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Unexpected Results in a Bioanalytical Laboratory – a Safety and Compliance Issue ?

Unexpected Results

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BI's procedures and experiences

- No dedicated SOP on unexpected/anomalous results
- Many scenarios covered in SOPs on sample analysis, method validation, sample re-analysis including pre-defined criteria and decision trees
- No formal root cause analysis plan and report
- Documentation in raw data and report
- QA usually not involved

- During recent FDA audit no concerns raised by auditor, no root cause analysis plan/report etc requested, but auditor was interested in good documentation of the rationale and the outcome of the measures taken in case of unexpected results

  The unexpected results in the audited BE studies were "single events" and had no impact on the subjects safety → no need to discuss unexpected results from the non-bioanalytical point of view

The Bioanalytical and the non-Bioanalytical Point of View

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From a classical bioanalytical point of view

- Samples with an unexpected result will be reanalysed
- In most cases the initial result will be confirmed
- Thus, the “strange” result is not caused by problems in the bioanalytical lab

Quod erat demonstrandum – case closed !

From a non-bioanalytical point of view

- The impact of the unexpected result on the subject/patient safety will be assessed as well
- established in the GMP area – “Out of Specification”
- established in clinical chemistry laboratories – “Out of Range“
- “knocking at the door” of our bioanalytical labs

EMA's Thoughts on Unexpected Results in a (Bio)Analytical Laboratory

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Excerpt from the EMA draft "Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples", released Aug 2010

6.1.7 Patient/subject safety

....**any issues that may impact on patient/subject safety are reported without delay**. These may include, but are not limited to, the reporting of **unexpected** or out of range **results and significant deviations from the protocol** or work instructions.

It is always appropriate to consider the need to expedite the reporting of results regardless of the nature of analysis or evaluation that is being conducted. For example, anomalous results or **unexpected values associated with pharmacokinetic analysis may indicate incorrect dosing or marked differences in a subject's ability to metabolise an investigational medicinal product which may potentially have safety implications**.

In all cases, results and observations should be reviewed by an appropriately qualified person to identify any anomalous or out of specification data. This review should be performed **in a timely manner** .

EMA's Thoughts on Unexpected Results in a Bioanalytical Laboratory

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Excerpt from the EMA "Guideline on bioanalytical method validation", effective 01 Feb 2012

5.4 Reanalysis of study samples

For bioequivalence studies, normally reanalysis of study samples because of a pharmacokinetic reason is not acceptable, as this may affect and bias the outcome of such a study. In this case, reanalysis might be considered as part of laboratory investigations, to identify possible reasons for results considered as abnormal and to **prevent the recurrence of similar problems in the future**.

The safety of trial subjects should take precedence over any other aspect of the trial. Consequently, there may be other circumstances when it is necessary to re-extract and/or re-analyse specific study samples, for example where an unexpected or anomalous result is identified that may impact on patient safety.

New Requirements for Bioanalytical Laboratories

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Is a bioanalytical laboratory able to

- Identify significant deviations from the protocol ?
- Identify misdosing ?
- Identify differences in a subject's ability to metabolise an investigational product ?
- Report this in a timely manner ?

And if the answer to all these questions is yes, can we or shall we as bioanalysts take over the responsibility ?

New Requirements for Bioanalytical Laboratories

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Is a bioanalytical laboratory able to

- **Identify significant deviations from the protocol ?**

  yes, e.g. in a non-placebo controlled trial with cross-over design some subjects had normal PK profiles for treatment 1 but hardly any profile for treatment 2

  → subjects did not take medication in treatment cycle 2 as no vomiting etc reported

  → clinic did not notice

  ☒ compliance issue due to misconduct

- **Identify misdosing ?**

  yes, e.g. placebo and active treatment mixed-up

  ⌒ may not be a safety issue for subject if the dose was approved for the trial

  ☒ compliance issue as it demonstrates that procedures at the clinic may be prone to error

New Requirements for Bioanalytical Laboratories

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Is a bioanalytical laboratory able to

- **Identify differences in a subject's ability to metabolise an investigational product?**

  yes, but may need help from pharmacokineticist and/or metabolism scientist
  e.g. profile differs significantly from others, no hint for analytical problem like matrix effect

  ☒ safety issue

- **report this in a timely manner ?**

  not always but very often, i.e. for clinical trials were the bioanalyst is unblinded and sample analysis is performed while the trial is still ongoing

New Requirements for Bioanalytical Laboratories

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And even while the answer to all these questions can be yes, shall we as bioanalysts really take over the responsibility or is that actually on someone else's plate ?

I think we as bioanalysts have to consider these topics, and should agree with colleagues from QA, Clinical and PK on a concept.

Does that mean a higher workload for the bioanalytical laboratory ?

From an analytical point of view probably not as we are discussing rather exceptional situations and not standard cases. And in these exceptional and obvious cases we would re-analyse the samples anyway.

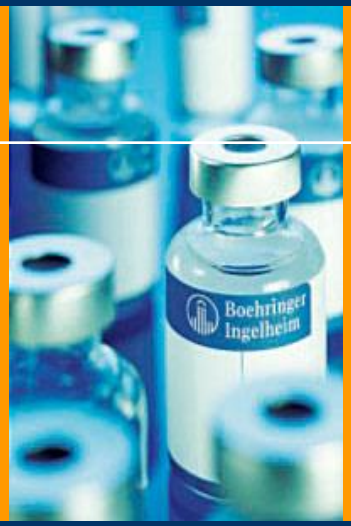
Thus, the “pivotal “part will be to agree on the “communication concept” and to implement it in the respective SOPs, and to allow “GCP QA” to enter our “GLP compliant” bioanalytical world.

And would higher workload be an acceptable excuse for potentially jeopardizing the subject/patient safety ?!

Summary

- A robust, accurate and precise bioanalytical assay is the pre-requisite for reliable data ensuring that the patient safety is not compromised by sample analysis
- But bioanalytical labs will also have to assess the impact of their data on the patients safety, i.e. in case of unexpected results,
  and may also get into the situation to identify non-compliance at a clinical site, supply unit or other function involved in a clinical trial
- Thus, applicable GCP requirements and related procedures should be considered and implemented in a bioanalytical laboratory.
  This is nothing we should be afraid of especially as "*The guidance [EMA reflection paper] is designed to complement existing quality systems …*

Finally, isn't more responsibility something we were actually asking for – we as a service function usually working in the background ?! And don't we want to take ownership for our data ?!



Thank you