Management of a Multi-Product Facility

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Introduction

- Cangene has discussed the development of an equine botulism antitoxin (BAT), a human IgG (IVIG) and the construction of a multi-use manufacturing facility (building C)

- Scale-up of the equine BAT product in building C

- Scale-up of the IVIG into building C

- Management of these products along with the Changeover strategy
Cangene currently produces several human plasma derived hyperimmune IgG products in our Building B including:

- WinRho SDF (anti-D IgG)
- HepaGam B (Hep B IgG)
- VariZIG (varicella zoster IgG)
- VIG (vaccinia IgG)
- AIG (anthrax IgG)

Cangene also manufactures an Equine plasma derived de-speciated BAT IgG (botulism anti-toxin) in our Building C
Equine BAT Product

- Reported on the development of the 200L BAT process at the 2005 PPB meeting in Crete
- Subsequently the process was scaled up from the 200L scale in Building B to 1000L plasma scale in Building C
- The process was transferred into the “multi-use facility” (Building C) described in a 2007 PPB meeting in Elba
Flexibility Design Goals

- Plant and equipment to be utilized for equine and human source plasma drove the need to establish a changeover plan at an early stage
- Modular equipment systems to allow re-organization of unit operations to suit different processes
- Standardized unit operations control code for scalability and flexibility to new processes
- Cleanroom air handling to allow for easy change of room pressurizations, as needed
- Cleanroom construction to allow for reconfiguration and movement of equipment skids within the plant
Building C (Multi-use Facility) Project Summary

- **Project Milestones:**
  - Design started: June 2004
  - Construction started: January 2005
  - Architectural construction completed: June 2006
  - Pharmaceutical utilities completed: July 2006
  - Process equipment installation completed: September 2006
  - BAT process transferred and first manufacture lot produced December 2007

- **Project Deliverables:**
  - 42,000 sq.ft. addition
  - 6 manufacturing suites with dedicated HVAC, entrances and support services
  - Process equipment to support two manufacturing platforms - equine antitoxin and human antibodies.
  - New PW, WFI, pure steam and compressed air utilities for new and existing manufacturing operations
• Product is the same for both scales
• Equine F(\(ab’)\(_2\) Fab blend of 7 anti-botulinum serotypes
• Bulk substance is frozen
• Liquid formulation
• 10% Maltose
• 0.03% Polysorbate 80
• pH 5.0 - 6.5
• \(\leq\) 2% monomeric IgG
• Solvent Detergent treated and Nanofiltered
Chromatography

200 L

1000 L
Buffer Make-up

1000L

200L
Ultrafiltration

200L

1000L
Virus Filtration

200L

1000L
Impact of BAT Scale-up

- Better process control (use of Delta V controller for UF and chromatography skids vs manual operation)
- Improved cleanability of equipment (all 1000L equipment validated CIP or SIP cycles compared to manual cleaning of much of the 200L equipment)
- Much higher throughput (over 40 X 1000L monovalent lots produced since end of 2007)
Human IVIG Product

- Reported on the lab-scale development at the PPB07 meeting on Elba
- The process was scaled up to a 30 L plasma pilot scale
- >25 Runs have been performed to develop the downstream purification and provide material for formulation studies
- Future runs will provide material for virus removal/inactivation studies and pre-clinical studies
Expanded Bed Columns

Lab scale

Pilot

Manufacturing
Human IVIG Product

- IQ/OQ and preliminary engineering runs will be performed by the end of 2009
- The BAT process will be changed out in the multi-use facility to allow for IVIG set-up
- After the engineering runs are complete the IVIG process will be changed out to allow for more BAT processing
Building C - Designed for Multi-Product Use

- From its original conception, the Building C process area has been designed for multi-product use:
  - Plant design to allow for easy reconfiguration and movement of equipment (wide hallways, large openings, high ceilings)
  - Cleanroom air handling to allow easy changes in room pressurization
  - Sufficient capacity and distribution of compressed air, PW, WFI and clean steam to support different processes
  - Modular process equipment skids to allow reconfiguration of process sequence
  - Standardized equipment control code for scalability and flexibility throughout entire equipment operating ranges
Building C Layout & HVAC Segregation
Building C - Designed for Multi-Product Use

- Equipment cleaning & sanitization planning included in original design concept:
  - Cleaning strategy developed for both equine and human plasma products
  - Three separate Clean-In-Place systems for tanks and equipment skids
  - Separate wash-up rooms for each process suite
  - Separate gowning for each process suite
  - All process equipment pressure rated for steam-in-place with clean steam
Previous Regulatory Discussions

- The original multi-product design of the facility and the product changeover sequence and presented to FDA / CBER in May 2005

- Subsequently, the following major activities have occurred:
  - Validation of all equipment cleaning for BAT
  - Re-validation of the cleaning for similar equipment used for human plasma products in Building B
Risk Management Approach

- Utilized a quality risk management approach to evaluate potential for cross-contamination between human and equine plasma products produced in Building C, using common equipment.

- Identified three areas of concern to be reviewed:
  - Product to product contamination
  - Viral contamination between products
  - Potential prion contamination between products

- FMEA approach to assess risks and identify mitigation activities
Key Risk Mitigation Activities

- Define specific changeover sequence of events
- Establish detailed checklists for equipment changeover
- Dedicated BAT blending equipment
- Ensure changeover sequence is appropriate for product contact materials, other than stainless steel
- Revise existing procedures to explicitly define practices for process changeover (e.g. cleanroom gowning, line clearances, etc.)
Equine & Human Plasma Process Similarities

- No live organisms to create starting material (e.g. bacteria, yeasts, viruses, etc.)
- Starting plasma is from pre-qualified donors
- Plasma is screened for viruses and pathogens before use in manufacturing - low starting viral load
- Liquid processes, conducted in closed process vessels and piping systems
- Both processes utilize solvent/detergent and nano-filtration steps for viral reduction
**BAT and IVIG Process Comparison**

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Common Equipment & Process Areas - Suite 1

- Process Tank
  - Used in both processes for solvent/detergent addition

- Process Skid - Plasma Filtration
  - Used in both processes for SD filtration with 8 & 1.2um filters
  - Filters are single use
Common Equipment & Process Areas - Suite 2

- **Process Tanks**
  - Used for both processes for S/D incubation
  - Product holding tanks for both processes
- **Process Skids UF/DF1 and UF/DF2**
  - Crossflow cassettes are not common equipment
- **Process Skid - Chromo Piping System**
  - Columns are not common equipment
Common Equipment & Process Areas - Suite 3

- Process Tank
  - Pre-filtration holding tank
- Process Skid
  - Nano-filter elements are single use
Common Equipment & Process Areas - Suite 4

- Process Tanks
  - Product holding & formulation tanks
- Process Skid - UF/DF 3
  - Crossflow cassettes are not common equipment
No active product is processed in these areas

- No product changeover procedure required

LLP and FSP tanks are used to hold solutions for delivery to the main floor process suites

- Used for buffers, WFI and solvents

- Dedicated CIP system for these two areas
# Changeover Sequence

## Process Equipment

1. Routine, post-use cleaning of all equipment, following completion of Product 1 operations

5. Perform enhanced CIP cycles on all common equipment

6. Steam in place (or autoclave) all common equipment

8. Replace all product contact gaskets

12. Perform pre-use cleaning of all equipment, prior to starting Product 2 operations

## Cleanroom Suites

2. Line closure for Product 1

3. Line opening for changeover activities

4. Remove all product dedicated components - columns, UF/DF cassettes, - from the suite

7. Full suite sanitization of walls, ceilings, floors, furniture and equipment exteriors

9. Changeout of all cleanroom garments

10. Line closure for all changeover activities

11. Line opening for Product 2 operations
‘Enhanced’ Cleaning

- Function - to provide additional prion inactivation and removal assurance for the unlikely event of prion contamination in either plasma donor pool

- Performed with Cangene’s CIP chemical at increased concentration, time and temperature

  OR

- Using sodium hydroxide with detergent additive, in accordance with PPTA recommendations
Changeover Sequence - Highlights

- Common equipment will be cleaned 3 times between products (2 standard cleanings, 1 enhanced cleaning)
- In combination with the cleaning, steaming of common equipment provides a second, orthogonal means of viral and bacterial reduction from the equipment
- Difficult to clean items - chromatography resins & columns, crossflow cassettes, gaskets, o-rings, etc. are product dedicated
Approach for Cleaning Validation

- The approach for cleaning of shared equipment between BAT and IVIG consists of:
  - Evaluation of the toxicity of the plasma and products
    - Safety data
    - Adventitious and non-adventitious agents (viruses, TSEs)
    - Denaturation studies
    - Use of No Observed Effect Level (NOEL) or 1-10 ppm as Maximum Allowable Carry Over (MACO), whichever is lower (dependant on equipment group)
  - Evaluation of the solutions in contact with the equipment (buffers, cleaning agents)
    - Many solutions are comparable between the two processes
    - Reagents are of low toxicity
Approach for Cleaning Validation

- Confirmation that the testing methods are suitable to ensure that any residual product/solution is below the MACO
  - Existing coupon studies for the equine plasma/product and for human plasma confirm that the soils are very soluble and have >80% recovery by TOC for stainless steel
  - New coupon studies will be executed for additional product contact materials (Teflon, Flex-hoses)
  - TOC used as indirect test for protein-based product; conductivity as indirect test for cleaning / buffer reagents
  - Worst-case assumptions and safety factors used to over-estimate potential risk
- Execute cleaning validations at scale for the worst-case product, based on MACO (based on product volume / equipment groups)
  - Execute confirmatory validation with the product at less risk
Equine & Human Plasma Cleaning

- **Equine Plasma Product CIP Cycle (Building C)**
  - Purified water rinse
  - Detergent added to 5mS/cm concentration
  - Detergent recirculation at temperature greater than 55°C
  - Purified water rinse
  - Phosphoric acid added to 1mS/cm concentration
  - Acid recirculation at temperature greater than 45°C
  - Water For Injection final rinse
  - Drying with compressed air

- **Human Plasma Products CIP Cycle (Building B)**
  - Purified water rinse
  - Detergent added to 5mS/cm concentration
  - Detergent recirculation at temperature greater than 55°C
  - Purified water rinse
  - Phosphoric acid added to 1mS/cm concentration
  - Acid recirculation at temperature greater than 45°C
  - Water For Injection final rinse
  - Drying with compressed air
Cleaning Validation Summary

- The existing cleaning procedures are considered to be appropriate for the BAT and IVIG change-over:
  - Both products are safe, of low toxicity and administered to humans
  - Cleaning methodologies for both human plasma products and equine plasma products are the same
  - Additional cleaning cycles and SIP will be executed for common equipment to minimize risk after Product Changeover
  - Cleaning validation acceptance criteria are the same for both human plasma products and equine plasma product
Summary

- Cangene’s Human Hyperimmune products are produced in our Building B
- Building C was designed and built as a multiuse facility
- The first product to go into Building C was the 1000 L BAT
- The next product will be a Human IVIG product
- A change-over program has been designed and risk analysis was used to ensure nothing has been missed
Acknowledgments

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