

Application of Disposable Technology for Formulation, Storage and Filling of an Aseptic Product

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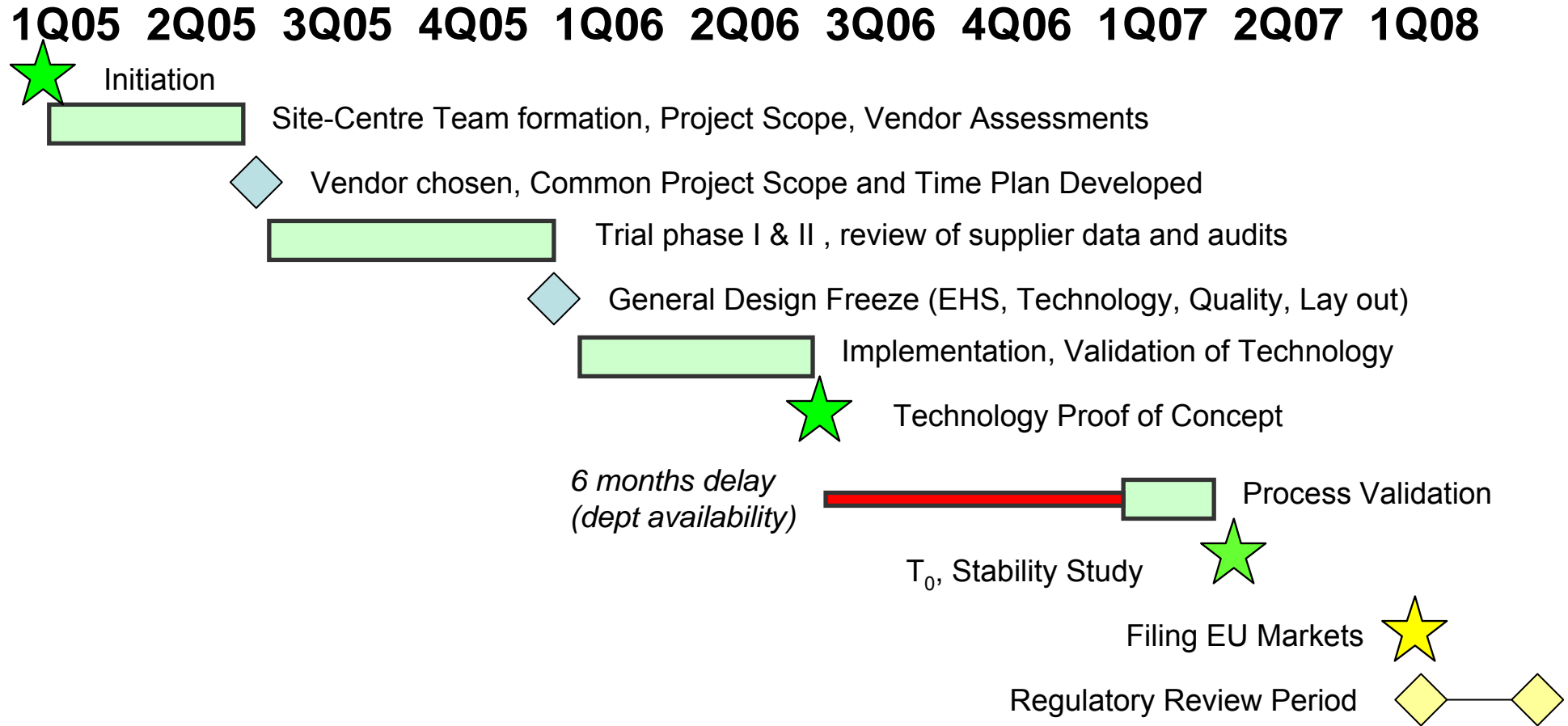
Project Overview

Project Objective

- Evaluate the use of a complete disposable process for formulation, storage and filling of cytotoxic products.

- Aspects assessed as part of the Scope
 - Technical Proof of Concept
 - GMP
 - EHS
 - Cost Evaluation
 - Procurement
 - Regulatory

Time plan



Q4 2008 Regulatory Approval for European Markets, **Project Complete**



Completed Project Activities

- Project formation, budget and disposable technology partner
- URS
- Validation project plan
- Design review
- Risk assessment
- Supplier technical review and audit
- Handling studies & design review
- Mixing studies
- Acerta® filling line assessment, installation and qualification: FAT, SAT, IOQ
- Compatibility studies, including extractable assessment and leachable study
- Trial batches, training and SOP documentation
- Environmental validation
- Media fills
- **Process Validation Batches Analyzed and on Stability**

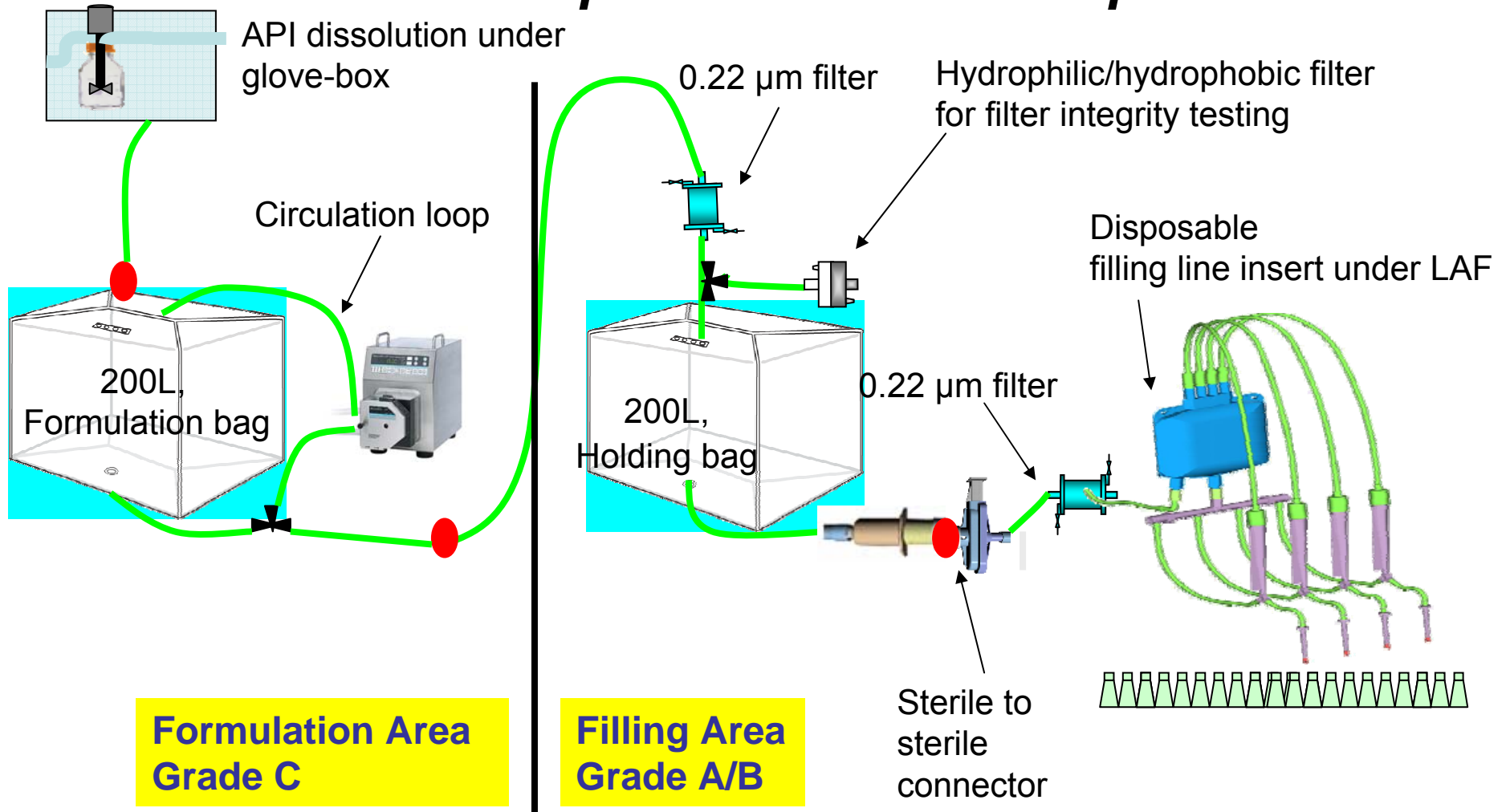
Remaining Activities

Complete Process Validation

- Leachable Study Report
- Validation Summary Report
- Complete Acerta[®] DS4 stability integrity testing (*Millipore*)
- File for Key European Markets
 - Milestone: Regulatory Approval
- Validation Batches available for Commercial Supply

Technical / Engineering Aspects

Disposable Set-up



**Formulation Area
Grade C**

**Filling Area
Grade A/B**

●: Connections between disposable units
NB: sampling & venting bags on sterilizing filter not shown

The Disposable Components

- Mixing bag and Holding bag
 - HyClone BioProcess Container of 200 L capacity
 - HyQ CX5-14 multi-layer, co-extruded polyolefin film
 - polyester, ethylene vinyl alcohol (gas barrier) and polyethylene (fluid contact)
 - HDPE fittings
- Pre-filtration bioburden sampling bags
 - HyClone Labtainer of 250ml capacity
 - HyQ CX5-14
- Acerta® reservoir bag
 - Millipore Pureflex® of 5 L capacity
 - Multi-layer, co-extruded polyolefin film
 - ethylene vinyl acetate, ethylene vinyl alcohol (gas barrier) and polyethylene (fluid contact)
 - Tubing and Sight tube - Platinum cured silicone
 - Dispense needles – Polycarbonate
 - HPDE Fittings
- Lynx® S2S connector (aseptic connection of disposable assemblies)
 - Polycarbonate

Trial period

- Easy to work with in process development
 - Develop process in non sterile mock area
 - Easily adapted and changed during process development for optimization
 - Flexibility and wide range of components
 - Millipore, Stedim, HyClone, PALL, CPC, Sartorius etc
- Worked closely with Millipore, Project Partner

Design trials



Handling Study

- Handling study considered:
 - Need to maintain integrity, cleanliness & sterility of disposables
 - Transfer of disposables into grade C and Grade B areas
 - Ease of assembly and operation
 - Tightness (no leaks) of connections
- Recommended improvements included:
 - Improved containment system
 - Better supports for heavier components (filter, pH)
 - Improvements to operability

Mixing Study

- Mixing Study (recirculation by peristaltic pump) included:
 - Placebo (same pH as process)
 - Vitamin B2, acidified to process pH
- Results:
 - Placebo:
 - 65 liters, time to uniform pH in less than 5 minutes @ 50 L/hr
 - 130 liters, time to uniform pH in less than 5 minutes @ 500 L/hr
 - 130 liter batches, time to uniform pH was increased to between 10 and 25 minutes @ 50 L/hr
 - Vitamin B2
 - All Vitamin B2 phosphate results were within 3% of one another at 0, 75 and 150 minutes
 - pH readings stabilized in less than 30 minutes
 - Addition of polypropylene glycol to increase viscosity had no effect on Vitamin B2 mixing



Mixing Study



Process simulation

- Placebo solution; identical to final manufacturing process
 - Filling station installed in Grade A but dispensing into bulk container
 - Ease of sampling for leachables analysis
 - Smallest batch size (worst case for leachables)
- Successfully assessed:
 - Operability and functionality of disposables
 - Leachables profile
 - Particulate profile
- Aseptic process simulation
 - Three media fills successfully executed

Filtration and filling



Summary – Mixing & Holding

Main Activities

- Supplier Review and Audit
- Trials including Handling and Mixing study
- Implementation
- Validation

Outcome

- Easy to use
 - Simplification - Limit operations to minimum
 - Visible process
- Flexible
 - Down scale or upscale easily achieved
 - Not limited to fixed stainless steel design
 - Can be integrated in current facility with minimal facility impact

Summary - Filling

Main Activities

- Integrated on aseptic filling line
 - Modular, can be implemented on existing filling line
- Fulfilled FAT criteria, environmental validation including 3 media fills.

Outcome

- Flexible Solution
- No Aseptic Connections
- Technical PoC for Acerta[®], not yet for Production use
 - Pilot scale – possible choice

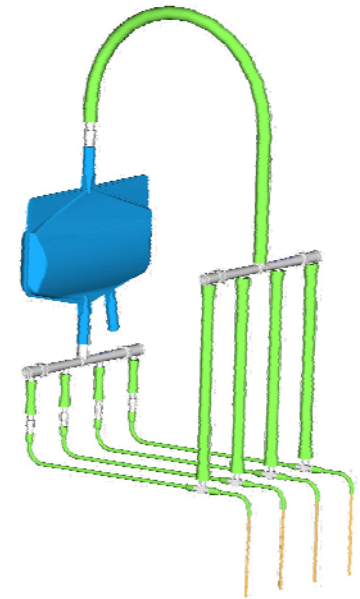


Implementation Learnings

Commercialization

For a drug product formulation / fill application:

- **Mixing & holding**
 - Multiple solutions available, multiple suppliers
 - Evaluate best mixing solution for particular product
- **Acerta[®] / filling**
 - ACERTA is a first beta test unit
 - Millipore, one supplier patented solution
 - No standard commercial filling line available
 - Integration of disposable insert onto filling line
 - Filling volume range
 - Aseptic design improvements suggested
 - Hardware, needles
 - Robustness & Reliability to be assessed
 - Mechanical / electrical, assembly integrity



Validation

- Supplier assessment
- Product compatibility
 - Biocompatibility/toxicity
 - Extractables & leachables
 - Product adsorption
 - Particle/fiber release
- Controlled and released as a batch/product component
- Disposable quality
 - Sterilisation
 - Depyrogenation/assessment of endotoxin levels (LAL/batch)
 - Integrity (100% tested)
 - Shelf life (2 years warranty for integrity & sterility)

Procurement

- Increased number of disposable integrator companies
 - HyClone
 - Millipore
 - Pall
 - Sartorius
 - Stedim
- New solutions evolving (bioreactors, mixing, filtration, chromatography)
- Dual sourcing achievable using same or similar components except for disposable filling line
 - HyClone has two equivalent plants for supply
 - Delivery time of disposable set up from order ~2-3 months
- Simplify development & release process by close supplier contact

Regulatory

Depends on what has been filed...

Case study assessed as:

- Europe Type I
 - Proposed submission will include validation summary and 6 months stability, plus accelerated stability
- Japan no regulatory impact
- USA
 - Can be filed for the US

A Viable Solution?

Cost Evaluation - existing facility

Technology can provide cost benefits but dependent on case

- Operational cost avoidance for existing facility balance increased disposable costs and disposable investment costs
 - Slight cost decrease to implement BPC for Formulation and Storage
 - Slight cost increase if include Acerta[®] disposable based filling line (One supplier solution)
- Not a cost improvement technology

Cost Evaluation – new investment

- New Investment provides full cost advantages
 - Significantly decreased investments
 - Less fixed process equipment investments
 - Less support systems & utilities, e.g. CIP, SIP and autoclaves
 - Reduces grade A requirement, as no aseptic connections
 - Decreased Implementation time compared to stainless steel
 - Process can to a great extent be developed in detail and validated in parallel with facility construction
 - Less facility and equipment validation

GMP Benefits

- Increased sterility assurance
 - No aseptic connections
 - Simplified set-up process
 - Full containment of pre-filtration bioburden samples
 - Aseptic pre-use, in situ filter integrity testing)
- Improved endotoxin control of product contact equipment
 - Manufactured in a way to prevent contribution of endotoxin load (under elevated temperatures, no water involved, controlled environment)
 - Regularly tested
- No risk for cross contamination

EHS Benefits

- Practical, ergonomic design
 - Working height
 - Reduced weight handling
 - Easy to install
 - Foldable carts
- Contained solution developed – reduced contact with product
- One time use, subsequently no CIP and SIP
- Environmental benefits difficult to assess
 - assume balance increased consumables against less CIP and SIP (WFI, steam...)

Operational Benefits

- Operational Savings
 - Increased efficiency, reduced non process activities
 - Reduced maintenance, due to less process and support equipment
 - Reduced Cleaning Validation
 - Reduced Environmental Monitoring, less Grade A area
 - Flexibility of batch size
- Efficiency increase
 - Disposable to decouple production, increase number of batches, increase / change batch size
 - Allows for increased back up capabilities

Conclusion

Project Summary

- Successfully applied disposable technology to formulation, storage and filling of aseptic cytotoxic products
 - Demonstrated improved operability, sterility assurance and containment
- Learnings
 - Commercialisation reservations for filling technology
 - Simple equipment design / development
 - Validation focussed on disposable, much less Commissioning & Qualification
- Benefits across all areas, accruing over time
 - Operational, EHS and GMP
- Increased ease of implementation as disposable suppliers continue to innovate and partner with industry

Acknowledgments



Federico Barberis, Sergio Borroni, Angela Molaschi, Ivano Morlacchi, Flavio Scandroglio, Antonella Uboldi



Penny Butterell, Paolo Dellavedova, Maria Diaz-Cabrera, Gary McNassor, Paola Tozzi, Tara Nestor, Per Sivertsson

MILLIPORE

Brett Belongia, Ernie Jenness, Myriam Jordan, Giuseppe Paganini, Ken Dolan

