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EU IVDR Performance Evaluation in 8 Steps

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The new revised EU Regulation 2017/746 is focusing specific guidelines on performance evaluation of In Vitro Diagnostic Medical Devices (IVD). The requirements are updated in Article 56 of the new In Vitro Diagnostics Regulation (IVDR). This new regulations are imposing manufacturer to prepare and submit a performance evaluation of the device to demonstrate its safety and performance according to the manufacturers' intended use. The technical documentation of performance evaluation report (PER) must be evidenced by three pillars: scientific validity, analytical performance and clinical performance. Collating data to reasonably address about each of the pillar which must be mandatory for IVD manufacturers. Some of the manufacturers are unsure about the preparation of PERs that are compliant with new regulations. Following steps on performance evaluation (PE) requirements stipulated under the IVDR2017/746 will help manufacturers to successfully introduce their IVDs in to the European Market.

Step 1: Understand Article 56

Article 56 states about general safety and performance requirements (GSPR) set out in Annex I, relating to performance characteristics referred to in Chapter I and Section 9 of Annex I. Also about the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 of Annex I that is based on the scientific validity, analytical and clinical performance aspects of the IVD device. Annexes XIII and ISO 20916:2019 specifies how IVD manufacturers have to plan, carry out and document the performance evaluation. Manufacturer must prepare a standard operating procedure (SOP) for IVD performance evaluations which should cover total device lifecycle and goes far beyond development.The IVDR describes that the PE is a continuous process that emphasizes the close interface with risk management (Annex VII, Section 4.5.4 and Annex XIII section 1.1).

Step 2: Performance evaluation plan (PEP) preparation

Device specific PEP must be prepared as per the Annex XIII, paragraph 1.1 of the IVDR requirements. It should explain about current state of the art, in regards to medical, diagnostic and technology related fields of the Device in question.Reference to relevant standards, common specifications, guidelines or best practice documents must be included. PEP should be included with intended purpose and characteristics of the device, analyte or biomarker used in the device, intended use, user, indications of use, General Safety and Performance Requirements (GSPR) supported by devices PE. Methods that were followed to examine the analytical and clinical performance of the device, benefit risk considerations, and Post-market Performance Follow-up (PMPF) plan should be explained in brief.

Step 3: About scientific validity

At the beginning of the device development cycle - scientific validity of the analyte(s) or biomarkers that has to be measured by IVD must be demonstrated. Furthermore, systematic literature search need to be conducted, 0 its search strategy, literature sourcesused, and data selection criteria are to be documented. Along with the database sources, scientific evidence can also be taken from statements from professional societies and expert opinions. If still the scientific validity is identified with gaps, IVD manufacturers need to generate additional data by performing proof of concept studies, pre-clinical studies or clinical performance studies particularly in the case of novel analytes. All the results need to be summarized in scientific validity report that has to be included in performance evaluation report.

Step 4: About analytical performance evaluation

Prepare analytical performance plan with detailed procedure and concrete experimental design. Usually analytical performance defined by specificity, sensitivity, reproducibility parameters. To evaluate in detail it is mandatory to conduct bench studies like cross-reactivity, interference, and stability testing and many other applicable criteria to the Device.Section 9.1 of Annex I of the IVDR describes all the parameters that need to be assessed. If the device is a complex IVD system -plan the verification ofindividual subsystems, its integration, and the sampling and sample handling aspects precisely for reproducibility, repeatability and accuracy of measurements of device. Once analytical performance plan is ready then summarize all the results in analytical performance report which will be included in PER.

Step 5: About conducting clinical performance evaluation

Clinical performance is the "ability of a device to yield results which are correlated with a defined clinical/physiological/pathological condition or state following the target population and intended user". Clinical performance provides evidence for how good the IVD is for delivering a result or diagnosis or guide treatment decisions. For conduct of clinical performance, one can only refer to scientific literature, to know if the device has well established technology, can refer to established, standardized tests. Clinical performance study protocol must be prepared in accordance with Annex XIII, paragraph 2 of the IVDR and in accordance with ISO 20916:2019. Collection of data for clinical evaluation plan parameters was described in Annex I, paragraph 9.1 b. Once the plan is ready the results are to be summarized in clinical performance report of IVD.

Step 6: IVD stability demonstration

Stability of a device needs to be demonstrated based on the type of the device, which is important for IVD assays and in vitro diagnostic reagents. To conduct stability study one can refer to EP25 guidance document from the Clinical and Laboratory Standards Institute (CLSI). While preparing stability plan one must ensure to follow all stability aspects mentioned by the IVDR in Annex II, paragraph 6.3 specifically about device's shelf life, device in-use stability, and transport stability.

Step 7: Prepare the clinical performance evaluation report (PER)

Once after completion of PEP, a report has to be prepared summarizing all the validated results of scientific validity, analytical performance and clinical performance. PER ensures the data obtained will demonstrate the sufficient clinical evidence. In the PER clinical evidenceto be evaluated in the light of the current state of the art in medicine, methodology used to search literature, the technology and the intended purpose of the IVD, and device's positive benefit-risk ratio.All the PER requirements were listed in Annex XIII, part A, section 1.3.2 of the IVDR.

Step 8: Post-market Performance Follow-up (PMPF) plan & report implementation

In the PER, a continuous update step is clinical evidence and its assessmentthroughout the life cycle of the IVDD. For any medical device PMPF has to be conducted to meet the post-market requirements to properly andcontinuously monitorthe device performance. So it is mandatory to collect clinical data. As a first step one must prepare PMPF plan and document the outcome in a PMPF evaluation report. PMPF plan must be included with methods and procedures that were followed to collect and evaluate scientific, performance, and safety data. The main goal of PMPF is to confirm the device safety and

performance throughout its lifecycle, and to identify previously unknown risks, limits to performance, or contra-indications etc. PMPF is also conducted to identify and analyze emerging risks, to ensure continued acceptability of the benefit-risk profile and to identify possible systemic misuse. If the IVD device belongs to class C or D the PMPF report must be updated annually whereas for low risk devices it not necessary to update annually. Along with PMPF report, for class C or D devicesa Periodic Safety Update Report (PSUR) also need to be included in the Technical file. PSUR is to be updated annually.

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