Novel Technologies in Plasma Fractionation

Dieter Fassnacht
“Developing new technologies to provide innovative solutions is a core value to Grifols”
Grifols Overview

Grifols is the world’s third largest producer of plasma derived medicines.

13,900 employees worldwide committed to serving patients affected by life-threatening conditions.

Hospital Division – Manufactures standard parental solutions, medical devices and logistics platforms for hospitals

Diagnostics Division - Supplies industry with clinical analysis and laboratory testing tools. Produces analyzers, reagents, instrumentation and products to collect, process and store blood

Bioscience Division - Treatment of medical conditions using blood components. Plasma collection and testing, manufacturing, marketing and sales, R&D

Bioscience manufacturing sites are located in Parets del Vallès, Spain; Clayton, North Carolina and Los Angeles.

Recent Acquisitions

2011: Grifols acquires Talecris Biotherapeutics for $ 3.4 billion
2014: Grifols acquires Novartis Diagnostics Unit for $ 1.7 billion

Stock Information

New York: GRFS
Madrid: GRF.MC
Grifols Engineering

Developing new technologies and expertise to provide innovative solutions is a core value for Grifols since founding of the company.

Inheriting this spirit, Grifols Engineering was established in 2001 to provide engineering solutions within the company but also to other pharmaceutical clients.

External Experience

**Engineering projects** include consulting, process engineering, feasibility studies, conceptual and detail design, construction and start-up services.

**Machinery projects** include specialized equipment for the fractionation industry, purification and fill lines.

Plasma Fractionation Technology

1. COLLECTION
2. TESTING
3. POOLING
4. FRACTIONATION
5. PURIFICATION
6. FILLING
Pooling
Combination of up to 11,000 frozen donations into single batch

Challenges of Pooling
• Thawing and combination process needs to be fast to minimize loses in product yield
• Difficulties in opening and emptying containers to remove frozen plasma
• Plasma containers are either bottles or bags
• Open product needs to be handled in Class C
• Large amount of material handling (donations in, frozen product out, pallets and totes out, wastes out)

Traditional Approach
• Labor intensive manual process with bio-burden and injury risks.
• Thawing and recovery rate of each individual donation is highly inconsistent

1 L Plasma Bottle
0.5 L Plasma Bag
Automatic Bottle Opener

Loading Side (Class D)
1. Manual Loading of Bottles
2. Skin-Thaw with Hot water
3. Rinse with AWFI

Unloading Side (Class C)
4. Air blow to dry bottles
5. Cutting station to open bottle
   • Bottle lids are discarded into waste chute
6. Robot empties frozen plasma slugs into chute to vessel
   • Detects failure to eject via weight change, then retry
7. Drip from empty bottles is collected for extra recovery
8. Empty bottles discarded into waste chute
Plasma Bag Opener

Method to skin-thaw is similar as for bottles
- Two parallel conveyers in single tunnel to increase throughput.
- Extended drying due to irregular bag shape

Novel Plasma Bag Opener
1. Robot grabs bag and pulls it across stationary knife
2. Two rollers squeeze frozen plasma block out of plastic.
3. Camera system automatically detects unsuccessful discharge.
- Two parallel robots work independently to increase pooling rate
Semi-Continuous Pooling

Minimization of residence time to increase cryoprecipitate yield

- Increase pooling rate to shorten process step
- Semi-continuous by starting product separation while still emptying plasma containers

Vertical Facility Integration

- Empty bottles and caps fall to ground floor
- Frozen plasma fall via chute to horizontal thaw vessels on mezzanine below
- Pallet lifts to transport plasma from ground floor and return empty pallets and totes
Fractionation

Successive additions of ethanol and buffers and temperature changes as low as -7ºC precipitates certain protein “fractions” from the plasma.

Proteins are then separated from the liquid via filtration or centrifugation

Traditional Challenges in Fractionation

- Sub-freezing process requires -5ºC harsh work environment
- Open processing requires extensive clean-room areas
- Separation equipment (centrifuges or filter-presses) often requires manual cleaning
- Open handling of ethanol requires expensive electrical installations
Minimize Clean Room Space

Move process equipment from clean room into technical space

- Improve cleanability of clean rooms
- Facilitate maintenance activities from non-clean room side
- Save construction cost and long term energy consumption

Process Vessels

- Unique manway neck and inclined plane allow vessel installation in technical space
Minimize Clean Room Space

**Process Vessels**
- Move vessels entirely into technical space
- Closed additions
- Permanent piping for CIP
- Aseptic sampling from instrument belt.

**Centrifuges**
- Clean room only contains rotating bowl and paste collection vessel.
- Motor, belt drive, lift for paste collection unit above clean room ceiling
- Processing support skid in technical space behind clean room wall.
Minimize Cold Production Space

Eliminate or reduce cold processing space
- Provide better work environment
- Improve cleanability of clean rooms
- Save construction cost and long term energy consumption

Dual temperature rooms
- Room is maintained at +5°C for standby, cleaning, equipment preparation
- Cool down to -7°C takes about 2 hours and is initiated when required (e.g. harvest for filter-presses)

Equipment innovations
- New centrifuge type does not require cold room.
- Product is fully enclosed and cooled via jacketed vessel
Maximize Use of Natural Light

**Increase natural lighting**

- Provide more pleasant work environment
- Increase of glass facilitates communication between areas
North Fractionation Facility

Key Figures
Location: Clayton, NC, USA
Size: 150,000 sq. ft.
Project Cost: $343 million
Construction Duration: 24 month
FDA Licensure: November 2014

without pre-approval inspection!

Highlights
Process: Plasma Fractionation through IV-1 paste
Separation Technology: Centrifugation
Capacity: up to 6 MML of plasma per year
Batch size: 9,000 L (world’s largest)
Maximized closed processing and automation
Minimized cold processing rooms and clean room space
North Fractionation Facility Expansion

Key Figures
Location: Clayton, NC, USA
Size: 39,000 sq. ft.
Project Cost: $28 million
Construction Duration: 12 month
FDA Licensure: November 2014
without pre-approval inspection!

Highlights
Process: Fractionation from IV-4 to Albumin
Separation Technology: Filtration
Tied into NFF utilities, process support and gowning
Optimal use of natural light
Fast-track project executed in-house; engineering, project and construction management
Fractionament IV

Key Figures
Location: Parets del Valles, Spain
Size: 1250 sq. m. footprint
3 stories
Project Cost: € 25 million

Timeline
Installation: May 2012 – Jul 2013
Validation: Sept 2013 – Jan 2014
EMA Licensure: May 2014
FDA Licensure: Dec 2014

Highlights
Process: Plasma Fractionation through V paste
Separation Technology: Centrifugation
Capacity: up to 4 MML of plasma per year
Batch size: 7,000 L
Fast Track construction
Minimized cold processing rooms and clean room space
Purification

Purification processes in Plasma Fractionation start with intermediate “pastes” and use typical purification unit operations used throughout the biotech:

- Ultrafiltration
- Chromatography
- CIP

The fractionation industry has special requirements related to viral inactivation / removal steps which include:

- Solvent Detergent treatment
- Thermal inactivation
- Nanofiltration
Skid Design and Manufacturing

Grifols as manufacturer of pharmaceuticals also designs and builds purifications skids in-house.

Main advantages:

- Better cost, schedule and scope control
- Design experience remains within company
- Automation can be developed specific to manufacturing needs and software design experience greatly supports future troubleshooting
- Turn-over packages assembled for specific business needs to support for IOQ
Innovations in Filling

Protective cap over stopper and vial guarantees sterility by providing labyrinth seal for microbes (principle of Pasteur flask).

Cap is removed only seconds before actual fill and stoppering providing maximum protection.
Innovations in Filling

Autoclave instead of depyrogenation oven provides decoupling of single equipment train to
- lessen impact of equipment failure
- allow staging of sterile vials before filling operation for fast product change-over

Autoclaving fully assembled vials also provides easy sterilization of stopper

Typical Filling Line

Grifols Sterile Filling Line

No separate stopper sterilization required

Protective cap maximizes protection

Decoupling of equipment

Sterile staging for fast change-over
SFF Expansion

Key Figures
Location: Clayton, NC, USA
Size: 23,000 sq. ft.
Project Cost: $22 MM
Construction Duration: 14 month
FDA Licensure: Expected May 2016

Highlights
Two new liquid fill lines
Fast-Track project engineered and constructed in-house
Viewing corridor provides complete visibility to vial preparation and filling processes
Novel design for Class A laminar flow recirculation