Death (or SAE) in First-in-Human Studies: What Next? Regulatory Perspective

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Background

- Deaths in FIH trials are exceedingly rare
- There are many safeguards in place to prevent these events
- Analysis of events often reveal etiologies that are obvious in retrospect – mitigating strategies are then introduced
- Unlikely that we will have a foolproof system

Why

- On-target toxicities
- Off-target toxicities
- Toxicity due to drug or metabolite
- Toxicity due to quality issues
- Non-clinical study issues
  - Toxicity unique to humans
  - Monitorable versus not monitorable

Management of IND post Event

- Clinical hold
- Most sponsors abandon development
- Assess event
  - Was it due to the drug
  - Was it predicted
  - Evaluate nonclinical and clinical data
  - Look at similar drugs
- Additional nonclinical MoA and pharmacological studies

Context

- Is molecule promising
- Is the intended use for a serious condition with unmet need
- Tolerance for adverse events
- Was it a metabolite or some idiosyncratic reaction that is monitorable

Going Forward?

- Consider low and slow
  - If toxicity observed in animal models
  - Narrow therapeutic index
- Use real-time pharmacokinetics with stopping criteria

EMA Draft Guidance

- Be smart – quality by design
- Incorporates lessons learned from publicized events
- Does not address what to do after an event


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