WHITEPAPER

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Companion Diagnostic (CDx) Products: EU Regulations

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INTRODUCTION

CDx products are specifically intended to identify patients who are targeted for therapy and who have a previously identified disease or genetic risk. A new classification system for companion diagnostics is introduced by the In Vitro Diagnostic Devices Regulation (Regulation (EU) 2017/746) along with the requirement to submit to conformity evaluation by a designated authority. The Regulation is in effect from May 26, 2022, after a five-year transition period.

A "regulation" is a law that has legal force. It must be implemented across the EU. For instance, the Council adopted a regulation when the EU wished to ensure that there are common safeguards on goods imported from outside the EU.

In vitro diagnostics (IVD) can be used alone or in combination with other devices and/or therapies, when used in combination with a therapeutic drug, they are referred as Companion Diagnostics (CDx). The development of CDx depends on companion biomarkers, intending to stratify patients based on their predicted response to a drug and its potential toxicity levels.

In the current legislation of IVDR 2017/746 CDx comes under Class C products, IVDs under Rule 3.

OBJECTIVES:

The principal objectives of a CDx are to

- Identify the appropriate patient group who are most likely to benefit from a therapeutic product.
- Identify the patient groups, for which the therapeutic product has been adequately proven safe and effective, allowing for adjustment of treatment to achieve optimal safety.
- Predict serious adverse reactions that some patients may present as an outcome of the therapeutic drug used.
- Monitor the response to treatment to improve/adjust the dosage scheme and to ensure continued patient safety.

THE REGULATORY PATHWAY FOR APPROVAL

According to IVDR (Annex IX, section 5.2), the conformity assessment process for CDx foresees a consultation procedure between a Notified Body and a Medical Authority. This could take place between any of the national regulatory authorities in the E.U. or the EMA, depending on who is responsible for the authorization of the corresponding medicinal product. The timeframe for the consultation is 60 days with the possibility to extend once for another 60 days. Regulatory Hurdles:

- CDx use is required for a label of an agent.
- If CDx development lags behind the agent it will take a longer time for an agent to be brought to market.

BACKGROUND

In May 2017, the term CDx was introduced in the EU regulation on IVDs, Regulation (EU) 2017/746. The new EU IVD regulation reveals two significant changes to the current situation. Firstly, CDx will be classified by

having a high individual risk or a moderate public risk (category C), will require a complex regulatory pathway including requirement for Design Examination Certification by a NB. CDx is a validated test for predictive biomarker (PBM), which enables the identification of subjects at a higher risk of developing adverse reactions to the medicine in question (safety) or the identification of a subset of patients who have an increased chance of efficacy.

According to the (old) IVD directive, notified bodies (NB) were responsible for all IVD. Now the proposal for a regulation of the European Parliament and of the Council on IVD medical devices is progressing in the legislative procedure. This regulation will for the first time in EU legislation specifically address CDx. This will be classified as high individual risk or moderate public risk (category C) requiring a conformity assessment not only by their manufacturer but also by NB. Although the proposed regulation makes the assessment of CDx more similar to the assessment of medicines than in the EU in the past, it upholds the split responsibilities for medicinal products and medical devices (including IVD and CDx). Since 2004, innovative medicines have been authorized for the European market virtually exclusively by EMA's centralized procedure. Responsibility for medical devices (including CDx) remains with the multitude of NB, even when the use of CDx and the treatment with a medicine are tightly linked. The discretion of the NB to consult either EMA or national competent authorities (NCA) in the member states on the assessment of CDx. Similarly, health technology assessment (HTA) bodies may want to include in their evaluations about the effects of CDx on cost–effectiveness of a treatment.

PROPOSED SOLUTIONS:

- → The new European regulation for in vitro diagnostics (IVD) divides the certification of IVD including companion diagnostics (CDx) by notified bodies (NB) from the market authorization of medicines. With the new regulation, CDx will require conformity assessment which is expected to include clinical evidence by NB. the benefit-risk balance of the medicine may depend on the performance (e.g., sensitivity and specificity) of its CDx, a close cooperation of EMA and NB will be necessary.
- → The Notified body will consult one of the competent authorities designated by member states in accordance with Directive 2001/83/EC or the European Medicines Agency (EMA) in accordance with the procedure set out in section 6.2 of Annex VIII and in section 3.6 of Annex IX. The ultimate goal of the guidance is to stimulate early collaborations that will result in faster access to promising new treatments for patients living with serious and life-threatening diseases. Therapeutic Products is intended to facilitate class labeling on diagnostic tests for oncology therapeutic products, where scientifically appropriate.

CDx is most often used in oncology; it is first used and is the largest segment.

Some biomarkers are present in more than one cancer type.

OVERVIEW OF EU - REGULATION IVDR 2017/746

Quality management system	General Safety and Performance Requirements (GSPRs) and Technical documentation	Conformity assessment
• The requirements for the Quality Management System	• Technical Documentation (TD) shall be in compliance	• Conformity Assessments Routes have been updated (Art. 9 of IVDD

of the manufacturer are described in Art. 10(8) and involve the following aspects:

- Verification/validation for business organization, including outsourced processes, design, and development, production process controls and quality control procedures, post-market surveillance, risk management, and performance evaluation.
- Although not yet harmonized with ISO 13485:2016, the new Regulation tries to align with the standard focusing on a risk-based approach for IVD regulation.
- Requirements for maintaining a risk management system (refer to Art. 10(2)) differs according to IVD class and must cover the entire lifetime of the device (see Annex I).

with Annexes II and III as per Art. 10(4) in order to provide evidence of conformity with General Safety and Performance.

- Adding completely new requirements with respect to the information on device description and specification, design information, the analytical performance of the device, stability, software verification, and validation.
- PMS updating requirements to design and manufacturing information, benefit-risk analysis and risk management, performance evaluation

has been replaced by Art. 48 in IVDR) to reflect the new classification rules and subsequent up-classification of most IVDs.

- Manufacturers must select an appropriate route to a conformity assessment as per Annexes IX to XI.
- NB involvement is required in all classes except class A (non-sterile).
- Class C and D IVDs now require the involvement of EMA and EU reference laboratories (refer to Chapter V, section 2, and Annexes IX, X, XI).

CONCLUSION:

Companion diagnostic product concludes that the development, opportunity, and growth of the CDx 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. To meet the complicated, growing regulatory demands of IVD technologies, an international consensus on the basic regulatory requirements for their approval and continuous monitoring should be seen as a step forward for public health. Currently, the lack of standardization and use of multiple platforms for the same biomarker raises concerns about the reproducibility and sensitivity of the specific analytical assay the platform assesses. 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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