Appendix 3: Clinical evaluation and post-market follow-up

The table below provides a snapshot of the detailed requirements for the clinical evaluation and post market follow-up documentation in Annex XIV of the EU MDR and the performance evaluation, performance studies, and post-market performance follow-up in Annex XIII of the EU IVDR.

For the **complete list** of European requirements, refer to:

- Annex XIV of EU MDR – Clinical evaluation and post-market clinical follow-up
- Annex XIII of EU IVDR – Performance evaluation and post-market follow-up

Clinical evaluation – EU MDR
To plan, continuously conduct and document a clinical evaluation, manufacturers shall:

- establish and update a clinical evaluation plan, which shall include at least:
  - an identification of the general safety and performance requirements that require support from relevant clinical data;
  - a specification of the intended purpose of the device;
  - a clear specification of intended target groups with clear indications and contra-indications;
  - a detailed description of intended clinical benefits to patients with relevant and specified clinical outcome parameters;
  - a specification of methods to be used for examination of qualitative and quantitative aspects of clinical safety with clear reference to the determination of residual risks and side-effects;
  - an indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device;
  - an indication how benefit-risk issues relating to specific components such as use of pharmaceutical, nonviable animal or human tissues, are to be addressed; and
  - a clinical development plan indicating progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a post-market clinical follow-up with an indication of milestones and a description of potential acceptance criteria;
- identify available clinical data relevant to the device and its intended purpose and any gaps in clinical evidence through a systematic scientific literature review;
- appraise all relevant clinical data by evaluating their suitability for establishing the safety and performance of the device;
- generate, through properly designed clinical investigations in accordance with the clinical development plan, any new or additional clinical data necessary to address outstanding issues; and
- analyse all relevant clinical data in order to reach conclusions about the safety and clinical performance of the device including its clinical benefits.

The results of the clinical evaluation and the clinical evidence on which it is based shall be documented in a clinical evaluation report which shall support the assessment of the conformity of the device.

A clinical evaluation may be based on clinical data relating to a device for which equivalence to the device in question can be demonstrated. The following technical, biological and clinical characteristics shall be taken into consideration for the demonstration of equivalence:

- - Technical: the device is of similar design; is used under similar conditions of use; has similar specifications and properties including physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength and software algorithms; uses similar deployment methods, where relevant; has similar principles of operation and critical performance requirements;
- - Biological: the device uses the same materials or substances in contact with the same human tissues or body fluids for a similar kind and duration of contact and similar release characteristics of substances, including degradation products and leachables;
- - Clinical: the device is used for the same clinical condition or purpose, including similar severity and stage of disease, at the same site in the body, in a similar population, including as regards age, anatomy and physiology; has the same kind of user; has similar relevant critical performance in view of the expected clinical effect for a specific intended purpose.
- The characteristics listed in the first paragraph shall be similar to the extent that there would be no clinically significant difference in the safety and clinical performance of the device. Considerations of equivalence shall be based on proper scientific justification. It shall be clearly demonstrated that manufacturers have sufficient levels of access to the data relating to devices with which they are claiming equivalence in order to justify their claims of equivalence.

The results of the clinical evaluation and the clinical evidence on which it is based shall be documented in a clinical evaluation report which shall support the assessment of the conformity of the device. The clinical evidence together with non-clinical data generated from non-clinical testing methods and other relevant documentation shall allow the manufacturer to demonstrate conformity with the general safety and performance requirements and shall be part of the technical documentation for the device in question. Both favourable and unfavourable data considered in the clinical evaluation shall be included in the technical documentation.

Post Market Clinical Follow-up – EU MDR
A post market clinical follow-up (PMCF) is a continuous process that updates the clinical evaluation (above) and shall be addressed in the manufacturer's post-market surveillance plan. The manufacturer shall proactively collect and evaluate clinical data from the use of the device when it has been supplied in the market, with the aim of confirming the safety and performance throughout the expected lifetime of the device, of ensuring the continued acceptability of identified risks and detecting emerging risks on the basis of factual evidence.

The PMCF plan shall specify the methods and procedures for proactively collecting and evaluating clinical data with the aim of:

- Confirm the safety and performance of the device throughout its expected lifetime
- identifying previously unknown side-effects and monitoring the identified side-effects and contraindications,
- identifying and analysing emergent risks on the basis of factual evidence,
- ensuring the continued acceptability of the benefit-risk ratio referred to in Sections 1 and 9 of Annex I, and
- identifying possible systematic misuse or off-label use of the device, with a view to verifying that the intended purpose is correct.

The PMCF plan shall include at least:

- the general methods and procedures of the PMCF to be applied, such as gathering of clinical experience gained, feedback from users, screening of scientific literature and of other sources of clinical data;
- the specific methods and procedures of PMCF to be applied, such as evaluation of suitable registers or PMCF studies;
- a rationale for the appropriateness of the methods and procedures;
- a reference to the relevant parts of the clinical evaluation report and to the risk management;
- the specific objectives to be addressed by the PMCF;
- an evaluation of the clinical data relating to equivalent or similar devices;
- reference to any relevant common specification (CS), harmonised standards when used by the manufacturer, and relevant guidance on PMCF; and
- a detailed and adequately justified time schedule for PMCF activities (e.g. analysis of PMCF data and reporting) to be undertaken by the manufacturer.

The manufacturer shall analyse the findings of the PMCF and document the results in a PMCF evaluation report that shall be part of the clinical evaluation report and the technical documentation.

The conclusions of the PMCF evaluation report shall be taken into account for the clinical evaluation and in the risk management. If, through the PMCF, the need for preventive and/or corrective measures has been identified, the manufacturer shall implement them.

Performance evaluation and performance studies – EU IVDR
Performance evaluation of a device is a continuous process by which data are assessed and analysed to demonstrate the scientific validity, analytical performance and clinical performance of that device for its intended purpose as stated by the manufacturer. 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.

Its depth and extent shall be proportionate and appropriate to the characteristics of the device including the risks, risk class, performance and its intended purpose.

1. Performance evaluation
1.1 Performance evaluation plan
As a general rule, the performance evaluation plan shall include at least the intended purpose of the device, specification of the characteristics of the device and the analyte or marker to be determined by the device, identification of certified reference materials or reference measurement procedures, clear identification of specified target patient groups with clear indications, limitations and contra-indications, the general safety and performance requirements that require support from relevant scientific validity and analytical and clinical performance data, specification of methods, including the appropriate statistical tools, used for the examination of the analytical and clinical performance of the device and of the limitations of the device and information provided by it, a description of the state of the art, including an identification of existing relevant standards, CS, guidance or best practices documents, an indication and specification of parameters to be used to determine the acceptability of the benefit-risk ratio for the intended purpose or purposes and for the analytical and clinical performance of the device, for software qualified as a device, an identification and specification of reference databases and other sources of data used as the basis for its decision making, an outline of the different development phases including the sequence and means of

determination of the scientific validity, the analytical and clinical performance, including an indication of milestones and a description of potential acceptance criteria, and a post-market performance follow-up plan.

1.2 Demonstration of the scientific validity and the analytical and clinical performance
As a general methodological principle the manufacturer shall identify through a systematic scientific literature review the available data relevant to the device and its intended purpose and identify any remaining unaddressed issues or gaps in the data; appraise all relevant data by evaluating their suitability for establishing the safety and performance of the device; and generate any new or additional data necessary to address outstanding issues.

1.3 Clinical evidence and performance evaluation report
The manufacturer shall assess all relevant scientific validity, analytical and clinical performance data to verify the conformity of its device with the general safety and performance requirements. The amount and quality of that data shall allow the manufacturer to make a qualified assessment whether the device will achieve the intended clinical benefit or benefits and safety, when used as intended by the manufacturer. The data and conclusions drawn from this assessment shall constitute the clinical evidence for the device. The clinical evidence shall scientifically demonstrate that the intended clinical benefit or benefits and safety will be achieved according to the state of the art in medicine.

2. 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. Clinical performance studies shall be performed on the basis of a clinical performance study plan (CPSP).

3. **Other performance studies**
The performance study plan and the performance study report shall be documented for other performance studies than clinical performance studies.

Post-market performance follow-up – EU IVDR
The post-market performance follow-up (PMPF) shall be a continuous process that updates the performance evaluation and shall be specifically addressed in the manufacturer's post-market surveillance plan. When conducting PMPF, the manufacturer shall proactively collect and evaluate performance and relevant scientific data from the use of a device with the aim of confirming the safety, performance and scientific validity throughout the expected lifetime of the device, of ensuring the continued acceptability of the benefit-risk ratio and of detecting emerging risks on the basis of factual evidence.

The PMPF shall be performed pursuant to a documented method laid down in a PMPF plan.

The PMPF plan shall specify the methods and procedures for proactively collecting and evaluating safety, performance and scientific data with the aim of: (a) confirming the safety and performance of the device throughout its expected lifetime, (b) identifying previously unknown risks or limits to performance and contra-indications, (c) identifying and analysing emergent risks on the basis of factual evidence, (d) ensuring the continued acceptability of the clinical evidence and of the benefit-risk ratio, and (e) identifying possible systematic misuse.

The PMPF plan shall include at least: (a) the general methods and procedures of the PMPF to be applied, such as gathering of clinical experience gained, feedback from users, screening of scientific literature and of other sources of performance or scientific data; (b) the specific methods and procedures of PMPF to be applied, such as ring trials and other quality assurance activities, epidemiological studies, evaluation of suitable patient or disease registers, genetic databanks or post-market clinical performance studies; (c) a rationale for the appropriateness of the methods and procedures referred to in points (a) and (b); (d) a reference to the relevant parts of the performance

evaluation report; (e) the specific objectives to be addressed by the PMPF; an evaluation of the performance data relating to equivalent or similar devices, and the current state of the art; (g) reference to any relevant CS, harmonised standards when used by the manufacturer, and relevant guidance on PMPF, and; (h) a detailed and adequately justified time schedule for PMPF activities, such as analysis of PMPF data and reporting, to be undertaken by the manufacturer.

The manufacturer shall analyse the findings of the PMPF and document the results in a PMPF evaluation report that shall update the performance evaluation report and be part of the technical documentation.

The conclusions of the PMPF evaluation report shall be taken into account for the performance evaluation. If, through the PMPF, the need for preventive and/or corrective measures has been identified, the manufacturer shall implement them.

If PMPF is not deemed appropriate for a specific device then a justification shall be provided and documented within the performance evaluation report.