Handling of Anomalous Results in Europe – Feedback from EBF Survey

"Finding the right level"

Silke Lüdtke
Boehringer Ingelheim on behalf of EBF

Presented at:

3rd Annual EBF Symposium, 01-03 Dec 2010

Scope of the Survey as well as the Presentation I

Current situation:

- According to current guidelines 1/3 of batch acceptance QC samples as well as ISR samples may show a higher deviation than actually specified
- Therefore, it is acknowledged that there is a certain probability that some study samples, QCs or calibrators won't meet the acceptance criteria
- **And** that this does not jeopardize the validity of the bioanalytical data and subsequent pharmacokinetic evaluation
- Some presentations on bioanalysis recently dealt with anomalous results, out of specification results etc – terms that are used within the GMP area

Scope of the Survey as well as the Presentation II

Question:

What do we as **Bioanalysts**, consider as an anomalous sample/result that requires special attention ?

Answer:

Do a survey within EBF !

To learn about the definition of anomalous results and related procedures within EBF member companies, and **to define the right level** how to handle these results **with respect to science and compliance**

Information about Survey

- Different scenarios during method validation and study sample analysis described
- Rather common scenarios described but not exceptional cases
- Question was „would you accept“, „repeat“ or „perform a more formal investigation“
- Questions on approval/documentation/reporting of measures included
- Input from 22 EBF member companies obtained
- Not all questions/answers displayed in detail here

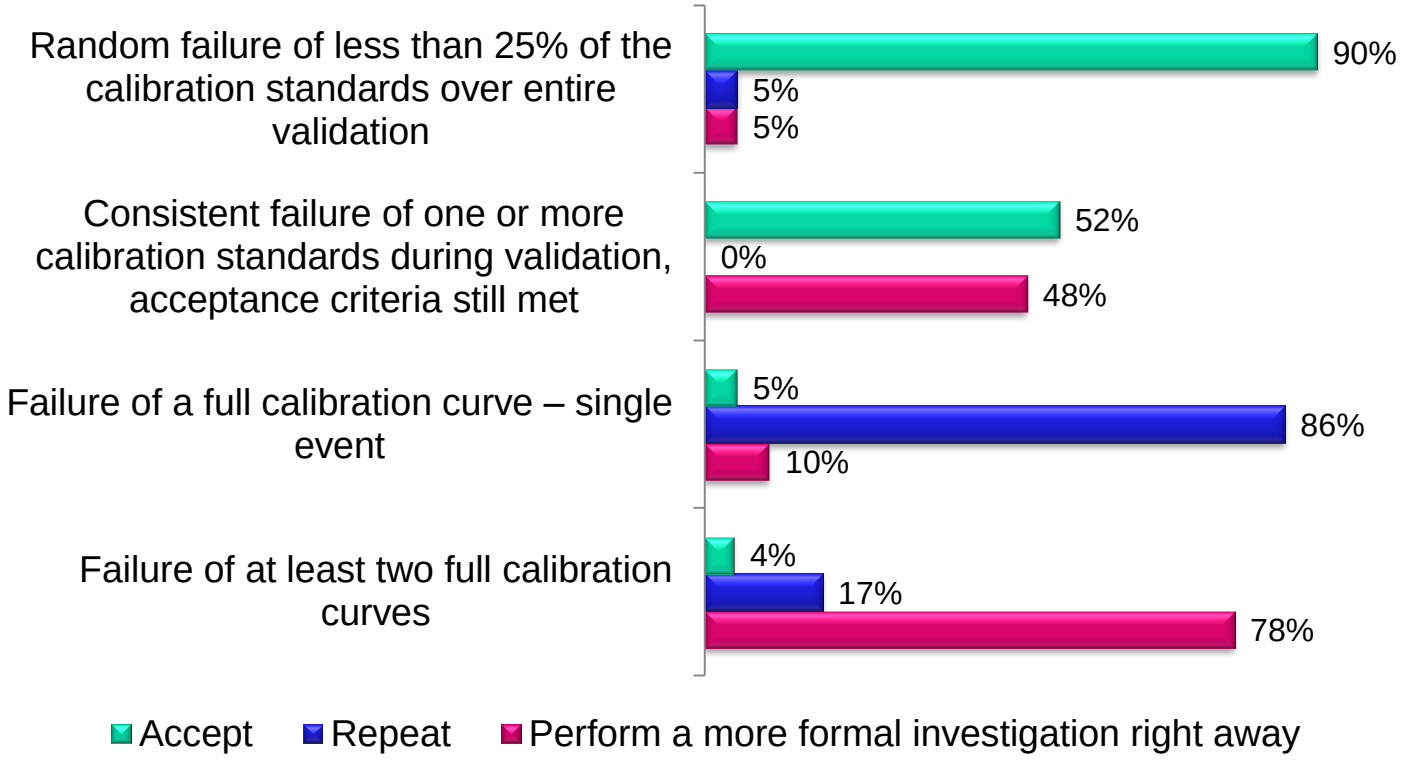
Questions on Method Validation

Dealing with

- failing calibration standards
- Failing validation samples assessing accuracy and precision of the method
- Failing validation samples used for stability testing, recovery etc.

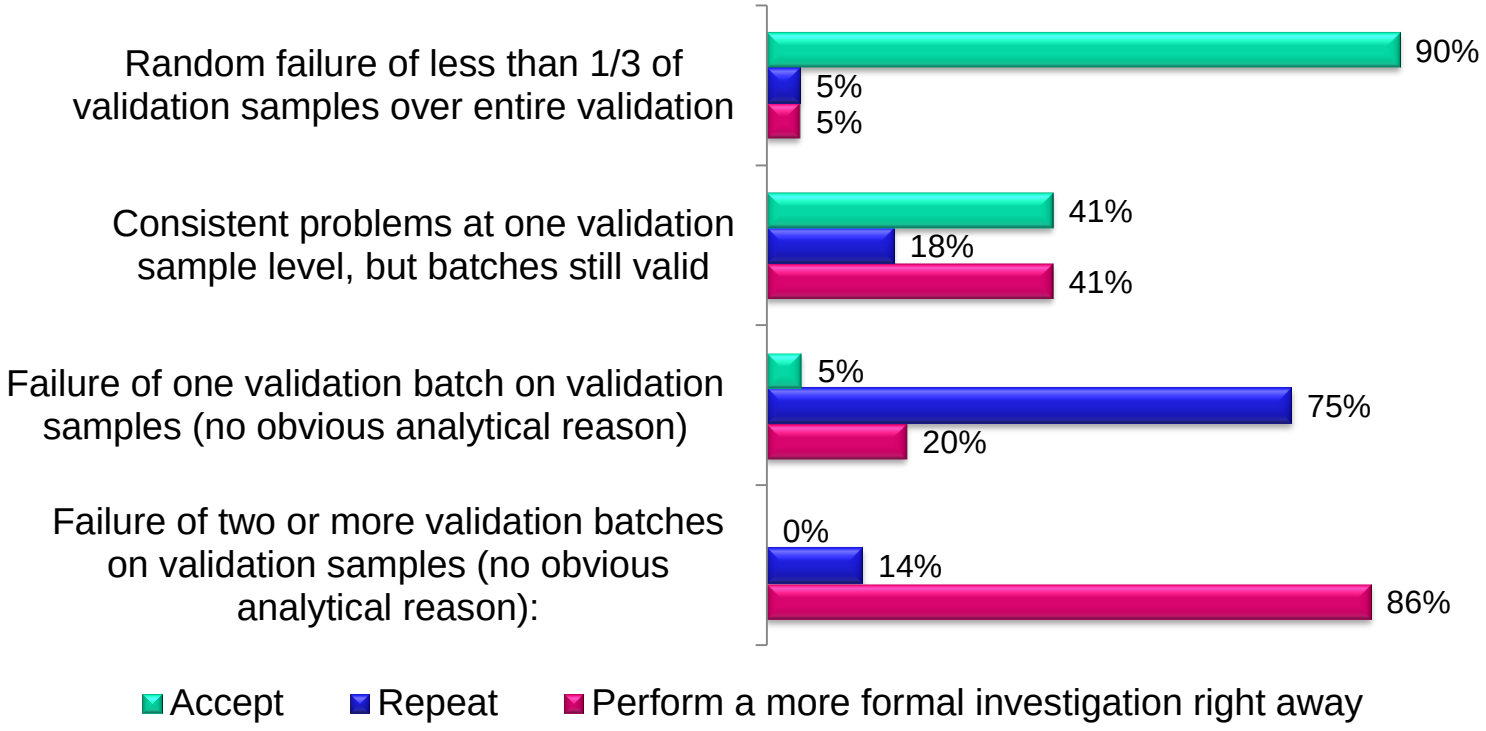
Questions on Method Validation

Failing Calibration Samples



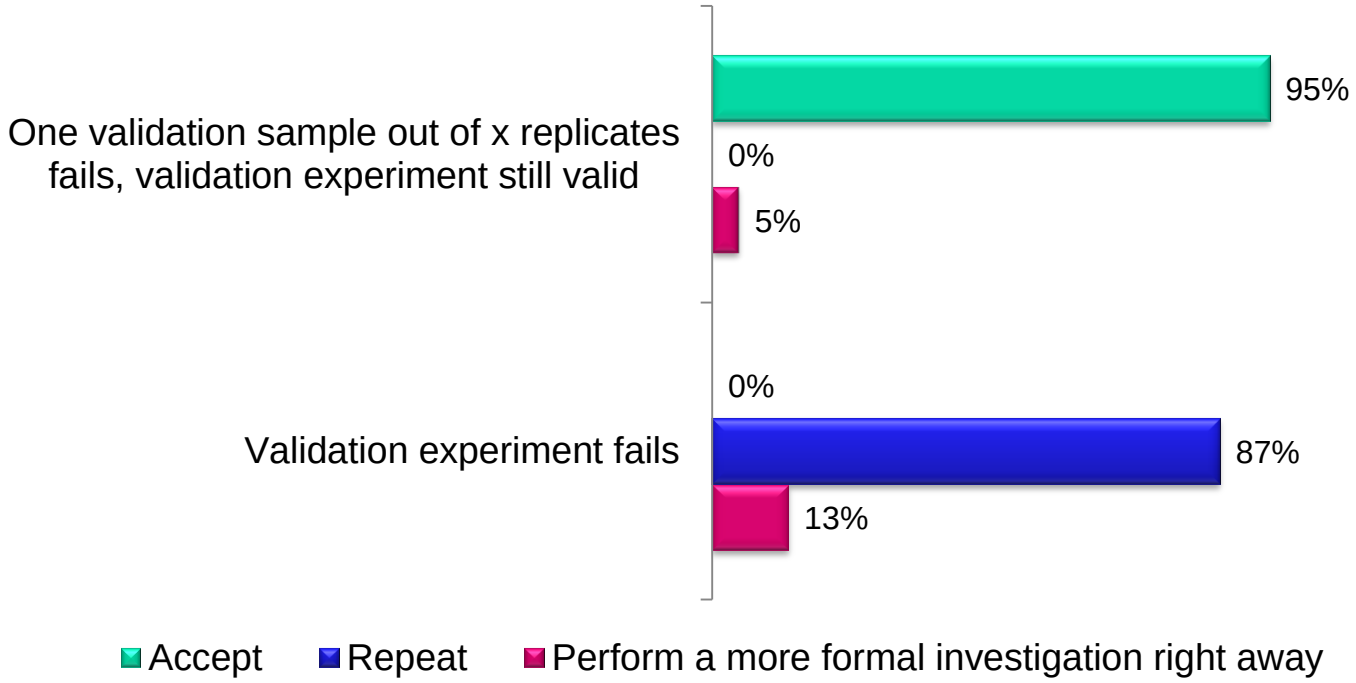
Questions on Method Validation

Validation Samples to assess Accuracy and Precision



Questions on Method Validation

Validation Samples used for Stability Testing, Recovery Testing etc



Questions on Method Validation

Rationale for accepting results

- Batch acceptance criteria met – batch valid
- Valid batches should not be rejected

However, many EBF members would re-spike the affected calibration standards or quality control samples in case these samples were also prepared for subsequent study sample analysis

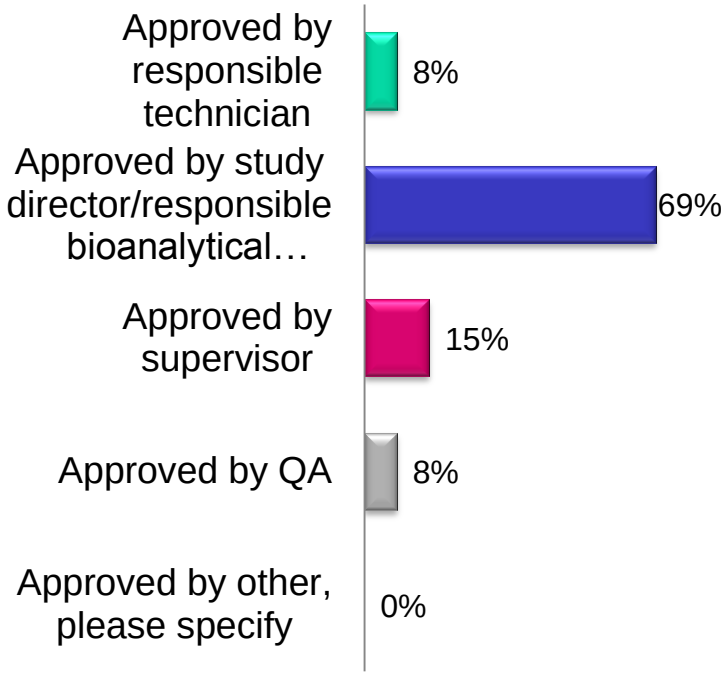
What is meant by a more formal investigation

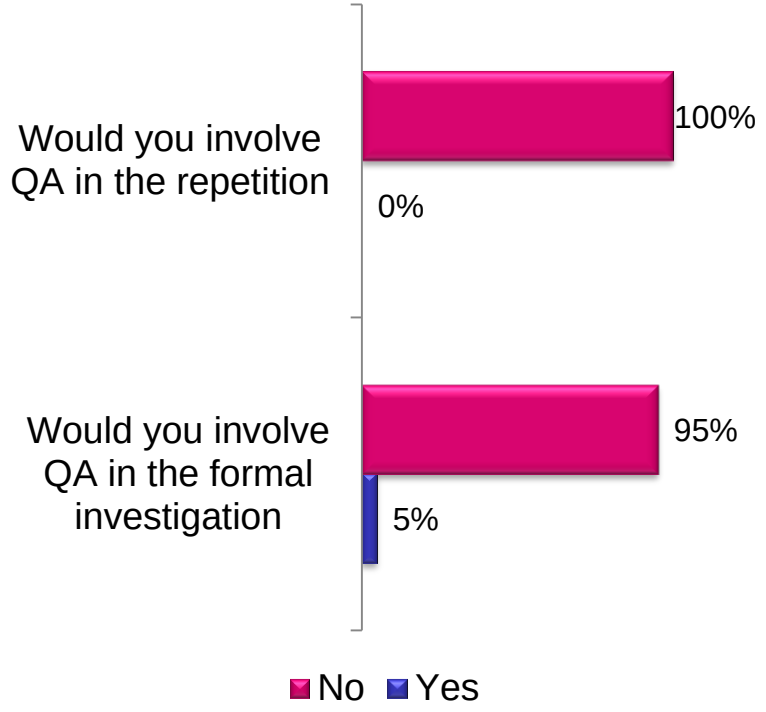
- Checking whether spiking process was correct
- Re-spike affected concentration level or entire calibration curve
- Check curve fitting

Aim is to avoid problems during study sample analysis

Questions on Method Validation

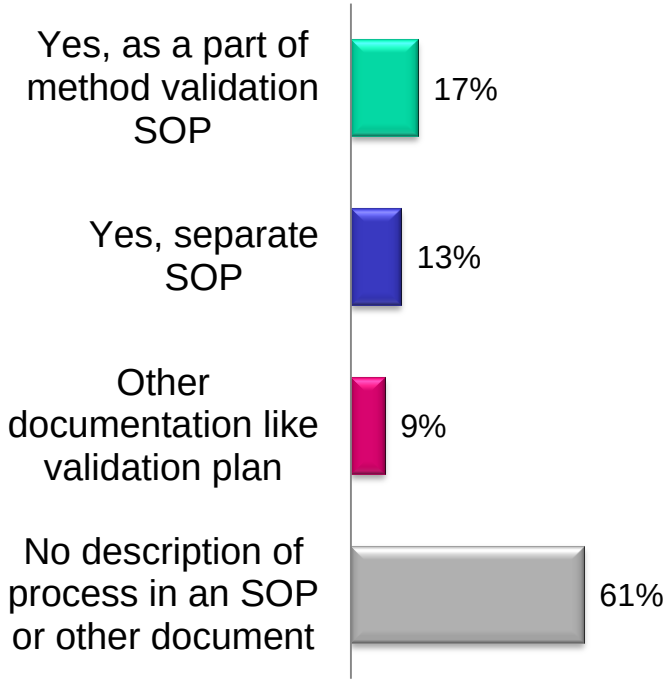
Approval of Measures / Involvement of QA



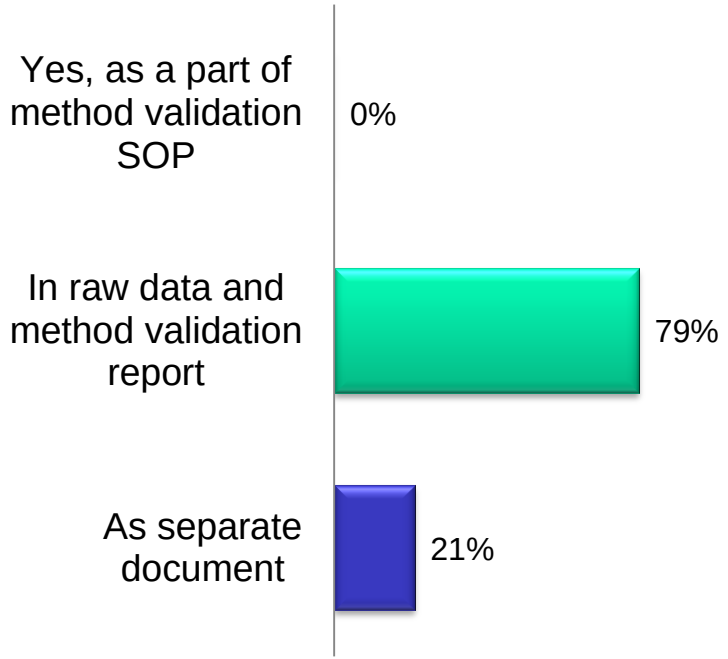


Questions on Method Validation

Pre-defined process ?



Documentation in Raw Data/ Bioanalytical Report ?



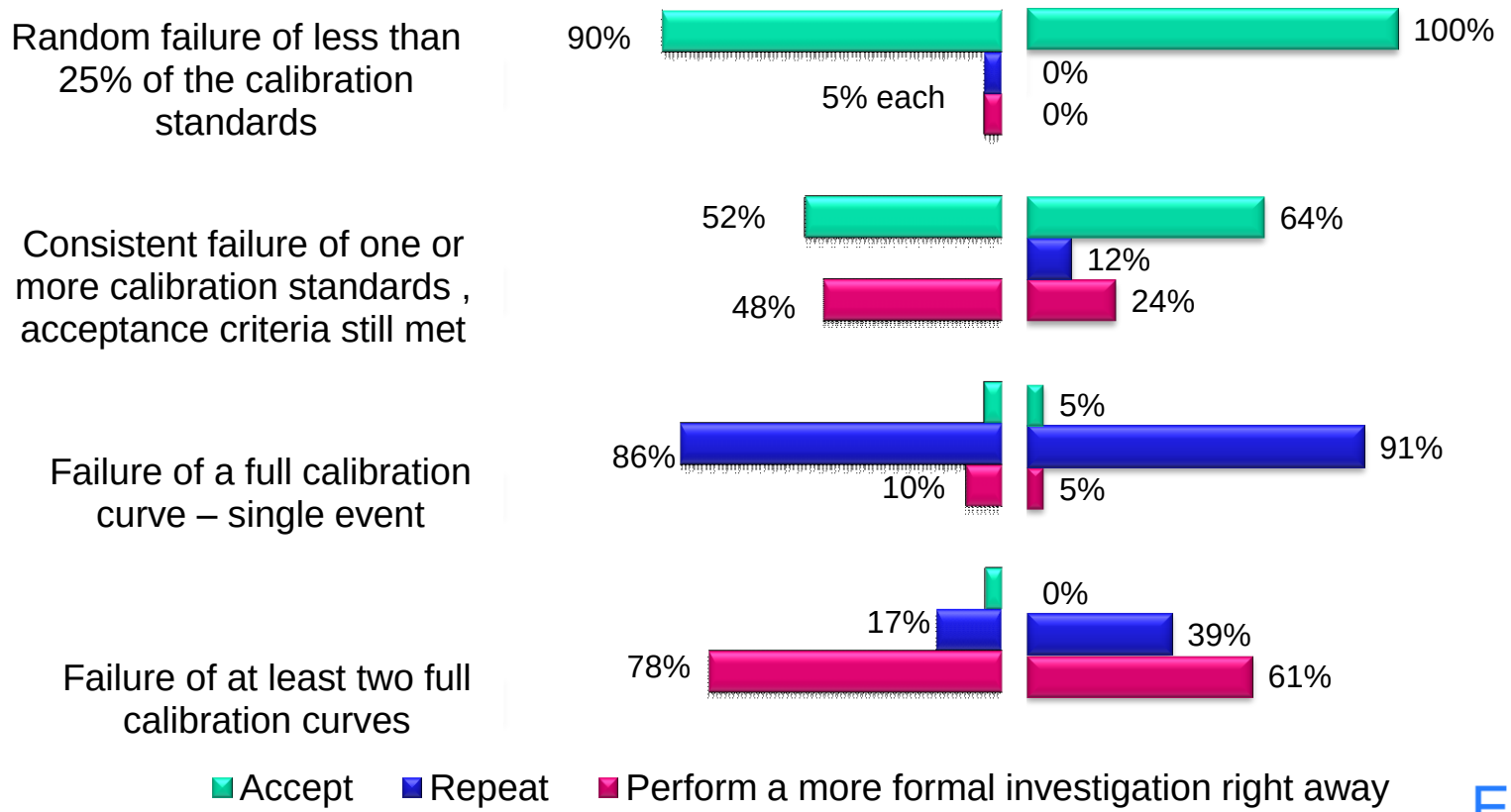
Questions on Study Sample Analysis

Dealing with

- Failing calibration standards
- Failing quality control samples
- Carry-over
- Differences in internal standard response
- „positive“ placebo/control group samples
- Unusual PK profile

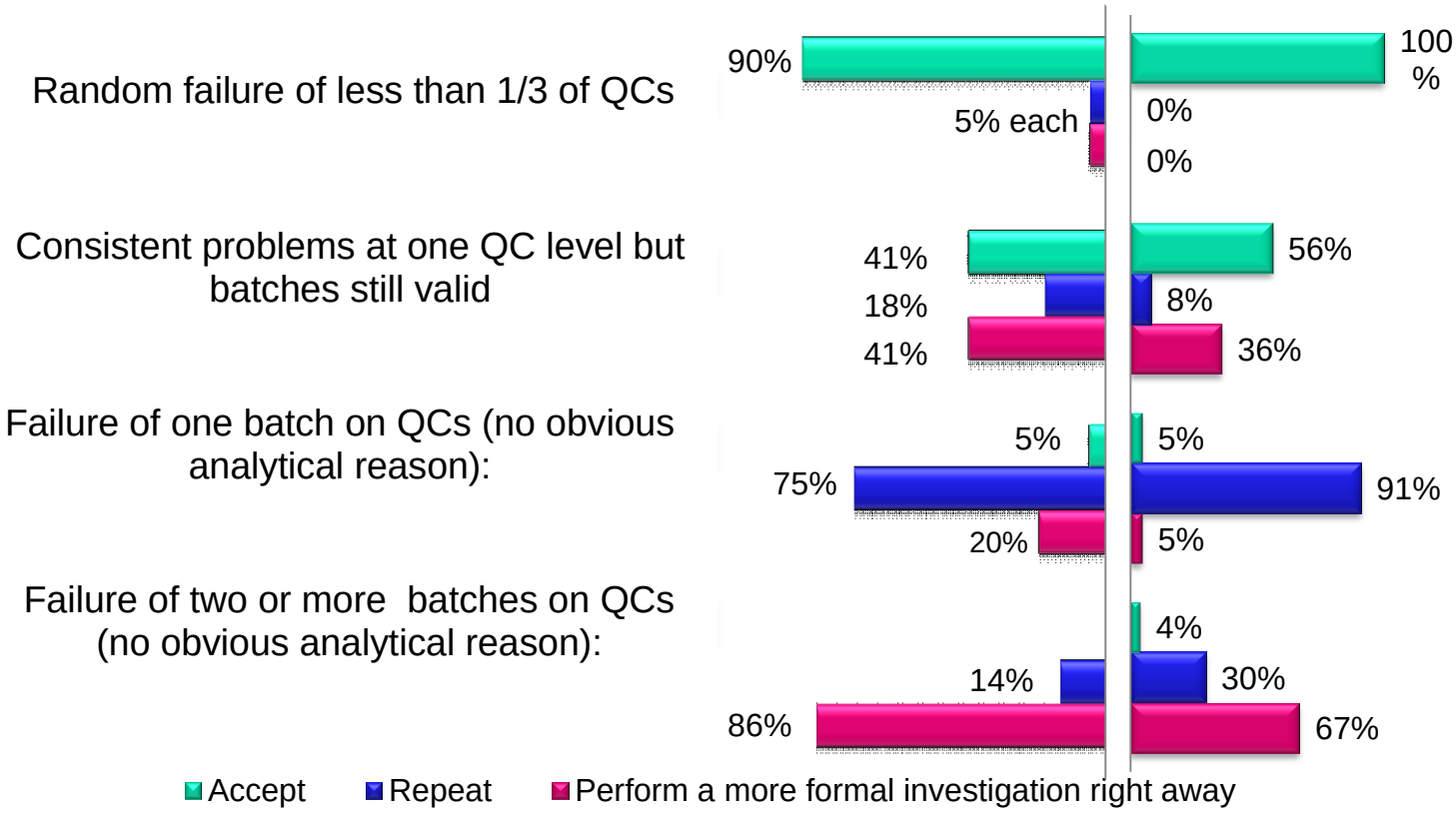
Questions on Study Sample Analysis

Calibration Standards: left side Validation, right side Study



Questions on Study Sample Analysis

Quality Control Samples: left side Validation, right side Study



Questions on Study Sample Analysis

Rationale for accepting results

- Valid batches should not be rejected

What is meant by a more formal investigation

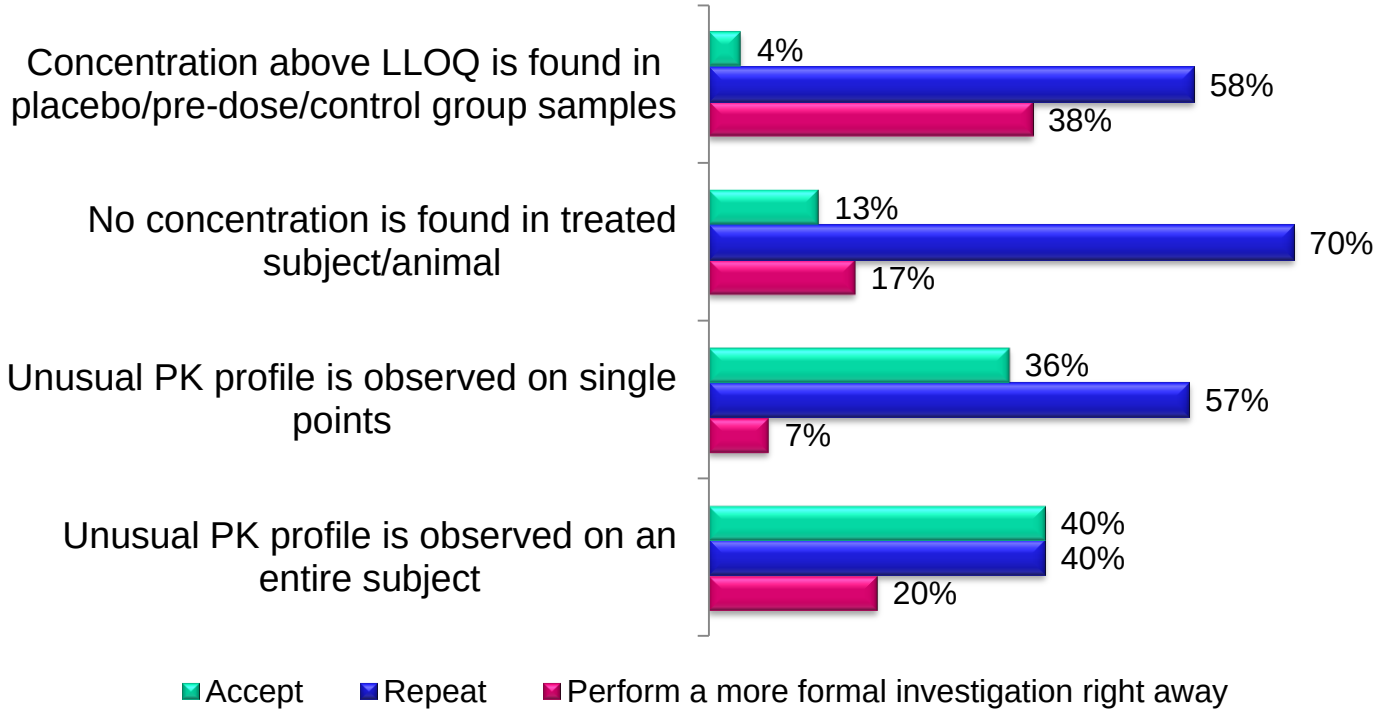
- Checking whether spiking process was correct
- Re-spike affected concentration level or entire calibration curve but accept valid batches analysed so far
- Check analytical system

Trigger for a more formal investigation

- Single event usually no trigger for a formal investigation
- Failure of two subsequent batches „sets off alarm“

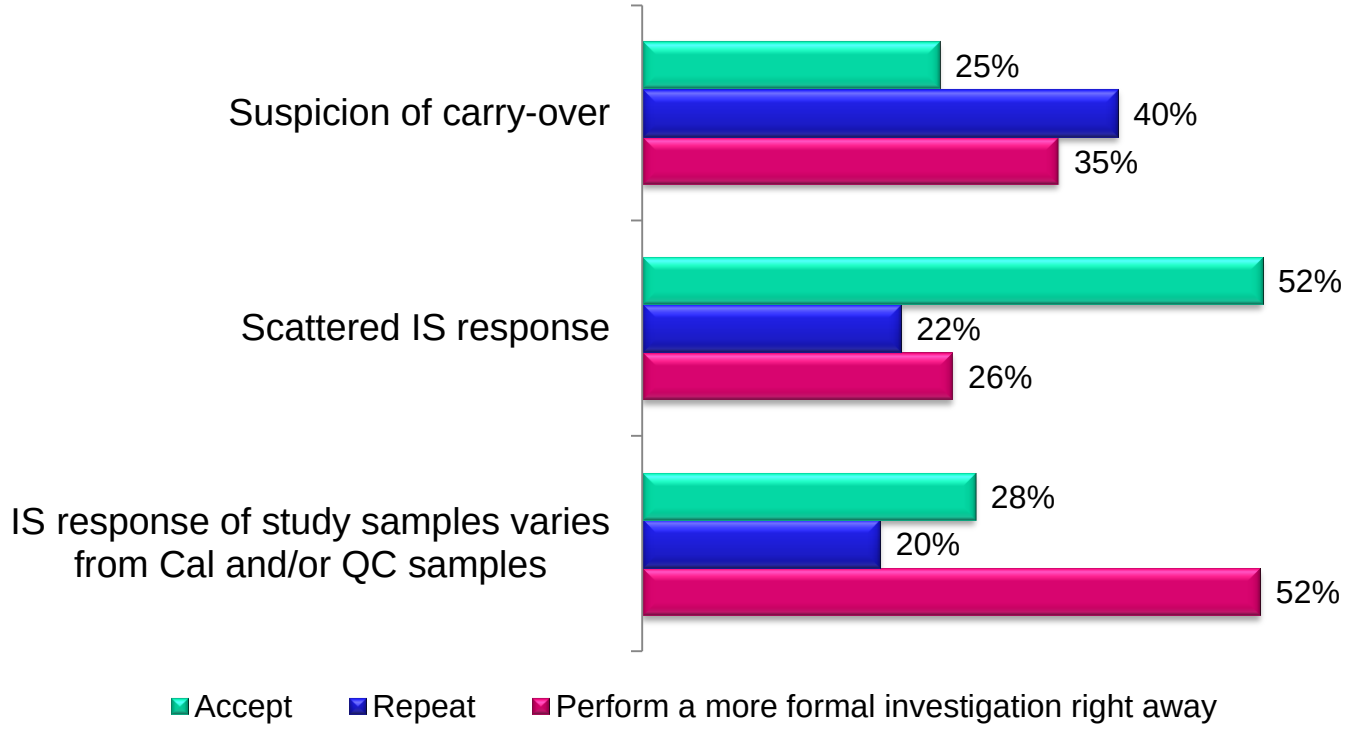
Questions on Study Sample Analysis

Study Samples – Answers reflect various Company Policies



Questions on Study Sample Analysis

Carry-over and Differences in IS Response



Questions on Study Sample Analysis

Differences in IS response

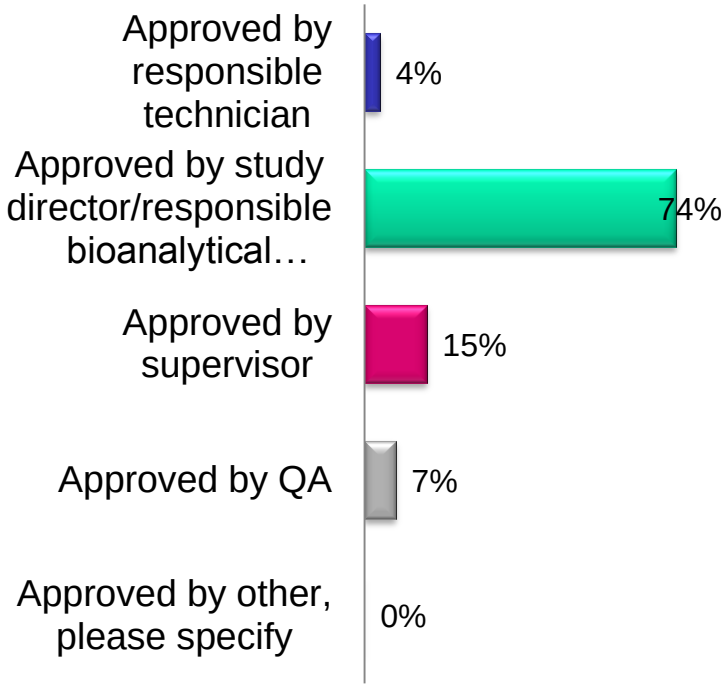
- Level of acceptance rather high in case a stable labelled IS is used – based on experiences made so far
- Situation is different in case a structural analogue compound is used as IS
- Pre-defined acceptance criteria hardly in place – based on experiences made so far and the predominantly use of stable labelled IS

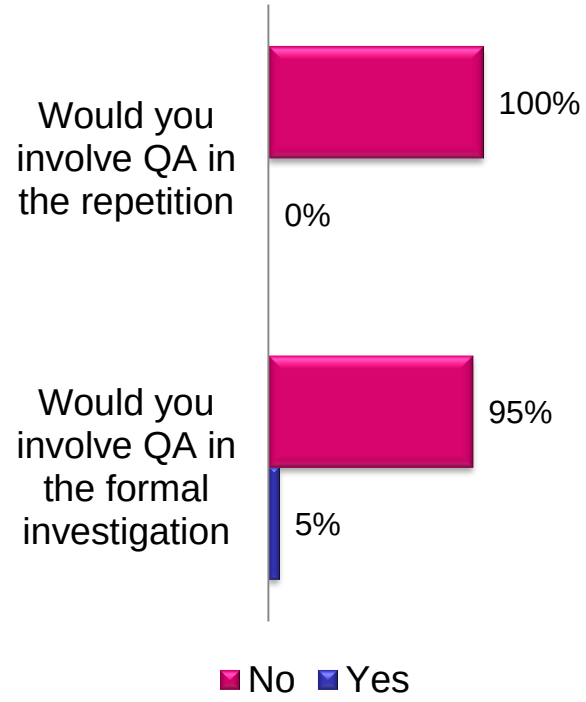
Carry-over

- Often assessed during study sample analysis
- Pre-defined acceptance criteria quite common

Questions on Study Sample Analysis

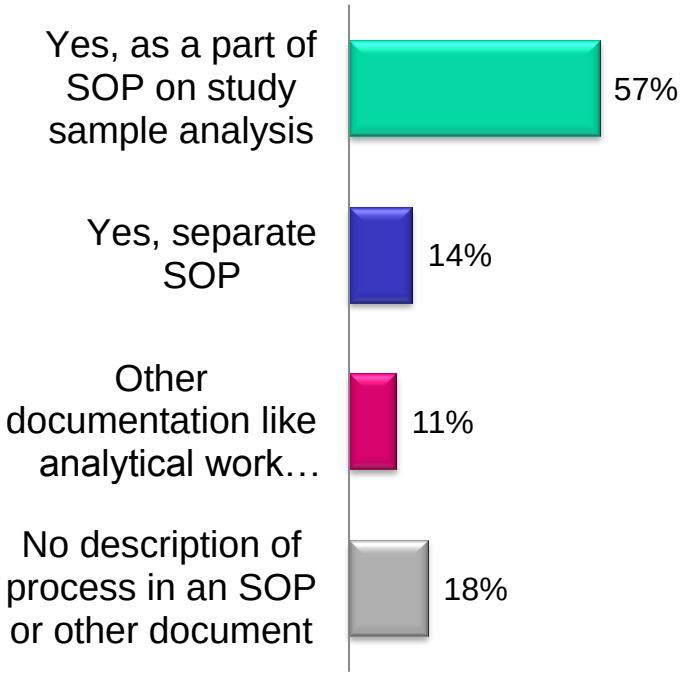
Approval of Measures / Involvement of QA



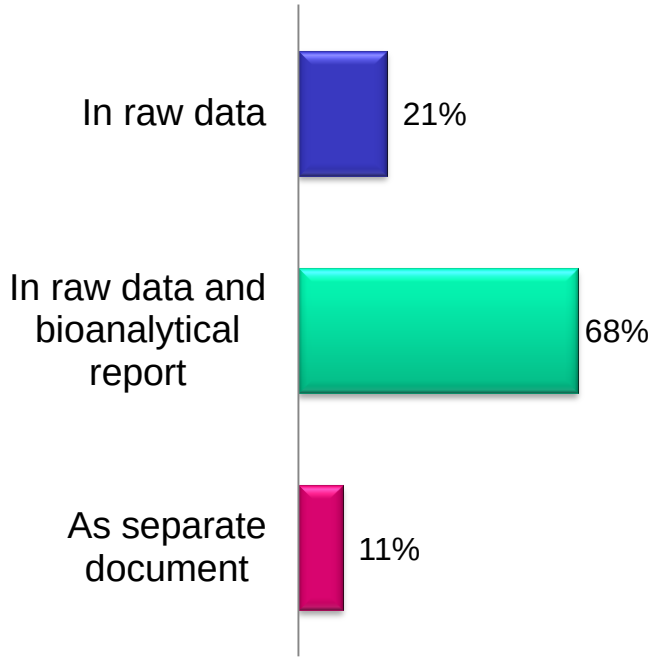


Questions on Study Sample Analysis

Pre-defined Process ?



Documentation in Raw Data/ Bioanalytical Report ?



Summary

Within EBF

- It is acknowledged that there is a certain probability that some samples won't meet the acceptance criteria/confirm the initial result, and that this does not jeopardize the validity of the data
- There is a common understanding that valid batches should not be rejected
- A lot of results are already checked – some call this check simply repetition others call it formal investigation
- Respective measures are documented at least in raw data but often in the raw data and the bioanalytical report so that traceability is given
- Good scientific practice established within EBF member companies - know-how and scientific expertise of bioanalyst can not be replaced by SOPs/CAPA documents

EBF

Acknowledgement

Thanks to

- All EBF members for completing the survey,
  and not being fed-up by the survey swamp
- The team responsible for the design/evaluation of the survey:
  Margarete Brudny-Klöppel, Sirpa Laakso,
  Berthold Lausecker, Magnus Knutsson,
  Peter van Amsterdam, Silke Lüdtke
- You - for your attention,
  and your active participation in the panel discussion