Personalised medicine: IVD’s and Companion Diagnostics

Competent Authority Perspective
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IVDR & Companion Diagnostics

Daryl Colombage, MHRA
Presentation Objectives

• CDx definition
  – classification

• IVDR requirements for CDx
  – clinical evidence requirements
  – additional requirements for performance studies
  – performance study evaluation application process

• Perspective on the current situation
IVDR & Companion Diagnostics (CDx)

CDx Definition:
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

CDx Classification: Class C, Rule 3(f) (Annex VIII)
Clinical Evidence

“… compliance … should be based on clinical evidence. … As a general rule, clinical evidence should be sourced from **clinical performance studies** …”

**Clinical evidence IVDR definition:**

“the clinical data and performance evaluation results, pertaining to a device of sufficient amount and quality to allow a qualified assessment of whether the device achieves the intended clinical benefit(s) and safety, when used as intended by the manufacturer;
# Performance indicators for IVDs

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<tr>
<th>Scientific Validity</th>
<th>Analytical Performance</th>
<th>Clinical Performance</th>
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<tbody>
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<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>
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Performance indicators for IVDs: CDx

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<td>• What is the evidence for the association between the <em>biomarker</em> and the likelihood of response to the corresponding <em>medicinal product</em>?</td>
<td>• How good is the IVD at detecting <em>biomarker</em>?</td>
<td>• How good is the IVD at predicting who is likely to respond to the corresponding <em>medicinal product</em>?</td>
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Performance studies

IVDR Article 57: General requirements on all studies
e.g. H&S of patients, user and others; data scientifically valid, reliable and robust

IVDR Article 58: Additional study requirements for:
- ‘interventional’ studies – affecting patient management decisions (e.g. drug/diagnostic co-development) and
- studies that involve invasive procedures or other risks for patients.

Competent authority approval for ‘interventional’ studies
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

6 days / 6 days

1d Trial sponsor submits changes
Within 1 week of the change
Stage 4. Running the trial

4f Corrective measures needed

4g Sponsor opinion

7 days

4h Member state opinion

4i Authorisation withdrawn

4a Study begins

4b Study continues (with modification or corrective measures - if needed)

4c Substantial modification

38 days (extendable by 7 days)

4d Member State opinion

4e Refusal
Stage 5. Performance study report

5a Study ended, suspended, or terminated early by sponsor
- 24 hours for early termination or suspension on safety grounds
- 15 days for end of study

5b Performance study report submitted
- 3 months for early termination
- 1 year for end of study

5c Performance study report publicly accessible
- Immediately (if study terminated early)
- On registration (if study ended)
- Within one year (if study ended but device not registered)
Co-development

Medicines legislation → Phase I trial → Phase II/III trial → Marketing Authorisation

Medicines Authority review → Devices Authority review/notification → Medicines Authority review → Medicines Authority opinion → Notified Body review → Clinical performance study → CE mark (Companion Diagnostic)

Planned Devices Regulation → Analytical study
Role of Notified Bodies and EMA

Notified Body

- Review of EMA opinion
- Review of IVD manufacturer
  - Request to EMA
    - Draft summary of safety and performance
    - Draft instructions for use
- Provide certificate to IVD manufacturer
- Convey decision to EMA
- Manufacturer applies CE mark (companion diagnostic)

EMA

- Opinion to NB
- Opinion on suitability of the device in relation to the medicinal product
- Public Assessment Report
Current situation (MHRA view)

1. Medicines legislation
2. Phase I trial
3. Phase II/III trial
4. Marketing Authorisation
5. Analytical study
6. Clinical performance study
7. CE mark
8. Planned Devices Regulation

Steps:
- Medicines Authority review
- Devices Authority review
- Medicines Authority review
- Notified Body review
- CE mark (Companion Diagnostic)

Notes:
- IVD for performance evaluation
- Crosses indicate failed steps
Current situation (MHRA view)

In Vitro Diagnostic Medical Devices (IVDs)

Unless an exemption applies, all IVDs being placed on the market or put into service in the EU are required to be CE marked.

This includes devices used in clinical trials of medicines to stratify patients for inclusion/exclusion in the trial or stratified to a cohort within a trial.

At the time of the clinical trial application, the CE mark need only be for the analytical performance of the IVD (eg detection of a biomarker) and will include reagents, equipment, calibrators, controls and software.

These are likely to be self-certified IVDs under the current medical device regulations.

Trials which determine the clinical performance of the assay (biomarker validity) will need to be registered as IVD performance evaluation studies.

The question of whether clinical performance studies involving non-CE marked IVDs can take place on a voluntary basis under the IVDR between now and 2020 is subject to further interpretation.

Building partnerships

What’s in the regulations?

What do the regulations mean?

What does the process look like?

How will it fit with our existing process?
Presentation Objectives - Recap

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