PROPOSED REGULATION ON IN VITRO DIAGNOSTIC MEDICAL DEVICES

EDMA – Clinical Evidence

28 September 2015

Clinical Evidence (articles 47-58, Annexes XII-XIII)

I. *Summary*

The introduction of clinical evidence is an essential component of the new IVD regulation and will have a crucial impact on the IVD sector when implementing this regulation. Clinical evidence requirements should be adapted to the specific needs of IVDs, and be feasible and realistic to implement for regulators and manufacturers alike. The three institutions have weighed in on the provisions of clinical evidence as follows:

The Commission has closely followed the international consensus, proposing a data and information driven approach and advocated for separated the requirements for studies where patients are at risk and where no patients are put at risk (a singular characteristic of IVDs is that studies can be carried out using leftover or biobank species without the involvement of patients).

The Parliament strengthened the safeguards for minors and incapacitated subjects participating in studies and put in place a clear mechanism for determining which studies constituted a risk to patients and which did not.

The Council focussed on a process driven approach rather than a data driven approach (how to do a performance evaluation rather than what information a performance evaluation should provide) and provided much more detail on how to carry out a study.

As such EDMA makes a proposal based on the following:

Maintains the framework of the international consensus of the commission proposal while including the safeguards for minors and incapacitated subjects as proposed by parliament and the mechanism for clarifying which studies constitute a risk. The overall performance evaluation process has been strengthened as per the Council proposal and all the relevant details on how to conduct studies involving a risk to patients have been included in the proposal.

EDMA believes that this is a balanced approach will be the basis for a strong legislation.

II. *Background*

The introduction of clinical evidence requirements for all IVDs is at the heart of the new IVD regulation.

As such the Commission in their proposal established a set of new requirements on clinical evidence based on the international consensus on clinical evidence for IVDs. These requirements push the need for pre-market data for IVDs to include not only analytical performance information but also a demonstration of the scientific validity of

IVDs (i.e. the relationship between the analyte being measured and the physiological or pathological state of the patient) and clinical performance, all bundled under the single concept of clinical evidence.

The commission proposal had the following key characteristics:

- **Data driven** – requirements were laid out in terms of the data that needed to be generated, while several mechanisms for generating that data were clearly acceptable the actual requirements where for data not for the process of generating it.
- **In line with new approach** – Clinical evidence requirements were laid out in a set of principles, which manufacturers would need to meet. This is in line with the new approach which does not include excessive technical detail in primary legislation to allow such details to be established and easily updated in secondary legislation and standards.
- **IVD Specific** – Clinical evidence requirements were defined as being IVD specific in particular taking into consideration the way in which clinical evidence can be gathered for IVDs given that most studies have no impact on patients and use of literature sources are key in many instances.
- **Interventional Studies** – A clear differentiation was made between situations where patient management decisions were taken as part of the study or a there was a risk to patients due to the specimen collection procedures and studies where there was no risk to the patient at all.

All of these points are in line with the international consensus for IVDs as defined by the GHTF.

The Council proposal has fundamentally modified this approach by seeking to align the requirements of IVDs with those of medical devices, as a consequence their approach is one which is driven by the process of gathering and assessing evidence rather than by the defining the data which underpins the evidence. Furthermore a significant amount of technical detail has been included in the council proposal.

III. *Study Requirements*

1. Defining study requirements: Most studies on IVD are conducted without any involvement of patients, e.g. by using leftover samples or samples from bio banks. The requirements for these studies are defined in Annex XII. It is only in exceptional cases that patients are directly involved in the study, i.e. where patient management decisions are taken as part of the study or the specific type of specimen collection poses some risk. Requirements for these studies are defined in Annex XIII, including more rigorous requirements.

Concern: Council text does not clearly differentiate between the requirements for studies where no patient are involved (Annex XII, General requirements for studies) and those where patients are involved and potentially at risk (Annex XIII, Specific requirements for interventional studies).

Proposal: Requirements for Annex XII (general requirements for studies) and Annex XIII (specific requirements for interventional studies) need to be adequately differentiated. In the implementation phase, a more precise definition of which specimen collection practices are considered to be a risk for patients and thus for which Annex XIII would apply are also needed.

IV. *Clinical Benefit*

2. Concept of clinical benefit: Clinical benefit refers to a patient outcome. While not directly defined in the legislation, clinical benefit is generally understood to be a favourable effect on a meaningful aspect of how a patient feels (e.g., symptom relief), functions (e.g., improved mobility) or survives as a result of treatment.

IVDs can provide information on the physiological or pathological state of a person, but they cannot directly determine a patient outcome or a care pathway for the patient as both are linked to the therapeutic options available in a healthcare system and the decisions made by healthcare professionals. (Ex: pregnancy test can determine if a woman is pregnant but not the outcome of the pregnancy, HIV screening and diagnosis can determine if a person is infected with the HIV virus but not the best course of treatment, etc.)

An appropriate requirement would be to assess IVDs against other diagnostic options and technologies, but not specifically against patient outcomes.

Concern: The Council text introduces the requirement that all IVDs need to be assessed against a clinical benefit. Assessing against a patient outcome as required by clinical benefit is not a feasible measure for IVDs.

Proposal: Criteria for assessment of clinical evidence applicable for IVDs, should be based on the information provided by the diagnostic technologies, not on subsequent healthcare pathways or patient outcomes.

V. *Post Market Assessment*

3. Post-market assessment: An IVD result is relevant for a given patient at a single point in time. For instance, a Hepatitis B test reflects the status of the patient at the specific moment when the test is performed. The test is not intended to follow the condition of that patient and is irrelevant for the assessment of the safety and performance of the IVD. This can be done through post-market assessment, whereby IVD manufacturers need to proactively monitor developments in epidemiology (emergence of new strains) and changes to clinical evidence, for instance through the emergence of new interference (e.g. caused by a new therapy). These developments would then trigger a post-market assessment by the manufacturer.

Concern: The Council text introduces the concept of a 'continuous assessment' for all IVDs. It leaves unclear whether this concept refers to the following-up of patients or the post-market surveillance of the IVD. Only the latter would be the appropriate method.

Proposal: The Council text on continuous assessment must be clarified to enable a feasible and appropriate post-market surveillance system for IVDs.

VI. *Pre-Market Evidence Generation*

4. Pre-market evidence generation: The method of how to gather clinical evidence and information can vary significantly depending on the IVD, e.g. there are significant differences in gathering data for a urine cup and an HIV blood screening assay. Rather than the process, it is the endpoints of evidence generation that are critical for IVDs.

Concern: Instead of the output-oriented concept proposed by the European Commission, the Council text proposes uniform procedural requirements on how data must be gathered.

Proposal: Information and data driven clinical evidence requirements, rather than process driven requirements are more appropriate to which avoid unnecessary burden for manufacturers and ensure adaptability to embrace innovative approaches.

EDMA proposals with regards to clinical evidence:

a) **Study type:** Better separation between the requirements for general studies and those which involve a risk to patients (Annexes XII & XIII)

b) **Concept of clinical benefit:** Criteria for assessment of clinical evidence based on the output of the diagnostic technologies, not on subsequent healthcare pathways or patient outcomes

c) **Post-market assessment:** The Council text on continuous assessment must be clarified to enable a feasible and appropriate post-market surveillance system for IVDs.

d) **Pre-market evidence gathering:** Information and data driven clinical evidence requirements, rather than process driven requirements.

Proposal

►**O** Commission Proposal - COM(2012) 541 of the 26/9/2012

►**P** Parliament First Reading - (COM(2012)0541 – C7-0317/2012 – 2012/0267(COD)) Adopted on 2/4/2014

►**C** Council Partial General Approach - 2012/0267 (COD) - 9770/15 PHARM 27 SAN 177 MI 392 COMPET 305 CODEC 859 – adopted 12 June 2015

Note – where not otherwise indicate the basic text of this proposal refers to this Commission text.

►O Article 47

General requirements regarding clinical evidence

1. The demonstration of conformity with the general safety and performance requirements set out in Annex I, under normal conditions of use, shall be based on clinical evidence ►**P** or additional safety data for general safety and performance requirements not covered by clinical evidence.◄

2. The clinical evidence shall support the intended purpose of the device as stated by the manufacturer.

3. The clinical evidence shall include all the information supporting the scientific validity of the analyte, the analytical performance and, where applicable, the clinical performance of the device, as described in Section 1 of Part A of Annex XII.

►**P** 3a. Where the manufacturer claims and/or describes an intended use, evidence attesting to this use shall constitute part of the requirements.◄

4. Where demonstration of conformity with the general safety and performance requirements based on clinical performance data or parts thereof is not deemed appropriate, adequate justification for any such exception shall be given based on the results of the manufacturer's risk management and on consideration of the characteristics of the device and, in particular, its intended purpose(s), the intended performance and the claims of the manufacturer. The adequacy of demonstration of conformity with the general safety and performance requirements based on the results of analytical performance evaluation alone shall be duly substantiated in the technical documentation referred to in Annex II. ►**P** Exemption from demonstration of conformity with general safety and performance requirements based on clinical data under the first subparagraph shall be subject to prior approval by the competent authority.◄

5. The scientific validity data, the analytical performance data and, where applicable, the clinical performance data shall be summarised as part of a clinical evidence report referred to in Section 3 of Part A of Annex XII. The clinical evidence report shall be included in the technical documentation referred to in Annex II relating to the device concerned.

6. The clinical evidence and its documentation shall be updated throughout the life cycle of the device concerned with data obtained from implementation of the manufacturer's post-market surveillance plan referred to in Article 8(6).

7. The manufacturer shall ensure that the device for performance evaluation complies with the general requirements of this Regulation apart from the aspects covered by the performance evaluation 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.

The manufacturer shall undertake to keep available to the competent authorities and the EU reference laboratories the documentation allowing an understanding of the design, manufacture and performances of the device, including its expected performance, so as to allow assessment of conformity with the requirements of this Regulation. This documentation shall be kept for at least five years after the performance evaluation of the device in question has ended.

Article 48

General requirements regarding clinical performance studies

1. Clinical performance studies shall be subject to this Regulation if they are conducted for one or more of the following purposes:

(a) to verify that, under normal conditions of use, the devices are designed, manufactured and packaged in such a way that they are suitable for one or more of the specific purposes of an in vitro diagnostic medical device referred to in number (2) of Article 2, and achieve the performance intended as specified by the manufacturers or sponsor;

(b) to verify that devices achieve the intended benefits to the patient as specified by the manufacturer;

►**P** to verify the clinical safety and efficacy of the device, including the intended benefits to the patient, when used for the intended purpose, in the target population and in accordance with the instructions of use.◄

(c) to determine any limits to the performance of the devices, under normal conditions of use.

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

3. Where the sponsor is not established in the Union, he shall ensure that a contact person is established in the Union. That contact person shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication to that contact person shall be considered as communication to the sponsor.

4. All clinical performance studies shall be designed and conducted in a way that the rights, safety and well-being of the subjects participating in such clinical performance studies are protected and that the clinical data generated in the clinical performance study are going to be reliable and robust.

►**P** Such studies shall not be conducted if the risks associated with the investigation are not medically justifiable in terms of the potential benefits of the device.◄

5. All clinical performance studies shall be designed, conducted, recorded and reported in accordance with Section 2 of Annex XII.

6. For interventional clinical performance studies, as defined in number (37) of Article 2, and for other clinical performance studies, where the conduct of the study, including specimen collection, involves invasive procedures or other risks for the subjects of the studies, the requirements set out in Articles 49 to 58 and in Annex XIII shall apply, in addition to the obligations laid down in this Article.

►**P** The Commission shall be empowered to adopt delegated acts in accordance with Article 85 concerning the provision of a list of **specimen collection procedures** with negligible risks, which allows a derogation to be made from the relevant Article.◄

ANNEX XII
CLINICAL EVIDENCE AND POST-MARKET FOLLOW-UP
PART A: CLINICAL EVIDENCE

The demonstration of conformity with the general safety and performance requirements set out in Annex I, under the normal conditions of use of the device, shall be based on clinical evidence.

The clinical evidence includes all the information supporting the scientific validity of the analyte, the analytical performance and, where applicable, the clinical performance of the device for its intended purpose as stated by the manufacturer.

1. SCIENTIFIC VALIDITY DETERMINATION

1.1. Scientific validity determination

1.1.1. The scientific validity refers to the association of the analyte to a clinical condition or a physiological state.

1.1.2. The determination of the scientific validity may not be necessary where the association of the analyte to a clinical condition or a physiological state is well known, based on available information, such as peer reviewed literature, historical data and experience.

1.1.3. For a new analyte and/or a new intended purpose, the scientific validity shall be demonstrated based on one or a combination of the following sources:

- information on devices measuring the same analyte with the same intended purpose that have marketing history;
- literature;
- expert opinions;
- results from proof of concept studies;
- results from clinical performance studies.

1.1.4. The information supporting the scientific validity of the analyte shall be summarised as part of the clinical evidence report.

1.2.0 Performance Evaluation

Performance evaluation of a device is a process by which data are assessed and analysed to demonstrate the adequacy of the clinical evidence of that device for its intended purpose as stated by the manufacturer.

►**C** To plan, continuously conduct and document a performance evaluation, the manufacturer shall establish and update a performance evaluation plan. The performance evaluation plan shall specify the characteristics and the performance of the device and the process and criteria applied to generate the necessary clinical evidence.

The performance evaluation shall be thorough and objective, considering both favourable and unfavourable data.◄

Interventional performance studies and other clinical performance studies involving risks for the subjects of the studies shall only be performed once the analytical performance of the device has been established and determined to be acceptable.

1.2.1. Analytical performance

1.2.1.1 The analytical performance characteristics are described in point (a) of Section 6(1) of Annex I.

1.2.1.2 As a general rule, the analytical performance shall always be demonstrated on the basis of analytical performance studies.

1.2.1.3 For novel devices, it may not be possible to demonstrate trueness since suitable higher order reference materials or a suitable comparative method may not be available. If there are no comparative methods, different approaches may be used (e.g. comparison to some other well-documented method, comparison to the composite reference method). In the absence of such approaches, a clinical performance study comparing test performance to the current clinical standard practice would be needed.

1.2.1.4 The analytical performance data shall be summarised as part of the clinical evidence report.

1.2.2. Clinical performance

1.2.2.1 The clinical performance characteristics are described in point (b) of Section 6(1) of Annex I.

1.2.2.2 Clinical performance data may not be required for established and standardised devices and for devices classified as class A according to the rules set out in Annex VII.

1.2.2.3 Clinical performance of a device shall be demonstrated based on one or a combination of the following sources

- clinical performance studies;
- literature;
- experience gained by routine diagnostic testing.

1.2.2.4 Clinical performance studies shall be performed unless it is duly justified to rely on other sources of clinical performance data.

1.2.2.5 Clinical performance data shall be summarised as part of the clinical evidence report.

1.2.2.6 When the clinical performance evaluation includes a clinical performance study, the level of detail of the clinical performance study report referred to in Section 2.3.3 of this Annex will vary based on the risk class of the device determined according to the rules set out in Annex VII:

- For devices classified as class B according to the rules set out in Annex VII, the clinical performance study report may be limited to a summary of the study protocol, results and conclusion;
- For devices classified as class C according to the rules set out in Annex VII, the clinical performance study report shall include the method of data analysis, the study conclusion and the relevant details of the study protocol;
- For devices classified as class D according to the rules set out in Annex VII, the clinical performance study report shall include the method of data analysis, the study conclusion, the relevant details of the study protocol and the individual data points.

2 CLINICAL PERFORMANCE STUDIES

2.1. Purpose of clinical performance studies

The purpose of clinical performance studies is to establish or confirm aspects of device performance which cannot be determined by analytical performance studies, literature and/or previous experience

gained by routine diagnostic testing. This information is used to demonstrate compliance with the relevant general safety and performance requirements with respect to clinical performance. When clinical performance studies are conducted, the data obtained shall be used in the performance evaluation process and be part of the clinical evidence for the device

2.2. Ethical considerations for clinical performance studies

Every step in the clinical performance study, from first consideration of the need and justification of the study to the publication of the results, shall be carried out in accordance with recognised ethical principles, as for example those laid down in the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and last amended by the 59th World Medical Association General Assembly in Seoul, Korea, in 2008.

2.3. Methods for clinical performance studies

2.3.1. Clinical performance study design type

Clinical performance studies shall be designed in such a way as to maximize the relevance of the data while minimising potential biases.

The design of the study shall provide the data necessary to address the clinical performance of the device.

2.3.2. Clinical performance study protocol

Clinical performance studies shall be performed on the basis of an appropriate 'clinical performance study protocol'.

The clinical performance study protocol shall set out how the study is intended to be conducted.

It shall contain information about the study design

such as the purpose, objectives, study population, description of test method(s) and interpretation of results, site training and monitoring, specimen type, specimen collection, preparation, handling and storage, inclusion and exclusion criteria, limitations, warning and precautions, data collection/management, data analysis, required materials, number of study sites and if applicable, clinical endpoints, outcomes, and requirements for patient follow-up.

In addition, the clinical performance study protocol shall identify the key factors which may impact the completeness and significance of results, such as intended participant follow-up procedures, decision algorithms, discrepancy resolution process, masking/blinding, approaches to statistical analyses, and methods for recording endpoints, outcomes and, where appropriate, communication of test results.

2.3.3. Clinical performance study report

A 'clinical performance study report', signed by a medical practitioner or any other authorised person responsible, shall contain documented information on the clinical performance study protocol, results and conclusions of the clinical performance study, including negative findings. The results and conclusions shall be transparent, free of bias and clinically relevant. The report shall contain sufficient information to enable it to be understood by an independent party without reference to other documents. The report shall also include as appropriate any protocol amendments or deviations, and data exclusions with the appropriate rationale.

►**P** The report shall be accompanied by the clinical evidence report as described in point 3.1 and be accessible through the electronic system referred to in Article 51.◄

3. CLINICAL EVIDENCE REPORT

3.1 The clinical evidence report shall contain the scientific validity data, the analytical performance data and, where applicable, the clinical performance data. If the analytical performance data is determined to be sufficient to declare conformity with the general safety and performance requirements set out to in Annex I without the need for clinical performance data, a rationale should be documented and included in the clinical evidence report.

3.2 The clinical evidence report shall in particular outline:

- the justification for the approach taken to gather the clinical evidence;

- the technology on which the device is based, the intended purpose of the device and any claims made about the device’s clinical performance or safety;

- the nature and extent of the scientific validity and the performance data that has been evaluated;

- how the referenced information demonstrate the clinical performance and safety of the device in question;

- the literature search methodology, if a literature review is the approach taken to gathering clinical evidence.

3.3 The clinical evidence and its documentation shall be updated throughout the life cycle of the device concerned with data obtained from the implementation of the manufacturer's post-market surveillance plan referred to in Article 8(5) which shall include a plan for the device post-market follow-up in accordance with Part B of this Annex.

►**P** The clinical evidence data and its subsequent updates through post-market follow-up shall be accessible through the electronic systems referred to in Articles 51 and 60.◄

Part B: Post-market follow-up

1. Manufacturers shall put in place procedures to enable them to collect and evaluate information relating to the scientific validity, as well as the analytical and clinical performance of their devices on the basis of data obtained from post-market follow-up.

2. Where such information becomes available to the manufacturer, an appropriate risk assessment shall be conducted and the clinical evidence report shall be amended accordingly.

3. Where changes to devices are necessary, the conclusion of the post market follow-up shall be taken into account for the clinical evidence referred to in Part A of this Annex and for the risk assessment referred to in Section 2 of Annex I.

If necessary, the clinical evidence or risk management shall be updated and/or corrective actions be implemented.

4. Any new intended purpose of a device shall be supported by an updated clinical evidence report.

ANNEX XIII

INTERVENTIONAL CLINICAL PERFORMANCE STUDIES AND OTHER CLINICAL PERFORMANCE STUDIES INVOLVING RISKS FOR THE SUBJECTS OF THE STUDIES

I. Documentation regarding the application for interventional clinical performance studies and other performance studies involving risks for the subjects of the studies

For devices for intended to be used in the context of interventional clinical performance studies or other performance studies involving risks for the subjects of the studies the sponsor shall draw up and submit the application in accordance with Article 49 accompanied by the documentation as laid down below:

1. Application form

The application form shall be duly filled out containing the following information:

1.1. Name, address and contact details of the sponsor and, if applicable, name, address and contact details of his contact person ►**C** or legal representative according to Article 48 paragraph 3◄ established in the Union.

1.2. If different from the above, name, address and contact details of the manufacturer of the device intended for performance evaluation and, if applicable, of his authorised representative.

1.3. Title of the performance study.

1.4. Single identification number in accordance with Article 49(1).

1.5. Status of the performance study (i.e. first submission, resubmission, significant amendment);

►**C** 1.5a. Details/reference to the performance study plan (e.g. including details of the design phase of the performance study).◄

1.6. If resubmission with regard to same device, previous date(s) and reference number(s) of earlier submission(s) or in the case of significant amendment, reference to the original submission. ►**C** The sponsor shall identify all of the changes from the previous submission together with a rationale for those changes, in particular, whether any changes have been made to address outcomes of previous competent authority or ethics committee reviews.◄

1.7. If parallel submission for a clinical trial on a medicinal product in accordance with Regulation (EU) No 536/2014, reference to the official registration number of the clinical trial.

1.8. Identification of the Member States, EFTA countries, Turkey and third countries in which the clinical performance study shall be conducted as part of a multicentre/ multinational study at the time of application.

1.9. Brief description of the device for performance evaluation**,** ►**C** its classification and other information necessary for the identification of the device and device type.◄

1.10. Summary of the performance study ►**C** plan.◄

1.11. If applicable, information regarding a comparator device, ►**C** its classification and other information necessary for the identification of the comparator device.

1.11a. Evidence from the sponsor that the clinical investigator and the investigational site are capable of conducting the clinical performance study in accordance with the performance study plan.

1.12. Details of the anticipated start date and duration of the performance study.

1.13. Details to identify the notified body, if the sponsor is using one at the point of application for performance study.

1.13a. Confirmation that the sponsor is aware that the competent authority may contact the ethics committee assessing the application.

1.14. The statement referred to in Section 4.1 of this Annex.◄

►P 1.a Incapacitated subjects and minors

1. Incapacitated subjects

In the case of incapacitated subjects who have not given, or who have not refused to give, informed consent before the onset of their incapacity, interventional clinical performance studies and other clinical performance studies involving risks for the subjects of the studies may be conducted only where, in addition to the general conditions, all of the following conditions are met:

- the informed consent of the legal representative has been obtained; consent shall represent the subject's presumed will and may be revoked at any time, without detriment to the subject;
- the informed consent of the legal representative has been obtained; consent shall represent the subject's presumed will and may be revoked at any time, without detriment to the subject;
- the explicit wish of an incapacitated subject, who is capable of forming an opinion and assessing this information, to refuse participation in, or to be withdrawn from, the clinical performance study at any time without giving a reason and with no liability or prejudice whatsoever being incurred by the subject or their legal representative as result shall be followed by the investigator;
- no incentives or financial inducements are given except compensation for participation in the clinical performance study;
- such research is essential to validate data obtained in a clinical performance study on persons able to give informed consent or by other research methods;
- such research relates directly to a medical condition from which the person suffers;
- the clinical performance study has been designed to minimise pain, discomfort, fear and any other foreseeable risks in relation to the disease and the developmental stage and both the risk threshold and the degree of distress are specially defined and constantly observed;
- the research is necessary to promote the health of the population concerned by the clinical performance study and cannot instead be performed on capacitated subjects;
- there are ground for expecting that participation in the clinical performance study will produce a benefit for the incapacitated subject outweighing the risks or will produce only a minimal risk;
- an ethics committee, with expertise regarding the relevant disease and the patient population concerned, or that has taken advice on clinical, ethical and psychosocial questions in the field of the relevant disease and patient population concerned, has endorsed the protocol;

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

2. Minors

An interventional clinical performance study and other clinical performance studies involving risks for the minor may be conducted only where, in addition to the general conditions, all of the following conditions are met:

- the written informed consent of the legal representative has been obtained, whereby consent shall represent the minor's presumed will;
- the informed and express consent of the minor has been obtained, where the minor is able to give consent according to national law;
- the minor has received all relevant information in a way adapted to his or her age and maturity,

from a medical doctor (either the investigator or member of the study team) trained or experience in working with children, regarding the study, the risks and benefits;

- without prejudice to second indent, the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical performance study at any time, is duly taken into consideration by the investigator;
- no incentives or financial inducements are given except payment for participation in the clinical performance study;
- such research 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;
- the clinical performance study has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage, and both the risk threshold and the degree of distress are specially defined and constantly observed;
- there are grounds to expect that some direct benefit for the category of patients concerned by the study may be obtained from the clinical performance study;
- the corresponding scientific guidelines of the Agency have been followed;
- the interests of the patient shall always prevail over those of science and society;
- the clinical performance study does not replicate other studies based on the same hypothesis and age-appropriate technology is used;
- the clinical performance study does not replicate other studies based on the same hypothesis and age-appropriate technology is used;

The minor shall take part in the consent procedure in a manner adapted to his or her age and maturity. Minors who are able to give consent according to national law shall also give their informed and express consent to participate in the study.

If during a clinical performance study the minor reaches the age of majority as defined in the national law of the Member State concerned, his/her express informed consent shall be obtained before the study may continue.◄

2. Investigator's Brochure

The investigator's brochure (IB) shall contain the information on the device for performance evaluation that is relevant for the study and available at the time of application.

►**C** Any updates to the brochure or other relevant information that is newly available shall be brought to the attention of the investigators in a timely manner. The IB shall be clearly identified and contain in particular the following information:◄

2.1. Identification and description of the device, including information on the intended purpose, the risk classification and applicable classification rule according to Annex VII, design and manufacturing of the device and reference to previous and similar generations of the device.

2.2. Manufacturer's instructions for installation, ►**C** maintenance, maintaining hygiene standards◄ and use, including storage and handling requirements, as well as the label and instructions for use to the extent that this information is available. ►**C** In addition, information relating to any relevant training required.◄

2.3. ►**C** Analytical performance◄

2.4. Existing clinical data, in particular the following:

- relevant ►**C** peer reviewed◄ scientific literature ►**C** and consensus expert opinions/positions from relevant professional associations available relating to the safety, performance, design characteristics, scientific validity, clinical performance◄ and intended purpose of the device and/or of equivalent or similar devices;

- other relevant clinical data available relating to the safety,►**C** scientific validity, clinical performance, design characteristics and intended purpose of similar devices including details of their similarities and differences.◄

2.5. Summary of the risk/benefit analysis and the risk management, including information regarding known or foreseeable risks and warnings.

2.6. In the case of devices that include tissues, cells and substances of human, animal or microbial origins detailed information on the tissues, cells and substances, and on the compliance with the relevant general safety and performance requirements and the specific risk management in relation to the tissues, cells and substances.

2.7. Reference to harmonised or other internationally recognised standards complied with in full or in

part.

►**C** A list detailing how the relevant general safety and performance requirements set out in Annex I are fulfilled, including the standards and Common Specifications applied, in full or in part, as well as a description of the solutions for fulfilling the relevant general safety and performance requirements, in so far as these standards and CS have not or only been partly fulfilled or are lacking.

2.7a. A detailed description of the clinical procedures and diagnostic tests used in the course of the performance study and in particular information on any deviation from normal clinical practice.◄

3. Clinical performance study ►C plan

Clinical performance studies shall be performed on the basis of a 'clinical performance study plan'.

The clinical performance study plan (CPSP) shall define the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical performance study.

It shall contain in particular the information as laid down below. If part of this information is submitted in a separate document, it shall be referenced in the CPSP.

(a) Identification of the clinical performance study and the CPSP.

(b) Identification of the sponsor – name, address of the registered place of business and contact details of the sponsor and, if applicable, the name, address of the registered place of business and contact details of his contact person/ legal representative pursuant to Article 48 paragraph 3 established in the Union.

(c) Information on investigator(s) (i.e. principal, coordinating, other; qualifications; contact details) and investigation site(s) (number, qualification(s), contact details) and, in the case of devices for self-testing, the location and number of lay persons involved. The roles, responsibilities and qualifications of the investigators shall be specified in the CPSP

(d) The starting date and scheduled duration for the clinical performance study.

(e) Identification and description of the device, its intended purpose, the analyte(s) or marker(s), the metrological traceability, and the manufacturer

(f) Information about the type of specimens under investigation, .

(g) Overall synopsis of the clinical performance study, its design type (eg observational, interventional) together with the objectives and hypotheses of the study, reference to the current state of the art in diagnosis and/or medicine

(h) A description of the expected benefits/risks of the device and of the clinical performance study in the context of the state of the art in clinical practice, the medical procedures involved and patient management.

(i) The instructions for use of the device or test protocol, the necessary training and experience of the user, the appropriate calibration procedures and means of control, the indication of any other devices, medical devices, medicinal product or other articles to be in- or excluded and the specifications on any comparator or comparative method used as reference,

(j) Description of and justification for the design of the clinical performance study, its scientific robustness and validity, including the statistical design, and details of measures to be taken to minimise bias (e.g. randomisation) and management of potential confounding factors.

(k) The analytical performance according to point a) of Section 6(1) of Annex I with justification for any omission.

(l) Parameters of clinical performance according to point b) of Section 6(1) of Annex I to be determined, with justification for any omission; specified clinical outcomes/endpoints (primary/secondary) used with a justification and the potential implications for individual health and/or public health management decisions

(m) Information on the performance study population: specifications of the subjects, selection criteria, size of performance study population, representativity to target population, if applicable, information on vulnerable subjects involved (e.g. children, immuno-compromised, elderly, pregnant women);

(n) Information on use of data out of left over specimens banks, genetic or tissue banks, patient or disease registries etc with description of reliability and representativity and statistical analysis approach; assurance of relevant method for determining the true clinical status of patient specimens.

(o) Monitoring plan;

(p) Data management;

(q) Decision algorithms;

(r) Policy regarding any amendments (incl. those according to Article 53) to or deviations from the CPSP, with a clear prohibition of use of waivers from the CPSP

(s) Accountability regarding the device, in particular control of access to the device, follow-up in relation to the device used in the clinical performance study and the return of unused, expired or malfunctioning devices.

(t) Statement of compliance with the recognised ethical principles for medical research involving humans and the principles of good clinical practice in the field of clinical performance studies as well as with the applicable regulatory requirements.

(u) Description of the informed consent process, including a copy of the patient information sheet and consent forms.

(v) Procedures for safety recording and reporting, including definitions of recordable and reportable events, and procedures and timelines for reporting.

(w) Criteria and procedures for suspension or early termination of the clinical performance study,

(x) Criteria and procedures for follow up of subjects following completion of a performance study, procedures for follow up of subjects in the case of suspension or early termination, procedures for follow up of subjects who have withdrawn their consent and procedures for subjects lost to follow up. Procedures for communication of test results outside the study, including communication of test results to the performance study subjects.

(y) Policy as regards the establishment of the clinical performance study report and publication of results in accordance with the legal requirements and the ethical principles referred to in Section 1 of Chapter I.

(z) List of the technical and functional features of the device indicating those that are covered by the performance study.

(aa) Bibliography.

Where any of the above-mentioned elements are not deemed appropriate for inclusion in the CPSP due to the specific study design chosen, a justification shall be provided.◄

4. Other information

4.1. A signed statement by the natural or legal person responsible for the manufacture of the device for performance evaluation that the device in question conforms to the general safety and performance requirements apart from the aspects covered by the clinical performance study and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the subject.

4.2. Where applicable according to national law, a copy of the opinion(s) of the ethics committee(s) concerned. ►**C** When according to national law the opinion(s) of the ethics committee(s) is not required at the time of the submission of the notification, copy of the opinion(s) of ethics committee(s) shall be submitted as soon as available.◄

4.3. Proof of insurance cover or indemnification of subjects in case of injury, according to Article 48c and the corresponding national legislation.

4.4. Documents to be used to obtain informed consent, including the patient information sheet and the informed consent document.

4.5 Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data, in particular:

- organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed;

- a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects concerned in clinical performance studies;

- a description of measures that will be implemented in case of data security breach in order to mitigate the possible adverse effects.

►**C** 4.6. Full details of the available technical documentation, for example detailed risk analysis/management documentation or specific test reports shall be submitted to the competent authority reviewing an application upon request.◄

II. Other sponsor's obligations

1. The sponsor shall undertake to keep available for the competent national authorities any documentation necessary to provide evidence for the documentation referred to in Chapter I of this

Annex. If the sponsor is not the natural or legal person responsible for the manufacture of the device intended for performance evaluation, this obligation may be fulfilled by that person on behalf of the sponsor.

2 ►**C**. The sponsor shall have an agreement in place to ensure that the serious adverse events are reported by the investigator(s) to the sponsor in a timely manner.◄

3. The documentation mentioned in this Annex shall be kept for a period of time of at least five years after the clinical performance study with the device in question has ended, or, when the device is subsequently placed on the market, at least five years after the last device has been placed on the market.

Each Member State shall make provision that this documentation is kept at the disposal of the competent authorities for the period indicated in the preceding paragraph in case the sponsor, or his contact person, established within its territory goes bankrupt or ceases its activity prior to the end of this period.

►**C** 4. The sponsor shall appoint a monitor that is independent from the investigation site to ensure that the clinical performance study is conducted in accordance with the Clinical Investigation Plan, the principles of Good Study Practice and this Regulation.

5. The sponsor shall establish follow-up measures for the investigation subjects.◄