Companion Diagnostics – a regulator’s perspective

Steve Lee
Monday 1st July
Aligning Research Standards with Clinical Standards

- Clinical evidence
- Notified Bodies and EMA
- CDx
- Drug and patient safety
- Challenges and opportunities
Disclaimer

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.
'companion diagnostic'

An in vitro diagnostic medical 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.
Companion Diagnostics

- Medicines legislation
- Phase I trial
- Phase II/III trial
- Medicines Authority review
- Devices Authority review/notification
- Medicines Authority review
- Medicines Authority opinion
- Notified Body review
- Clinical performance study
- CE mark (Companion Diagnostic)
- Marketing Authorisation

- Analytical performance/Scientific validity
- Medicines legislation
- Devices Regulation
- Medicines legislation
Intended purpose

Previously
For the measurement of serum rhubarb

Now
For the quantitative measurement of rhubarb in human serum on the SL+ instrument.

For use as a companion diagnostic in people with specific symptoms to identify those likely to benefit from treatment with rhubarbimab.

Only for use by qualified laboratory professionals.

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Performance evaluation report

Scientific validity report
- Other device
- Literature review
- Expert opinion
- Studies

Analytical performance report
- Specimen type
- Accuracy
- Sensitivity/specificity
- Measuring range/cut-off
- Novel markers

Clinical performance report
- Clinical performance studies
- Peer reviewed literature
- Published experience
- Equivalence?

Clinical evidence
... a qualified assessment whether the device will achieve the intended clinical benefit or benefits and safety, when used as intended by the manufacturer. The data and conclusions drawn from this assessment shall constitute the clinical evidence for the device. The clinical evidence shall scientifically demonstrate that the intended clinical benefit or benefits and safety will be achieved according to the state of the art in medicine.

Other studies
- Stability (shelf-life, in use, shipping)
- Software V&V
- Sterility
- AHM origin
- Measuring fx
- Combination
Companion Diagnostics

1. Medicines legislation
2. Phase I trial
3. Phase II/III trial
4. Marketing Authorisation

Analytical performance/Scientific validity

- Devices Authority review (Phase II/III trial)
- Medicines Authority review (Phase I trial)
- Notified Body review
- Medicines Authority opinion
- CE mark (Companion Diagnostic)
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
Subjects in a CTIMP are tested for a biomarker that allows detection of early signs of drug-induced liver injuries - eg ALT, miRNA etc

**Question:** How should the biomarker test be regulated?

<table>
<thead>
<tr>
<th>Answer</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory tests do not need to be regulated</td>
<td>A</td>
</tr>
<tr>
<td>Biomarker validation is part of the clinical trial application</td>
<td>B</td>
</tr>
<tr>
<td>Assay validation is an IVD performance study</td>
<td>C</td>
</tr>
<tr>
<td>A clinical test on patient samples should be CE-IVDR</td>
<td>D</td>
</tr>
</tbody>
</table>
Challenges and opportunities

Coordination, coordination, coordination
Health Institution Exemption

Devices that are made or modified and used within a health institution do not need to meet all the requirements of the regulations

Exempt devices must:

• Meet the relevant requirements for safety and performance
• Have a justification for the exemption based on target patient group’s specific need
• Have formal technical documentation in place
• Be made and used within an appropriate quality system
• Have some information made publicly available

Performance studies?
# Immunotherapy

<table>
<thead>
<tr>
<th>Drug INN</th>
<th>Cancer</th>
<th>Marker(s)</th>
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<tbody>
<tr>
<td>everolimus</td>
<td>breast</td>
<td>Hormone receptor HER2/neu</td>
</tr>
<tr>
<td>trastuzumab</td>
<td>breast</td>
<td>HER2/neu</td>
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<td>pembrolizumab</td>
<td>lung</td>
<td>PD-L1</td>
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<tr>
<td>abixabtagene ciloleucel</td>
<td>NHL</td>
<td>Tumour Specific Antigen</td>
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<tr>
<td>Aid to prescribing</td>
<td>range</td>
<td>Tumour Mutation Burden</td>
</tr>
</tbody>
</table>
Can sandboxing help to bridge from research to practice?

**RUO**
- Observational study
  - Art 57
- Intervenional study/CDx
  - Art 58

**CE**
- Intended purpose #1
- PMPF
- PMS

**CE**
- Intended purpose #2

**Bridging study?**
- Data may not be submissible
- Data should be submissible
- Limitations
- SANDBOX
- Reduced Limitations

**No patient management**
- Patient management OK
Other challenges and opportunities

- Follow on (2\textsuperscript{nd} gen) IVDs (equivalence)
- Early access to medicines
- Labelling (SPC)
- Clinical compliance
- Established CDx
- Reference materials
- ‘Complementary’ diagnostics: Define ‘essential’
- Real World Evidence
- Software as a medical device (SaMD)
- Performance monitoring (eg EQA)
- CDx developed and/or used outside of EU