XIV.

2 Within one week of any change occurring in relation to the documentation referred to in Chapter I of Annex XIV, the sponsor shall update the relevant data in the electronic system referred to in Article 69 and make that change to the documentation clearly identifiable. The Member State concerned shall be notified of the update by means of that electronic system.

3 Where the Member State concerned finds that the performance study applied for does not fall within the scope of this Regulation or that the application is not complete, it shall inform the sponsor thereof and shall set a time limit of maximum 10 days for the sponsor to comment or to complete the application by means of the electronic system referred to in Article 69. The Member State concerned may extend this period by a maximum of 20 days where appropriate.

Where the sponsor has not provided comments nor completed the application within the time limit referred to in the first subparagraph, the application shall be deemed to have lapsed. Where the sponsor considers that the application falls under the scope of this Regulation and/or is complete but the Member State concerned does not agree, the application shall be considered to have been rejected. The Member State concerned shall provide for an appeal procedure in respect of such refusal.

The Member State concerned shall notify the sponsor within five days of receipt of the comments or of the requested additional information, whether the performance study is considered as falling within the scope of this Regulation and the application is complete.

4 The Member State concerned may also extend the period referred to in paragraphs 1 and 3 each by a further five days.

5 For the purposes of this Chapter, 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 periods referred to in paragraphs 1, 3 and 4 respectively.

6 During the period when the application is being assessed the Member State may request additional information from the sponsor. The expiry of the deadline pursuant to the point (b) of paragraph 7 shall be suspended from the date of the first request until such time as the additional information has been received.

7 The sponsor may start the performance study in the following circumstances:

a in the case of performance studies carried out pursuant to point (a) of Article 58(1) and where the specimen collection does not represent a major clinical risk to the subject of the study, unless otherwise stated by national law, immediately after the validation date of application described in paragraph 5 of this Article, provided that a negative opinion which is valid for the entire Member State, under national law, has not been issued by an ethics committee in the Member State concerned in respect of the performance study;

b in the case of performance studies carried out pursuant to points (b) and (c) of Article 58(1) and Article 58(2) or performance studies other than those referred to in point (a) of this paragraph, as soon as the Member State concerned has notified the sponsor of its authorisation and provided that a negative opinion which is valid for the entire Member State, under national law, has not been issued by an ethics committee in the Member State concerned in respect of the performance study. The Member State shall notify the sponsor of the authorisation within 45 days of the validation date of the application referred to in paragraph 5. The Member State may extend this period by a further 20 days for the purpose of consulting with experts.

8 The Commission is empowered to adopt delegated acts in accordance with Article 108 amending, in the light of technical progress and global regulatory developments, the requirements laid down in Chapter I of Annex XIV.

9 In order to assure the uniform application of the requirements laid down in Chapter I of Annex XIV, the Commission may adopt implementing acts to the extent necessary to resolve issues of divergent interpretation and practical application. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 107(3).

Article 67

Assessment by Member States

1 Member States shall ensure that the persons validating and assessing the application, or deciding on it, do not have conflicts of interest, are independent of the sponsor, the investigators involved and of natural or legal persons financing the performance study, as well as free of any other undue influence.

2 Member States shall ensure that the assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience.

3 Member States shall assess whether the performance study is designed in such a way that potential remaining risks to subjects or third persons, after risk minimization, are justified, when weighed against the clinical benefits to be expected. They shall, while taking into account applicable CS or harmonised standards, examine in particular:

a the demonstration of compliance of the device(s) for performance study with the applicable general safety and performance requirements, apart from the aspects covered by the performance study, and whether, with regard to those aspects, every precaution has been taken to protect the health and safety of the subjects. This includes, in case of performance studies, the evaluation of the analytical performance, and in case of interventional clinical performance studies, the evaluation of the analytical performance, clinical performance and scientific validity, taking into consideration the state of the art;

b whether the risk-minimisation solutions employed by the sponsor are described in harmonised standards and, in those cases where the sponsor does not use harmonised standards, whether the risk-minimisation solutions provide a level of protection that is equivalent to that provided by harmonised standards;

c whether the measures planned for the safe installation, putting into service and maintenance of the device for performance study are adequate;

d the reliability and robustness of the data generated in the performance study, taking account of statistical approaches, design of the performance study and methodological aspects, including sample size, comparator and endpoints;

e whether the requirements of Annex XIV are met.

4 Member States shall refuse the authorisation of the performance study if:

a the application dossier submitted pursuant to Article 66(3) remains incomplete;

b the device or the submitted documents, especially the performance study plan and the investigator's brochure, do not correspond to the state of scientific knowledge, and the performance study, in particular, is not suitable for providing evidence for the safety, performance characteristics or benefit of the device on subjects or patients;

c the requirements of Article 58 are not met; or

d any assessment under paragraph 3 is negative.

Member States shall provide for an appeal procedure in respect of a refusal pursuant to the first subparagraph.

Article 68

Conduct of a performance study

1 The sponsor and the investigator shall ensure that the performance study is conducted in accordance with the approved performance study plan.

2 In order to verify that the rights, safety and well-being of subjects are protected, that the reported data are reliable and robust, and that the conduct of the performance study is in compliance with the requirements of this Regulation, the sponsor shall ensure adequate monitoring of the conduct of a performance study. The extent and nature of the monitoring shall be determined by the sponsor on the basis of an assessment that takes into consideration all characteristics of the performance study including the following:

a the objective and methodology of the performance study; and

b the degree of deviation of the intervention from normal clinical practice.

3 All performance study information shall be recorded, processed, handled, and stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection.

4 Appropriate technical and organisational measures shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves transmission over a network.

5 Member States shall inspect, at an appropriate level, performance study site(s) to check that performance studies are conducted in accordance with the requirements of this Regulation and with the approved investigation plan.

6 The sponsor shall establish a procedure for emergency situations which enables the immediate identification and, where necessary, an immediate recall of the devices used in the study.

Article 69

Electronic system on performance studies

1 The Commission shall, in collaboration with the Member States, set up, manage and maintain an electronic system:

a to create the single identification numbers for performance studies referred to in Article 66(1);

b to be used as an entry point for the submission of all applications or notifications for performance studies referred to in Articles 66, 70, 71 and 74 and for all other submission of data, or processing of data in this context;

c for the exchange of information relating to performance studies in accordance with this Regulation between the Member States and between them and the Commission including the exchange of information referred to in to Articles 72 and 74;

d for information to be provided by the sponsor in accordance with Article 73, including the performance study report and its summary as required in paragraph 5 of that Article;

e for reporting on serious adverse events and device deficiencies, and related updates referred to in Article 76.

2 When setting up the electronic system referred to in paragraph 1 of this Article, the Commission shall ensure that it is interoperable with the EU database for clinical trials on medicinal products for human use set up in accordance with Article 81 of Regulation (EU) No 536/2014 of the European Parliament and of the Council[(1)] as concerns performance studies of companion diagnostics.

3 The information referred to in point (c) of paragraph 1 shall only be accessible to the Member States and the Commission. The information referred to in the other points of that paragraph shall be accessible to the public, unless, for all or parts of that information, confidentiality of the information is justified on any of the following grounds:

a protection of personal data in accordance with Regulation (EC) No 45/2001;

b protection of commercially confidential information, especially in the investigators brochure, in particular through taking into account the status of the conformity assessment for the device, unless there is an overriding public interest in disclosure;

c effective supervision of the conduct of the performance study by the Member State(s) concerned.

4 No personal data of subjects shall be publicly available.

5 The user interface of the electronic system referred to in paragraph 1 shall be available in all official languages of the Union.

Article 70

Performance studies regarding devices bearing the CE marking

1 Where a performance study is to be conducted to further assess, within the scope of its intended purpose, a device which already bears the CE marking in accordance with Article 18(1) (‘PMPF study’), and where the performance study would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome, the sponsor shall notify the Member States concerned at least 30 days prior to its commencement by means of the electronic system referred to in Article 69. The sponsor shall include the documentation referred to in Section 2 of Part A of Annex XIII and in Annex XIV. Points (b) to (l) and (p) **[**[X1]of Article 58(5), Articles 71, 72 and 73, and Article 76(5) and (6), and the relevant provisions**]** of Annexes XIII and XIV shall apply to PMPF studies.

2 Where a performance study is to be conducted to assess, outside the scope of its intended purpose, a device which already bears the CE marking in accordance with Article 18(1), Articles 58 to 77 shall apply.

Editorial Information

X1 Substituted by Corrigendum to Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (Official Journal of the European Union L 117 of 5 May 2017).

Article 71

Substantial modifications to performance studies

1 If a sponsor intends to introduce modifications to a performance study that are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the data generated by the study, it shall notify, within one week, by means of the electronic system referred to in Article 69, the Member State(s) in which the performance study is being or is to be conducted of the reasons for and the nature of those modifications. The sponsor shall include an updated version of the relevant documentation referred to in Annex XIV as part of the notification. Changes to the relevant documentation shall be clearly identifiable.

2 The Member State shall assess any substantial modification to the performance study in accordance with the procedure laid down in Article 67.

3 The sponsor may implement the modifications referred to in paragraph 1 at the earliest 38 days after the notification referred to in paragraph 1, unless:

a the Member State in which the performance study is being or is to be conducted has notified the sponsor of its refusal based on the grounds referred to in Article 67(4) or on considerations of public health, of subject and user safety or health, or of public policy; or

b an ethics committee in that Member State has issued a negative opinion in relation to the substantial modification to the performance study, which, in accordance with national law, is valid for that entire Member State.

4 The Member State(s) concerned may extend the period referred to in paragraph 3 by a further seven days, for the purpose of consulting with experts.

Article 72

Corrective measures to be taken by Member States and information exchange between Member States on performance studies

1 Where a Member State in which a performance study is being or is to be conducted has grounds for considering that the requirements set out in this Regulation are not met, it may take at least any of the following measures on its territory:

a revoke the authorisation for the performance study;

b suspend or terminate the performance study;

c require the sponsor to modify any aspect of the performance study.

2 Before the Member State concerned takes any of the measures referred to in paragraph 1 it shall, except where immediate action is required, ask the sponsor or the investigator or both for their opinion. That opinion shall be delivered within seven days.

3 Where a Member State has taken a measure referred to in paragraph 1 of this Article, or has refused a performance study, or has been notified by the sponsor of the early termination of a performance study on safety grounds, that Member State shall communicate the corresponding decision and the grounds therefor to all Member States and the Commission by means of the electronic system referred to in Article 69.

4 Where an application is withdrawn by the sponsor prior to a decision by a Member State, that information shall be made available through the electronic system referred to in Article 69 to all Member States and the Commission.

Article 73

Information from the sponsor at the end of a performance study or in the event of a temporary halt or early termination

1 If the sponsor has temporarily halted a performance study or has terminated a performance study early, it shall inform within 15 days the Member States in which that performance study has been temporarily halted or terminated early, through the electronic system referred to in Article 69, of the temporary halt or early termination. In the event that the sponsor has temporarily halted or terminated early the performance study on safety grounds, it shall inform all Member States in which that performance study is being conducted thereof within 24 hours.

2 The end of a performance study shall be deemed to coincide with the last visit of the last subject unless another point in time for such end is set out in the performance study plan.

3 The sponsor shall notify each Member State in which that performance study was being conducted of the end of that performance study in that Member State. That notification shall be made within 15 days of the end of the performance study in relation to that Member State.

4 If a study is conducted in more than one Member State, the sponsor shall notify all Member States in which that performance study was conducted of the end of the performance study in all Member States. That notification shall be made within 15 days of that end of the performance study.

5 Irrespective of the outcome of the performance study, within one year of the end of the performance study or within three months of the early termination or temporary halt, the sponsor shall submit to the Member States in which a performance study was conducted a performance study report as referred to in Section 2.3.3. of Part A of Annex XIII.

The performance study report shall be accompanied by a summary presented in terms that are easily understandable to the intended user. Both the report and summary shall be submitted by the sponsor by means of the electronic system referred to in Article 69.

Where, for scientific reasons, it is not possible to submit the performance study report within one year of the end of the study, it shall be submitted as soon as it is available. In such case, the clinical performance study plan referred to in Section 2.3.2. of Part A of Annex XIII shall specify when the results of the performance study are going to be available, together with a justification.

6 The Commission shall issue guidelines regarding the content and structure of the summary of the performance study report.

In addition, the Commission may issue guidelines for the formatting and sharing of raw data, for cases where the sponsor decides to share raw data on a voluntary basis. Those guidelines may take as a basis and adapt, where possible, existing guidelines for sharing of raw data in the field of performance studies.

7 The summary and the performance study report referred to in paragraph 5 of this Article shall become publicly accessible through the electronic system referred to in Article 69,

at the latest when the device is registered in accordance with Article 26 and before it is placed on the market. In cases of early termination or temporary halt, the summary and the report shall become publicly accessible immediately after submission.

If the device is not registered in accordance with Article 26 within one year of the summary and the performance study report having been entered into the electronic system pursuant to paragraph 5 of this Article, they shall become publicly accessible at that point in time.

Article 74

Coordinated assessment procedure for performance studies

1 By means of the electronic system referred to in Article 69, the sponsor of a performance study to be conducted in more than one Member State may submit, for the purpose of Article 66, a single application that, upon receipt, is transmitted electronically to all Member States in which the performance study is to be conducted.

2 The sponsor shall propose in the single application referred to in paragraph 1 that one of the Member States in which the performance study is to be conducted acts as coordinating Member State. The Member States in which the performance study is to be conducted shall, within six days of submission of the application, agree on one of them taking the role of the coordinating Member State. If they do not agree on a coordinating Member State, the coordinating Member State proposed by the sponsor shall assume that role.

3 Under the direction of the coordinating Member State referred to in paragraph 2, the Member States concerned shall coordinate their assessment of the application, in particular of the documentation referred to in Chapter I of Annex XIV.

However, the completeness of the documentation referred to in Sections 1.13, 4.2, 4.3 and 4.4 of Chapter I of Annex XIV and point (c) of Section 2.3.2. of Part A of Annex XIII shall be assessed separately by each Member State concerned in accordance with Article 66(1) to (5).

4 With regard to documentation other than that referred to in the second subparagraph of paragraph 3, the coordinating Member State shall:

a within six days of receipt of the single application, notify the sponsor that it is the coordinating Member State (‘notification date’);

b for the purpose of the validation of the application, take into account any considerations submitted within seven days of the notification date by any Member State concerned;

c within 10 days of the notification date, assess whether the performance study falls within the scope of this Regulation and whether the application is complete and shall notify the sponsor accordingly. Article 66(1) and (3) to (5) shall apply to the coordinating Member State in relation to that assessment;

d establish the results of its assessment in a draft assessment report to be transmitted within 26 days of the validation date to the Member States concerned. By day 38 after the validation date, the other Member States concerned shall transmit their comments and proposals on the draft assessment report and the underlying application to the coordinating Member State which shall take due account of those comments and proposals in its finalisation of the final assessment report, to be transmitted within 45 days of the validation date to the sponsor and the other Member States concerned.

The final assessment report shall be taken into account by all Member States concerned when deciding on the sponsor's application in accordance with Article 66(7).

5 As regards the assessment of the documentation referred to in the second subparagraph of paragraph 3, each Member State concerned may request, on a single occasion, additional information from the sponsor. 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. The expiry of the last deadline pursuant to point (d) of paragraph 4 shall be suspended from the date of the request until such time as the additional information has been received.

6 For class C and D devices, the coordinating Member State may also extend the periods referred to in paragraph 4 by a further 50 days, for the purpose of consulting with experts.

7 The Commission may, by means of implementing acts, further specify the procedures and timescales for coordinated assessments to be taken into account by Member States concerned when deciding on the sponsor's application. Such implementing acts may also set out the procedures and timescales for coordinated assessment in the case of substantial modifications pursuant to paragraph 12 of this Article and in the case of reporting of adverse events pursuant to Article 76(4) and in the case of performance studies involving companion diagnostics, where the medicinal products are under a concurrent coordinated assessment of a clinical trial under Regulation (EU) No 536/2014. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 107(3).

8 Where the conclusion of the coordinating Member State concerning the area of coordinated assessment is that the conduct of the performance study is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of all Member State(s) concerned.

Notwithstanding the first subparagraph, a Member State concerned may only disagree with the conclusion of the coordinating Member State concerning the area of coordinated assessment on the following grounds:

a when it considers that participation in the performance study would lead to a subject receiving treatment inferior to that received in normal clinical practice in that Member State concerned;

b infringement of national law; or

c considerations as regards subject safety and data reliability and robustness submitted under point (d) of paragraph 4.

Where one of the Member States concerned disagrees with the conclusion on the basis of the second subparagraph of this paragraph, it shall communicate its disagreement, together with a detailed justification, through the electronic system referred to in Article 69 to the Commission, to all other Member States concerned, and to the sponsor.

9 Where the conclusion of the coordinating Member State concerning the area of coordinated assessment is that the performance study is not acceptable, that conclusion shall be deemed to be the conclusion of all Member States concerned.

10 A Member State concerned shall refuse to authorise a performance study if it disagrees with the conclusion of the coordinating Member State as regards any of the grounds referred to in the second subparagraph of paragraph 8, or if it finds, on duly justified grounds, that the aspects addressed in Sections 1.13, 4.2, 4.3 and 4.4 of Chapter I of Annex XIV are not complied with, or where an ethics committee has issued a negative opinion in relation to that performance study which is valid in accordance with national law for that entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.

11 Each Member State concerned shall notify the sponsor through the electronic system referred to in Article 69 as to whether the performance study is authorised, whether it is

authorised subject to conditions, or whether authorisation has been refused. Notification shall be done by way of one single decision within five days of the transmission, pursuant to point (d) of paragraph 4 of this Article, by the coordinating Member State of the final assessment report. Where an authorisation of a performance study is subject to conditions, those conditions may only be such that, by their nature, they cannot be fulfilled at the time of that authorisation.

12 Any substantial modifications as referred to in Article 71 shall be notified to the Member States concerned by means of the electronic system referred to in Article 69. Any assessment as to whether there are grounds for disagreement as referred to in the second subparagraph of paragraph 8 of this Article shall be carried out under the direction of the coordinating Member State, except for substantial modifications concerning sections 1.13, 4.2, 4.3 and 4.4 of Chapter I of Annex XIV and point (c) of Section 2.3.2 of Part A of Annex XIII, which shall be assessed separately by each Member State concerned.

13 The Commission shall provide administrative support to the coordinating Member State in the accomplishment of its tasks under this Chapter.

[[X1]14 The procedure set out in this Article shall, until 25 May 2029, be applied only by those of the Member States in which the performance studies are to be conducted which have agreed to apply it. From 26 May 2029, all Member States shall be required to apply that procedure.**]**

Editorial Information

X1 Substituted by Corrigendum to Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (Official Journal of the European Union L 117 of 5 May 2017).

Article 75

Review of the coordinated assessment procedure

By 27 May 2028, the Commission shall submit to the European Parliament and to the Council a report on the experience gained from the application of Article 74 and, if necessary, propose a review of Article 74(14) and point (g) of Article 113(3).

Article 76

Recording and reporting of adverse events that occur during performance studies

1 The sponsor shall fully record all of the following:

a any adverse event of a type identified in the performance study plan as being critical to the evaluation of the results of that performance study;

b any serious adverse event;

c any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

d any new findings in relation to any event referred to in points (a) to (c).

2 The sponsor shall report without delay to all Member States in which a performance study is being conducted all of the following by means of the electronic system referred to in Article 69:

a any serious adverse event that has a causal relationship with the device, the comparator or the study procedure or where such causal relationship is reasonably possible;

b any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

c any new findings in relation to any event referred to in points (a) and (b).

The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the sponsor may submit an initial report that is incomplete followed up by a complete report.

Upon request by any Member State in which the performance study is being conducted, the sponsor shall provide all information referred to in paragraph 1.

3 The sponsor shall also report to the Member States in which the performance study is being conducted any event referred to in paragraph 2 of this Article that occurred in third countries in which a performance study is performed under the same clinical performance study plan as the one applying to a performance study covered by this Regulation by means of the electronic system referred to in Article 69.

4 In the case of a performance study for which the sponsor has used the single application referred to in Article 74, the sponsor shall report any event as referred to in paragraph 2 of this Article by means of the electronic system referred to in Article 69. Upon receipt, this report shall be transmitted electronically to all Member States in which the performance study is being conducted.

Under the direction of the coordinating Member State referred to in Article 74(2), the Member States shall coordinate their assessment of serious adverse events and device deficiencies to determine whether to modify, suspend or terminate the performance study or whether to revoke the authorisation for that performance study.

This paragraph shall not affect the rights of the other Member States to perform their own evaluation and to adopt measures in accordance with this Regulation in order to ensure the protection of public health and patient safety. The coordinating Member State and the Commission shall be kept informed of the outcome of any such evaluation and the adoption of any such measures.

5 In the case of PMPF studies referred to in Article 70(1), the provisions on vigilance laid down in Articles 82 to 85 and in the implementing acts adopted pursuant to Article 86 shall apply instead of this Article.

6 Notwithstanding paragraph 5, this Article shall apply where a causal relationship between the serious adverse event and the preceding performance study has been established.

Article 77

Implementing acts

The Commission may, by means of implementing acts, establish the detailed arrangements and procedural aspects necessary for the implementation of this Chapter, as regards the following:

(a) harmonised electronic forms for the application for performance studies and their assessment as referred to in Articles 66 and 74, taking into account specific categories or groups of devices;

(b) the functioning of the electronic system referred to in Article 69;

(c) harmonised electronic forms for the notification of PMPF studies as referred to in Article 70(1), and of substantial modifications as referred to in Article 71;

(d) the exchange of information between Member States as referred to in Article 72;

(e) harmonised electronic forms for the reporting of serious adverse events and device deficiencies as referred to in Article 76;

(f) the timelines for the reporting of serious adverse events and device deficiencies, taking into account the severity of the event to be reported as referred to in Article 76;

(g) uniform application of the requirements regarding the clinical evidence/data needed to demonstrate compliance with the general safety and performance requirements set out in Annex I.

The implementing acts referred to in the first paragraph shall be adopted in accordance with the examination procedure referred to in Article 107(3).

(**1**) 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 (OJ L 158, 27.5.2014, p. 1).

Status:
Point in time view as at 05/05/2017.

Changes to legislation:
There are currently no known outstanding effects for the Regulation (EU) 2017/746 of the European Parliament and of the Council, CHAPTER VI.