Lyfjastofnun
Icelandic Medicines Agency

The European Regulatory Landscape

Perspectives on development and validation of endpoints

Kerstin Wickström, Lyfjastofnun (Icelandic Medicines Agency)

Ocular Disease Forum 1

May 15, 2023

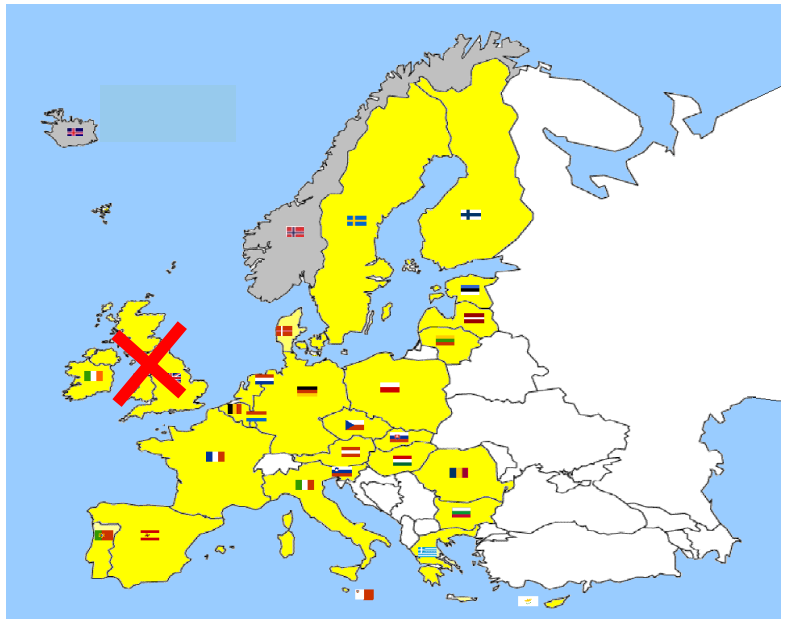
Disclosure: No conflicts of interest

Disclaimer: All views expressed are personal and not necessarily the views of EMA, the CHMP or Lyfjastofnun

EU regulatory system

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Created in 1995
- Permanent secretariat
- Coordinate procedures & scientific resources
- www.ema.europa.eu/

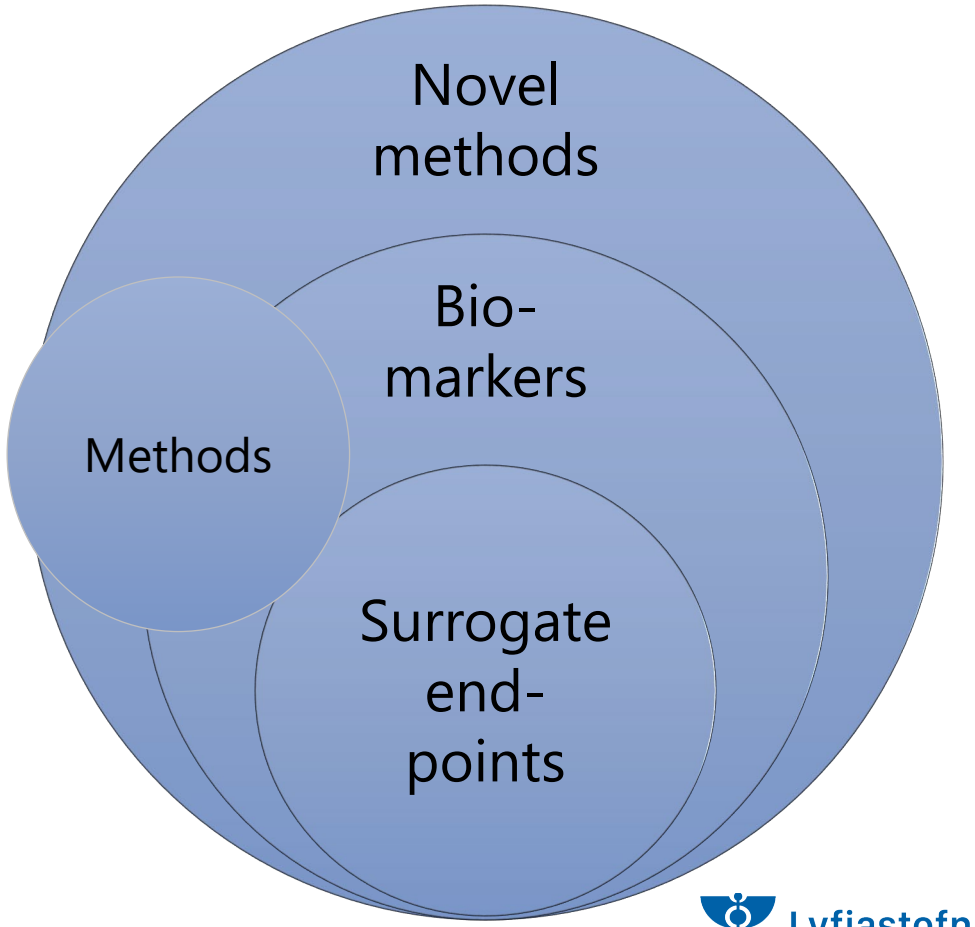


- National agencies
  - scientific resources
  - > 4000 experts
- CHMP
  - Scientifically responsible
  - From EU member states + IS, NO and 5 co-opted members
  - Provide positive or negative opion on approval of drugs
- SAWP
  - Members based on expertise, not country
  - Provides scientific advice on drug development
    - On specific drugs, novel methods, biomarker and endpoint development
    - Dialogue between developer and EU regulators

Lyfjastofnun
Icelandic Medicines Agency

Definitions

- **Biomarker:** An objective measure of normal, pathogenic, or pharmacological processes in response to intervention.
- **Surrogate endpoint:** A biomarker that is intended to substitute for a clinical endpoint.
- **Clinical endpoint:** Reflects how a patient feels, functions, or survives



Lyfjastofnun
Icelandic Medicines Agency

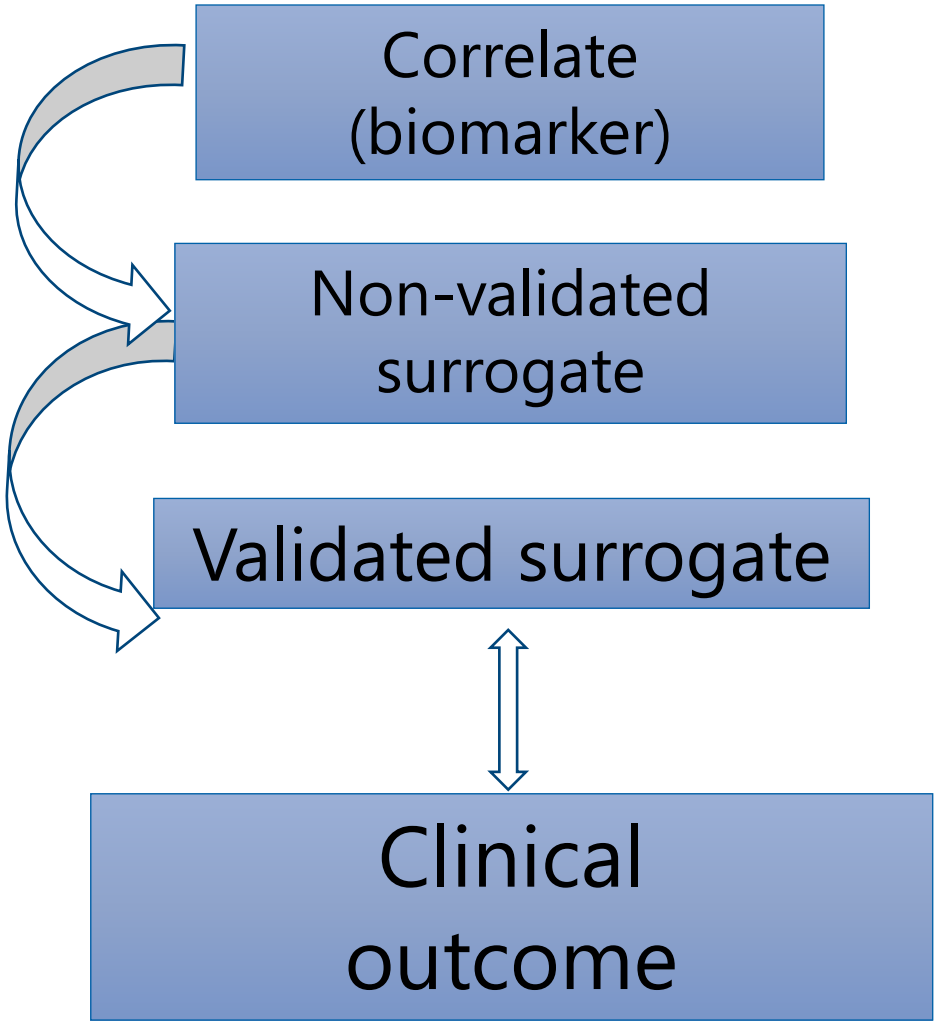
Validation?

» Google says:

"the action of checking or proving the validity or accuracy of something"

Strengths and weaknesses characterised

The "marker" captures what it is intended to

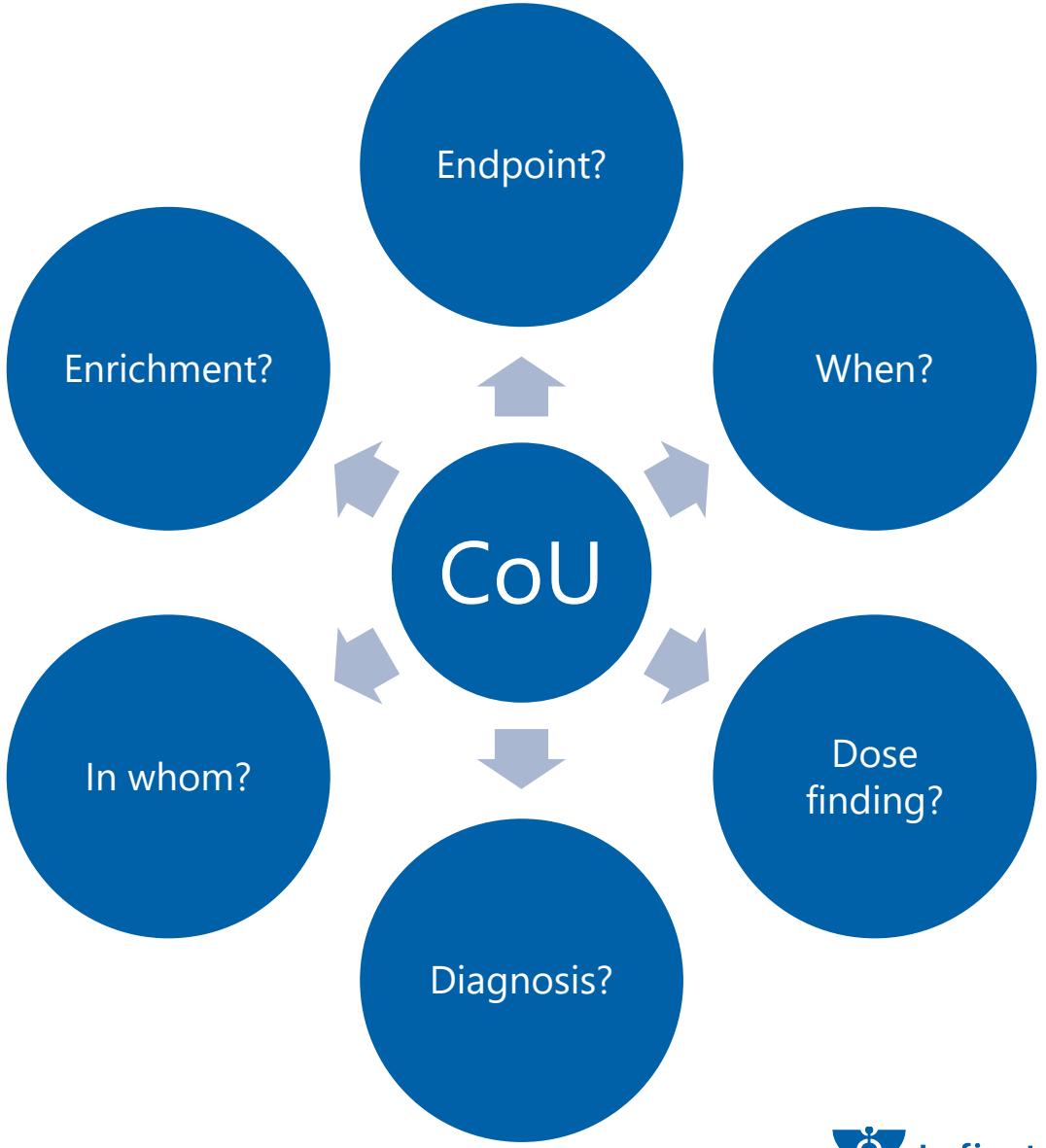


Lyfjastofnun
Icelandic Medicines Agency

Validation - Context of use?

- How should the "marker" be used?
- Which weight is it given?
  - By the Sponsor
  - By the Regulator
- What are the associated claims?

- Starting point: define the "Context of use"



Lyfjastofnun
Icelandic Medicines Agency

Context of Use vs Requirements

Exploratory trials

- Primary or secondary endpoint – biomarker or surrogate
  - proof of concept
  - aid in dose selection

Relaxed

Risk to developer in case of wrong conclusions from "poor" marker

Confirmatory trials

- Primary (and key secondary) surrogate endpoint

Not relaxed

Link to and relevance for clinical outcome to be established

Validation

- secondary or exploratory endpoints
  - supportive efficacy
  - support mechanism of action
  - sub-group characterisation

More relaxed

Depends on associated claims

The basis for validation of a surrogate endpoint

Context of Use: Primary endpoint in registrational trial(s) in a moderate to severe patient population with disease Y

Plausible

Reliable

Content validity

Construct validity

Change to intervention/ Predictable

Responsive

Surrogate endpoint

Correlation only not sufficient

THE LINK TO AND THE RELEVANCE BETWEEN MARKER AND CLINICAL OUTCOME TO BE ESTABLISHED

- What does a change of the surrogate mean in terms of loss or gain of visual function/functional vision? Over time?
- What to tell the patient?

- At the end of the day
  - A fully validated surrogate (primary endpoint) in a confirmatory trial, should work across trials with different interventions.

Challenges

- Link to and relevance between marker and clinical outcome
- In often slowly progressing conditions such as IRDs, GA, DR etc?
  - Learn from natural disease history data
  - Info from previous trials
  - Learn from failures
  - Anchoring using quality of life instruments and other, more rapidly progressing measures of likely importance
  - Support from other biomarkers and/or anatomical markers
  - Enrich study population
  - Modelling – e.g. the time to severe visual impairment/blindness
- Totality of data
- Remaining uncertainties – are they acceptable?

EU process for qualification of “biomarkers”

- Qualification advice
  - Voluntary, scientific pathway
  - Confidential advice letter

- Qualification opinion
  - CHMP issues an opinion on the acceptability of a specific use of a marker

» http://www.ema.europa.eu/

Thanks for your attention!

Lyfjastofnun
Icelandic Medicines Agency