EBE-EFPIA Personalised Medicine Working Group Manifesto

FINAL - 12 September 2017

Purpose and content of the Manifesto

The EBE-EFPIA Personalised Medicine Working Group Manifesto aims to highlight policy elements that are considered essential to ensure that personalised medicines and their paired diagnostic tests, also called companion diagnostics, successfully reach patients.

The Manifesto consists of three distinct parts, supported by a glossary, addressing the following policy needs:

• A clear and coordinated process for the regulatory approval of personalised medicine (Part I)
• A clear and predictable process for the economic/value assessment of and access to personalised medicine (Part II)
• A European regulatory framework that is supportive of innovation – creating a flexible and “forward-looking” regulatory and reimbursement environment (Part III) – which includes:
  o The use of multi-marker signatures
  o The use of electronic health record systems that facilitate clinical research, ease the collection and processing of real-world data and improve clinical practice
  o Data protection legislation that effectively facilitates the use of “big data” in healthcare research.

For each of the three parts above, barriers as well as related solutions are highlighted.

This document constitutes Part I of the Manifesto:

A clear and coordinated process for the regulatory approval of personalised medicine
Part I: A clear and coordinated process for the regulatory approval of personalised medicine

It is essential to clarify the role and responsibility of each player participating in the various phases of bringing personalised medicine (medicinal product and test) to patients. For each of these phases, key barriers as well as proposed solutions are outlined.

1 - Coordination of scientific advice for personalised medicine

Barrier:
The registration pathways for medicinal products and diagnostic tests are independent of each other in the European Union. This is anticipated to lead to a lack of coordination between decision makers, such as the European Medicines Agency (EMA), National Competent Authorities (CAs), Health Technology Assessment (HTA) bodies and Notified Bodies (NBs). Such a lack of coordination could pose a significant challenge for medicine developers and diagnostic manufacturers during the development and registration of the medicinal product and its associated companion diagnostic test.

Solution:
Specific scientific advice procedures should be developed to allow a collaborative approach between the EMA and NBs, taking the positive experience of parallel EMA-HTA advice into account.

2 - Regulatory assessment (including labelling)

Barriers:
The role and responsibility of the EMA or the relevant CA of an EU Member State in the evaluation of the suitability of a companion diagnostic for a given medicinal product is unclear, as stated in the recently adopted In-Vitro Diagnostic Medical Devices Regulation (IVD Regulation – Regulation (EU) 2017/746). It may lead to an unpredictable pathway and delays if there is duplication of work with NBs or conflicting assessments. More granularity is required, detailing how the interaction between the EMA, CAs and NBs will work in practice. The following points highlight key questions related to regulatory requirements throughout the IVD development process:

• The EMA or a CA will deliver an opinion to the NB on the companion diagnostic test and its suitability in relation to the concerned medicinal product. The conceptual elements and their management are unclear.
• How will the assessment or opinion on the companion diagnostic be integrated by the EMA or relevant CA into the formal medicinal product approval procedures and what role is
foreseen for the industry regarding the interactions with regulators, to ensure that concerns or questions are resolved in the most efficient manner?

• What is the mechanism for the resolution of conflict in cases of misalignment between NB and EMA or CA to avoid delay of approval for medicinal product or companion diagnostic?

• What are the regulatory requirements for investigational IVD tests used in the context of personalised medicine clinical trials? Standardisation of investigational IVD requirements is a challenge since the clinical trial application process governing medicinal clinical trials depends on the individual CA in each Member State.

• How will labelling decisions be coordinated between the medicinal product and companion diagnostic? Under the IVD Regulation, in its instructions for use, the companion diagnostic will refer to the International Non-Proprietary Name (INN) of the associated medicinal product for which it is a companion diagnostic. As for medicinal products, precedence of centrally approved products uniformly shows a requirement to use “a validated test”. Formal guidance on medicinal products’ labels should be developed when a companion diagnostic is used for patient selection (e.g. regarding the appropriate level of description of companion diagnostic test performance needed in the label).

• The pharmaceutical legislation has several provisions to enable accelerated approval and earlier access to innovative medicinal products for patients (e.g. accelerated assessment, PRIME scheme, conditional marketing authorisation, compassionate use, adaptive pathways, etc.) with the possibility of gathering real-world evidence. The independence of the medicinal product and companion diagnostic registration pathways could lead to a lack of coordination and potential delays in the companion diagnostic test registration for medicinal products that make use of an accelerated regulatory pathway.

Solutions:

The EMA’s and CAs’ new role and responsibility in the assessment of companion diagnostics should be clearly defined and effectively communicated. Furthermore, the EMA’s and CAs’ assessment of the suitability of the companion diagnostic in relation to the medicinal product must be coordinated closely with the NB to prevent delaying the availability of both the medicinal product and the companion diagnostic.

As part of the assessment, the companion diagnostic test’s analytical and clinical validation requirements expected by the NB, EMA or CA must be identified clearly and consistently with each other. This information should be made publicly available or shared through guidance documents.

Furthermore, during early dialogue with the medicines regulators, there should be an opportunity for developers of both medicinal products and companion diagnostics to discuss and agree on a single, integrated development plan with both medicines regulators and NBs. This would allow for the target (biomarker), diagnostic test and medicinal product to all mature together during development. Appropriate guidance should be developed by the EMA to support this process and clarify the performance data that will be requested, together with a procedural timeframe.
As well, adaptive regulatory pathways that can incorporate additional scientific evidence are needed, as they are particularly suitable for biomarker-selected populations. These flexible pathways would allow the updating of the intended use of the diagnostic tests and prescribing information of the medicinal products whenever novel clinical safety and efficacy information becomes available (e.g. new genomic targets).

Finally, the publication of precedents would be helpful in creating additional transparency with regard to review criteria. There is a critical need in personalised medicine for a publicly accessible database that lists all approved medicinal products along with their companion diagnostic test that have been appropriately validated for the relevant intended clinical use. This database should be updated frequently and provide links to publicly available performance data for both the medicinal product and companion diagnostic test. The example provided by the US FDA could be considered for this purpose (link available HERE).

**Specific considerations for targeted topics**

Four targeted topics require specific considerations: follow-on companion diagnostic tests; in-house testing; clinical evidence of a biomarker; and large genetic panels.

**Follow-on companion diagnostic tests:**

**Barrier:**

EU requirements for clinical validation of a “follow-on” companion diagnostic test that comes onto the EU market after the original registration of the medicinal product remains to be clarified.

**Solution:**

Development of regulatory guidance is needed to highlight the analytical performance requirements and potential clinical evaluation for “follow-on” companion diagnostic tests that come onto the market after the original registration of the medicinal product.

**In-house tests – devices manufactured and used only within health institutions established in Europe:**

**Barrier:**

In the EU, companion diagnostic testing can be performed using CE-marked IVD tests or in-house tests. Currently, in-house companion diagnostic tests with non-transparent performance data are widely used. Therefore, safety and efficacy of these laboratory-developed tests may be questioned when used in conjunction with a specific medicinal product.
Solutions:
In-house companion diagnostic tests should be held to the same quality standard as commercially developed companion diagnostic tests, specifically when they are used to make identical clinical decisions regarding a medicinal product. Further guidance is required on the subject of standards for validation of in-house companion diagnostic tests.

The widespread use of in-house tests also requires precise instructions and careful quality control, to ensure that all patients receive a reliable result to help guide their treatment. The introduction of an “in-house labelling” requirement to increase transparency about the performance of each of these assays is needed. The labelling should include analytical performance data that will improve the understanding of the test.

Lastly, given that the local implementation of a companion diagnostic in clinical practice is highly variable and very often dependent on in-house tests, the EMA and academic societies should cooperate to define EU-wide quality assurance schemes, with a view to ensure that both commercially-available diagnostics and in-house developed tests retain high quality and reproducibility in clinical practice. This could be realised with the support of pathology professional societies, or National Quality Assurance systems.

Clinical evidence of a biomarker

Barrier:
The utilisation of previously generated scientific and technical information related to the companion diagnostic’s development process is currently unclear.

Solutions:
In cases where appropriate clinical relevance for a biomarker has previously been confirmed, it should be sufficient to use retrospective data to establish the analytical and clinical performance of a new companion diagnostic test for this same marker.

This should be feasible if the following requirements are met:
- The generation of high-quality observational data with linked biologic specimens for a biomarker assessment as the basis for other clinical utility assessments
- Facilitating the use of retrospective bridging studies, demonstrating that an already existing diagnostic test could be used for another approved medicinal product.

Large genetic panels

Barrier:
The current regulatory system operates under a “one medicinal product – one companion diagnostic” paradigm. However, genetic biomarkers are typically part of larger genetic panels.
Solution:
The approval of diagnostic platforms on general performance metrics (e.g. next generation sequencing platforms) should be introduced, rather than basing the regulation on individual diagnostic targets. This would facilitate the validation of additional biomarkers as well as multi-market genetic signatures. Furthermore, all stakeholders need to join in the discussions to understand current clinical practice and where the technology is evolving. Based on this understanding, a flexible and dynamic regulatory framework for genetic panels should be discussed to promote future innovation in genetic testing.

3 - Post-authorisation

Barrier:
The approval of future extensions of a medicinal product’s use to new indications or patient groups could be delayed by the inefficient coordination of the intended use change of a companion diagnostic with regards to the existing registration.

Solution:
Efficient coordination between the medicinal product and companion diagnostic registration pathways is critical for new product indications to reach patients in a timely manner. Therefore, the link between the independent medicinal product (EMA, CA) and companion diagnostic (NB) registration pathways must be revised to arrive at a better-integrated process for approving changes in the post-authorisation phase.