Clinical phase drug manufacturing line based on Single Use Integrated Solutions

A Biotech User Perspective

PDA Israel
Single Use Equipment
Tel Aviv, 7th May 2018

Claudia Gagliardini – Pall Biotech
Daniel Martinez - Nuova Ompi
Case Study: Actors

- OMPI
- Pall
- Adienne
ADIENNE is active in national and international pharmaceutical markets and focuses its activities in the fields of onco-hematology, auto-immune diseases and transplant of solid organs and bone marrow.

ADIENNE S.A. Corporate (Lugano-Switzerland)
ADIENNE S.r.l.S.U. Manufacturing (Caponago-Italy)
ADIENNE S.L.U. Subsidiary (Barcelona-Spain)
ADIENNE US Inc. Subsidiary (New York-USA)

Commercial activity in the Middle East, Asia-Oceania and Latin America is managed through local distributors.
TEPADINA® (INN thiotepa) was recognized in 2007 Orphan Drug with the indication "Conditioning treatment prior to transplantation of haematopoietic progenitor cells" from EMA and the indication "Conditioning treatment prior to transplantation of stem cell" by the FDA. Currently on the market.

BEGEDINA® (anti-CD26 antibody) has been recognized Orphan Drug with the indication “Treatment of graft versus host disease (GvHD)" both from EMA (2010) and FDA (2011). Currently in phase II.

MUBODINA® (anti-C5 miniantibody) has been recognized Orphan Drug with the indications "Treatment of atypical hemolytic uremic syndrome associated with hereditary abnormality of the complement system" both from EMA (2008) and FDA (2011), and "Treatment of primary membranoproliferative glomerulonephritis," both from FDA (2009) and EMA (2011). Currently in pre-clinical phase.

ERGIDINA® (anti-C5-RGD miniantibody) has been recognized Orphan Drug with the indication "Prevention of ischemia/reperfusion injury related to solid organ transplant" both from EMA (2008) and FDA (2009). Currently in pre-clinical phase.
Within Pall Life Sciences, the Biotech division is the largest and fastest-growing division, delivering exceptional process solutions for:

- Biotech
- Biologics (Vaccines & Plasma)
- Classic Pharmaceuticals
Biotech Clinical Phases Production Challenges

- Financial Pressure
- Process Scalability
- Speed To Market
- Quality Requirements

Biotech Clinical Phases Production
Biotech Process Requirements

Increase
- Flexibility
- Productivity
- Quality

Reduce
- Foot Print
- Cost of Goods
- Capital Expenses
Adienne Approach:
Single Use End-to-End integrated Solution
Evolution in Biotech Process Approach: End-to-End Continuous Integrated Platform

Discrete Batch Unit Operations

Fully Continuous
Islands of Continuous Processing

Single-Use Facilities

Current single-use technology for batch processing

Process Intensification

Adoption of discrete technologies to maximize productivity within a batch environment

Integrated Unit Ops

Two or three unit operations fully integrated to maximize efficiency

Continuous Processing

Fully continuous or semi-continuous process using Continuous Ready Technologies to deliver best process economics and product quality

‘Islands of Continuous’
Evolution in Biotech Process Approach: 
End-to-End Continuous Integrated Platform

Initial cost modeling suggests this is an attractive scenario for mAb manufacturing

Biotech Integrated Platform: Upstream
Biotech Integrated Platform: Downstream
Single-Use Mixing

Final Bulk Sterile Filtration

Single-Use Needles

Final Sterile Filtration

Single-Use Leak Testing
The filling system is completely disposable. It has been designed specifically for ADIENNE process by PALL Biotech. Every component in contact with the product is SU and pre-sterilized.
Main facts

From cell culture to product filling

- Smarter solutions to improve process
- *Unique* solutions customized for process
- Lower COGS

Example (real) of a very customised disposable sampling system
Sterile filling with Single Use systems

Final recovery and storage

Sterilizing filter

KPC Sterile Disconnector

KPC Sterile Connector

Storage bag (optionally freezeed)
Final Sterile Filtration

1. KPC Sterile Connector from storage bag
2. Peristaltic pump
3. N2 for integrity testing
4. Sterilizing filter
5. Product bag hanging outside the filling machine
6. To filling machine
7. KPC Sterile Connector
Sterile filling with Single Use systems

Final Sterile Filling

KPC Sterile Connector

Allegro Single Use Needle

double channel peristaltic dosing pump
Single-Use Technology (SUT) Adoption Involves Shared Risks

Quality Ownership

Supplier → End-User

Supplier → End-User

Shared risk = shared responsibility
Life Cycle of SUS from Manufacture to Final Disposal

(1) and (2) are tests performed upon customer request
From Supplier’s Data To User Process Validation

What are the validation needs for the specific application? Are the supplier data sufficient, high-quality and brackets process conditions?

**YES**
Data can be used for process validation

**NO**
User-specific process validation must be performed
Process Specific Validation

What should be considered when validating filters and single-use technologies (SUT)?

- Does the product/process impact the filter/SUT?
  - Integrity Testing
  - Compatibility
  - Microbial Viability & Retention

- Does the filter/SUT impact the process?
  - Extractables
  - Leachables
  - Adsorption
Standardized Extractables Data

Brackets >80% Biologics Applications


by Weiling Ding, Gary Madsen, Ekta Mahajan, Seamus O'Connor, and Ken Wong

BPOG component testing guidelines towards suppliers

- 6 extraction solvents
- Standard analytical techniques
- 2 extracting temperatures
- Multiple time points
Certificate of Quality

We hereby certify that:

Pall\textsuperscript{\textregistered} Allegro\textsuperscript{\textregistered} Single Use System
System Part Number: SUS Sterile
System Lot Number: EXAMPLE
System Expiry Date: September/2015
Filter Part Number: EXAMPLE
Filter Lot Number: EXAMPLE

is manufactured, inspected and conforms in all aspects to Pall Corporation agreed specifications and drawings. The manufacturing conditions, product requirements, sub-assemblies, raw material purchasing specifications, as well as batch records of these products are fully traceable within Pall. The fluid path of this system is STERILE.

Materials of Construction
The fluid contact components of the Allegro system have met the requirements for biological reactivity, in vivo, under the United States Pharmacopoeia (USP<88>) for Class VI plastics.

This product does not contain materials of construction in contact with fluid that are considered specified TSE or BSE risk materials according to current legislation and guidelines (reference European CPMP/EMRA/410/01 and US Code of Federal Regulations, Title 21 Part 189.5).

Contact Pall for further information regarding materials of construction.

Product Quality
System Integrity: Allegro systems utilize documented processes that have been validated to ensure that systems are leak free at the time of production. All Pall Allegro biocontainers are 100% leak tested during manufacture.

Dimensions: Allegro systems are 100% inspected during manufacture to ensure dimension compliance with Pall specifications.

Visual Appearance: Allegro systems are 100% inspected during manufacture to ensure compliance to Pall design and for cleanliness.

Fluid Path Endotoxins: Periodically, effluents from representative samples of Allegro systems are tested for endotoxins in accordance with USP <85> Bacterial Endotoxins Test using Limulus Amebocyte Lysate (LAL) reagent. Fluid path rinses meet the internal specification of <0.25 EU/mL.

Fluid Path Cleanliness: Periodically, effluents from representative samples of Allegro systems are tested for particulates. Fluid path rinses meet the current limits under USP <788> Particulate Matter in Injectons.

Sterilization by Gamma Irradiation
Each system of this lot is subjected to a validated gamma irradiation dose. Sterilization of the fluid path has been validated per AAMI/ANSI/ISO 11137 and AAMI TR33.

This product is manufactured in a controlled environment (Class 7 in operation according to ISO 14644) under a Quality System certified to ISO 9001. Consider only unopened, undamaged packages for use. Further information is available by contacting Pall.

David Bowen, Quality Manager, Pall Ilfracombe
Pall Ilfracombe, Station Road, Ilfracombe, Devon EX34 8BH
26/September/2013

www.pall.com
25 Documentation for Single Use filling systems
The filling system is completely disposable. It has been designed specifically for ADIENNE process by PALL Biotech. Every component in contact with the product is SU and pre-sterilized.

**Aseptic filling: the critical step**
EZ-fill Packaging Details: Chosen Configuration

- **Tyvek Lid**
- **Tyvek Sheet**
- **10R format Glass Vials (borosilicate type I)**
  - 96 pcs in Tray: no glass to glass contact

Tray protected by a double steribag

Box packaging configuration:
- 960 pcs/box
- 24,000 pcs/pallet
**EZ-fill Benefits for Small Scale Applications**

- **Reduce Total Cost of Ownership**
  (capex – validation costs – business risk reduced)

- **Increase Flexibility**
  (tray configuration and single-use solutions)

- **Increase Quality**
  (no glass-to-glass contacts)

- **Reduce Time-to-Market**
  (if used from early stages to industrial phase)

---

EZ-fill configuration as the best option for small scale applications
Glass Forming Process: from Bulk to EZ-fill
Production Area
Designed and developed on GMP standard.

Different Clean Rooms
(from ISO8 to ISO5)

Internal Laboratories
(chemical, environmental and functional testing)
EZ-fill Vial Process Steps

Containers Feeding

Washing (WFI) and Dying

Depyrogenation

Nesting, Tub Insertion & Tyvek sealing

Double bagging in steribags

Final sterilization

No-Glass-to-Glass Contact Packaging
OMPI Pharma Manufacturing Layout EZ-fill Vials Line

1. FEEDING
2. WASHING (WFI)
3. SILICONIZATION (CARTRIDGES) & DEPYROGENATION
4. NESTING, TUB INSERTION & SEALING
5. PRINTING & BAGGING

Capping and crimping station for cartridges

EZ-fill Line Video
Quality System Involves All the Process Steps from Raw Material to Final Product

- Incoming controls of raw materials
- Environmental controls
- QC controls before sterilization
- Microbiological controls after sterilization

EZ-fill material is released compliant with dimensional, cosmetic, microbiological requirements
Every Batch is Delivered with Certificate of Conformity to Guarantee the Quality Level

<table>
<thead>
<tr>
<th>Nuova Ompl.</th>
<th>S.r.L.</th>
<th>Conformity Certificate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Via Melchese, 17 - 20117</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CERTIFICATO DI CONFORMITÀ**

**CONFORMANCE CERTIFICATE**

<table>
<thead>
<tr>
<th>Norse del prodotto EZ-EE</th>
<th>MASTER</th>
<th>Cod.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ez-EEIM Product name</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Numero Lotto</th>
<th>Data di rilascio lotto</th>
<th>Data di scadenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch number</td>
<td>Date of batch release</td>
<td>Expiration Date</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data di produzione (1)</th>
<th>Data di sterilizzazione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Production</td>
<td>Date of sterilization</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ciclo di sterilizzazione</th>
<th>Data di sterilizzazione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterilization cycle</td>
<td>Date of sterilization</td>
</tr>
</tbody>
</table>

1. CONFORMITA' VEIRO (Glass conformity)
Sulla base del certificato del lotto vevo si dichiara che i contenitori super monto sono stati ottenuti da tubi di vetro borosilicato di 1° classe identificato, in accordo alla USP e Farmacopea Europea edizioni vigenti.

The type I glass used for the manufacturing of the above-mentioned containers is in compliance with the USP and the European Pharmacopoea current editions.

2. CONFORMITA' PRODOTTO FINITO (Product conformity)
Il prodotto viene sottoposto a controlli durante e al termine del processo produttivo.
- Cualitativa
- Dimensionale
- Contestualità particolare

The following process and final inspections are performed on the product.
- Cosmetic
- Dimensional
- Particular counts

3. STERILITA' (Sterility)
Il lotto super montato è certificato sterile se contenuto in contenitore integro o non danneggiato. Tuttavia la sorga di sterilità della Farmacopea Europea e USP, edizioni correnti.

The referenced batches certified sterile in unopened or undamaged packaging, it meets the sterility test which is based on the European Pharmacopoea, and the USP, current editions.

4. ENDOTOSISSE BATTERICHE (Bacterial endotoxins)
Ricerca endotoxica in accordo con la Farmacopea Europea e USP, edizioni vigenti. Soddisfa il limite di 0.2 µg/ml.

Bacterial endotoxins search based on the European Pharmacopoea and USP, current editions. It meets the limit of < 0.25 µg/ml.

5. RESIDUI (Residuals)
Residuo di ossido di etilene ≤ 1 µg/ml e residuo di Cloridrina etililenica ≤ 0.5 µg/ml, in accordo con CPMP (linee guida per l'uso di ossido di etilene nella produzione di prodotti farmaceutici).

Ethylene oxide residue ≤ 1 µg/ml and Ethylene chlorohydrin residue ≤ 0.5 µg/ml, according to CPMP (note for guidance on limitations to the use of ethylene oxide in the manufacture of medicinal products).

Prodotto sterilito con Ossido di Etilene, non pirogenico, non tossico, monouso. Il prodotto in vetro viene garantito sterile solo a confusione integra e non danneggiato.

Product sterilized with Ethylene Oxide, non pyrogenic, non toxic, single use. Product guaranteed sterile if package is not opened or not damaged.

Certification of:

- Glass and Product conformity
- Sterility
- Shelf Life
- Endotoxin level
- Sterilization gases residual

Customizations are feasible through Addendum to Certificate
Secondary Packaging to Preserve Cosmetic Aspect and Mechanical Resistance and to Reduce Particle Generation

Nest and Tub made in PoliPropilene (PP)

All the packaging material and suppliers are validated
Why a no Glass-to-Glass Solution is the Best Option for Packaging our Sterile Containers?

**Traditional Tray (Glass-to-Glass)**

- Risks of breakages, cosmetic issues and particle generation

- Packaging Supplier
- Shipment to Pharma Site
- Pharma Site
- Filling/Inspection Operations

**Ompi EZ-fill (No Glass-to-Glass)**

- Strong mitigation of the Risk of breakages and cosmetic issues
## Performances of Different Packaging Configuration

<table>
<thead>
<tr>
<th>Test</th>
<th>EZ-fill Vials No glass-to-glass</th>
<th>Steel Tray without Dividers</th>
<th>Thinwall PP Tray without Dividers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packaging Visual Inspection</td>
<td>Conforming</td>
<td>Conforming</td>
<td>Non-Conforming</td>
</tr>
<tr>
<td>Seal Integrity of the Packaging</td>
<td>Conforming</td>
<td>Conforming</td>
<td>Conforming</td>
</tr>
<tr>
<td>Glass Container Cosmetic Defects</td>
<td>Conforming</td>
<td>Non-Conforming</td>
<td>Non-Conforming</td>
</tr>
<tr>
<td>Particle Contamination</td>
<td>Conforming</td>
<td>Non-Conforming</td>
<td>Non-Conforming</td>
</tr>
<tr>
<td>Sterility Test</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Non Sterile</td>
</tr>
</tbody>
</table>

### Vials Subjected to

- Random Vibration Test (ASTM D-4728)
- Test Method for Impact Testing for Shipping Containers and Systems (ASTM D-880)
- Test Method for Drop Test of Loaded Containers by Free Fall (ASTM D-5276)
EZ-fill is Suitable from the Early Stages to Industrial Production of Parenterals

FROM THE SMALL LABORATORY TO THE BIG MANUFACTURING SITE

- Presterilized package Fully compatible with SUS systems
- Flexible Solution applicable to Small Scale Productions
- Reduced Total Cost of Ownership
- High Quality from Manufacturing to Shipping
Thank you!