

# Global clinical trials - Challenges for Bioanalysis

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# Global clinical trials - challenges

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- Challenges involved with global clinical trials
  - Clinical sites can be anywhere in the world. Sites can be in developing countries where compliance awareness is not that established
  - The bioanalytical department instructs as detailed as possible on bioanalytical requirements related to sampling, storage and shipment (see further)
  - Monitored by site monitors, the bioanalytical department can't follow up
  - Not all sites have all needed equipment
  - Site might say they comply
  - Site personnel doesn't always understand the impact of a deviation

# Global clinical trials - challenges

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- Timely shipment of samples to central laboratory
- Correct shipment of the samples
- The results of PK samples may be unreliable if the sites don't comply with the requirements

# Global clinical trials - Requirements clinical sites

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- Instructions given to clinical sites
  - Via lab manual
  - Via the clinical protocol
  - Via Statement of Work (SOW) written by central lab
- Instructions include
  - Sampling conditions
  - Sampling tubes to be used (volume, anticoagulant)
  - Time between sampling and centrifugation
  - Time between centrifugation and freezing
  - Storage conditions at the site
  - Shipment conditions and timing of shipments
  - Courier to be used (door to door delivery, dry ice)

# Recent example

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- In a recent filing, Janssen received questions from FDA. One of the questions was:

*"Please clarify whether the temperature(s) that long term sample stability was evaluated at (-20°C) for both compound 1 and compound 2 was the storage temperature(s) throughout the life cycle of the PK samples from the following trial: ABC-123 at the clinical trial sites, the bioanalytical laboratories and, if applicable, at any storage facilities for the samples."*

- Background information:
  - Method for compound 1 and compound two is a combined method
  - Validated at sponsor and transferred to CRO
  - During validation, stability testing was done at -20°C

# Recent example

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- Documents set up at start of the trail were consulted:
  - SOW stated storage at -20°C at the clinical sites
  - SOW stated storage at -20°C at the central laboratory
  - Bioanalytical Study plan stated storage at -20°C at the bioanalytical lab
- Bioanalysis consulted the different parties:
  - the clinical team to confirm that SOW was followed
  - the bioanalytical lab involved to confirm that the correct storage conditions were used

# Recent example

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## Response to FDA:

*The samples from trial ABC-123 were stored at -20°C at the clinical site. They were shipped on dry ice to the central lab, stored there at -20°C, shipped on dry ice to the bioanalytical lab, and upon arrival stored again at -20°C until analysis. After analysis, they were stored again at -20°C at the bioanalytical lab.*

- For the same study, an EMA inspection was conducted at some of the clinical sites involved
- The EMA inspection revealed that some sites used -70°C freezers

# Recent example

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- The EMA inspection report also included a lot of observations for one of the clinical sites, not directly related to the PK samples
  - Calibration of equipment not adequate
  - Personnel training logs not adequate
  - Identification of protocol deviations not adequate
  - Unsigned or missing laboratory reports
  - No adequate reporting of AE
  - And so on
- The EMA inspection report was shared with FDA



# Recent example

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## Question from FDA:

*The clinical site inspection reports mention the use of -70C freezers to store samples. Please confirm whether plasma samples were stored at -70C at the trial sites , intermediate storage site (if applicable) or at the Bioanalytical lab.*

- Investigation: what sites used what freezers, and how long were samples stored at the individual sites?
- Result: some samples were stored at -70°C, we provided a list of number of samples stored at what temperature, and maximum time of storage at -70°C
- Long term stability testing was started at -70°C
- Long term stability was proven at -70°C for the maximum period the samples were stored (37 days)

# Recent example

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- Consequences
  - Results from the one site with lots of observations had to be excluded because authorities decided the site was not reliable, PK analysis had to be repeated after exclusion of these results
  - Extra stability testing had to be set up to cover the storage of the PK samples at all sites. If we had not been able to prove extra stability, all results from sites using -70°C freezers would most likely have been excluded

# Possible impact

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- Exclusion of part of the results for a study
- Exclusion of the whole study
- Need to repeat an entire study
- Delay in approval of a product

# Lessons learned

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- Bioanalysis is the first point of contact for the PK samples throughout their whole lifecycle in the study
- Increased focus on sample management aspects by all stakeholders in clinical trials from sampling onwards is necessary
  - Bioanalysis needs to be closely involved in set up of the study and bioanalysis instructions need to be followed
  - The correct storage conditions need to be used at all times and there is a need for close follow-up by the study monitors
  - Timely shipment of samples to central lab or bioanalysis and timely analysis of the samples is needed to stay within the proven stability window
  - Any deviation from the prescribed instructions in the lab manual or SOW needs to be communicated to Bioanalysis for impact analysis and corrective action

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# Questions? Comments?

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