Fit-for-purpose approach to biomarker assay deployment in medicinal product clinical trials

26 February 2019

This discussion paper provides MedTech Europe's perspectives on the role of predictive biomarker assays in clinical trials and applicable regulatory frameworks and practices across Europe, to achieve a harmonised understanding of how the regulatory framework of the IVD Directive should be applied. It proposes that biomarker assays used in early clinical trials may be validated using a fit-for-purpose approach. It is intended as a basis for dialogue with authorities and other stakeholders. The scope of this paper applies to situations where a predictive biomarker assay is used in a clinical trial context. Good study practice must be followed in all cases where there is an impact for patients, in particular the oversight by an ethics committee and all considerations due to ensure patient safety and consent.

Introduction

Regulation of companion diagnostics[1] is a relatively new field. Assays to identify or measure predictive biomarkers[2], commonly named 'predictive biomarker assays,' are used in several phases of medicinal product development. In many cases, particularly for new biomarkers, no commercial assays will be available for the specific intended use; in this situation assays are co-developed with the drug. The intended purpose of these assays varies and evolves during the drug development process, from early discovery or research to e.g. selecting, classifying or monitoring subjects in late stage clinical trials. Those late stage trials often provide a key part of the evidence to support the regulatory marketing authorisation of the medicine and the CE-marking of the assay as a companion diagnostic.

In a broader context, predictive biomarker assays are a *critical component* of personalised medicine. 'Paving the way for personalised medicine for citizens is part of the vision of several ministries and funders across the EU. Ensuring that these, often innovative, assays can be used as intended without undue delay will also contribute to this goal.

[1] 'Companion diagnostic' is defined for the first time in Europe in the IVD Regulation 2017/746/EU under Article 2(7). While the scope of this paper is on the IVD Directive 98/79/EC, rather than on the IVD Regulation, the below definition from the regulation can be used:
"'companion diagnostic' means 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;"

[2] Biomarkers are biological measurements that can be used to e.g. predict risk of disease, to enable early detection of disease, to improve treatment selection and to monitor the outcome of therapeutic interventions.

Concerns – Authority and Industry Perspectives

While most competent authorities in the EU support that predictive biomarker assays used in clinical trials are regulated as devices for performance evaluation, some competent authorities are requesting that such assays must be CE-marked prior to use in a clinical trial. Presumably the request for CE-marking is based on a desire to ensure that any assay used in clinical research shall be appropriately validated and ultimately as safe as possible for the clinical trial subject. **The industry agrees with these overarching safety goals**. We believe that consensus on the appropriate regulatory avenue should be found while keeping these goals in mind. CE-marking of predictive biomarkers used in clinical trials as IVDs is leading to challenges in the areas of legal status of the clinical trial assay and its intended use, lack of harmonised approach by regulators, the impracticality of having full validation/analytical performance established on some occasions and the additional impact which CE-marking brings in terms of time delays and administrative burden.

CE-marking of an assay requires *inter alia*, full validation of the analytical performance, establishing technical documentation, labelling the device and registering with the competent authority. By contrast, following the procedure for performance evaluation requires fulfilling all the essential requirements and having full validation of the analytical performance except for those aspects which are being investigated. CE-marking means a time delay of several months if not more, beyond the time necessary to follow the procedure for a device performance evaluation. This leads to delay in clinical trial initiation which in turn could delay the availability of medicinal products to clinical trial subjects (during the trial) and once in the routine healthcare system (to patients).

It is agreed that analytical performance and demonstration of assay suitability is needed prior to use of an assay in a clinical trial or study. Such assays are used in research or investigative settings and are not meant for commercialisation. Where they are used in a clinical trial setting involving study subjects an appropriate fit-for-purpose regulatory pathway should be taken. Good study practice must be followed in all cases where there could be an impact on patients, in particular the oversight by an ethics committee and all considerations due to ensure patient safety and consent.

Note: this paper discusses the current regulatory regime under the IVD Directive 98/79/EC. While the sector is transitioning to a new regulatory regime under the IVD Regulation 2017/746/EU, the IVD Directive will continue to be relevant until May 2022.

Guiding Principles

To find a solution to the above concerns, MedTech Europe suggests that the following guiding principles are used by drug trial sponsors, assay manufacturers, authorities and others involved in the assessment of the trial/study:

Principle 1: Clarity on the purpose of a trial/evaluation and the parties involved

The intended purpose of the assay component needs to be clearly identified early on. This, in turn, will determine what is the nature of the trial/evaluation. E.g. it could qualify as a *clinical trial* (for the investigational drug aspects), as a *performance evaluation* (for the assay aspects), or as an early-phase drug trial using an assay as a tool for the trial, without the assay having a medical diagnostic purpose and thereby falling out of the scope of the IVD Directive. To determine the nature of the trial/evaluation requires early dialogue between the assay provider and the drug manufacturer (usually the clinical trial sponsor), and ideally also with relevant authorities. Based on this discussion, the regulatory requirements can be identified and obligations for each party clarified.

Principle 2: Fit-for-purpose approach to the use of the assay

A biomarker assay used in a clinical trial setting must be assessed based on its intended purpose and to what extent the test results will drive treatment assignment or otherwise influence the clinical management of study subjects. Guiding questions to consider in making a risk determination could be:

- Will use of the results of the assay lead to some study subjects not being treated with or lead to a delay for a known effective therapy?
- Will use of the results from the assay expose study subjects to risks (e.g., adverse events) that exceed the risks encountered with the control arm therapy or non-trial standard of care?
- Is it likely, based on existing knowledge about the relationship between the biomarker and the investigational medicinal product, that incorrect results from the biomarker assay would present a potential for serious risk to study subjects? The safety profile of the drug must also be taken into account.

Analytical performance is a general requirement for devices for performance evaluation. A certain level of analytical performance evidence should always be available (and certain parameters such as sample stability of DNA in blood will be known and remain consistent across different biomarkers). Depending on the context of the trial, it can make sense not to require full validation of the analytical performance before the test is used. In this scenario, it is important to consider the risks to subjects participating in the trial (i.e. the consequences of a false positive or false negative result) and the integrity of the data generated by the test. Based on this assessment, it could be considered acceptable to not generate the full data for some analytical parameters subject to a suitable justification. Every case should be evaluated on its own.

The biomarker assay must be reliable and produce accurate data. It must also be suitable for its specified intended purpose – which in this case is the clinical trial or study. Some analytical parameters should always be generated before a test is used in a trial where its use could influence treatment of patients, e.g. for the following:

- analytical sensitivity
- analytical specificity
- accuracy
- repeatability
- limits of detection

For other parameters, in particular where assays are deployed in early clinical trials (even selection assays) and pose a low risk to trial subjects, a technical validation based on fit-for-purpose approaches should be sufficient. Depending on the context of the trial, outstanding analytical data could be collected in parallel with the clinical trial/study e.g. for the following parameters:

- reproducibility (**justification** – the test will be deployed in a limited number of central laboratories. These laboratories are under clinical trial protocol and would be trained extensively, utilizing a defined test site protocol and be closely monitored and controlled during the conduct of the clinical trial/study)
- control of known relevant interfering substances (**justification** – the sample type is routinely used in diagnostic tests; the manufacturer has conducted several studies with different biomarkers with the same sample type and technology to confirm the impact of any potential interfering studies). The context of the trial and intended purpose should always be considered in risk management however: for example, for a trial involving subjects with melanoma, melanin is a known interferent with polymerase chain reaction, so this is an example where a study would need to be performed in advance to gain data on known interferences.
- stability (**justification** – real time stability studies might be ongoing but not yet finalised; stability is particularly important to ensure the continued safety and performance of the test once on the market)

A more detailed overview is provided below showing the proposed minimal analytical validation criteria for a biomarker assay used in a clinical trial which follows a fit-for-purpose approach.

	Biomarker Assay use in medicinal product clinical trials		**For reference Commercialised assay**
Context of Use	Exploratory (including retrospective; not for patient selection)	Selection or Enrichment	Commercial / EU
Sample Types	Contrived samples, spike-ins acceptable	Clinical samples matching tissue/disease type	Clinical samples matching target population
Range/Sensitivity	(✓)	✓	✓
Specificity	(✓)	✓	✓
Robustness	--	(✓)	✓
Stability - Sample/specimen	✓	(✓)	✓
Stability – Reagent	-- /(✓)	(✓) within period of trial	✓
Stability - Onboard (for use on instruments)	-- /(✓)	(✓) preliminary	✓
Shipping stability	--	(✓) within context of trial	✓
Accuracy (results from trueness and precision)	✓	✓	✓
Repeatability	✓	✓	✓
Reproducibility	-- /(✓)	(✓) within context of trial	✓
Cut-off	--	✓	✓
Interferences	--	(✓) within context of specimen & technology	✓
Cross reactions	-- /(✓)	(✓) within context of specimen & technology	✓
Clinical performance	--	--	✓
Scientific validity	--	Scientific rationale	✓

Following a fit-for-purpose approach which considers the assay intended purpose, the scientific needs of the study and the risk to the patients, it could be considered as appropriate to run interventional performance studies without having finalized the data for the above points.

Principle 3: Use of the most appropriate 'regulatory pathway'

There are different pathways which can be taken regulating the assay, depending on the intended purpose and the context of the use of the assay:

- clinical trial assay which is outside the scope of the IVD Directive;
- clinical trial assay with performance evaluation (i.e. Annex VIII statement and procedure);
- clinical trial assay which is CE-marked only for the purpose of that trial;
- clinical trial assay which is both a device for performance evaluation and CE-marked

3.1. Clinical trial assay which is outside the scope of the IVD Directive

Early-phase drug trials use the assay as a research tool for the trial. In this situation the assay is not used for any medical diagnostic purpose. The assay is also not under investigation as a device for performance evaluation. Therefore, it does not fall under the scope of the IVD Directive 98/79/EC. The purpose of including the assay in the clinical trial is not to gather evidence in support of CE-marking nor, should it follow the procedure for performance evaluation.

In many cases, an IVD manufacturer will provide a biomarker assay or components thereof to a pharmaceutical company with no intent to develop the test further for future commercialisation. The product provided by the assay maker has no stated medical objective or intended use and is provided without any clinical interpretation instructions.

3.2 Clinical trial assay which is a device for performance evaluation

Where the IVD manufacturer has a device for performance evaluation they must follow Annex VIII (statement and procedure). The requirements include establishment of analytical performance[3,4] and, among others, implementation of risk mitigation measures in the design. The requirements and documentation obligations established by legislators aim to ensure patient safety. Importantly, they are specific to the performance evaluation study in question. Devices for performance evaluation should not be CE-marked[5] and EU countries are not allowed to create obstacles for making them available. The declaration submitted by IVD manufacturers to their local competent authority prior to making devices available for performance evaluation under Annex VIII of the IVD Directive can be considered as broadly equivalent to the manufacturer's registration of self-declared CE marking.

Performance evaluation procedure under Annex VIII of the IVD Directive is an appropriate and valid regulatory pathway to ensure that the device in question conforms to the requirements of the Directive, apart from the aspects covered by the evaluation and apart from those specifically itemised in the statement, and that every precaution has been taken to protect the health and safety of the patient, user and other persons."[6]

[3] 'Analytical performance' is the ability of a device to *correctly detect or measure* a particular analyte (IVD Regulation (IVDR) Article 2 (40)) 2017/746). In the case of predictive biomarker assays, the analytical performance shows whether the test can 'find' and 'measure' correctly the biomarker in question, and how precisely.
[4] IVDD Article 9 (4) and Annex VIII requires that the Essential Requirements (Annex I) are fulfilled, except the ones which are the purpose of the performance evaluation study. In the case of predictive biomarker assays, this means that e.g. analytical performance and implementation of risk mitigation measures must be established *before* the clinical trial.
[5] IVDD Article 4 (2) and Article 9.
[6] IVDD Annex VIII.2, 5th bullet point

This is most appropriate and typical regulatory status for a predictive biomarker assay, considering that many such assays are aspiring to become companion diagnostics and are therefore subject to co-development together with a corresponding drug.

3.3 Clinical trial assay which is CE-marked

Some EU regulators request assays to be CE-marked under the IVD Directive before they are used in clinical trials.

MedTech Europe is aware of the following issues which arise when predictive biomarker assays are required to be CE-marked before use in a clinical trial:

- Lack of harmonised approach in EU leads to regulatory confusion – some regulators require CE-marking whereas others require the Annex VIII statement and procedure. For some multi-country studies, CE-marking and performance evaluation of the same clinical trial assay are required by different competent authorities. The clinical trial assay is in an ambiguous situation of being CE marked but used for performance evaluation only, as the scope of the clinical trial is outside of the CE marked (un)intended purpose.
- The intended purpose of a device for performance evaluation is different to that of a CE-marked IVD. CE-marking an assay only for the purpose of using it in a clinical trial appears to bring the two regulatory pathways into contradiction. Requiring a CE-mark for assays deployed in early clinical trials may misrepresent the identity/purpose of the trial assay and cause later confusion.
- Requiring a manufacturer to comply with all the documentation and procedures (technical documentation, labelling, registration etc.) necessary to CE mark a clinical trial assay which may only be used in a single clinical trial/study, is burdensome and seems disproportionate. Many predictive biomarker assays do not transition from the trial to the market as a companion diagnostic. For assays which later become companion diagnostics a procedure to CE-mark the assay again is required to place the final configuration on market.

3.4 Clinical trial assay which is both a device for performance evaluation and CE-marked

Often clinical trials are run as multi-country and/or international investigations. Depending on in which European country a study is held, competent authorities could ask for the device to follow the procedure for performance evaluation or to be CE-marked. Where EU competent authorities have different perspectives on how to regulate multi-country clinical trial assays this can and does result in the same clinical trial assay attempting to comply with the requirements for performance evaluation and for CE-marking at the same time. This puts the status of the assay in a legally ambiguous position and means double sets of paperwork and procedures as well as further delays in starting the clinical trial.

According to the IVD Directive, a device intended for performance evaluation must follow the procedure under Annex VIII; moreover, the IVD Directive states that a device which is intended for performance evaluation

should not be CE-marked[7]. Once CE-marked, the device can be placed on the EU market. These two regulatory pathways are in direct contradiction to each other. IVD manufacturers or clinical trial sponsors seeking a legal basis for CE-marking of clinical trial assays – including those whose use could influence the patient management of study subjects – will not find it in national transposition of the IVD Directive nor in the Clinical Trials Regulation 536/2014/EU.

Opportunity for Discussion

MedTech Europe brings the above as discussion points with regulators to clarify the appropriate regulatory pathways. Requiring CE-marking of predictive biomarker assays before they are used in clinical trials/studies raises a number of practical issues. At the same time, following a fit-for-purpose approach can help inform the level of assay validation needed for the use of an assay in an interventional study. A lack of a harmonised approach between regulators causes additional administration, lack of legal certainty and in some cases stops trials from taking place in Europe.

We welcome a discussion on suitable approaches to ensuring patient safety whilst ensuring that innovation can continue to be promoted in Europe.

* * *

About MedTech Europe

MedTech Europe is the European trade association for the medical technology industry including diagnostics, medical devices and digital health. Our members are national, European and multinational companies as well as a network of national medical technology associations who research, develop, manufacture, distribute and supply health-related technologies, services and solutions.

For more information, visit www.medtecheurope.org.

[7] Directive 98/79/EC, Article 16 "1. Devices, other than devices for performance evaluation, considered to meet the essential requirements referred to in Article 3 must bear the CE marking of conformity when they are placed on the market"