WHITEPAPER

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EU has been overhauling its rules on in-vitro diagnostics (IVD), particularly companion diagnostics, tobring them more into line with internationally agreed standards. But despite the changes, it is still retaining a regulatory system that keeps the approval of IVDs separate from those for pharmaceuticals.

CDx companion Diagnostics products

IVDR recognizes that "Companion Diagnostics (CDx) are essential for defining patients' eligibility for specific treatment with a medicinal product. In the current legislation of IVDR 2017/746CDx comes under Class C products.

Further companion diagnostic, or CDx, informs the use of personalized treatment options for advanced cancer patients by identifying FDA-approved treatment options that may be appropriate based on the unique drivers of their individual cancer. A companion diagnostic is a medical device, often an in vitro device (IVD), which provides information that is essential for the safe and effective use of a corresponding drug or biological product.

As a result of the division of regulatory responsibilities, the NB's main task is to assess the technical quality and performance of the CDx. Both the NB and the medical agency, either EMA or the national authorities, have to assess, in the light of evidence from clinical trials, whether the CDx has sufficient sensitivity and specificity to be safe and effective.

Companion diagnostic (CDx), form a subset of ***In vitro Companion Diagnostics Devices*** where by definition a CDx assay is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. Further, the FDA specifies three areas where a CDx assay is essential:

1. To identify patients who are most likely to benefit from a particular therapeutic product;
2. To identify patients likely to be at increased risk of serious adverse reactions as a result of treatment with a particular therapeutic product; and
3. To monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness.

So according to the FDA, a CDx assay can be used both to predict outcome (efficacy and safety) and to monitor the response.

CDx in the current Regulation:

In the classification system proposed in the IVDR, IVDs will be assigned to four classification groups A, B, C, and D, depending on device risk, with class A being the lowest risk class. The four-class system resembles that of the Canadian and Australian regulations, and is similar, but not equal, to what has been proposed by a Global Harmonization Task Force.

In the current IVDR Guidelines all CDx assays will be **Class C devices** and will require a complex regulatory pathway including a requirement for a Design Examination Certification by an NB. The review

by the NB may possibly also be linked to a consultation with the European Medicines Agency (EMA) or, alternatively, compliance to a Common Technical Specifications (CTS) will be required. The CTS for new devices will be drafted as part of the review process. No matter which of the proposed pathways (EMA consultation or CTS) becomes final, the time to the market for a CDx assay will be extended essentially.

Regulatory Pathway for CDx companion Diagnostics products

Legal definition for CDx in Europe is set and subject to the requirements specified in the IVDR, CDx are defined by Article 2 (7) as devices which are essential for the safe and effective use of a corresponding medicinal product to:

A. Identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or

B. Identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal products

For CDx furthermore, a requirement will also be that an independent notified body should perform the conformity assessment, and that this notified body has to consult the European Medicines Agency (EMA) or one of the medical product national competent authorities Medicines regulatory authorities' in EU will be required to be consulted during the review of CDx conformity assessment and so, there is opportunity for more consistent and transparent information on CDx to be provided. The In-Vitro Diagnostic Devices Regulation introduces a new obligation that CDx to undergo a conformity assessment by a notified body. Notified body has to consult EMA for issue of a CE compliance certificate, the Notified Body must seek a scientific opinion from the Agency (EMA) on the suitability of the companion diagnostic to the intended purpose.

From a regulatory perspective, because the development of CDx combines pharmaceutical and medical devices, their regulatory requirements must reflect the complexity and costs associated with scientific, clinical, operational, and commercial decisions. The new Regulation applies to all IVDs and their accessories and introduces new definitions and rules not only for CDx but also for in-house tests, kits, and single-use IVDs.

CDx, and most software that is a part of IVD instruments (SaMD), single-use IVDs, and genetic tests will fall into the Category **Class C**.

The conformity assessment for CDx foresees a consultation procedure between the NB and a medical authority, depending on who is responsible for the authorization of the corresponding medicinal product.

New IVDR Guidelines and process for CDx:

Manufacturers are expected to provide a summary of safety and performance with Instructions For Use (IFU), and to evaluate the IVD for the associated medicinal product. However, because a CDx is dependent on a therapeutic agent, it is expected that new CDx consultations will primarily be performed in collaboration with the EMA.

The Competent Authority must provide its opinion within 60 days, but this period may be extended once for a further 60 days if there is sufficient justification for this extension. Manufacturers of CDx should allow for 120 days for the regulatory procedure to take place. Unlike reference laboratory testing, if the scientific and technical feedback is unfavorable, the certification process may continue based on the recommendation of the NB, provided there is a justification for this overruling..

The therapeutic indications granted EMA will be reviewed in parallel to, applications for medicinal products in view of related CDx associated to a drug or medicinal product.

CDx development, opportunity, and growth of the market have the potential to further personalize therapeutic strategies and improve patient access, outcomes and their response to innovative pharmaceutical agents and/or diagnostic methods. Therefore, approval of CDx must be aligned with the scrutinized assessment of their analytical validity. Implementation of IVDR 2017/746, although a challenging regulatory shift for CDx, opts to optimize the field through the alignment of European requirements with the American and Japanese ones and the continuous, dynamic monitoring of the real-world use of IVDs.

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