

EBF view on ISR

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on behalf of the EBF*

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10 – A New Journey Begins**

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CCIII 2006

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.

Incurred sample evaluation performed using samples from one study would be sufficient for all other studies using that same species.

Current Guidance/Guidelines

The use of calibration standards and QC samples during validation may not mimic the actual study samples.

Differences for instance in protein binding, back-conversion of known and unknown, sample inhomogeneity or concomitant medications, may affect the accuracy and precision of the analyte in such samples during processing and storage.

It is therefore recommended to evaluate accuracy of incurred samples by reanalysis of study samples in separate runs at different days.

EMA/CHMP/EWP/192217/2009 Rev.1Corr. 2**

Current Guidance – Requirements to ISR

Requirement	FDA (2013 draft)	EMA	MHLW*	CFDA**	CC Workshop
Scope	TK/species All BE, <u>pivotal</u> PK and <u>PD</u>	TK/species BE, FIH, FIP, hepatic/renal	TK/species BE, FIH, FIP <u>with</u> hepatic/renal	TK/species BE, FIH, FIP, hepatic/renal	TK/species BE, <u>by discretion</u> (e.g. FIH, FIP, DDI, disease)
Amount	Fixed 7%	10% first 1000 5% > 1000	~10% first 1000, ~5% > 1000	10% first 1000 5% > 1000	Fixed 5-10%
Selection	Near C _{max} and elimination phase “for all subjects”	Near C _{max} and elimination phase	Near C _{max} and elimination phase, “As many subjects as possible”	Near C _{max} and elimination phase	Near C _{max} and elimination phase “fewer samples from more subjects”
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)	2/3 (67%) within 20% (LC/MS), 30% (LBA)	2/3 (67%) within 20% (LC/MS), 30% (LBA)
Failures	General: <u>SOP</u> based investigation	General: Investigate	General: Cause investig. <u>and</u> <u>impact</u>	General: Investigate	General: Investigate

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* Ministry of Health, Labour and Welfare, Japan

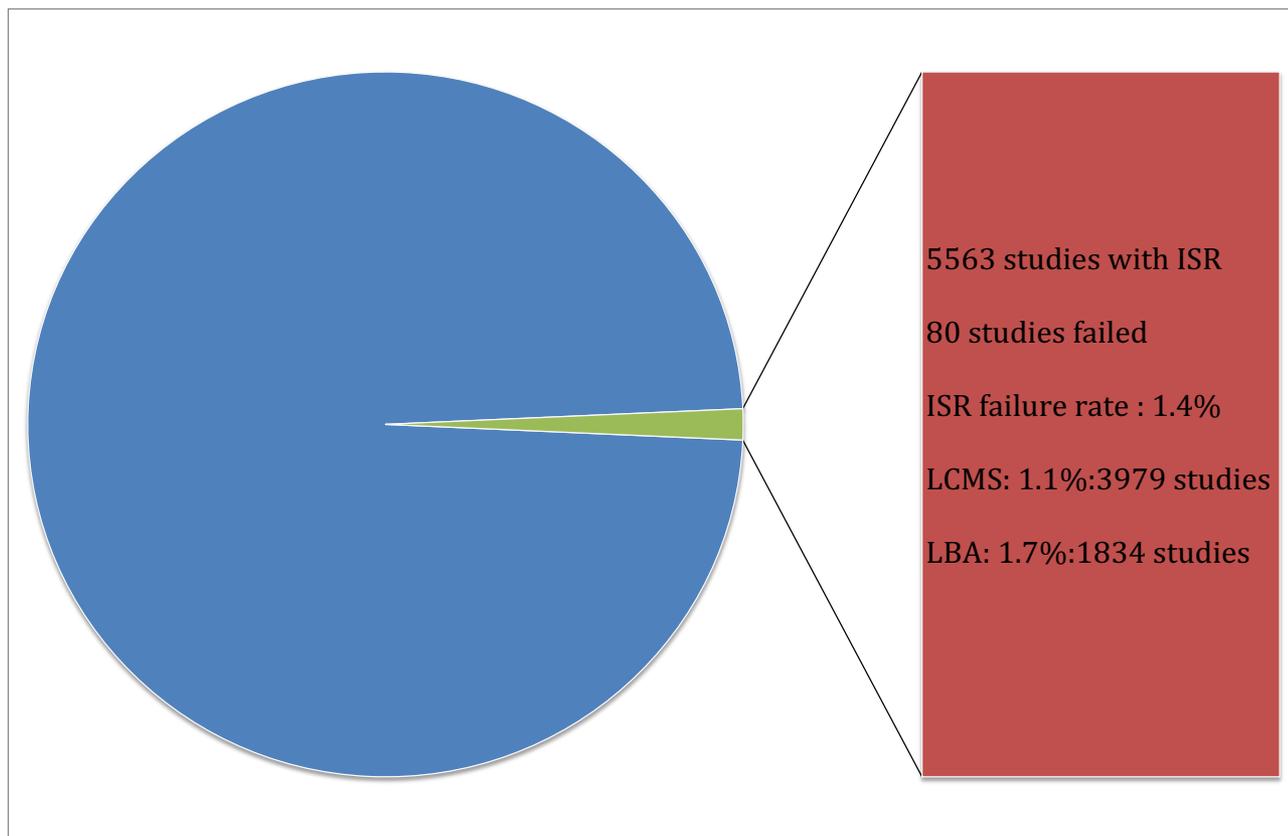
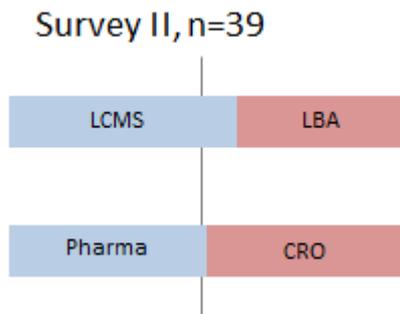
** Unofficial translation from Chinese

*Do we, as industry,
follow the Guidance/Guidelines?*

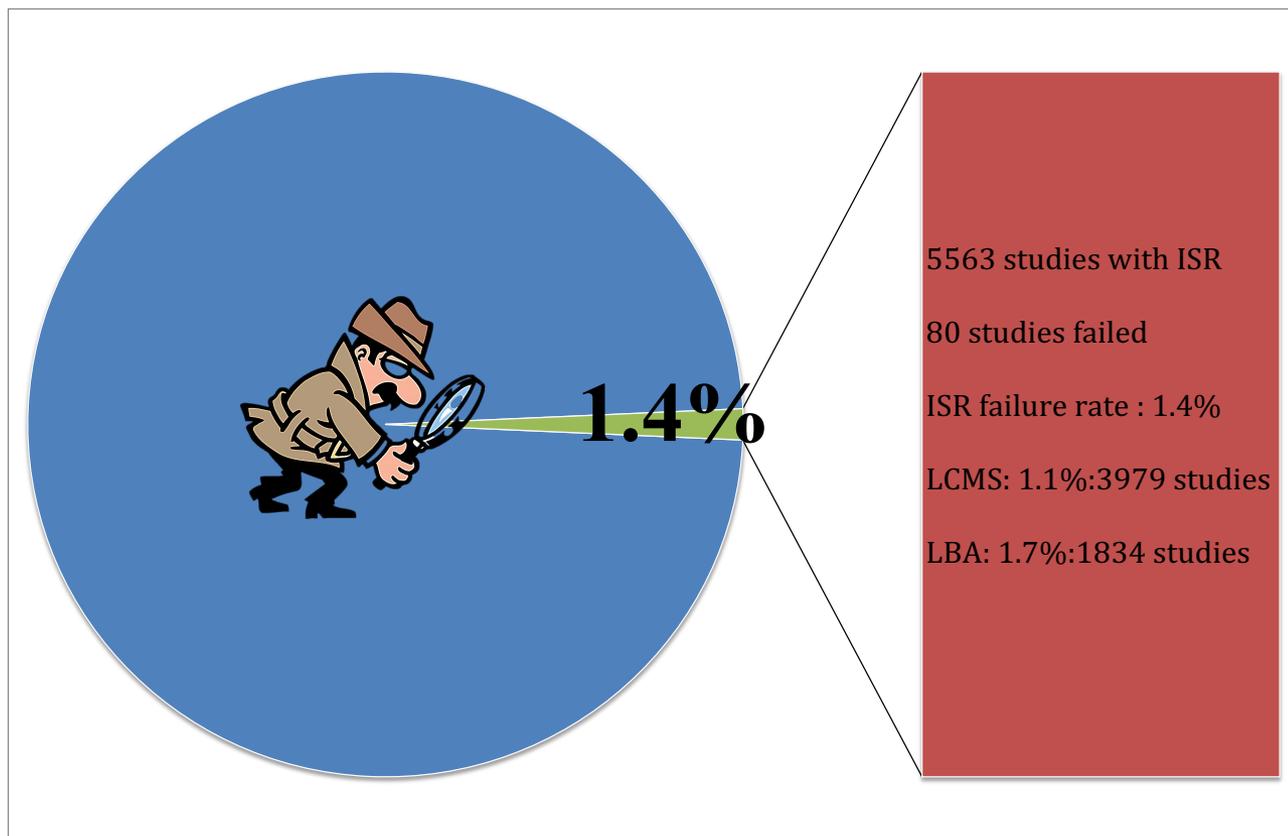
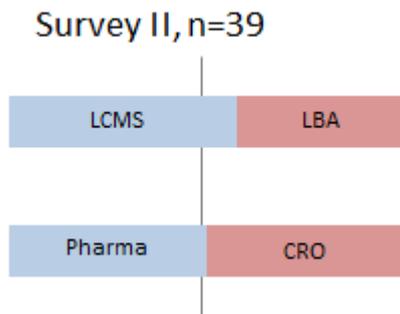
ISR revisited

- What are the EBF experiences with ISR 10 years after introduction.
- Do we as industry agree how to interpret the guidance.
- 3 EBF member surveys were conducted in 2016 and 2017 - results discussed during EBF meetings.
- Focus on ISR failures; study types, cause and impact.
- Consolidated reflection from EBF

ISR revisited

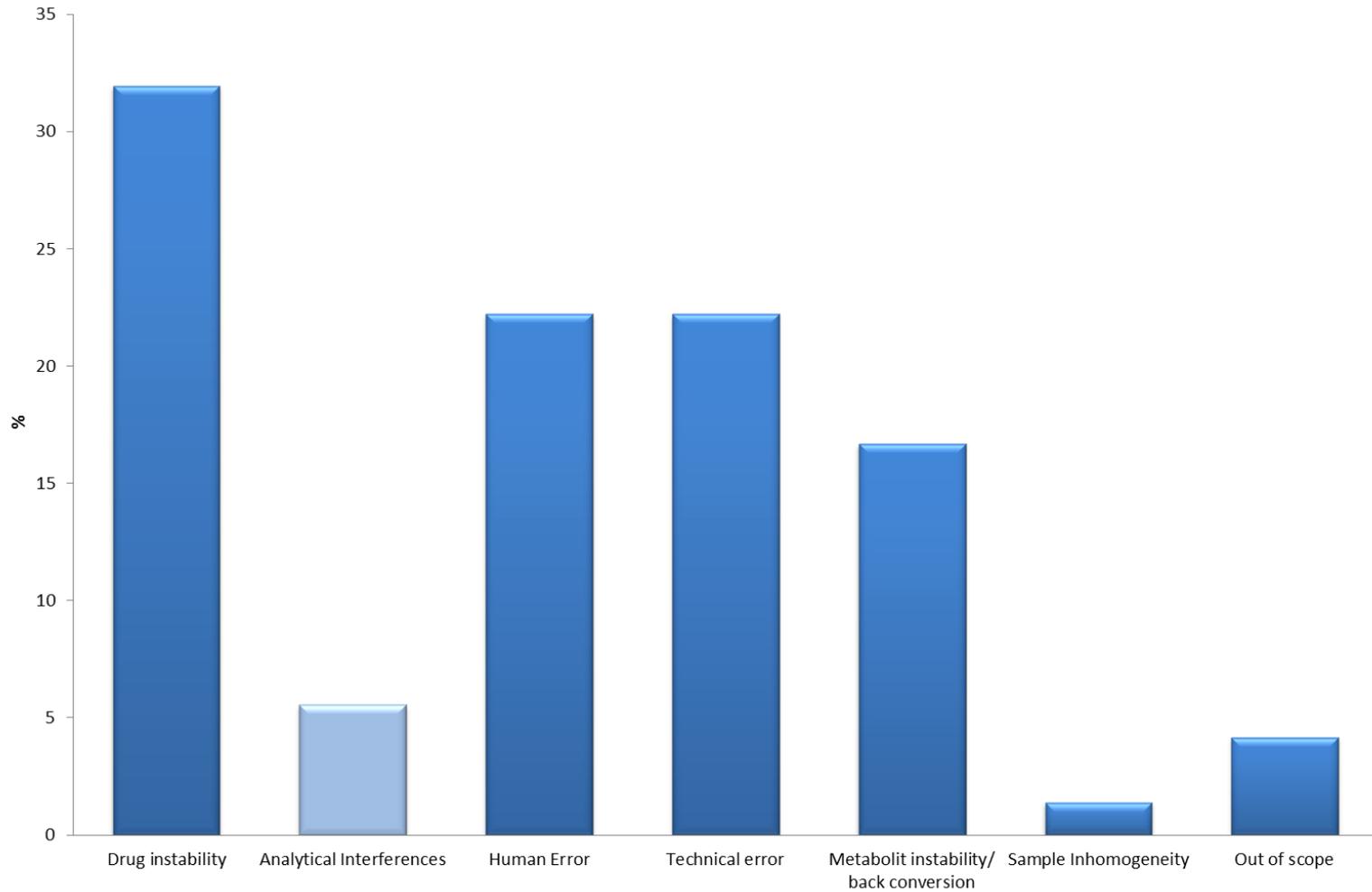


ISR revisited





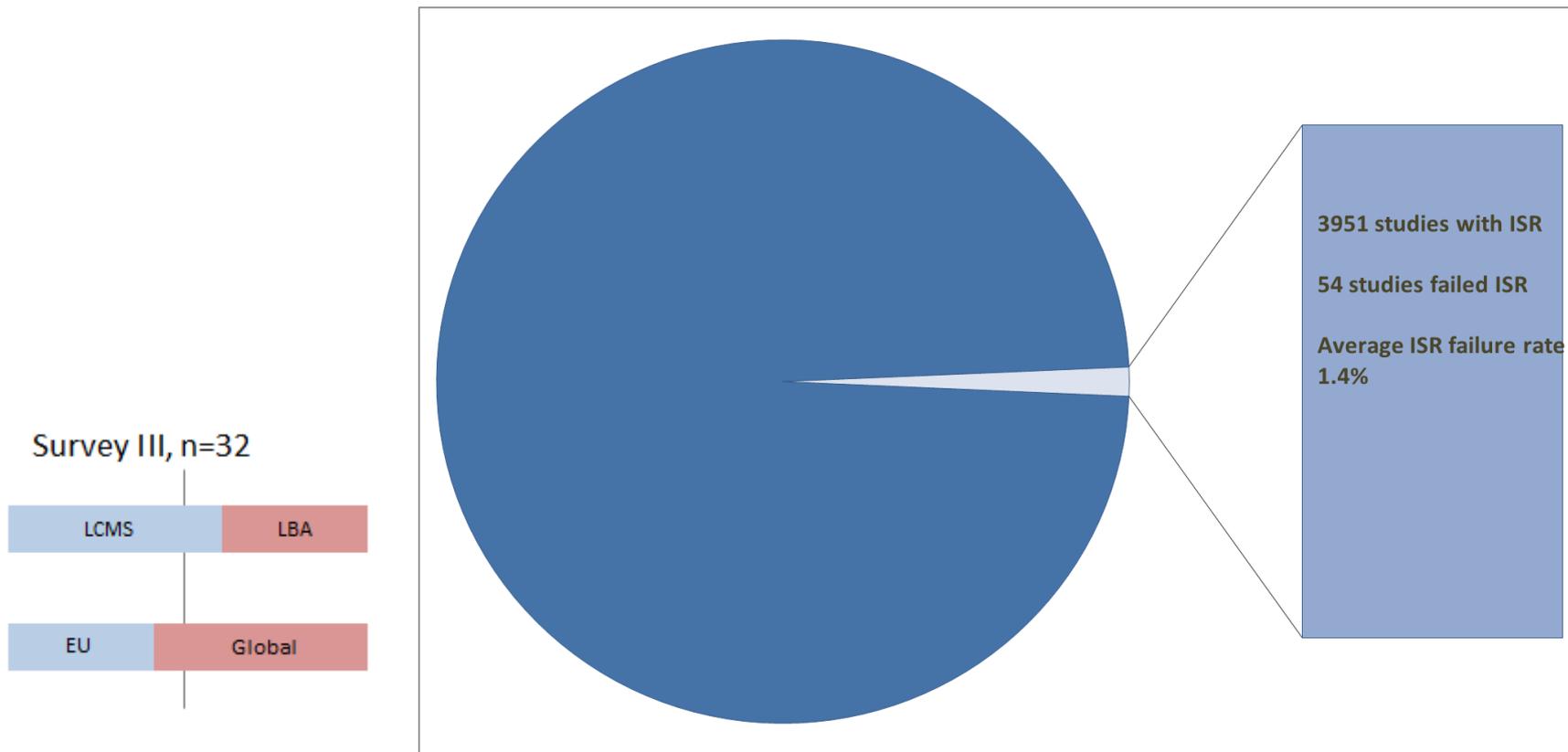
ISR: Cause of failures (1.4%)



(Inconsistent feedback)

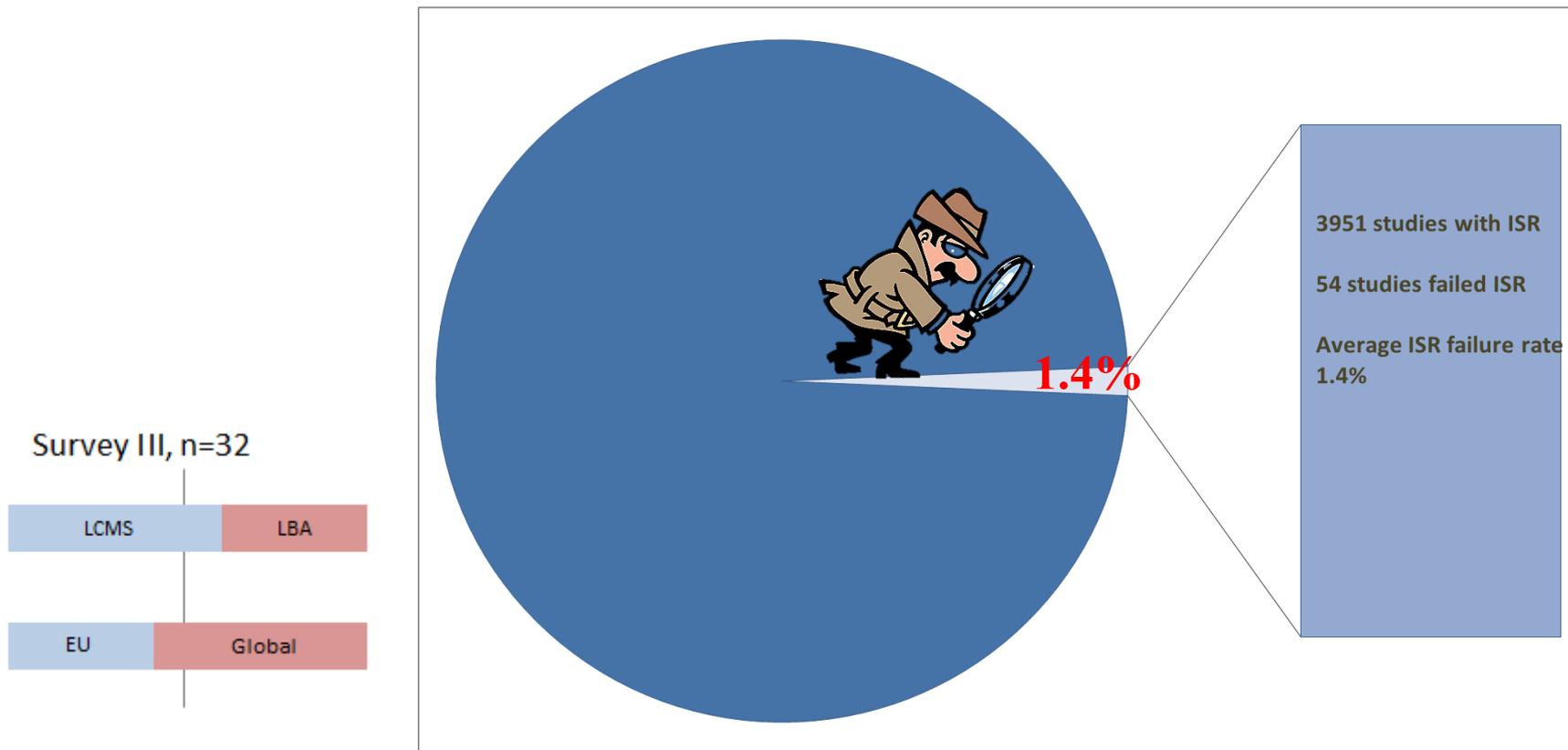
ISR failures

New survey with more details on studies, causes and impact

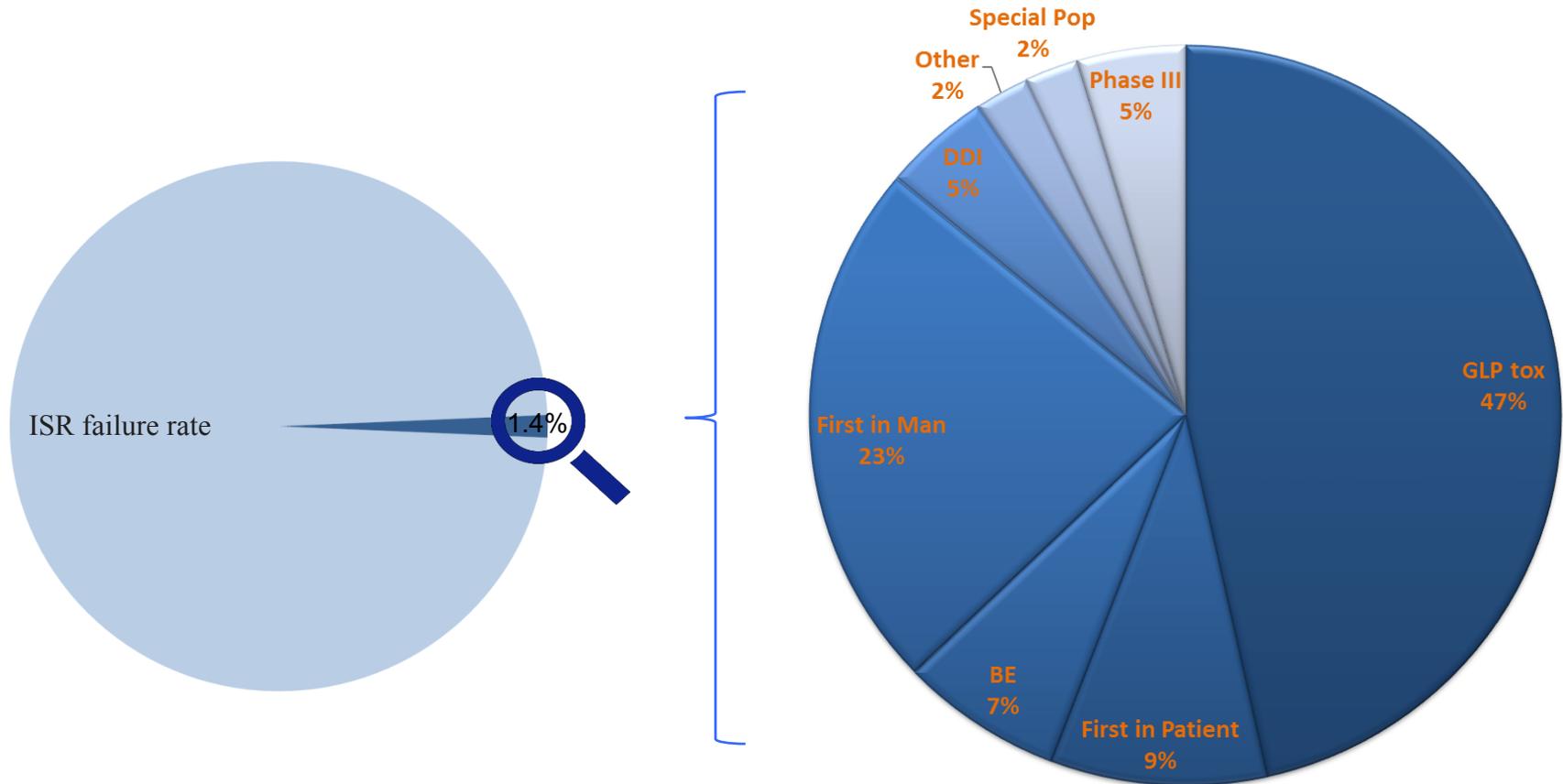


ISR failures

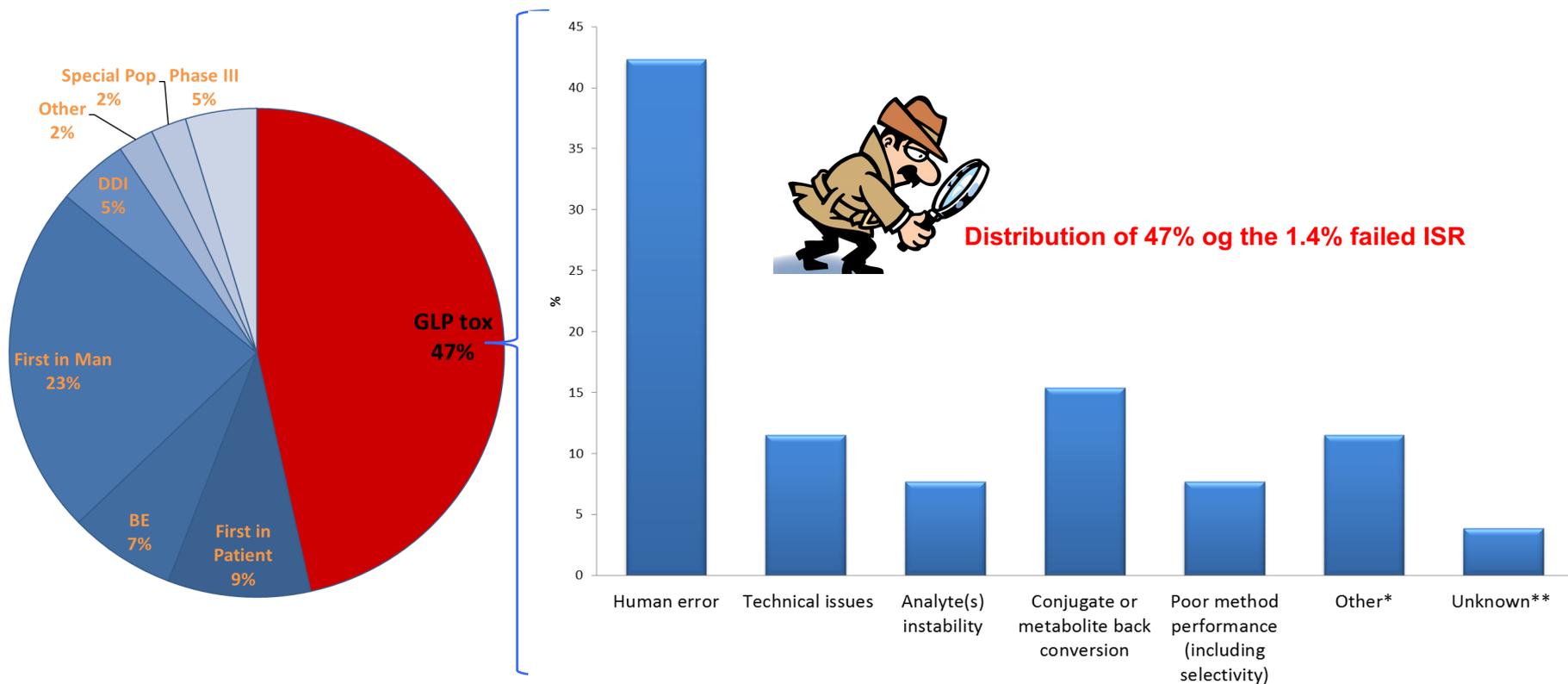
New survey with more details on studies, causes and impact



1.4% ISR failures: Distribution between study types



ISR failures in GLP tox – Reasons

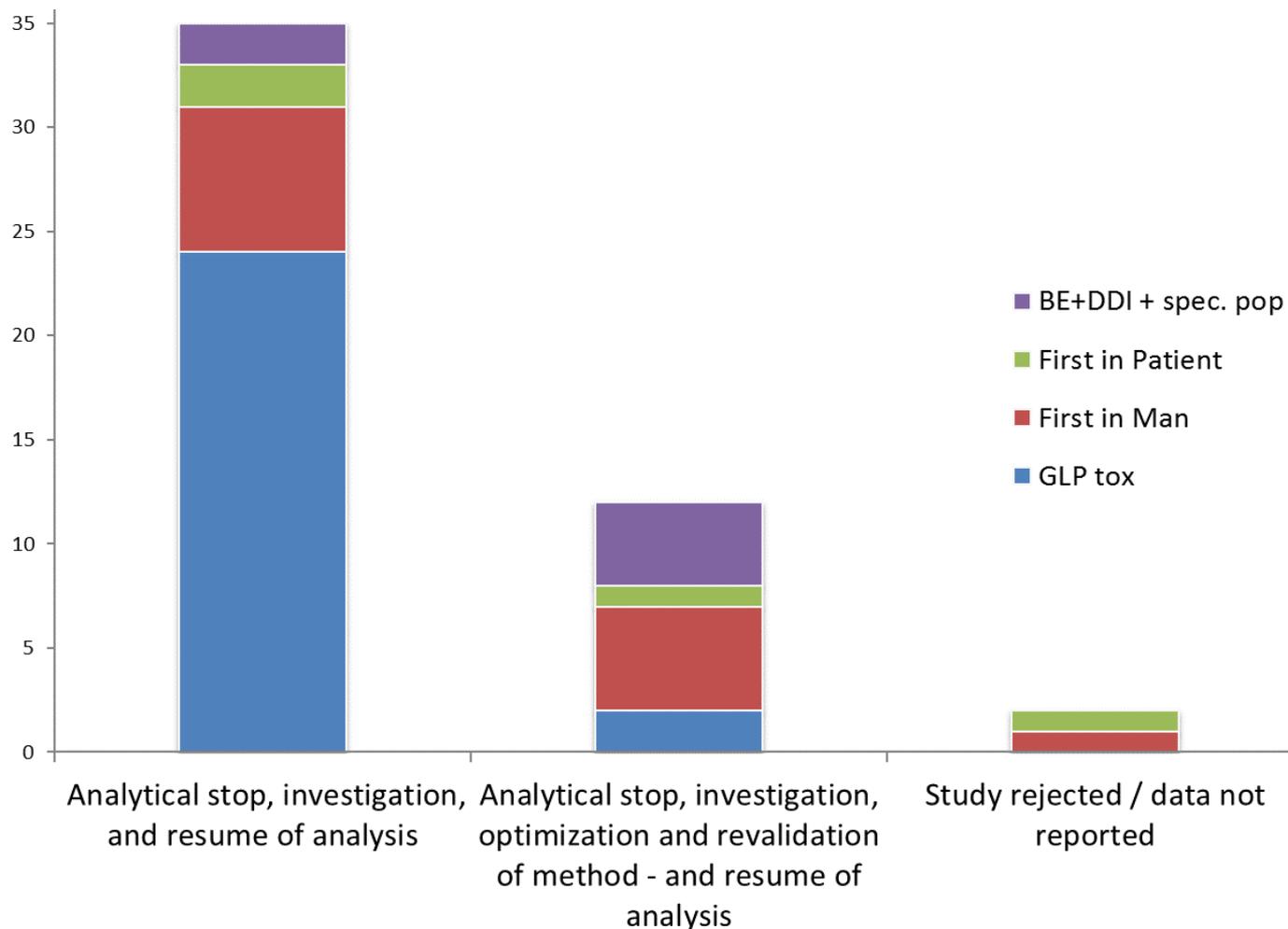


Other*

- Presence of antibodies
- Solubility of the analyte (in animal bile)
- Unexpected excipient matrix effect for an oral administration



1.4% ISR failures: Impact and elucidation



Comment from one lab

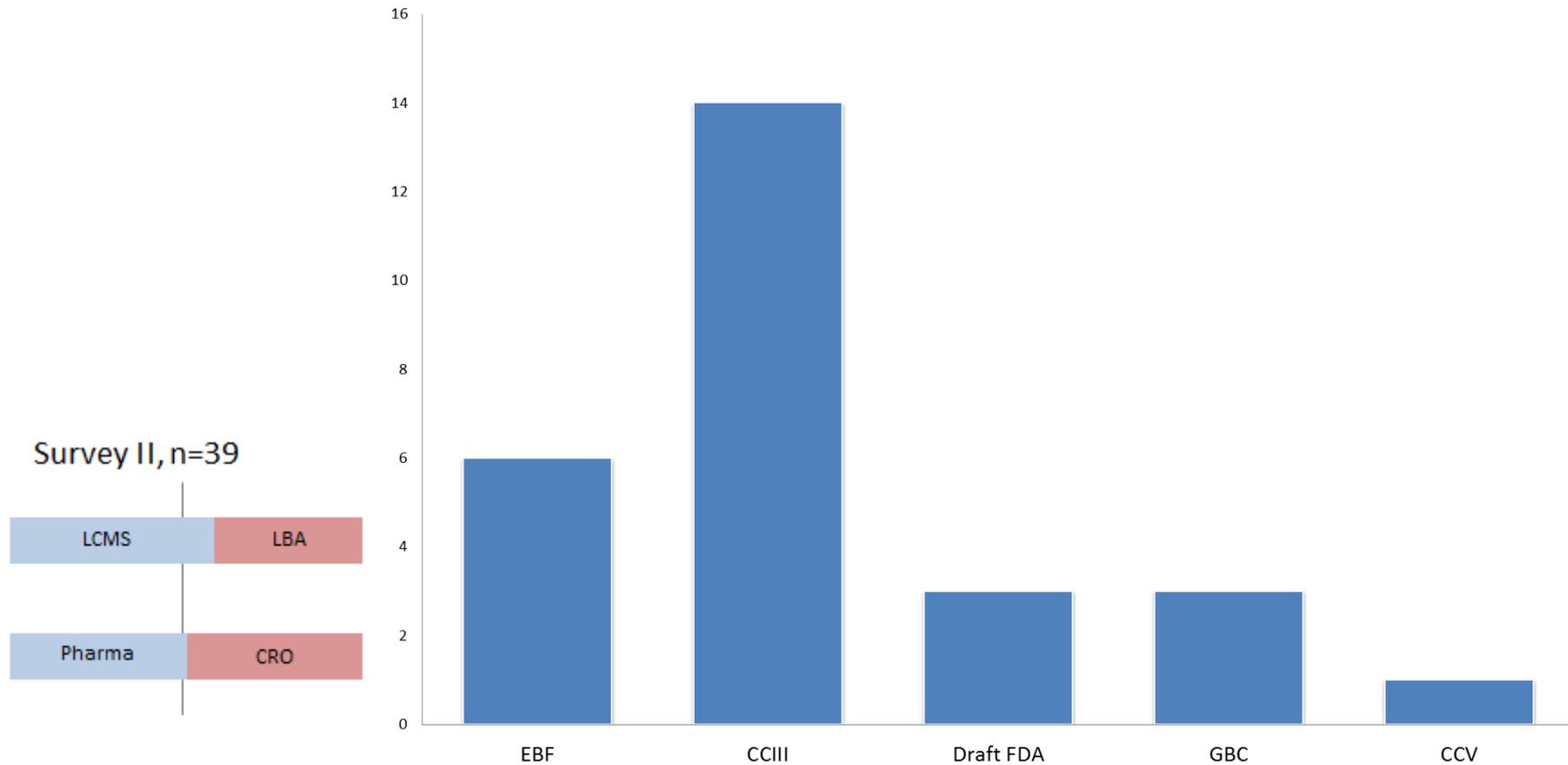
For GLP tox, failures on human and technical errors are not be flagged as ISR failure, 5% of all runs fail because of errors like these, but are easily fixable and repeated



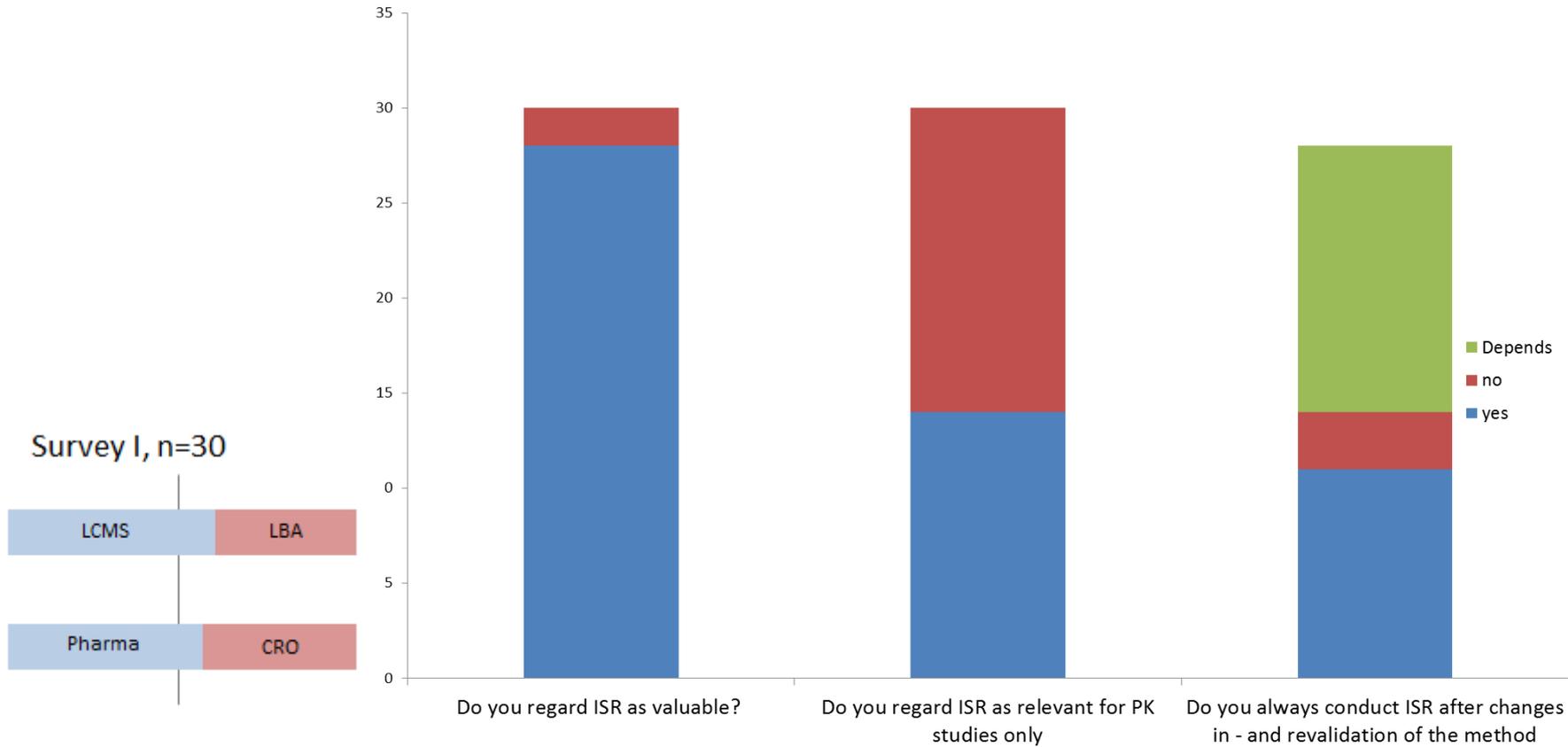
ISR failures: Reflections

- In GLP tox studies, most ISR fail due to human or technical error.
- First in Man to late (pivotal) studies - distribution seems more even, but data set is too small to conclude.

Which documents besides EMA guideline do you follow on ISR?

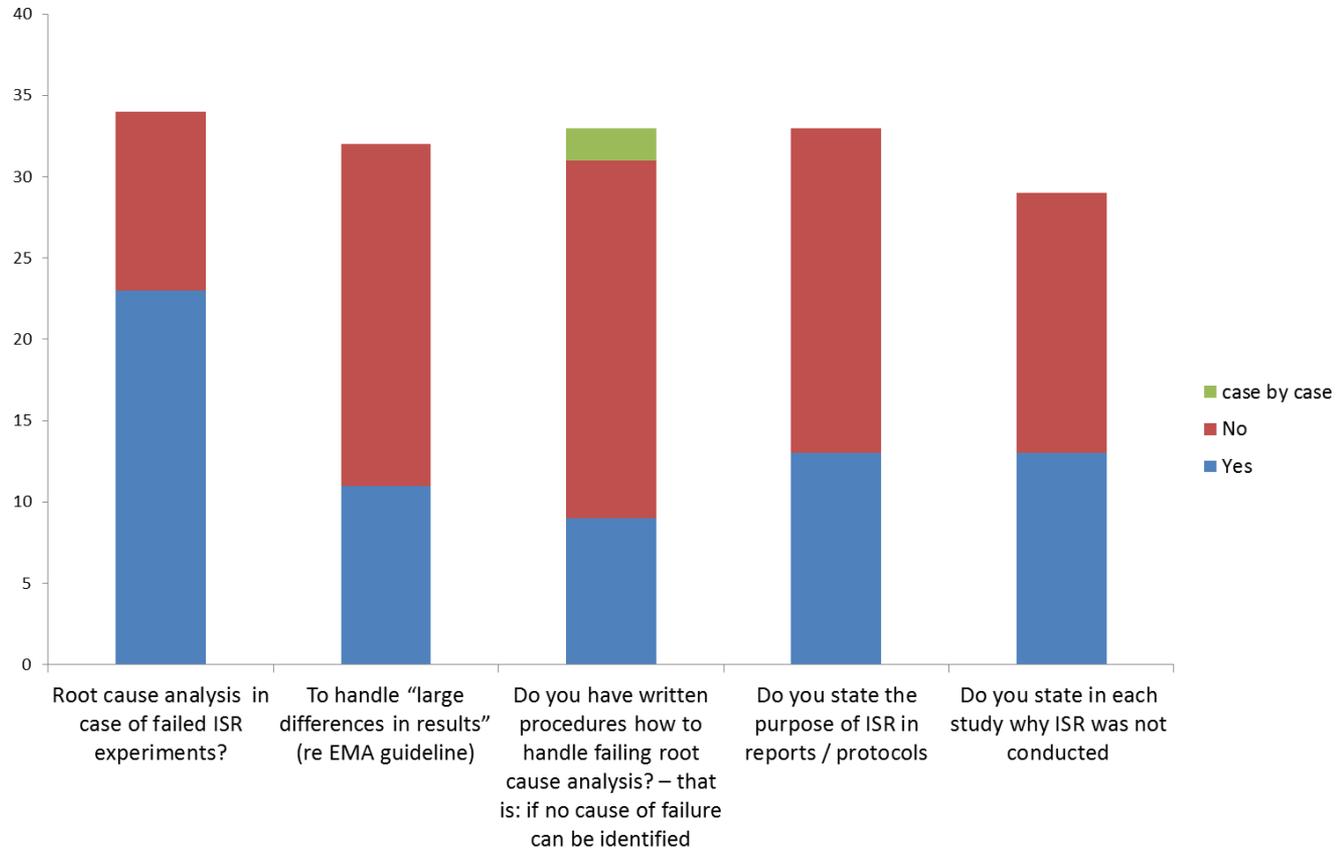
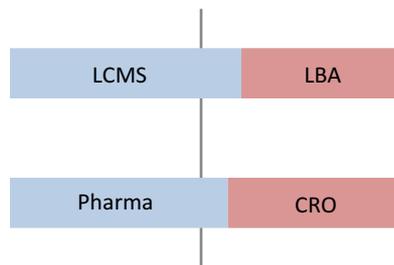


Do you?



Do you have written procedures

Survey II, n=39



Open Question:

What aspects or formulations in the current guidance that you do not find sufficiently unambiguous to serve as clear guidance?

Comments:*

- “The EMA Guidance is very clear”
- What makes a clinical study with PK sampling “pivotal”?
- In what studies should ISR actually be done?
- What constitutes a large difference in a single sample, especially if ISR passes?

- We conduct ISR for each and every study
- ISR should be measured regardless of the means of samples
- We conduct ISR for all regulatory studies
- Clinical we run ISR in all studies
- Follow AAPS paper and EMA with regard to which studies we apply ISR. However, as CRO we may only have a few studies and ISR must be confirmed in our lab with our method (and as such, that may be a pop PK study or non-pk study)

* Selected as representative of a large data set

An observation from the data

- Industry continues to perform ISR in more studies than called for in guidance/guideline, even though failure rate remains low.
- Although data not shown, it can be assumed that the number of studies with a failed ISR which also impact any downstream safety decision is even significantly lower.



- Are resources used and associated cost of performing ISR in its current application by industry balanced with the benefit of conducting ISR?
- If industry would limit ISR to those studies called for in the Guideline/Guidance, would this sufficiently ensure data quality?

Conclusion

- ISR failure rate is low (app. 1.5%) and failures are 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.
- Hence, 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.

Recommendation: to us - as industry

The scope for ISR study selection is unambiguously clear from the guidance. However, many labs execute ISR as an in-study validation parameter / process control in studies and numbers not called for in the guideline.

- **We recommend industry to limit the number of studies and study types with ISR to that as a regulatory requirement**

Recommendations: To ICH M10 EWG

Industry is uncomfortable when dealing with sporadic flyers (single samples with large variations).

- **Single-sample variation in passed ISR should not be an issue for investigation in the ICH M10 guideline**

Based on current experiences (1.5% ISR failure rate), causes and impact of failed ISR, the 10 + 5 % repeats is a high number not adding value. The number of ISR should be aligned with number of spiked QC's in a run (5%).

- **Reduce ISR to 5 % and recommend a minimum number for ISR analysis**

Acknowledgement

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EBF Community