Regulatory Considerations for Rare Disease Drug Development and approval in the EU

Regulation & Considerations

Organisers: THE CYPRUS INSTITUTE OF NEUROLOGY & GENETICS
DEPUTY MINISTRY OF RESEARCH, INNOVATION AND DIGITAL POLICY
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Navigating the regulatory landscape

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Where We Are

Progress has been made…

- Orphan Regulation born in 2000
- Over 3000 orphan drug designations
- Already over 260 orphan medicines approved

… But still too far to go

- > 6000 orphan diseases characterized
- Only over 260 orphan drugs approved
- Uneven momentum across disease groups
- Ultra rare diseases lag even more

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EU Regulatory Orphan Framework

- **Core Criteria for Orphan Status**
- Identification of rare disease
- Medical plausibility based on functional outcome data
- Seriousness
- Low disease prevalence
- Significant benefit over existing treatments (Europe)

- **Regulatory and Financial Incentives**
- Protocol assistance (free with SME status)
- Academic Office support
- Fee reductions & Market exclusivity
- Conditional Licencing with orphan designation
- Need for a Paediatric Investigational Plan

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Significant Benefit a European thing for Designation

- **Significant benefit remains a cornerstone for OD**
- Indirect Comparisons have already become unavoidable
- MAIC / STC / IPD-adjusted methods

- **No silver bullet to overcome weak comparator choice or compensate for missing prognostic factors**
- Planning and transparency
- **Important for Maintenance of Orphan Designation**

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Challenges for Developers

- Limited knowledge of condition
- Primarily a paediatric condition (only a third of conditions are adult only)
- Small patient populations.
- Phase 2 data only, single arm studies, limited safety data.
- Insufficient knowledge of end-points to measure.
- Difficulty to recruit.
- No registries or natural history studies
- Advanced therapies requiring different Quality requirements

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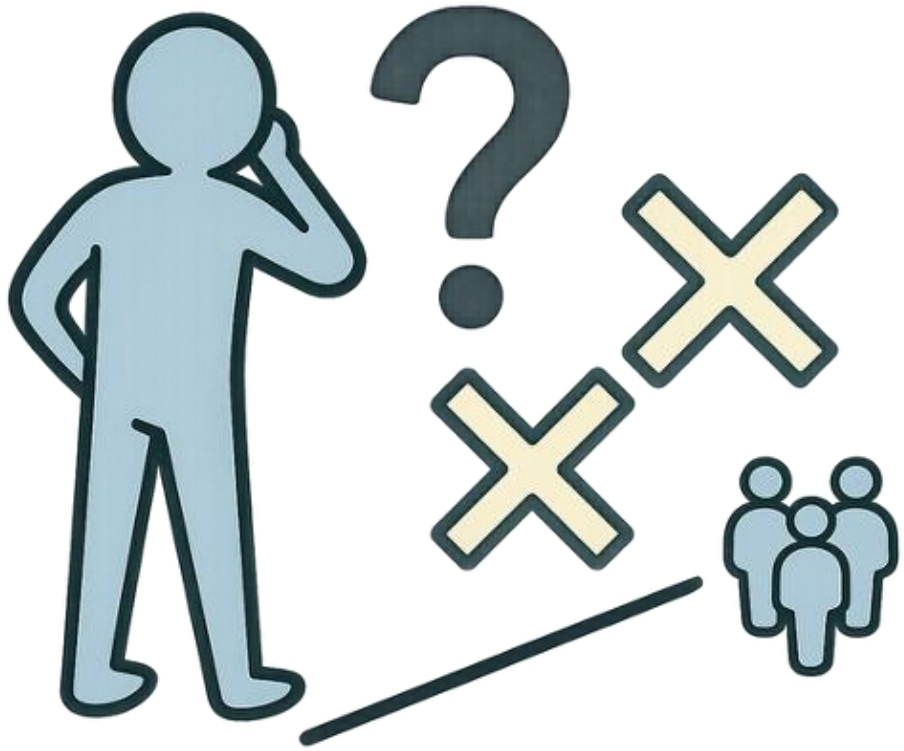
Classic RTC limitations

Challenges of Conventional RCTs in (very) rare diseases

- Small to n-of-1 populations
- no Phase 3 study possible
- Ethical concerns

Alternative Trial Designs

- Natural history studies
- Single-arm trials
- External comparator arms
- Adaptive designs



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Regulatory Strategy? Timing is of essence.

- When to approach to the Regulator.
  - Orphan designation can be obtained with non-clinical data pharmacodynamic data so the earlier the better. Two cases histories can make a difference (FDA as well) (6-9months)
  - Assistance should be sought for SMEs or Academics through the SME office or Academic Office at EMA.
  - Discuss a PRIME designation if you have compelling Phase II data.
  - Refer to European Guidelines such as n=1 trials. These are available on the EMA website.
  - If a new active substance and you have a paediatric population seek a PIP after Phase I (1 year to obtain)
  - Discussion of Clinical development can be obtained through a request for a joint FDA-EMA scientific advice meeting. These are held monthly.
  - Comparator Data might be needed for Significant Benefit to maintain the orphan designation at time of Licencing.

Approval

- Depending on the data you have and the type of condition study the optimal licencing pathway for CHMP.
  - Is it normal, conditional, exceptional or accelerated.
  - Accelerated is offered when you obtain PRIME designation or is requested to CHMP before submission for licencing.
  - Conditional is offered if you have an orphan designation or your condition is considered life-threatening and you have incomplete data.
  - Seek advice from EMA Scientific Advice Working Party as this will be at a reduced fee or free (for SMEs) if you have Orphan Designation.
  - Can time this in parallel with end of Phase II with the FDA so you can align your advices and avoid problems at assessment time.

Where We're Going

Reform of the Pharmaceutical Regulation

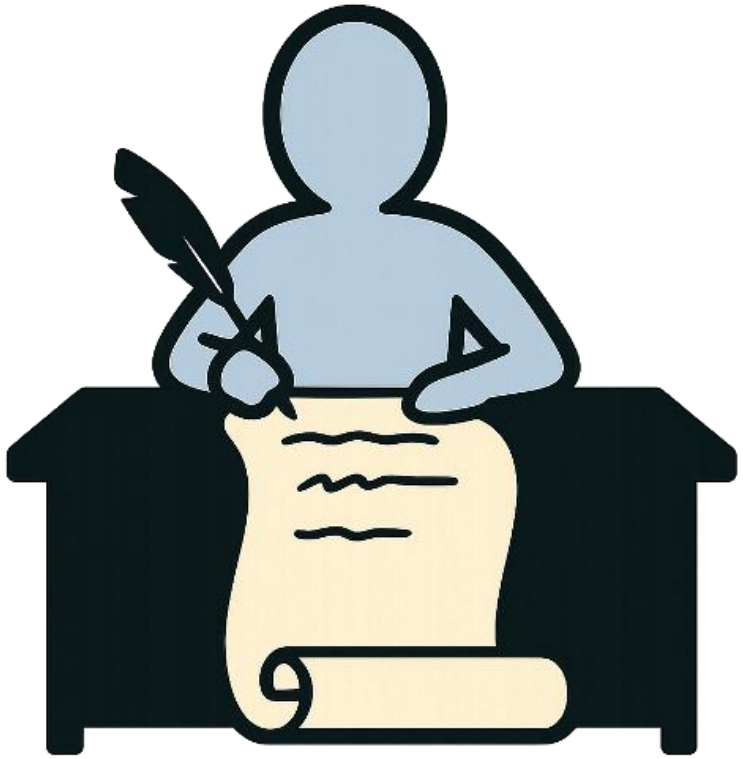
Main principles of orphan designation remain

Operational context will change

Focus on unmet need

Expert-based approach

EU HTA Regulation > JCAs, comparative evidence



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Conclusions

- Early Orphan Designation provides more regulatory flexibility and access to the European and US regulator
- Rare Diseases are a challenge due to the small patient populations, often paediatric nature of the condition and do not follow traditional development pathways.
- Licencing options are available in Europe to help overcome some of these limitations such as conditional, exceptional circumstances and accelerated licencing

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- Thank you and open for questions

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When the comparator turns out to be incomparable

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From NAM to MAN

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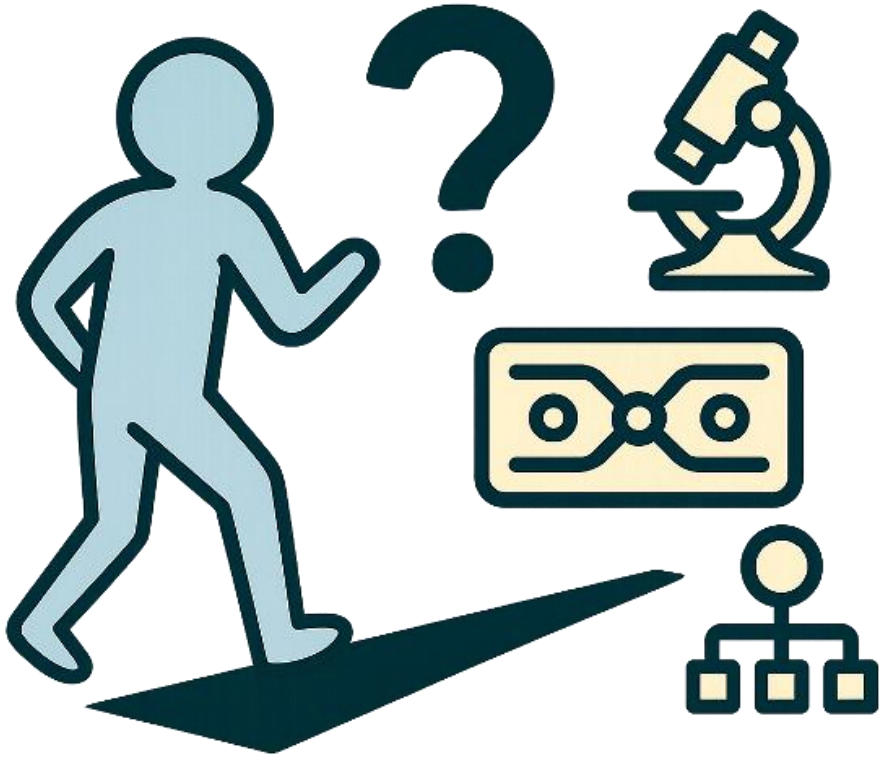
Challenges ahead

Replace or minimise in-vivo testing

- scientific and ethical progress
- organ-on-chip, organoids, computational models, advanced in-vitro systems

Significant benefit remains a cornerstone for OD

- Based on the foundation of functional outcome data
- Certain rare diseases are characterised by complex multisystem involvement



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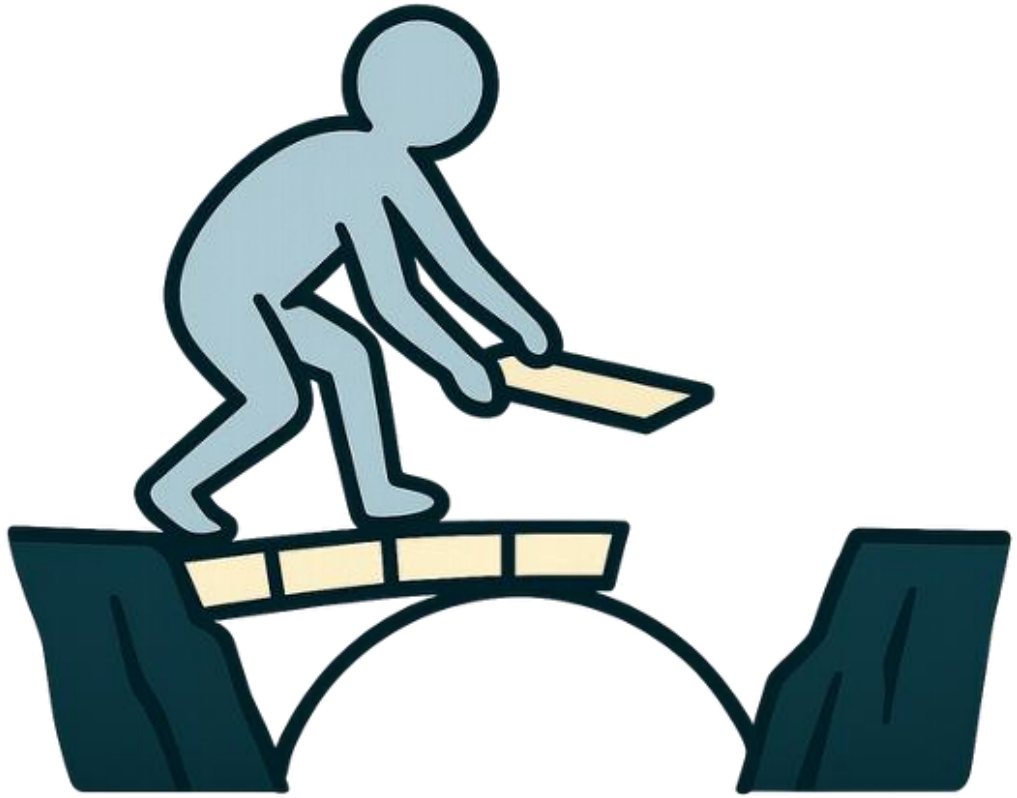

Bridging the Gap

Currently a regulatory vs science gap exists

- NAM approach is not rejected outright
  - functional endpoint bar remains for the time being
  - Human relevance is key
  - Solely mechanistic engagement is not sufficient
- Integrate multiple evidence streams, avoid ’anyone can see this’ extrapolation claims

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Chasing the horizon

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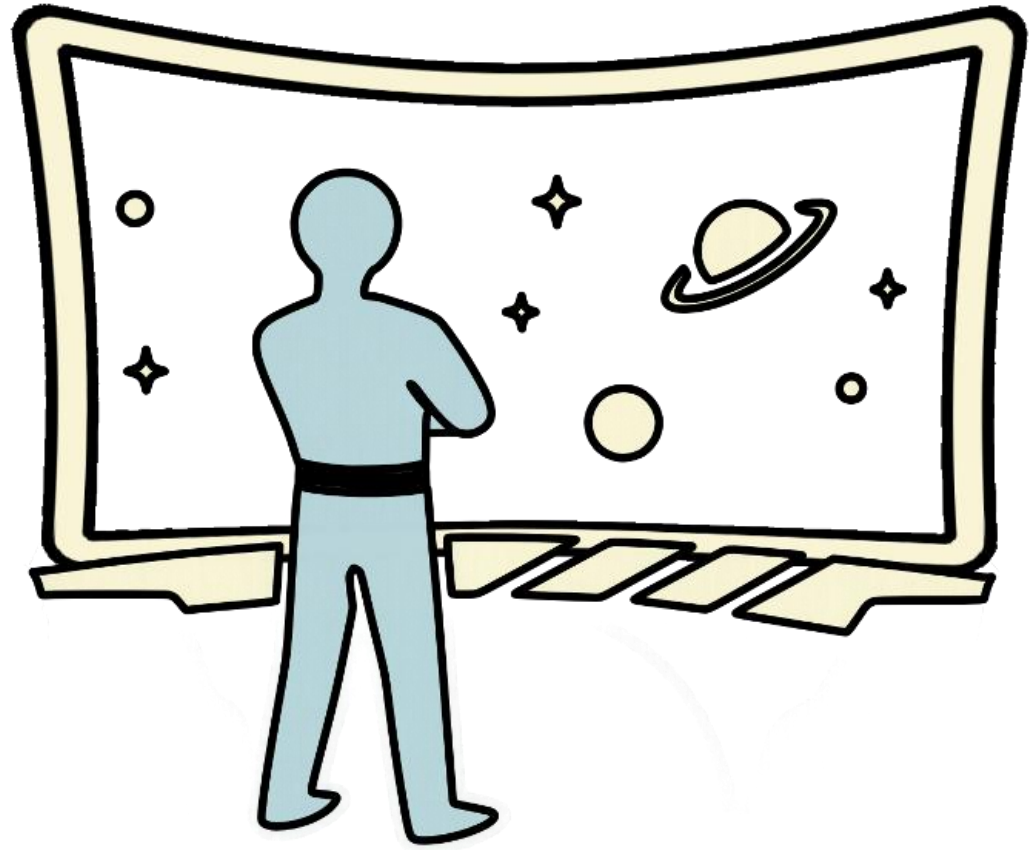
To Boldly Go

Increased importance of JCA

- Integrated evidence packages (clinical + NAM + RWE).
- Consistency between SB claims and HTA comparative needs.
- design "HTA-ready trials" from day one

Multi-stakeholder considerations

- Above all: patient involvement



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Key Challenges

Evolving Rare Disease Regulation

- Keeping up with scientific progress.

Aligning Science, Reality and Regulation

- Dealing with new realities such as indirect comparisons and non-animal methods.
- Flexible rigorousness

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