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EMA Draft Guidance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