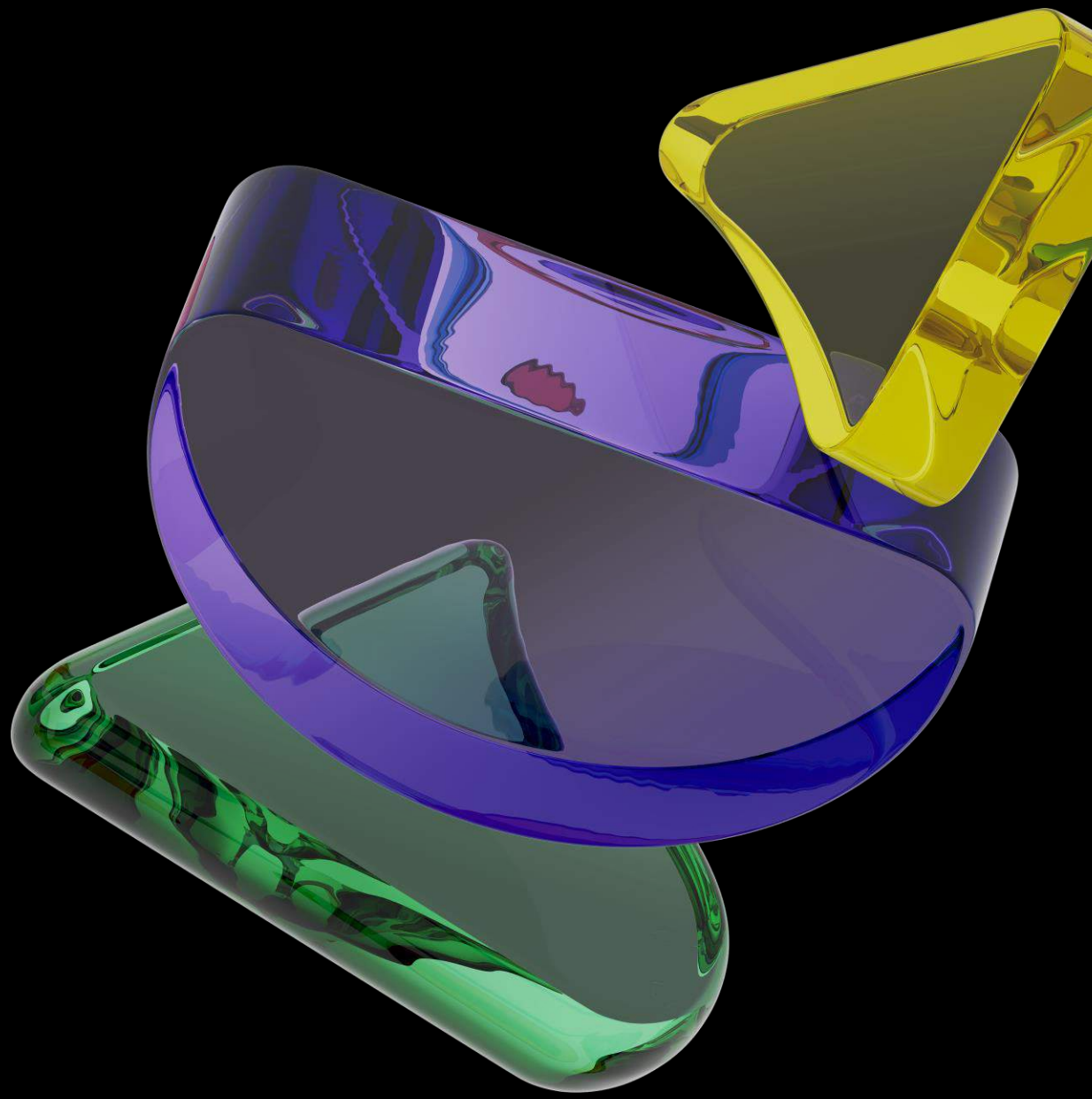
Orphan & Paediatric Devices

Regulatory Challenges - NB Perspective



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Understanding the Medical Device Regulation

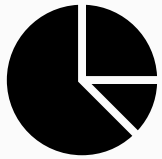
- The EU Medical Device Regulation 2017/745 (MDR) applies to all medical devices placed on the EU market, without specific provisions dedicated to paediatric or orphan devices.

- Although the MDR allows for the principle of proportionality to be applied, compliance requirements are still determined through a risk-based classification system.

- Regardless of manufacturer size or annual device sales volume, all manufacturers must meet the applicable legislative requirements based on the device's assigned risk class.

Sufficient Clinical Evidence

Quality



Quantity

CHAPTER VI

CLINICAL EVALUATION AND CLINICAL INVESTIGATIONS

Article 61

Clinical evaluation

1. Confirmation of conformity with relevant general safety and performance requirements set out in Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the
providing sufficient clinical evidence,
. 1, shall be based on clinical data
rred to in Annex III.

The manufacturer shall specify and justify the level of clinical evidence

To that end, manufacturers shall plan, conduct and document a clinical evaluation in accordance with this Article and Part A of Annex XIV.

Tell the story...

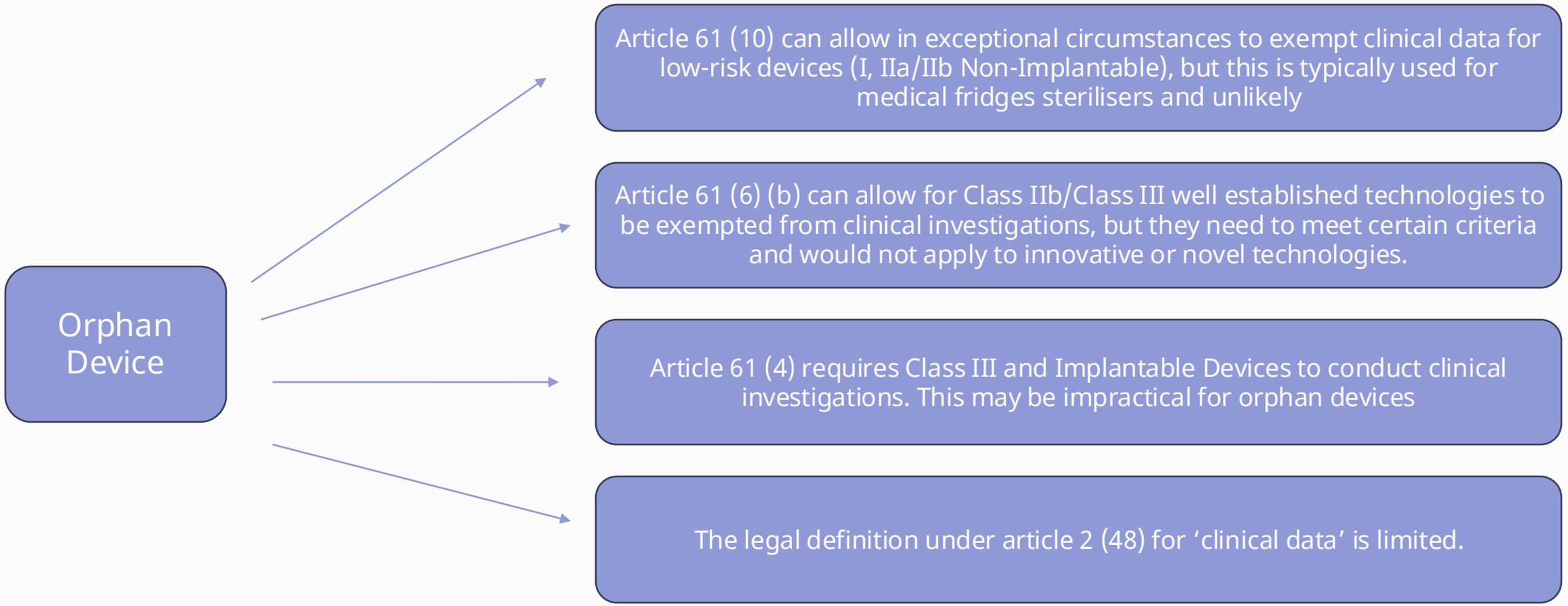
Proving Sufficient Clinical Evidence

- Low Risk
- Indirect Clinical Benefit
- Known Market History
- Known Behaviours
- Unethical/Inappropriate to collect evidence
- Technical Standards
- Established Generic Device Group

Lower **Higher**

- High Risk
- Direct Clinical Benefit
- Novel Technology
- Residual Risks
- Potential Opportunities to Collect Pre-Market Evidence
- Absence of Technical Standards
- Longer Lifetime

Regulatory Options:

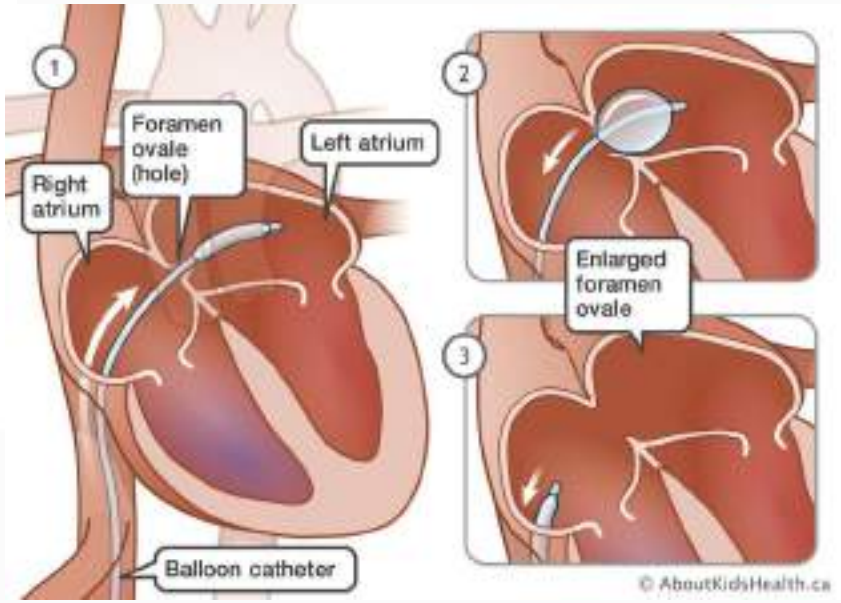


Background to the Creation of the MDCG 2024-10 Guidance…

Orphan Medical Devices and Pediatric Cardiology – What Interventionists in Europe Need to Know, and What Needs to be Done

Abstract

Introduction



https://pubmed.ncbi.nlm.nih.gov/36258097/

The EU Solution…

Medical Devices

Medical Device Coordination Group Document MDCG 2024-10

MDCG 2024-10

Clinical evaluation of orphan medical devices

June 2024

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The document is not a European Commission document and it cannot be regarded as reflecting the official position of the European Commission. Any views expressed in this document are not legally binding and only the Court of Justice of the European Union can give binding interpretations of Union law.

[Link to MDCG2024-10]

Orphan device status enables *proportionate* regulatory pathways not reduced safety expectations.

- Orphan devices address rare diseases / small patient populations (≤12,000 patients/year in EU) and often significant unmet medical need

- MDR does not relax Annex I General Safety & Performance Requirments (GSPRs) for orphan devices → All applicable GSPRs must still be met

- **MDCG 2024-10 recognises that:**
  - Pre-market clinical evidence may be limited, but
  - This must be explicitly justified, transparent, and post-market clinical follow up (PMCF) activities are critical

  Notified Bodies must balance:
  - Proportionality & feasibility
  - Scientific uncertainty
  - Patient safety and public trust


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The Role of the Notified Body in Orphan Device Conformity Assessment

NBs remain fully accountable for conformity decisions under the MDR.

What the NB must do

- Verify orphan device status early (structured dialogue or application review)
- Assess technical documentation using the same conformity principles as non-orphan devices

Critically evaluate:

- ✓ Whether Annex I GSPRs are met
- ✓ Whether limitations in pre-market clinical data are acceptable and justified
- ✓ Whether the benefit-risk profile is favourable

What the NB cannot do

- Accept orphan status as a reason for lower clinical scrutiny
- Accept vague or aspirational PMCF plans
- Ignore unresolved safety or performance uncertainties

Key Regulatory Tool

Certificates with conditions / provisions (Annex VII, Article 56)→ Common and appropriate for orphan device

We recognise the challenges – but scientific justification must lead the strategy

Acknowledged realities

- Small patient populations
- Ethical and practical limits on clinical investigations
- Disproportionate cost vs. sales volume
- Vulnerable populations (paediatrics, emergencies)

What proportionality looks like in practice

- Robust use of pre-clinical data to support GSPRs
- Clearly articulated expected clinical benefit
- Transparent identification of clinical evidence gaps
- Justification that:
  - Further pre-market data is not feasible or proportionate
  - Residual uncertainty is controlled and monitored

For orphan devices, PMCF is the backbone of the lifecycle evidence strategy

Why PMCF matters more

- Accepted pre-market limitations must be resolved post-market
- Lifecycle benefit-risk determination depends on PMCF data

What Notified Bodies expect

- A detailed, structured, credible PMCF plan
- Clear linkage between:
  - Identified pre-market evidence gaps
  - Specific PMCF activities designed to address them
- Realistic timelines aligned with actual usage volumes

•Use of:

- Registries
- Prospective PMCF investigations
- Real-world clinical data

Honest acknowledgement

- Small numbers and slow data accrual are expected
- But “difficult” is not a justification for “undefined”

Regulatory reality

Failure to deliver on PMCF commitments→ Risk to certificate validity

Structured Dialogue, Expert Panels, and Working Together

Early engagement prevents late failure.

Structured Dialogue

- Best opportunity to:
  - Align on orphan status justification
  - Discuss clinical evidence limitations
  - Set realistic PMCF expectations
- Does not replace conformity assessment
- Must respect NB independence and impartiality

Expert Panel Advice

Expert panel opinions are scientifically critical

They provide:

- Validation of orphan status
- Advice on clinical data sufficiency and uncertainty

Important distinction:

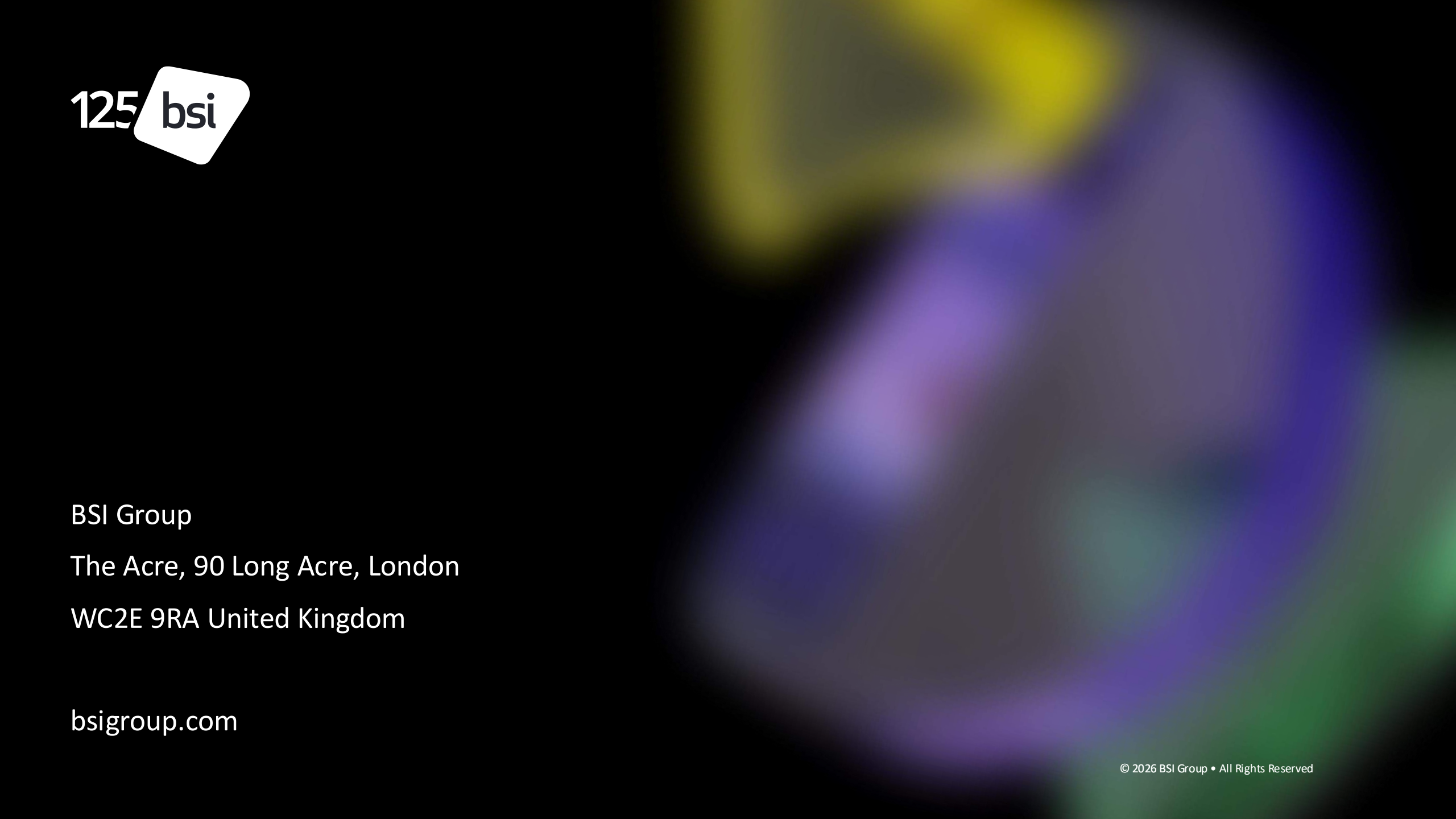
Scientific advice ≠ automatic regulatory compliance

Notified Bodies must:

- Consider expert panel advice carefully
- Explain and justify any divergence from the panel opinion
- Maintain accountability for MDR conformity decisions

To Conclude…

- **A pragmatic, collaborative approach is needed** to address orphan and paediatric device challenges while ensuring continued patient access and maintaining regulatory compliance.
- **Notified Bodies must operate within the legal framework**, but should be proactive, adaptable, and open to working with manufacturers to identify appropriate risk-based solutions.
- **Risk mitigation strategies should be considered**, including enhanced post-market surveillance and greater reliance on robust pre-market data where clinical evidence is inherently limited.
- **Manufacturers have a responsibility to engage early and proactively with Notified Bodies** to support ongoing device availability for orphan and paediatric indications.
- **High-quality justification is essential**: manufacturers must provide clear, well-documented rationales for limited or absent clinical evidence, creating the foundation for Notified Bodies to assess risks and agree appropriate regulatory pathways.



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