Production Assistance for Cellular Therapies

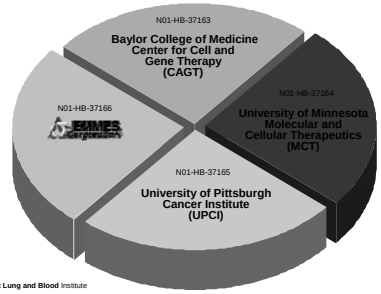
Welcome to the

Educational Web Seminar
"Validation Processes"

July 31, 2008
12:00 Noon - 1:00 PM ET

About PACT

A National Heart Lung and Blood Institute-funded initiative



National **Heart Lung and Blood** Institute

MISSION

- PACT manufactures quality cell therapy products on behalf of investigators with funded clinical trials requiring support in product development
- PACT's educational training focuses on three general areas: translational development/scale-up and manufacture of cell therapy products, quality assurance, and regulatory issues
  - Workshops (on-site)
  - Web Seminars

Today's Education Web Seminar

"Validation Processes"
Carolyn Keever-Taylor, PhD

Medical College of Wisconsin

Web Seminar Description
The speaker will provide an overview of a Quality System, the principles for validation, and discuss the three types of validation processes: prospective, concurrent, and retrospective and what elements should be addressed in each

Web Seminar Objectives

- How to prepare and execute a validation plan
- How to set up and monitor a process validation program
- When validation and revalidation is required

Faculty Disclosure

The Accreditation Council for Continuing Medical Education (ACCME) is the governing body that accredits AABB to provide continuing medical education credits for physicians. In accordance with the ACCME Standards for Commercial Support℠, all faculty for this event have signed a conflict of interest form in which they have disclosed any significant financial interests or other relationships with the industry relative to the topics they will discuss during this program.

Presentation Slides

The presentation slides for this web seminar are available publicly on the main page at:

www.pactgroup.net

PACT Webinar July 2008

Validation Processes

Carolyn A. Keever-Taylor –Medical College of Wisconsin

MEDICAL COLLEGE OF WISCONSIN

Objectives

* How to prepare and execute a validation plan
* How to set up and monitor a process validation program
* When validation and revalidation is required

Define terms

Explain value

Provide example template

Illustrate with examples

Terms

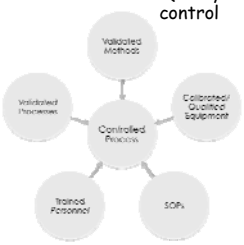
* **Validation:** Confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled.
* **Verification:** The confirmation of the accuracy of something or that specified requirements have been fulfilled.
* **Qualification:** The establishment of confidence that equipment, supplies, and reagents function consistently within established limits. Qualification is part of the validation process.

Validation

* Types of Validation Studies
  * Prospective- Before a procedure or process is implemented.
  * Concurrent- Usually some studies done prior to implementation with completion during (e.g. CD34-enrichment).
  * Retrospective- For procedures that have been in place that were not formally validated.
  * Revalidation- Secondary to major changes in the procedure or process.

Why Required?

* Standards
  * FACT
  * AABB
* Regulations
  * CGTP
  * CGMP
* Each product unique
* Quality requires process control



What to Validate?

* Processes, Policies & Procedures
  * Processing (including cryopreservation)
  * Storage
  * Distribution & Transport
  * Product assays and testing
* In-house prepared reagents
* Labels
  * Creation, accuracy of identity and content
  * Suitability under conditions of use
* Computer systems provided they:
  * Are required to adhere to core GTP functions
  * Perform user defined calculations
  * Constitute an inventory control system

Procedure vs. Process

* Procedures- A description of how an activity is to be performed.
  * New procedures require full validation
  * Established procedures adopted into the laboratory should be verified
  * Equipment considered with focus on the product, not the mechanics of the equipment. Does require that equipment be qualified.
* Process- A set of interrelated tasks and activities to accomplish a work goal.
  * Broader in scope
  * Validation must considers impact of addition or change on established practices

Overall Approach

* Consistent format specified by SOP, e.g. study template
* Defined responsibilities for:
  * Writing plan- Lab Director or QM/QA designee
  * Performing study- QM/QA personnel or technical Staff
  * Review of results- Lab Director or QM/QA designee
  * Approval of plan and of results- QM/QA personnel
* Conclusion as to outcome-based on data analysis
* Implementation plan, including staff notification and training

Validation Study Design

Define in Advance:

* What will be measured?
* How will the measurements be done?
* How many measurements will there be?
* What are the key elements and critical control points that must be controlled?
* What are the expected results?
* What is an acceptable outcome?

Validation Study Results

* Include all raw results or reference their location
* Prepare a summary of results, use tables or figures if appropriate
* Use statistical analysis suitable for the data
* Explain unexpected failing results or repeated testing
* Come to an overall conclusion as to the validation of the procedure or process based on the study results

Key Aspects to Validate

* Analytical systems Qualification- Focus on instrumentation. Equipment qualification includes:
  * Installation Qualification (IQ)- May be by vendor or lab. Ensures all parts present and equipment functions.
  * Operational Qualification (OQ)- Verifies equipment operates as per specification for accuracy, linearity and precision.
  * Performance Qualification (PQ)- Verifies equipments performs as expected under regular working conditions and within the ranges required.
  * Regular maintenance and quality control- Required to ensure the equipment continually functions within the OQ and PQ criteria.

Key Aspects (2)

* Method Validation
  * Precision- Ruggedness, repeatability, reproducibility at different levels. Express using standard deviation and/or coefficient of variation of replicates.
  * Accuracy- Closeness to an acceptable value. Can be precise but not accurate
  * Limits- Highest and lowest values that can be handled.
  * Specificity, Linearity and range- Usually apply to assay validation
  * Robustness- Effect of deliberate variations in method parameter (e.g. reagent concentration, temperature)

Key Aspects (3)

* System suitability- Refers to the overall process.
  * Determine potential for affects on other parts of the system
  * Measure effects on other parts of the system

Method Validation Study Template (1)

* Title- Describes what is being tested.
* Purpose- Type of study, description of the parameters and outcomes to be assessed
* Acceptable Results- What is required for the process or method to be considered verified. Includes requirements for:
  * Precision
  * Accuracy
  * Specificity
  * Linearity and Range
  * Ruggedness

Not all aspects apply to every study

Example

* Title - Effect of overnight storage on CD3 and CD34 phenotype
* Purpose- Is there a significant difference in %CD3 or CD34 in products tested at receipt versus stored.
* Acceptable Results-
  * Precision- Mean, sd, cv of within assay for fresh vs overnight to be assessed.
  * Accuracy-At receipt result considered as true value. A difference of ≤10% is required. Paired t Test must be p >0.05 for no difference.
  * Specificity-Product must contain >0.20% CD34 or CD3 to ensure specificity of measurement.
  * Linearity and Range-Not evaluated in this study.
  * Ruggedness-Not evaluated in this study.

Method Validation Study Template (2)

* Procedure- Include details of how the study is to be performed and/or reference to existing SOPs.
* System Description to include:
  * Expected results.
  * Critical control points (where can things go wrong)
  * Key elements- Steps that must be managed.
* Target replicates- may need to vary to meet statistical endpoints. Statistical endpoints defined.
* Responsibilities- Individuals who are to perform or are responsible for each aspect of the study.

Example

* Procedure- Instructions for staining and reference to relevant SOPs and workforms. May design a study specific workform.
* System Description to include:
  * Expected results.-Here we thought there would be a difference with a higher % of CD34 and CD3 due to death of granulocytes. Also results might be affected by product MNC content.
  * Critical control points –Included MNC content of product. Wanted a mixture of above and below 70%. Panel with replicate tubes for CD3 and CD34 to determine intra-assay variability.

Example

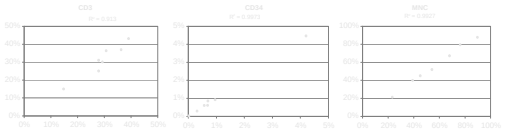
* Key elements- Accurate sampling, strict adherence to flow protocols, product storage at 1-6^{o}C.
* Target replicates- Six products with >0.20% CD34, 3 with >70% MNC and 3 with <70% MNC were targeted. More allowed if statistical analysis was inconclusive.
* Responsibilities- Standard approval of study by Director. Technologists routinely doing testing performed assays. BMT program QI chair has final review and approval.

Method Validation Study Template (3)

* Results
  * Workforms
  * Raw data
  * Statistical analysis
  * Graphs
  * Data summary
* Summary Evaluation
  * General description of results
  * Approval or disapproval with reason
  * Required additional studies after implementation, if approved

Example

* Results
  * Workforms-Were attached
  * Raw data-Were attached
  * Statistical analysis-Showed a within assay CV of <5% for CD3 and CD34. Overnight vs. at receipt CVs similar. No difference based on MNC and paired t Tests showed no difference with overnight storage.
  * Graphs-



Example

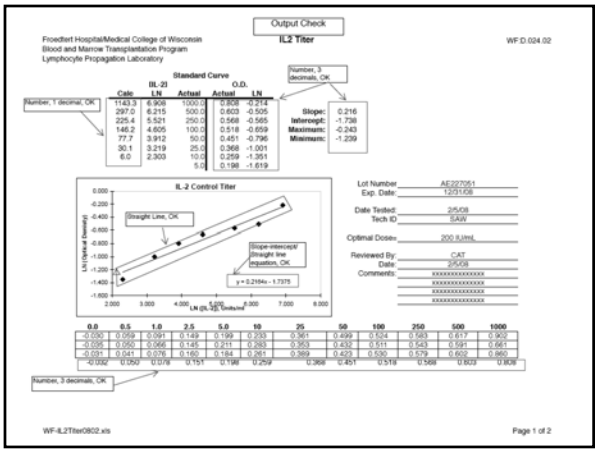
* Data summary-Included description of stats and of one product under the 0.20% limit for CD34 eliminated from stats for CD34, but showed no change in overnight assay. A 7th product was tested to replace the one <0.20%. A Table of results was prepared that included all statistics that were done.
* Summary Evaluation
  * General description of results-Takes narrative form, included discussion that no difference was seen even though one was expected.
  * Approval or disapproval with reason-Study was approved. Testing at receipt is routinely performed and is not repeated the next day.
  * Required additional studies after implementation, if approved-Additional data added to study on occasions when two analysis are done

Method Validation Study Template & Example

* Implementation Plan
  * Need for new or revised SOP- Revision was required since practice had been to repeat testing.
  * Personnel notification and training if needed- Documented discussion at laboratory meeting. Sign off on revised SOP.
  * Effective dates- Change was effective with all study approvals and final SOP revision.
* Authorization review and signatures- Study documents reviewed within lab, then by program QI committee chair before change is final.

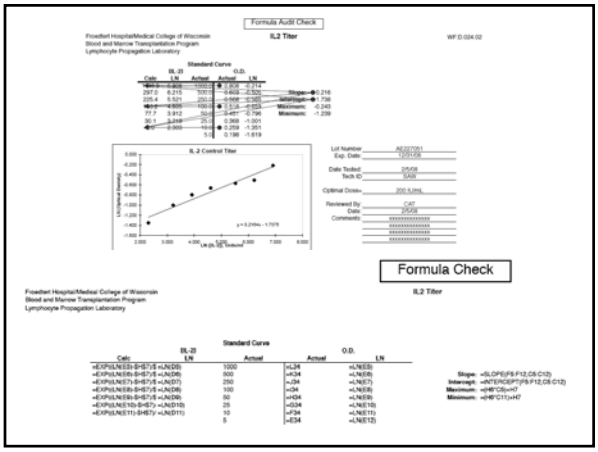
Spreadsheet Validation Template

* Spreadsheet Information
  * Document identifiers
  * Designer or modifier identity and date
  * Workform title
  * Workform purpose
  * List of changes for modified workform
* Checklist of required design elements based on SOP.
* Documentation that input cells are in the acceptable format and check of any input cells with limits.
* Documentation that output cells are in the acceptable format and check of any output cells with limits.



Spreadsheet Validation Template

* Printout and check of all formulas for syntax and reference to other cells.
* Manual calculations and checks for all formulas with sample data.
* Individual check of all macros.
* Checklist of performance requirements for current equipment. Computers and printers.
* Checklist for consistency of user interface parameters.



Spreadsheet Validation Template

* Validation of charts for X and Y axis units and range with range of sample data input.
* Review of functioning of programmed error messages.
* Security and data safety features. Password assignment.
* Confirmation that default values are in agreement with SOP.
* Listing of any unacceptable results and corrections or recommendation for corrections.
* Approvals.

When to Revalidate/Verify?

Changes in:

* Procedures
  * Critical reagent, supply, equipment-new source or model, not new lot
  * Source material (e.g. HPC, Marrow vs. HPC, Apheresis product)
* Process
  * One or more procedures- assess how other steps affected
  * Key personnel- Ensure proper training, qualifications
  * Location- effect of travel distances, potential barriers
* Computer Systems
  * Equipment- assess capacity, backup requirements
  * Programming- effects on entire system

Challenges

* Starting material for prospective validations
  * Mobilized products
  * Need for mock products
* Validation of backup reagents, supplies, equipment
* Adequate testing of all possible conditions, e.g. Product transport
* Time and personnel

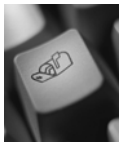
Take Home

* Validation is Good! Ensures a controlled process.
* Requires pre-planning and stepwise procedures.
* Includes data collection and data analysis.
* Requires implementation plan.
* Is an ongoing process.

Production Assistance for Cellular Therapies

Validation Processes

Speaker Contact E-mail



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Web Seminar Presentation Slides

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CME Information

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CME Credit

If you are interested in obtaining CME credit for attending this web seminar, please note that each attendee must:

~Sign and fax roster to 240-306-2527~

~Complete the online survey~

http://www.surveymonkey PACT Web Seminar #11 Survey
(survey link above embedded in the reminder email sent Wednesday, July 30th)

Note: Please complete within 48 hrs of the web seminar

AABB Live Learning Center

After the rosters have been processed, you will receive an email from AABB with instructions on how to print your CME/CE certificates for this web seminar

Thank you for attending!

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