Progress with the implementation of the Companion diagnostics framework under the EU In-vitro Diagnostic Regulation (IVDR)

Update on the final guidance

8th Industry Stakeholder Platform on R&D support

Monday 11 July 2022

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Why In-vitro diagnostics? Oncology examples

About 1/3 of marketing authorisations in the field of oncology, approved in EU between 2010 and 2020, required a diagnostic test for patient identification.
Medicinal product & IVD/CDx interplay in Europe

Medicines NCA
Clinical development phases
I II III (pivotal)
Cut off establishment
Cut off confirmation
Predictive power BM

EMA - EC
Benefit/risk assessment
Initial MA application Opinion & MA
PhV Post approval changes

SmPC Indication
Intended Use SSP/IFU

Initial consultation Opinion *
Follow-up consultation

Conformity assessment
Notified body
CE
PhV Post approval changes

Companion diagnostic (EU IVD Regulation)

Scientific validity Feasibility
Analytical performance Clinical performance
Clinical development phases
IVD-NCA

Prototype assay
BM Hypothesis

Abbreviations: BM: Biomarker; CDx: Companion Diagnostics; EC: European Commission; EMA: European Medicines Agency; IVD: In vitro diagnostic medical device; MA: Marketing Authorisation, NCA: National Competent Authority; R&D: Research & Development
Need for systematic review of predictive biomarker & assay (CDx) data

Consideration to reflect information on the biomarker & assay in the SmPC

D80 AR template - In vitro biomarker test for patient selection for efficacy and safety

Scientific rationale for the choice of the predictive in vitro biomarker test (e.g. prevalence, relation to disease mechanism)

Analytical method including assay platform, specimen, pre-analytical processing requirements and read-out method.

Consideration of the status of the assay in pivotal trial in relation to the intended CDx

Analytical and clinical validation strategy:
• Analytical validity: For verifying the suitability of an assay, robustness, accuracy, specificity, sensitivity and linearity should be considered depending on the analytical platform
• Clinical validity (sensitivity/specificity) should be described either by correlation with a clinical endpoint (for novel assays) or -if available- by concordance study with a clinically valid reference assay
• Cut-point selection should be described and discussed in detail since it is of particular importance for the benefit /risk assessment

Medicinal product & IVD/CDx interplay in Europe

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CDx definition - Art. 2(7) IVDR

“(7) ‘companion diagnostic’ means a device which is essential for the safe and effective use of 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.”
What the legislation states on CDx

**Conformity assessment** - IVDR Article 48

For **companion diagnostics** the **notified body** shall consult the concerned **competent authority** designated in accordance with Directive 2001/83/EC or the European Medicines Agency (EMA), as applicable.

- Scientific validity
- Analytical performance
- Clinical performance

**SSP & IFU** - ANNEX IX, Chapter II - 5.2

The **notified body** shall, before issuing an **EU technical documentation assessment certificate** for the companion diagnostic and on the basis of the **draft summary of safety and performance** and the **draft instructions for use** [...] consult one of the competent authorities [...] regarding the **suitability of the device in relation to the medicinal product concerned**.
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Opinion*

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Conformity assessment
Notified body

Companion diagnostic (EU IVD Regulation)
Scientific validity  Feasibility
Analytical performance  Clinical performance

R&D  Prototype assay  BM Hypothesis
Clinical Trial Assay  GMP Assay
Clinical development phases
IVD-NCA

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Scope of assessment: Suitability of the CDx for use with the concerned medicinal product(s)

“Suitability” relates to the use of a CDx with a particular medicinal product(s), given the performance and use claimed by the manufacturer.

Aspects that are considered when assessing the suitability of a CDx:

• Scientific validity (scientific rationale)
• Analytical performance
• Clinical performance
Different scenarios of the CDx consultation procedure

- **Co-developed CDx:** a device that is developed in a clinical development program together with the concerned medicinal product, either in view of an initial marketing authorisation or a change of the indication. This can mean that the device was developed in the framework of:
  - A pivotal clinical trial with the concerned medicinal product
  - A bridging study assessing the concordance of the CDx and the device used in the pivotal clinical trial of the corresponding medicinal product

- **Follow-on CDx:** a device that seeks the same indication in its intended use as the co-developed CDx (hereafter, original CDx). The follow-on CDx targets the same biomarker but is not developed in parallel with the clinical development programme of the medicinal product and is not necessarily based on the same technology as the original CDx.

- **Devices already marketed under Directive 98/79/EC on in vitro diagnostic medical devices (IVDD).** The two scenarios above are possible depending on how the device was initially developed. → For Class C devices, transitional period for application of IVDR requirements until 26 May 2026
Overview of steps for implementation of CDx consultation

- **Dec 2022**: Publication of draft guidance and procedural documents
- **Jan 2022**: First CDx consultation submitted to the EMA
- **Feb 2022**: End of public consultation on the procedural guidance
- **Jun 2022**: Adoption of guidance and procedural documents by CHMP/CAT
Relevant guidance published on the EMA webpage

- **Guidance on the procedural aspects** for the consultation to the EMA by a notified body on CDx
- **Assessment Report template** for consultation on CDx
- **Application forms** for initial and follow-up consultation on CDx
- **Letter of intent-template** for the submission of a consultation
- **Q&A** on practical arrangements on the CDx consultation procedure

| Adoption by CAT for release for consultation | 10 December 2021 |
| Adoption by CHMP for release for consultation | 16 December 2021 |
| End of consultation (deadline for comments) | 20 February 2022 |
| Adoption by CHMP | 13 June 2022 |
| Adoption by CAT | 17 June 2022 |
| Date for coming into effect | Publication date |

Keywords: Consultation, notified body, companion diagnostic, in vitro diagnostic, medical device, biomarker

[Medical devices | European Medicines Agency (europa.eu)](https://www.europe.eu)
Initial consultations (60-day TT with a possible extension of 60 days)

• Pre-submission phase
• Submission & validation
• Assessment (ad hoc CHMP/CAT discussion)
• Adoption of Opinion or List of Questions (LoQ)

Follow-up consultations (30-day TT, no extension)

Procedural timetables | European Medicines Agency (europa.eu)
Topics for further discussion...

- **Publication of the CHMP assessment report** on the CDx consultation
- Reflection of information on **CDx in the SmPC** of the medicinal product
- Clarification of **scope of NB and CHMP/CAT assessments**
- Opportunities to get more accurate **estimates for expected CDx consultations**

→ Learning curve for all stakeholders involved
→ Need for further close interactions between stakeholders, including medical device and pharmaceutical industry, to facilitate and optimize this process
Thank you for your attention

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Further information

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