CASE STUDY

Epigenetic MoA drug development: Navigating regulatory barriers to enable an hAME study in healthy volunteers

A KEY QUESTION

How can well-supported regulatory strategy and scientific justification help navigate a clinical pathway that regulators often view as challenging?

KEYWORDS Clinical Trials, Regulatory Strategy, Oncology, hAME, Healthy Volunteers (HV)

This case study explores how Fortrea collaborated with a sponsor developing an oncology therapy with an epigenetic mechanism of action (MoA). Because healthy volunteer studies are often viewed as challenging for such programs, Fortrea worked with the sponsor to develop a scientifically justified approach that supported regulatory review of a feasibility pathway for a study in healthy volunteers.

Challenges

- **Genetic modification concerns:** The modification of genetic pathways by epigenetic products in healthy participants is generally deemed inappropriate and is typically refused by regulators
- **Regulatory resistance:** Regulators have questioned whether it is appropriate to administer such agents to healthy subjects, reflecting a cautious regulatory posture
- **Patient-based study complications:** An hAME study in cancer patients would require radiolabeled drug administration in a hospital setting. Patients' health status, logistical complexity and the investigational product's short stability window posed significant risks to successful trial delivery
- **Sponsor preference:** The client strongly favored minimizing operational complications and avoiding the scientific limitations of a patient-based design

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Actions

1. Global regulatory landscape assessment

Fortrea analyzed historical feedback from both the FDA and MHRA. Findings:

- **FDA = high regulatory risk** with near-certain non-acceptance
- **MHRA = pragmatic and flexible.** Had previously provided feedback indicating openness to considering such proposals on a case-by-case basis where supported by strong scientific rationale

2. Specialist scientific and ethical justification

Fortrea guided and refined a comprehensive justification document addressing:

- Mechanistic rationale for the drug's epigenetic effects
- Preclinical safety data supporting HV dosing
- Ethical arguments for HV participation over patient involvement
- Stability and logistical considerations
- Precedent, including prior Fortrea-led epigenetic HV work

3. Strategic MHRA Submission

The Clinical Trial Application (CTA) was constructed to address MHRA's stated considerations for such submissions:

- Clear, evidence-based scientific narrative
- Robust safety rationale
- Operational safeguards tailored to HV dosing

Results

The MHRA accepted the submission with no additional queries at that stage.

This approval:

- Supported a study design that aligned with the sponsor's preferences for operational simplicity and scientific control
- Avoided compromised patient-based alternatives
- Provided a pathway that avoided the operational complexities associated with a patient based trials
- Demonstrated that regulators may consider proposals differently when provided with compelling scientific evidence

Lessons learned

- **Understand regulatory diversity:** Global regulatory positions differ—select the jurisdiction that aligns with your scientific justification
- **Lead with strong science:** Thorough scientific narratives can shift regulatory expectations
- **Pragmatism matters:** When patient-based studies introduce unnecessary complexity, alternative pathways may be both safer and more efficient
- **Collaborative alignment:** Early coordination between Fortrea and the sponsor helped align expectations and support a clear submission strategy

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References

Jones PA, Issa JP, Baylin S. Targeting the cancer epigenome for therapy. Nat Rev Genet. 2016 Sep 15;17(10):630-41. doi: 10.1038/nrg.2016.93. PMID: 27629931.

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