Regulation of companion diagnostic IVDs
Overview of CDx regulation – 30 minutes

IVDR basics
Clinical evidence requirements
Development models
Assessment of performance studies
Health Warning!

These views on the interpretation of the Regulations represent my own best judgement based on the information currently available. MHRA would always advise you to seek the views of your own professional advisers.
Contents

I Legislative acts

REGULATIONS


However, most requirements will not fully apply until 26th May 2020 for Medical Devices, and 26th May 2022 for In Vitro Diagnostic Medical Devices.
IVD development

Performance evaluation

Interventional study

NCA assessment

Performance study

Scientific Validity
Analytical performance
Clinical performance

MA/EMA assessment

NB assessment

Companion Diagnostic

CE mark

Health Institution Exemption

Clinical use
Clinical evidence is …

- based on performance studies
- used to demonstrate compliance with the regulations
- updated through the lifecycle of the product
Performance evaluation

Performance study
“To allow for a structured and transparent process, generating reliable and robust data, sourcing and assessment of available scientific information and data generated in performance studies should be based on a performance evaluation plan.” (recital 61 IVDR)

“As a general rule, clinical evidence should be sourced from performance studies …” (recital 62 IVDR)

“(42) ‘performance study’ means a study undertaken to establish or confirm the analytical or clinical performance of a device;” (Article 2 IVDR)
## Performance indicators for IVDs

<table>
<thead>
<tr>
<th>Scientific Validity</th>
<th>Analytical Performance</th>
<th>Clinical Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• the association of an analyte to a clinical condition or a physiological state</td>
<td>• the ability of a device to correctly detect or measure a particular analyte</td>
<td>• the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user</td>
</tr>
</tbody>
</table>
General requirements for all IVD performance studies

• the health and safety of patients, users and other subjects
• the circumstances of the study
• rights, safety, dignity and well-being of the subjects in the study
• studies involving left over samples
• data generated by the study

data generated are going to be scientifically valid, reliable and robust
Additional requirements may apply

- Surgically invasive samples
- Interventional studies
- Additional risks to subjects
- Companion diagnostic IVDs
- Studies that involve people from specific groups
- Emergency situations
Additional requirements may apply

- Prior authorisation by a Member State(s)
- Review by an independent ethics committee
- Protection of vulnerable subjects
- Management of risks and benefits to the subject
- Informed consent and not exerting undue influence
- Demonstrating analytical performance and scientific validity
- Qualifications of those involved in the study
- Study facilities
'companion diagnostic'
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** of serious adverse reactions as a result of treatment with the corresponding medicinal product

*This includes devices used in clinical trials to stratify patients for inclusion/exclusion in the trial or stratified to a cohort within a trial.*
Performance indicators for IVDs
(clinical condition with a companion diagnostic ~ likely to respond to the medicinal product)

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</tr>
<tr>
<td>• What is the evidence for the association between the biomarker and the likelihood of response to the corresponding medicinal product?</td>
<td>• How good is the IVD at detecting biomarker?</td>
<td>• How good is the IVD at predicting who is likely to respond to the corresponding medicinal product?</td>
</tr>
</tbody>
</table>
**CDx development**

<table>
<thead>
<tr>
<th>Medicinal Product</th>
<th>IVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novel</td>
<td>Novel</td>
</tr>
<tr>
<td>Novel</td>
<td>CE-CDx</td>
</tr>
<tr>
<td>Approved</td>
<td>Novel</td>
</tr>
<tr>
<td>Approved</td>
<td>CE-CDx</td>
</tr>
</tbody>
</table>

Equivalence (MDR) Clinical, Technical, Biological (performance?)
CDx development

1. Medicines legislation
2. Phase I trial
   - Medicines Authority review
   - Devices Authority review/notification
3. Phase II/III trial
   - Medicines Authority review
   - Notified Body review
4. Clinical performance study
5. Marketing Authorisation
   - Medicines Authority opinion
   - CE mark (Companion Diagnostic)
6. Analytical performance/Scientific validity
7. Devices Regulation
8. Medicines legislation
9. Devices Regulation
10. Medicines Authority review
11. Notified Body review
12. Medicines Authority opinion
13. CE mark (Companion Diagnostic)
Application process for Competent Authority assessment of companion diagnostic IVD performance evaluation studies

Stage 1. Application and coordination

1a Trial sponsor notifies application
1b Commission assigns SIN via electronic system
1c Agree coordinating Member State and inform sponsor
1d Trial sponsor submits changes

Stage 2. Verification

2a Coordinating member state verifies application
2b In scope and complete?
2c Return to sponsor
2d In scope and complete?
2e Rejected
2f Member State appeals process

Stage 3. Assessment

3a Member State opinion

Stage 4. Running the trial

4a Study begins
4b Study continues (with modification or corrective measures - if needed)
4c Substantial modification
4d Member State opinion
4e Refusal

Stage 5. Performance study report

5a Study ended, suspended, or terminated early by sponsor
5b Performance study report submitted
5c Performance study report publicly accessible

45 days (extendable by 20 days)

Within 1 week of the change

4a Sponsor opinion
4b Sponsor opinion
4c Authorisation withdrawn

Stage 5. Performance study report

24 hours for early termination or suspension
15 days for end of study

3 months for early termination
1 year for end of study

Immediately (if study terminated early)
On registration (if study ended)
Within one year (if study ended but device not registered)
### Follow on companion diagnostics (aka me2)

<table>
<thead>
<tr>
<th>Equivalent?</th>
<th>Samples?</th>
<th>New clinical performance study?</th>
<th>Notify to competent authority?</th>
<th>Assessed by competent authority?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Only left over samples</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>Only left over samples</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>New samples</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>Only data??</td>
<td>??</td>
<td>Yes</td>
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CDx development

Medicines legislation

Phase I trial

Medicines Authority review

Analytical performance/Scientific validity

Clinical performance study

Phase II/III trial

Medicines Authority review

Devices Authority review/notification

Notified Body review

Marketing Authorisation

Medicines legislation

Devices Regulation

CE mark (Companion Diagnostic)
Role of Notified Bodies and EMA
Health Warning!

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Summary of CDx regulation

IVDR basics
Clinical evidence requirements
Development models
Assessment of performance studies
Thank you

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