High Volume Rapid Turn-around Clinical Sample Analysis: Obstacles, Solutions and Lessons Learned

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1 ABSTRACT

Objectives: Methodological and process optimization to streamline sample receipt, bioanalysis, quality control/assurance to meet data deliverables in a series of rapid turn-around clinical programs exceeding 24,000 study samples.
Methods: A pre-program stake-holder meeting was held between the Sponsor, the central clinical laboratory, and Charles River Laboratories for process optimization including: electronic sample manifest receipt, sample reconciliation, sample analysis, QC and QA of the data, reporting, and data transfers. Method optimization was performed to streamline the ELISA method previously used for lower throughput studies. Partial method validation of the optimized method included steps involved with: sample extraction, centrifugation, coating stability, extracted plate stability.
Results: The electronic sample manifests were revised to facilitate the 64 samples shipments received from the clinical site. Rolling dates for data submission were scheduled, so that QA'ed data was available every second week. Data was sent to the PK scientist in a rolling basis, to accelerate the PK analysis, while a final set of data was transferred to the central clinical laboratory using a revised data transfer process.
Implications: Due to the above process improvements, the assay failure rate was at approximately 6%, while the ISR sample pass rate was >96%. Using the new electronic manifest process, 20 of the 24000 samples received required reconciliation. The Sponsor requested deliverable dates were all met. These processes were implemented to other clinical studies in order to maximize throughput and to minimize manifest discrepancies.

2 INTRODUCTION

Multiple clinical studies yielding a high volume of bioanalytical study samples requiring rapid turn-around were presented to the bioanalytical team (sponsor and CRO). A data flow optimization meeting was held to ensure deliverables (on-time provision of QC'ed and QA'ed data and final report) would be met.

Optimization topics included the following: bioanalytical method and reagents, sample shipment, sample management, personnel, QC process, QA process, data transfer, communication plan, risk assessment and mitigation strategy, escalation plan and archiving (refer to Figure 1).

A stake-holder meeting was held face-to-face, including representation from the Sponsor, clinical site, the central clinical laboratory, and the bioanalytical laboratory.

The bioanalytical method to determine concentrations of free LY-X in human serum consisted of an initial PEG-precipitation step, followed by a sandwich ELISA.

3 METHODS / OPTIMIZATION / RESULTS

Figure 1. Processes Improvement Occurring During Large Clinical Program

Topic	Existing Procedure	Optimization	Result
Method Partial Validation	-Bioanalytical method to detect free LY-X in human serum involving an initial PEG precipitation followed by a sandwich ELISA. -96 well ELISA plates coated with drug specific capture reagent with demonstrated 24 hour stability refrigerated. -Sample dilutions performed in matrix with individual micro-centrifuge tubes and PEG precipitation extraction performed in micro-centrifuges. -Extracted supernatant diluted 3-fold before application to the coated and blocked ELISA plates and incubated for 2 hours. Remainder of procedure is standard.	-Inefficiencies caused by short plate stability. Plate coating stability extended to 96 hours. -Tube labelling and the use of a micro-centrifuges for dilutions and extraction was rate limiting. Transition to a 96 well high speed plate centrifugation system. Partial validation performed to evaluate the reduced speed of the plate centrifuge relative to the micro-centrifuge (10 000 g(av) compared to 6 000 g(av)). -Immediate assay of the extracted supernatant prevented running the ELISAs in a batch wise manner. Stability of the extracted supernatant was evaluated for 7 days with the plates kept covered and refrigerated requiring a partial validation.	-Extension of plate stability to 96 hours allowed bulk preparation of coated plates with little wastage caused by plate expiration. -Transitioning to a 96 well plate sample dilution and extraction procedure eliminated the need to label micro-centrifuge tubes. Throughput for samples (standards, QCs and study samples) with a single micro-centrifuge was 24 samples per run compared to 196 samples with the micro-plate centrifuge. Efficiency in sample throughput was increased by 2-fold. -Establishing storage stability of the extracted sample introduced a break in the procedure so that extraction activities and ELISA activities were separated by as much as 7 days. This introduced flexibility and efficiency in scheduling and batch wise processing of the extraction and ELISA procedures.
Sample shipment	-Several weekly shipments received during a short period of time. -High level of discrepancy -Extensive follow-up	-Manifest design was simplified/updated -Central laboratory verified samples prior to shipment	-Manifest fields match data transfer fields -20 of the 15 000 samples received had discrepancies, which were resolved quickly
Sample management	-Samples logged in freezers -Staff handles sample reception	-Due to large bolus of samples, additional freezers were purchased. -Back-up personnel were assigned for handling of samples to accommodate large numbers.	-All samples were logged in upon reception. -Sufficient freezer space was available to accommodate large number of samples.
Reagents	-Reagents ordered to cover a study.	-Critical reagents ordered ahead of time to cover a 3-month period. Stocks maintained for an on-going 3-month analysis period -Matrix volume ordered to cover entire clinical program. -Bulk spiking to cover entire program, spiking matched to previous preparation.	-Enough reagents were available to cover analysis. -All analysis, dilutions and spiking performed with the same pre-qualified lot of matrix, and thus no selectivity issues noted. -Spikings were always matched against a gold standard, as such ISR results were all within acceptance (>96% success rate).
Personnel	-Staff performs the analytical work.	-With the large number of samples to be analyzed, and the high workload demands during a short period of time, additional staff were hired and qualified on the sample analysis method. In addition, technicians from other department were cross-trained on the method.	-Sample analysis peaks were able to be handled with the pool of technical analysts available.
QC Process	-Data is QC'ed on an on-going basis, with results QC'ed at end of study.	-Data was audited on a rolling basis, and results table was QC'ed on a bi-weekly period. -Submissions to QA department were also done on a bi-weekly basis.	-Smaller data batches were QC cleared on a rolling basis, aiding the QA unit review the data. -QC'ed data transfers occurred on a bi-weekly manner with the Sponsor, to allow for a transient PK analysis check.
QA Process	-Data and report are submitted to the QA group at the end of a study.	-Data was submitted to the QA group on a bi-weekly basis, and data was cleared in batches. -Report was submitted at the end of the study.	-Rolling QA'ed data transfer were submitted to the central laboratory. -Potential issues with the data/results were addressed on an on-going basis. -When final set of samples arrived, turnaround time was significantly decreased, due to the batching of data to QA.
Data Transfer	-Data generated containing multiple fields, which needs to be reconciled at the end of a study. -Data transferred via e-mail or portal to Sponsor.	-New process implemented with central clinical laboratory, in which data was uploaded to Watson LIMS containing less data fields (no collection date and time entries contained, only a unique accession number). -Data transfer occurred via a secure File Transfer Protocol (sFTP) server established between CRL and the central clinical laboratory.	-A total of 21 data transfers occurred during a three month period. -No reconciliation was required for any of these transfers, as the data format was greatly simplified with internal codes used at the central clinical laboratory
Communication Plan	-E-mail sent to main Sponsor contact to address any issues.	-During the stakeholder meeting, various topics were assigned owners, and the media type (e-mail, Excel file, conference calls) was established, as well as the frequency of these communications.	-Due to this clarification, this aided in identifying which people should be contacted in specific cases. -Accelerated issue resolution, by having the correct personnel involved in the communication right from the start.
Risk Assessment	-Potential risks with a study discussed internally.	-During the stakeholder meeting, various potential risks involved with such a large clinical program were identified, and assigned an impact and priority rating, with a potential risk response attributed to an owner(s).	-This process allowed all team members to know what potential risks were at play, and who would respond to remedy these risks should they arise during the program.
Escalation Plan	-Potential problems are communicated to the Sponsor.	-During the stakeholder meeting, an escalation plan was outlined, with types of issues and main point of contact for each.	-Allowed for a smoother escalation of potential issues with either the Sponsor, central clinical laboratory and the bioanalytical laboratory..
Archiving	-Samples and data are archived at study finalization.	-Due to large number of samples to be archived at the same time, additional freezers were purchased to ensure all materials could be archived on the finalization date.	-Once study finalization occurred, all material was archived on the finalization date with no issues.

4 CONCLUSION

A pre-program stake holder meeting was held prior to the clinical program, with attendees including the Sponsor, the clinical site, the central laboratory and the bioanalysis laboratory. Items of discussion included the sample receipt process, sample logging process, the bioanalytical method, the reagent inventory, QC and QA review, data transfer/reporting, an escalation process, and a communication plan.
The central laboratory shipped samples to the bioanalysis laboratory (CRL) following complete reconciliation of sample records. The emphasis was not on shipping samples from the central clinical laboratory to the bioanalytical laboratory rapidly, but shipping samples that had complete and accurate manifests provided to the bioanalytical laboratory prior to receipt.
The optimization of the PEG precipitation method allowed for a higher sample throughput per day per analyst. A 96-well plate centrifuge was used to increase throughput, and avoid the use of a microfuge. In addition, the stability of the PEG precipitation solution was extended to 7 days at 4°C.
For the data transfer, the electronic manifest details were simplified, so that less entries were provided. Collection date and time of the samples was not provided in the electronic sample manifest, only a specific accession number, which could be tracked by the central laboratory.