# Workshop

# Towards harmonised implementation of the ICH M10 Guideline

## Chapter 5: ISR

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**on behalf of the EBF**

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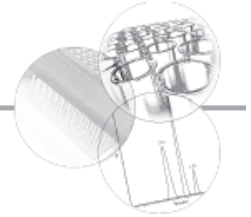
# Flow of the session

- Background – Any news?
- Survey results
  - Investigation of failed ISR
  - Definition of Pivotal
  - How to select samples for ISR
- Panel discussion



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White Paper

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# ISR revisit - prior to ICH M10

- *ISR failure rate was low (app. 1.5%) and failures were mostly in earlier development studies.*
- *Agreement among EBF members that ISR creates value as a post method-validation parameter.*
- *ISR criteria are clear on pass/fail, however the scope for study selection is not clear for all.*
- *Industry perform ISR in more studies than called for in guidance/guideline.*
- *Guidance on handling sporadic flyers (single samples with large variations) is not clear.*

***Conclusion on "EBF view on ISR" at 10th EBF Open Symposium November 2017***

# Evolution of ISR

*There are several situations where the performance of standards and QCs may not adequately mimic that of study samples from dosed subjects (incurred samples).*

*Examples include metabolites converting to the parent species, protein binding differences in patient samples, recovery issues, sample inhomogeneity, and mass spectrometric ionization matrix effects.*

*These factors can affect both the reproducibility and accuracy of the concentration determined in incurred samples. While these effects are often characterized and minimized during method development using QC samples, it is important to ensure that they are under control when the method is applied to the analysis of incurred samples.*

*Viswanathan, et al., The AAPS Journal 2007, 9(1) E30-42 (CCIII 2006)*

# Evolution of ISR - Purpose

- *EMA 2012:*
  *It is therefore recommended to evaluate accuracy of incurred samples by reanalysis of study samples … (in separate runs at different days).*

- *FDA 2018:*
  *ISR is a necessary component of bioanalytical method validation and verifies the reliability of the reported study sample analyte concentrations.*

- *ICH M10:*
  *ISR is intended to verify the reliability of the reported sample analyte concentrations.*

# Evolution of ISR

| Requirement | ICH M10 | FDA | EMA |
|---|---|---|---|
| **What** | TK species<br>FIH<br>Pivotal BA/BE<br>(Pivotal) FIP<br>(Pivotal) hepatic/renal | All Pivotal for labelling or approval:<br>TK/species<br>All BE, pivotal PK and PD | TK/species<br>BE, FIH, FIP, hepatic/renal |
| **When** | Not on the same day as the original analysis | In separate runs | In separate run, at different days |
| **Amount** | 10% first 1000 | 10% first 1000 | 10% first 1000 |
| | 5% > 1000 | 5% > 1000 | 5% > 1000 |
| **Selection** | Near $C_{max}$ and elimination phase - representative for the whole study | Near $C_{max}$ and elimination phase | Near $C_{max}$ and elimination phase |
| **Acceptance Criteria** | 2/3 (67%) within 20% (LC/MS), 30% (LBA) | 2/3 (67%) within 20% (LC/MS), 30% (LBA) | 2/3 (67%) within 20% (LC/MS), 30% (LBA) |
| **Failures** | SOP based investigation | SOP based investigation | Investigation |

# Any news: more work, less work, ambiguous?

- “Flyers' do not need to be investigated” *Yes!, clear guidance*
- “ISR not required for all studies” *Never was!*
- *Pivotal?*
- *Investigations* for failed ISR

# A few nuts to crack

- Definition of Pivotal and Patient Population.
- How, when and where to conduct and document investigation for failed ISR?
- How to set objective criteria for choosing the subset of study samples for ISR?

# Panel discussion

1. How do you define Pivotal and how do you ensure that the BioA Scientist/ Sponsor is aware of the overall scope and intentions of a given study (in relations to a submission)?

2. What would trigger an investigation of failed ISR in your lab and how do you document?

3. Please share how you define objective criteria for selection of samples for ISR

# Proposal

- Know your project and understand the purpose of each and every study you conduct.

- ISR is indented as a Post Validation tool.  Be clear how to distinguish between ISR conduct pr. guidance requirements and how to used ISR to mitigate business risks for pivotal studies.

# Acknowledgements


- EBF
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# Contact Information

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