RSNN EXPERT MEETING – COMPANION DIAGNOSTICS – CHALLENGES AND OPPORTUNITIES

BACKGROUND

According to the European In Vitro Diagnostic Medical Devices Regulation (IVDR)[1] a companion diagnostic (CDx) is a device which is 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 product.

On 26 May 2022, the requirements for safe and effective use of In Vitro Diagnostics (IVDs) became more stringent, when European Directive 98/79/EC for In Vitro Diagnostic Medical Devices (IVDD) was replaced by European Regulation (EU) 2017/746 (IVDR). The current transition to IVDR is a long and complex process with an emerging number of challenges. These include the lack of European reference laboratories (EURLs) and concerns around gathering clinical evidence under the IVDR's requirement. Last year, a survey was conducted by the Dutch Health and Youth Care Inspectorate (IGJ) among Netherlands-based manufacturers of medical devices for IVDs to gain insight into how the transition to the IVDR is progressing.[2] The survey showed that the percentage of legacy IVDs (currently CE marked under the IVDD) that will transition to the IVDR is only 58%. For 20% of legacy IVDs, manufacturers already know that they are not going to make the transition to the IVDR. Factors such as the high cost of meeting the IVDR requirements, limited market potential or the availability of new versions of the device all play a role.

Currently, the Medicines Evaluation Board (MEB) is conducting a CDx Horizon Scan together with the HMA-EMA EU-Innovation Network. The CDx Horizon Scan is the systematic examination of information to detect early signs of scientific and technological developments with previously unknown regulatory challenges or public health opportunities. It aims at enabling the European Medicines Agency (EMA) and the European Medicines Regulatory Network (EMRN) to proactively respond to forthcoming challenges and opportunities and identify aspects of the product and technology of IVDs and the corresponding medicinal

[1] https://eur-lex.europa.eu/eli/reg/2017/746/oj
[2] https://english.igj.nl/documents/publication/2023/09/05/appeal-to-manufacturers-take-action-to-meet-ivdr-requirements

products that may require new or adapted regulatory tools or approaches or which may be used to assist regulators. This topic also concerns the Dutch Central Committee on Research Involving Human Subjects (CCMO). The change from a Directive (IVDD) to a Regulation (IVDR) means among others stricter European requirements for IVD, with a new classification system. CCMO also deals with the interplay between the Clinical Trial Regulation (CTR) and the IVDR when jointly developing a medicine and a CDx.

EXPERT MEETING

On 28 May 2024, RSNN organised an expert meeting with the title 'Companion Diagnostics – Challenges and Opportunities'. The goal of this RSNN Expert Meeting was to retrieve information from the field in terms of developments, missed topics or technologies, challenges and opportunities related to CDx. The invited experts shared their knowledge, experiences, and personal views in accordance with the Chatham House Rule. The group comprised 18 experts from various backgrounds including academia, industry, governmental bodies and health care professionals (HCPs).

The discussion was guided by the following pre-defined questions:

1. What sort of issues do you foresee to play an important role from a regulatory perspective with respect to CDx in the coming decade?
2. Which technological developments do you expect to pose a challenge or opportunity in the coming decade?
    a. With respect to emerging IVD technological developments?
    b. With respect to developments in personalized medicine?
3. CDx play an important role in oncology. Are there other therapeutic fields where CDx may play an important role in the coming decade?
4. What regulatory challenges and opportunities do you foresee in the context of co-development of CDx and the corresponding medicinal product?

This report provides a summary of the discussion held and is arranged per question.

SUMMARY

At the start of the meeting, it became clear that a good understanding of the definition of CDx is important. It became clear that in the discussion at hand CDx are defined as IVDs that are only used to test whether or not to start with a specific medicine. Tests designed to modify treatments are *not* considered a CDx.

1) What sort of issues do you foresee to play an important role from a regulatory perspective with respect to CDx in the coming decade?

Researchers highlighted the speed at which new biomarkers are being discovered which may lead to new CDx. Innovations in algorithms and artificial intelligence are facilitating these advancements. The process of making new diagnostics IVDR-compliant is time-consuming and complex, because of the need for assessment by a Notified Body. In practice this may result in attempts to circumvent the IVDR by using diagnostics in research settings rather than commercial application. The extensive validation process required by IVDR means that by the time an IVD is validated, newer, more advanced versions of the technology may already be available. This lag can hinder the timely adoption of cutting-edge diagnostics, delaying potential benefits for patients. HCPs stressed that lab-developed tests should be allowed, even if there was a validated CDx. It is not feasible, either financially or practically, to sequentially test multiple CDx, especially when considering tissue limitations in the oncology setting. In-house lab-developed tests offer a tailored approach that can be more efficient and effective in certain clinical settings. Someone from the industry pointed out the stricter requirements for lab-developed tests in the IVDR.

The industry indicated to struggle with early clinical research. The different regulations (IVDR and CTR) that are in place are not always clear. These regulations are all useful in their own right, but because of improper coordination and differences in terms of definitions, their interplay complicates developments. There seem to be signs that clinical research is pulling out of Europe because of the IVDR, presumably because of difficulties in patient enrolment in early clinical studies. Premature classification of assays as CDx, to fall in scope of IVDR in early clinical phases, was also mentioned. In most cases those assays will never become CDx. The time and resources required in the early phase of clinical trials needed to qualify those assays within the IVDR might be disproportionate to the additional safety it provides for patients if the assay ultimately turns out not to be a CDx. Moreover, assays used in clinical trials tend to be already validated according to widely adopted guidelines such as ICH M10.

It was also noted that CDx will influence medicines reimbursement and potential price negotiations. Developing a CDx is costly and the test results will have an impact on reimbursement. The interaction between the product information and reimbursement will become increasingly important. Additionally, if the use of a validated test is mentioned in the product information, is that mandatory? Or can an alternative (in-house) test be used? Would this be considered off-label use? From a research and hospital point of view, flexibility was mentioned to be important, as was the need for the ability to adapt. The industry indicated that the wish for flexibility is understandable, but legislation sets strict limits on in-house

testing,[3] and that this is also recognized in the *'Guidance for the use of in-house developed IVD tests'*[4] drawn up by the Dutch IVDR Taskforce of laboratory professionals.

Finally, whole genome sequencing (WGS) tests a wide range of biomarkers simultaneously. Currently in oncology, WGS is performed with fresh frozen tissue samples. However, in the near future, WGS will be feasible on other types of samples, including liquid biopsies, greatly simplifying the process.

2) Which technological developments do you expect to pose a challenge or opportunity in the coming decade?

a. With respect to emerging IVD technological developments?

b. With respect to developments in personalized medicine?

An industry representative identified the internet as a critical factor influencing the future of personalized medicine: the vast amount of user data with wearables, collected by companies like Google and Meta, suggests a potential shift towards these companies providing medical services. However, wearables currently seem far from achieving the capability of CDx, which are in vitro tests that determine the suitability of specific medicines.

The field of point-of-care testing is also developing rapidly, mostly in population screening. While testing at home offers convenience for patients, there are concerns about the reliability and validity of these tests. The experts believed that self-administered CDx tests are not likely to become a reality in the near future due to these reliability issues.

The increase in available health information raises significant privacy concerns. With tools like the gene passport, patients will have extensive health data stored throughout their lives, similar to the information from the heel prick test conducted at birth. This abundance of information brings ethical challenges, including how patients manage and understand their data.

Healthcare professionals expressed concerns that the rise of commercial diagnostics and home screening methods could lead to overdiagnosis, potentially overwhelming the healthcare system. More screening can lead to identifying conditions that may not require immediate treatment, resulting in unnecessary stress for patients and increased healthcare costs.

[3] The In Vitro Diagnostic Regulation (IVDR) and the MDCG 2023-1 Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746.

[4] 'Handvat gebruik lab-developed tests zoals beschreven in de IVDR (versie 3.0, 2023).

In daily practice, lab-developed tests are becoming increasingly comprehensive, such as broad tests like WGS, Whole Exome Sequencing (WES) and larger targeted panel tests. For validation, clinical evidence is necessary. A clinician wondered: if a WGS test has been validated for BRAF mutations in melanoma, is it required to complete the extensive validation process to for instance the intended use of the BRAF test for lung cancer as well?
For medicines this is understandable, but perhaps not for a test: it stays the same.

Academia anticipates that tumor-agnostic tests will gain traction in a few years. Must these tests be validated for each tissue type? Technically, future diagnostics will be possible with less material or at earlier stages of the disease. While it is unclear if this will impact CDx, it will certainly affect treatment.

Additionally, rare diseases were mentioned. Developing medicines and CDx for these diseases is challenging. While biomarker-based selection is helpful, collecting sufficient evidence is difficult.

3) **CDx play an important role in oncology. Are there other therapeutic fields where CDx may play an important role in the coming decade?**

In addition to oncology, other areas mentioned are hemophilia, amyotrophic lateral sclerosis (ALS), clotting disorders and pain medication. It is anticipated that in a few years, genetic profiling may also play a role in targeted therapies for psychiatry. Transplantation medicine was also highlighted as a field where CDx may play an important role in the future.

In general a growing emphasis on biomarkers was mentioned by the participants. This could mean that CDx will play a role in a growing number of therapeutic areas. According to some participants, the growing emphasis on biomarkers also encompasses situations where adverse events may occur.

4) **What regulatory challenges and opportunities do you foresee in the context of co-development of CDx and the corresponding medicinal product?**

The main challenge identified by many participants was the co-development of a medicine and a CDx. Participants felt that both they and the entire field were on a learning curve with new regulations such as MDR, CTR, and IVDR. However, not everyone is progressing at the same pace or in the same manner, and some may not even be fully aware of the increased regulatory stringency. Many obstacles could be overcome through collaborative efforts and shared learning. Most discussions arose from differing definitions or interpretations. Participants recognized the need to navigate the learning curve together, emphasizing the

importance of consistency. For instance, Medical Ethics Review Committees (METCs) in the Netherlands operate individually without an umbrella organization. Given the multitude of stakeholders, the idea of a multidisciplinary think tank was proposed.

It was noted that the different stakeholders form a peer community of scientists. It was mentioned to keep in mind that in discussions and collaborations, regulators do not per se participate as scientists.
Importantly, participants stressed that the purpose of regulations must remain focused on patient well-being and quality of care.

One healthcare professional pointed out that the IVDR approaches CDx from the perspective of the biomarker and the medicine, rather than from a broader disease and patient perspective.

Costs were also discussed, with concerns that more CDx could lead to higher expenses, although better patient selection might result in more effective medicine use. This complexity might affect Health Technology Assessments (HTAs). Participants emphasized the need for cooperation among HTAs, National Competent Authorities (NCAs), Notified Bodies (NBs), and other stakeholders, to save time and money by avoiding redundant efforts.

Everyone works in their own "bubble" and participants agreed that understanding and acknowledging each other's environments is crucial. Regulations exist for a reason.

From a hospital perspective, it was suggested that lessons could be learned from the field of orphan medical devices and their specific CE-conditions. This field concerns different subjects, but the same challenges.

Participants concluded that while everyone is engaged in a collective effort, they share common challenges. The end-user and regulatory field both anticipated that the IVDR would pose difficulties.

TAKE HOME MESSAGES

- The process of making CDx IVDR-compliant is time-consuming and complex
- The field of diagnostics develops faster than the IVDR might keep up with
- The co-development of a medicine and a companion diagnostic is an important challenge
- The entire diagnostics field is on a learning curve with new regulations such as CTR and IVDR
- Understanding and acknowledging each other's environments is crucial