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Committee for medicinal products for human use (CHMP)

Frequently asked questions on medicinal products development and assessment involving companion diagnostic (CDx)

Taking into consideration the recent implementation of the Regulation 2017/746 (*In vitro* diagnostic regulation (IVDR)), this Questions and Answers (Q&As) document aims to provide an overview of the Agency's current line of thinking on specific issues related to predictive biomarker-guided medicinal products development and assessment including a companion diagnostic (CDx) development. It is proposed to address issues that may require further clarity, considering their recurrence in pre-authorisation interactions and in the context of marketing authorisation/variation applications of medicinal products (hereafter referred to as drug regulatory submissions).

This Q&As document does not address assessment requirements for clinical trial approval by National Competent Authorities (NCA) or conformity assessment of candidate CDx by a notified body but provides guidance for generating adequate data for the marketing authorisation application for medicinal products.

These Q&As should be read in conjunction with the relevant regulations, scientific and regulatory guidelines and procedural guidance documents. In particular, the following Regulation is of relevance for CDx development and assessment as *in vitro* diagnostic medical device:

- Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices (IVDR) (1)

Within the current regulatory framework, 'companion diagnostic' is defined in the Art. 2 (7) of the IVDR, as 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.

Further, according to the IVDR, "…tests that provide information to predict treatment response or reactions, such as companion diagnostics, are in vitro diagnostic medical devices.

Companion diagnostics are essential for defining patients' eligibility for specific treatment with a medicinal product through the quantitative or qualitative determination of specific markers identifying subjects at a higher risk of developing an adverse reaction to the medicinal product in question or

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identifying patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective. Such biomarker or biomarkers can be present in healthy subjects and/or in patients. Devices that are used with a view to monitoring treatment with a medicinal product in order to ensure that the concentration of relevant substances in the human body is within the therapeutic window are not considered to be companion diagnostics."

For questions related to the requirements of the In vitro diagnostic medical devices regulation (IVDR) (Regulation (EU) 2017/746)) on IVDs in the context of medicinal products development, applicants are referred to relevant Medical Device Coordination Group (MDCG) guidance documents, in particular MDCG 2022-10 endorsed jointly by the MDCG and Clinical Trial Expert Group (CTEG), and advised to consult with the respective National Competent Authorities (NCAs) regarding IVD requirements in the context of Clinical Trial application(s) (CTA), such as:

- MDCG 2022-2 Guidance on general principles of clinical evidence for In Vitro Diagnostic medical devices (IVDs) (2)
- CTEG/MDCG 2022-10 Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) (3)
- MDCG 2023-1 guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746 (4)

Furthermore, in accordance with the IVDR, *in vitro* diagnostic medical device(s) falling under the definition of CDx (Art 2(7) of IVDR) require a conformity assessment by a notified body with consultation of the relevant medicinal product competent authority (EMA for centrally authorised medicinal product) to obtain CE marking. The consultation procedure by the CHMP/CAT focuses on the suitability of the CDx for use with the concerned medicinal product(s).

The applicant or the device manufacturer is strongly encouraged to contact timely a notified body with regards to the conformity assessment procedure considering also the timing of the CDx consultation procedure. For information on the CDx consultation procedure, please refer to the following:

- "Guidance on the procedural aspects for the consultation to the EMA by a notified body on companion diagnostics" and other related documents (Q&A on practical arrangements, application form and Assessment Report template, available at https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices). (5)

The conformity assessment of the CDx performed by the notified body as part of the CDx certification is outside the scope of the marketing authorisation evaluation of the related medicinal product. The robustness of clinical data as determined by the reliability and suitability of a test (also referred as assay in the context of drug development in this Q&A) used in a pivotal clinical trial(s) (that might be a candidate CDx of the final to-be-marketed CDx) is a part of the benefit-risk assessment. The supporting validation data on the biomarker assay(s) (candidate CDx) should be provided as part of marketing authorisation applications for medicinal products given their importance for the assessment of the benefit/risk balance of the related medicinal product. In this context, it is possible to discuss aspects related to the concerned predictive biomarker assay(s) (candidate CDx) as part of scientific advice procedures.

Other scientific and regulatory guidelines and procedural guidance documents are:

- ICH guideline E18 on genomic sampling and management of genomic data (EMA/CHMP/ICH/11623/2016) (6)

- Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection (EMA/446337/2011) (7)
- Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development (EMA/CHMP/641298/2008) (8)
- Guideline on predictive biomarker-based assay development in the context of drug development and lifecycle (EMA/CHMP/800914/2016, concept paper) (9)
- CHMP Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6) (10)
- Qualification of novel methodologies for drug development: guidance to applicants EMA/CHMP/SAWP/72894/2008 (11)
- Q&A on Complex clinical trials - Q5.3 What are the requirements with regard to the biomarker assays when results of complex clinical trials are submitted to support MAAs (12)
- Day 80 assessment report templates - sections 3.6 (clinical efficacy) and 4.6 (clinical safety) (13)
- Day 120 assessment report templates (section 3.3.4.5 and 3.3.7.5, respectively) (14)
- Pharmacogenomics information in SmPC – SmPC advisory group (15)
- Guideline on summary of product characteristics (SmPC) (16)

1 - What are the elements to consider when predictive biomarker assay(s) developed as companion diagnostic(s) are used for defining patients' eligibility for specific treatment with medicinal product in clinical trials intended to support drug regulatory submissions?

The Agency's position on (predictive) biomarker investigations in the context of drug development is described in relevant clinical efficacy and safety guidelines. In particular, the guideline on the evaluation of anticancer medicinal products (10) addresses the (predictive) biomarker-guided medicinal product development. Additional methodological considerations are covered in the Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection (7). With regards to sampling considerations, applicants are advised to consult the ICH guideline E18 on genomic sampling and management of genomic data (6).

When development of a medicinal product is associated with testing by an *in vitro* diagnostic (IVD) medical device, additional guidance and Q&As should be consulted (2, 3, 8, 12).

As a general principle, the strategy for development of a biomarker assay for defining patients' eligibility for specific treatment with a medicinal product should be scientifically sound and planned as early as possible, to aim for a CDx co-development with the medicinal product. Due to their importance for the evaluation of the robustness of data for the medicinal product, adequacy of the selected biomarker(s) and assay(s) for the intended purpose should be ensured during medicinal product development and substantiated by a sound scientific rationale (e.g. for biomarker-negative data collection), valid scientific criteria (e.g. for a clinical cut-off selection in case of (semi-) quantitative assays) and reliable evidence/data.

In general, the processes of development and validation for predictive biomarker assays refer, respectively, to efforts to develop and optimise a testing system for biomarkers and to demonstrate that the assay performance is adequate for the intended use.

Therefore, the extent of scientific knowledge on the biomarker guides the development strategy for the biomarker assay defining patients' eligibility for specific treatment with a medicinal product, including but not limited to:

- biological/pharmacological rationale, functional role of the biomarker, intended context of use,
- biomarker measurement approach, whether it is categorical, continuous (with further categorisation e.g. to biomarker-positive and biomarker-negative subpopulations) and/or composite,
- hypothesis regarding the relationship between the biomarker and the clinical outcomes,
- biomarker prevalence, clearly defined and pre-specified population in which the biomarker is measured, reflective of the target population (claimed indication),
- specific characteristics of biomarkers, such as biological variability and range of expression,
- analytical method(s) and cut-offs used to measure the biomarker throughout clinical development(s)

With regards to the (pre-)analytical methods and the biomarker assay development and validation the following elements should be considered:

- overall strategy for the biomarker assay development depending on the intended use,
- Pre-analytical (sample-related) factors, choice of the source/matrix of tissue/biomaterial in which the biomarker is measured, sample collection including sample transport and storage,
- analytes, technologies and platforms used and their respective limitations,
- selected analytical performance parameters, such as sensitivity and specificity considering pre-defined acceptance criteria and their justification,
- central and/or local testing.

From a clinical validation perspective, the following elements are essential:

- strategy to generate relevant data in the context of the specific medicinal product development depending on the strength of the relationship between the biomarker and clinical outcomes,
- rationale for the patient population eligibility in the clinical trial (regardless of the biomarker status or defined by biomarker(s) status), extent of available non-clinical and/or clinical data in subpopulation not enriched (such as biomarker-negative subpopulation),
- relevant clinical cut-off values based on semi quantitative measurement e.g. biomarker-negative and biomarker-positive subpopulations (including a rationale for the cut-off, preferably supported by a sound derivation and subsequent validation of the predictive performance of the biomarker and its cut-off).

Finally, biomarkers can be initially qualified for a specific context of use in the regulatory qualification procedure (10).

References: 2, 3, 6, 7, 8, 10, 11, 12

2- What are the elements to present in drug regulatory submissions when predictive biomarker assays have been used for defining patients' eligibility for specific treatment with a medicinal product in clinical trial(s)?

When submitting an application, companies should identify in the application form if the medicinal product is to be used with (a) CDx within the meaning of Article 2(7) of the IVDR. If the candidate CDx has not been CE marked or submitted for conformity assessment yet, preliminary information on the possible CDx should still be provided with anticipated timelines for the conformity assessment.

In the submitted dossier (module 2.5 and module 5), the Applicant should clarify whether the assay is considered as a predictive biomarker assay for efficacy/safety of the corresponding medicinal product and specify which assay version was used in the pivotal trial(s). Further, the testing laboratories should be stated as well as their adequate accreditation should be demonstrated. A discussion on the scientific rationale for biomarker selection and methodology used for analytical and clinical validation should be provided (refer to question 1 above).

Elements to be described include but are not restricted to:

- Intended use and scientific rationale for the choice of the biomarker and predictive biomarker assay, including their validation status (please refer to the question 1),
- Biomarker assay clinical development and validation strategy (prospective/retrospective),
- Detailed information on analytical validation of the assay used in the pivotal study and whether it was performed centrally,
- Eligibility criteria of the pivotal trial; whether the assay population/specimen is identical or representative for the target population,
- Data supporting the cut-point selection (since it is of particular importance for the benefit /risk assessment)
- Completeness of data collection (how the handling of missing data was prespecified and which data in terms of samples or results of testing are missing),
- Consistency of recruitment and assay performance between different study sites when local testing has been used.

In addition, information related to the different assay versions used during development and their concordance, as well as their analytical and clinical validity, may be expected (see question 3).

Lastly, the Applicant should make a proposal to adequately reflect the target population (i.e. claimed indication for the treatment) and the study results in relevant sections of the summary of product characteristics (see question 4).

References: 1, 2, 12, 13, 14

3- What are the elements to consider when more than one assay has been used to measure the same biomarker for defining patients' eligibility for specific treatment with a medicinal product in a clinical trial intended to support drug regulatory submission?

When several assays to measure the same biomarker are used in a clinical trial, the general principles described above apply for each of the assays used. If the assays are intended to be used interchangeably (e.g. different tissue-based assays; liquid biopsy proposed to be used as surrogate for tissue biopsy) concordance analyses should be provided.

When a sequential testing approach is used for patient selection, the testing strategy should be justified. Examples of such sequential testing are the use of assays of increased sensitivity or the use of different methods with different sensitivity and specificity (e.g. liquid biopsy followed by reflex

tumour testing). The use of several assays with different performance characteristics may lead to a certain degree of heterogeneity in the selected populations which could hamper interpretation of the clinical trial results. Heterogeneity in the populations could also have a negative impact on the interpretability of clinical results relating to concordance data between assays. To reduce such heterogeneity central testing is recommended. This should be taken into account when designing the study.

4- How should the information about biomarker-based assays used as companion diagnostic be reflected in the summary of product characteristics (SmPC) of the medicinal product?

Information about the biomarker should be included in relevant sections of the SmPC in line with the SmPC guideline and considering the recommendations from the SmPC advisory group on pharmacogenomics information in the SmPC.

Guiding principles regarding information regarding the IVD/CDx in the SmPC based on regulatory practice/experience are as follows:

- Inclusion of the biomarker (including cut-off if needed) in the indication wording (4.1) or in the contraindication (4.3) when applicable,
- Inclusion of information about the biomarker and the biomarker-based assay in 4.2, 4.4, 4.8 and 5.1 as relevant,
- It is recommended that the wording in section 4.2 of the SmPC makes reference to a CE-marked in vitro diagnostic (IVD) or a validated test, e.g. "… should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used."
- Information on specific aspects of treatment with the medicinal product related to its use with the validated test or assay should be described in the relevant sections of the SmPC to an extent sufficient to ensure safe and effective use of medicinal product. In the section 5.1 of the SmPC, additional mitigation of risks to safe and/or effective use of medicinal product can necessitate specification of brand names (e.g. when distinctive information on concurrently used tests/assays is needed).

References: 14, 15

5- To facilitate access to medicines, can a validated assay manufactured and used only within a health institution located in the EU be used for defining patients' eligibility for specific treatment with a medicinal product?

In accordance with the IVDR, CDx devices require a conformity assessment by a notified body to obtain CE marking and be placed on the market. Applicants are advised to plan biomarker assay/CDx development as early as possible during drug development to ensure timely access to new medicines approved for patients. Co-development of biomarker assay/CDx and drug candidate is recommended.

Devices manufactured and used only within health institutions established in the Union ("in-house devices") are exempted from most of the requirements of the IVDR provided that a number of conditions is satisfied. Regarding the possibility of their use for defining patients' eligibility for treatment with a medicinal product, applicants are referred to the IVDR and relevant guidance documents from the MDCG. To be noted, the use of "in-house" devices is limited to within one legal entity.

References: 1, 2, 3, 4

6- If the IVD assay/test is used outside its intended purpose for defining patients' eligibility for specific treatment with a medicinal product, what level of scientific evidence is required to justify such use?

If the assay is assigned an intended purpose that fulfils the definition of an IVD according to IVDR Article 2, then it must comply with the relevant requirements of the IVDR. This is the case for assays used for defining patients' eligibility for treatment with a medicinal product.

Applicants/sponsors are referred to relevant MDCG guidance documents and advised to consult with the respective NCAs regarding IVD requirements in the context of CTAs.

In the context of drug regulatory submissions, sponsors should clarify the regulatory status of the assay(s) used in the clinical trial(s) (i.e., in-house assay, certified in other regions, CE-marked in EU under IVDD, CE-marked in EU under IVDR as CDx, device for performance study under IVDR as CDx, etc.). If already CE-marked in EU, the sponsor should specify whether the proposed use is within or outside its prescribed intended purpose.

When IVD(s) are used in the context of drug development, it is the applicant/sponsor responsibility to provide sufficient information to ensure compliance with relevant requirements of the IVDR, justify the suitability of the IVD(s) for the intended use and to allow evaluation of the robustness of data to be generated for the benefit/risk assessment of the drug and for patient safety with regards to false testing results. In that respect, adequate analytical validation of the assay should be demonstrated, and scientific validity of the biomarker substantiated with data (see Q2).

References: 1, 2, 3, 12, 13, 14

7- Is a completed conformity assessment for an IVD intended to be used as CDx with a specific drug required to support the regulatory approval of the concerned drug?

From the medicine authorisation perspective, sufficient documentation on the IVD assay/test needs to be provided to support the robustness of the clinical data generated. There is no legal requirement that the evaluation of the medicinal product and the device certification take place in parallel, and therefore they do not have mandatory simultaneous review periods. As a general principle, early interactions between the NCA/EMA and the relevant notified body are recommended to enable timely access for patients to both the medicinal product and the CDx.