EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle

Agreed by Pharmacogenomics Working Party	7 April 2017
Adopted by CHMP for release for consultation	20 July 2017
Start of public consultation	28 July 2017
End of consultation (deadline for comments)	15 November 2017

The proposed concept paper is intended to be developed into a guideline which will replace 'Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development' (EMA/CHMP/641298/2008).

Comments should be provided using this template. The completed comments form should be sent to PGWPSecretariat@ema.europa.eu

Keywords	*companion diagnostic (CDx), in vitro diagnostics (IVD), co-development, biomarkers, assay development, platforms, genetic testing, -omics, drug development*

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1. Introduction

A subset of personalised medicine is the use of predictive biomarkers (BM) to decide treatment or dose selection. As the science progresses, more personalised medicines are being developed and approved. In some cases, the assay used to measure the BM will be considered a companion diagnostic (CDx) as defined in the new in vitro diagnostic (IVD) medical devices regulation (IVDR) for the first time:

Companion diagnostic means a device which is essential for the safe and effective use of a corresponding medicinal product to:

- *identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or*
- *identify, before and/or during treatment, patients likely to be at increased risk for serious adverse reactions as a result of treatment with the corresponding medicinal product.*

In view of the publication of the new IVDR it is timely to consider developing guidance relating to the interface between medicinal products and predictive BM assays, including CDx.

2. Problem statement

In Europe, the legislations covering the marketing of medicinal products and IVD medical devices are not directly linked. The new IVDR envisages cooperation between notified bodies and medicines regulators in the evaluation of new CDx for obtaining a CE mark, although this will not lead to approval by medicines regulators of one or more specific CDx for use in conjunction with a given drug.

If it is recommended in the labelling that a medicinal product should be used in conjunction with a predictive BM, any commercial assay used for this purpose will be considered a CDx and will require an appropriate conformity certificate (CE mark).

Developments of medicinal products and IVDs are often independent, coming together only superficially towards the end. This may not be ideal as there remain gaps in evidence and validations. Therefore it would be helpful to provide guidance on using a close knit development programme linking the two, and use of clinical trials to generate evidence required to support validation of the diagnostic. The proposed guideline intends to highlight possible options to achieve this.

Also in the post-approval setting, it is essential that any CDx used to select patients for treatment with a medicinal product is adequately validated and sufficiently quality assured. This is important to ensure patients are not withheld potentially efficacious therapy and/or do not receive a potentially harmful therapy.

3. Scope

The guideline will provide recommendations relating to the interface between predictive biomarker-based assays including CDx, and the development and lifecycle of medicinal products.

4. Discussion (on the problem statement)

4.1. Clinical development phase

A CE-marked IVD may not be available to measure potentially predictive BMs during drug development, particularly in the case of novel BMs. In this scenario, the assay used in clinical development may itself be co-developed as an eventual CDx.

An important consideration for this guideline is the impact this may have on the clinical development program. The potential to align technical assay validation and clinical evidence requirements for drug approval with technical and clinical performance requirements for CE marking will be discussed.

The technical performance requirements of assays used to measure predictive BMs will vary in a stepwise fashion depending on the stage of development (early explorative study vs pivotal study), and whether the BM status affects study entry, subject eligibility and treatment allocation. The timing of the assay development in relation to drug development, and the use of central laboratory testing (particularly for highly complex tests), are also relevant considerations.

4.2. Post-approval phase

When a predictive BM test is recommended for the safe and effective use of an approved drug, the continued evaluation of benefit risk will depend in part on the availability of a suitably validated and quality assured assay, whether CE-marked or 'in-house'.

For the scenario discussed in section 4.1 above, the assay used during the pivotal trial in support of drug approval could be considered a reference test for the development and validation of subsequent CDx.

In order to facilitate the development of suitable tests for use in the clinic, the guideline will discuss concordance testing and bridging studies, including testing of stored patient samples. The interchangeability of assays that have been co-developed with more than one drug, but measure the same predictive BM, will also be considered.

A related aspect is the information provided in the Summary of Product Characteristics (SmPC) of the medicinal product regarding predictive BM-based assays that were used during the pivotal study; this is particularly relevant when predictive BM testing is mentioned in the SmPC. Information relating to assay performance characteristics could facilitate the development of suitable CDx post-approval.

Consideration will also be given to the role of the risk management plan for medicinal products to be used in conjunction with a predictive BM assay if there could be important risks associated with incorrect patient selection.

The impact of potentially non-harmonised life cycles of medicinal products and CDx including medicinal product labelling variations (e.g. new indications or patient populations) and test assay modifications will be considered.

4.3. A Glossary defining used terms in EMA guidelines and in the IVD Regulation

The guidance will define and explain regulators' understanding of specific terms in a glossary, e.g. analytical / clinical validation / performance, clinical utility, concordance studies and training and validation sets.

5. Recommendation

The Committee for Human Medicinal Products' (CHMP) Pharmacogenomics Working Party (PGWP) recommends drafting a Guideline on predictive biomarker-based assay development in the context of drug development and lifecycle.

6. Proposed timetable

It is anticipated that a draft guideline will be available 9-12 months after the end of the public consultation of the concept paper and will be released for 6 months external consultation.

7. Resource requirements for preparation

- Development of the guideline will be led by the PGWP, involving other relevant CHMP working parties including Scientific Advice Working Party (SAWP), Oncology Working Party (ONCWP), Biostatistics Working Party (BSWP) as necessary and the (EC) IVD working group.
- Expertise from stakeholders including notified bodies and competent device authorities will be included when drafting the guideline.

8. Impact assessment (anticipated)

The guideline will help to optimise the co-development of medicinal products and companion diagnostics. The anticipated effect is to better define the patients in whom the benefit/risk will be positive.

9. Interested parties

Medicinal product developers, Notified bodies, National Competent Authorities, IVD medical device developers, in-house test developers, HTA bodies, clinicians, pathologists and other pharmaceutical and device regulators.

10. References to literature, guidelines, etc.

- Reflection paper on co-development of pharmacogenomic biomarkers and assays in the context of drug development (draft)
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/07/WC500094445.pdf
- Guideline on good pharmacogenomic practice (draft)
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/05/WC500205758.pdf
- Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection (draft)
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/07/WC500108672.pdf
- ICH guideline E18 on genomic sampling and management 4 of genomic data (Step 3)
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/02/WC500200837.pdf

- ICH E16 Genomic biomarkers related to drug response: context, structure and format of qualification submissions
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097060.pdf

- Reflection paper on pharmacogenomic samples, testing and data handling
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003864.pdf

- Reflection paper on pharmacogenomics in oncology
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003866.pdf