A Single-Use ADC Process: From Development to Clinical

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Agenda/Content

• Manufacturing needs for ADC development
• Regulatory requirements
• Scale and containment considerations of Bayer
• Feasibility study for disposable based processing to bulk
• Conclusions from the user perspective
• Sartorius capabilities and technologies
• Looking forward
ADCs = Bioconjugates – Bridging Large & Small Molecules

- **Macromolecule**: Large Molecule (Proteins & Antibodies for targeted therapy)
- **Linker**: Stable or cleavable bridge
- **Effector Payload**: Small Molecule (Toxins)

Focus on Physical Stability

Focus on Chemical Stability
Consequences for ADC Drug Substance Production

- Produce mAb in standard mammalian cell culture facility with usual segregation
- Do conjugation in a separate facility suited for handling of toxic compounds as well as proteins
- Produce drug product in special DP production suite
ADC Production Scale-Up Concept

Starting point at Bayer
  • Production of clinical supplies of ADCs at the 10 g / batch scale in chemical development
  • Scale not sufficient to support later phase clinical demand

Goal
  • **Additional capacities for clinical supplies of ADCs** at the 30 to 500 g / batch [6/30/100L] scale
  • Handling of highly potent substances and production of different ADCs in existing mammalian cell culture pilot facilities (downstream processing areas)
  • Minimize toxic waste streams
  • Low capital investment
  • Basic process (incl. dilution and pH adjustment) but no single solution specialization

Challenge
  • Cross-contamination avoidance
  • No jeopardizing of environmental & work safety

Diagram:
- Linker coupling
- Toxophore conjugation
- Ultra-/diafiltration
- Fill / finish
Regulatory Guidance

According to the EMA publication (December 2009) on the guidance of the GMP/GDP Inspectors Working Group, shared facilities can be used for the production of highly potent drug substances, provided that certain risk management measures and input from toxicological experts are taken into consideration.
ADC Production Concept for Clinical Trial Material at Bayer

- Use existing mAb Pilot Plants for conjugation

- Do conjugation as last processing step using isolator technologies in the final mAb formulation downstream suite (class C area)

- Enable closed systems concept including use of disposables for conjugation up to ADC filling and storage –

  - Feasibility study together with Sartorius, how to realize this concept
Concept Case Study for ADC Production Using Disposables (BHC/Sartorius)

This concept study is about developing functionally closed disposable based ADC processing in a highly protected environment (isolator)

- handling highly toxic compounds
- including filling of drug substance in bags
- up to a scale of 100 L batch size
Block Flow Diagram (BFD) – Example of an ADC Process

Linker coupling
Toxin coupling
UF / DF (to remove excessive toxin)
Chromatography
Sterile Filtration
Sterile Filtration
Bulk Drug Substance (BDS)

Optional steps

Final Form & Fill

MAb Production

Sartorius Stedim Biotech
In this step the Antibody and the connected hydrophilic linker are conjugated with the cytotoxic drug that is later responsible for inactivating the target cells.
Ultra-Filtration and Diafiltration of ADCs

1. Removing excessive toxins
2. Concentrating and re-buffering/washing of ADCs.
Bulk Drug Substance (BDS) Preparation

- Linker coupling
- Toxin coupling
- UF / DF (to remove excessive toxin)
- Chromatography
- Sterile Filtration
- UF / DF
- Sterile Filtration
- Bulk Drug Substance (BDS)

Formulation and filling of homogenized product. Transport via storage or freeze-thaw bags.
Summary of Main Equipment for Fully Single-Use ADC System

**Palletank**
Jacketed Palletank for mixing and cooling with load cells for Antibody Drug Conjugation

**FlexAct UD**
for excessive toxin removal, concentration and diafiltration of ADCs

**Pre- and sterile filter**
for final filtration of ADCs

**Palletank**
for homogenization, formulation and filling of BDS into transportation bags

**Flexboy bags**
for transportation to final form and fill via storage bags or freeze/thaw bags
Summary – ADC Manufacturing Based on FlexAct

- Process scale-up realizable from 10 – 100L, other sizes seem possible
- Fully single-use process for UF|DF, sterile filtration and BDS preparation
- Combined equipment based on FlexAct platform family for conjugation, UF|DF, sterile filtration and BDS preparation
- Process realized in an isolator environment for highest operator protection

Mock-up study 2012
Glove Box / Isolator

Personnel is protected from exposition to hazardous material

• Glove box is closed
• Filter system retains particles and aerosols
• Low pressure inside glove box
• In case of hazard solution is retained in glove box
Disposable Reactor

- „Ready-to-use“ γ-sterilized PE bag with temperature and pH probes installed
- Wireless measurement values transfer to external data system
- Dynamic volume range from 10 to 100 L (same reactor footprint, increased height)
- Double jacket for temperature control
- Supra conductive magnetic stirrer without bag contact
- Addition of solids (top) and liquids (bottom) possible
- Closed sampling
- Modification of front-door and drive unit has been performed to allow for operation within isolator
- Compatibility with organic solvents (e.g. EtOH, DMSO* up to 10%) and biologicals
- In addition reactor is also retentate vessel for UF/DF step
Bayer ADC Project

6 Steps from Concept to Realization

- Pre-Conceptual Design
- Conceptual Design
- Basic Engineering
- Detailed Engineering
- Acceptance
- Execution
Conclusions from the user perspective

• With the combination of single-use systems, closed processing and isolator technologies, ADCs can be manufactured in classical multi-purpose pilot-scale facilities without jeopardizing work safety or higher risk of cross-contamination.

• Avoidance of additional investments for the construction of a dedicated ADC facility (equipment and space)

• HSEQ concept to proof absence of any contamination in working area between manufacturing campaigns

• Realized at 2 scales for GMP production in 2 biotech pilot plants:
  • 30–40 L for prePoC clinicals
  • 100 L for post PoC clinicals
Scalability: From Lab to Process ...

- Bayer project was a valuable and exciting learning experience
- Increased interaction and capabilities in ADC market
  - Discussed needs and concerns
- Identified technologies suitable for ADC processing at each scale
- Looking forward to tomorrow's development and processing needs
Main challenges for ADC manufacturing

- Cross-contamination / cleaning validation
- Handling of cytotoxic components - Operator risk
- Use of solvents (DMA|DMSO) – Chemical compatibility
- Leachables & Extractables
- Contaminated waste handling
Scalability: From Lab to Process...

Membrane areas 0.1 m² to 14m² for flexible development and manufacturing.

All sets including bags and filter cassettes, fully gamma irradiated and fully self contained.
SARTOFLOW® Alpha Plus SU

- Self-contained units
- Gamma-sterilized
- Fully enclosed sterile pathway
- Single-use sensors
- Separate control unit
  - placed outside of the glovebox
- 5-20L SU bags available for use
**PD Scale Single-Use Crossflow**

<table>
<thead>
<tr>
<th>SARTOFLOW® Slice 200 Benchtop System</th>
<th>SARTOFLOW® Alpha Plus SU</th>
<th>SARTOCON® Slice SC Cassette</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Min Volume: 25mL</td>
<td>✓ Plug &amp; Play</td>
<td>✓ pre-flushed</td>
</tr>
<tr>
<td>✓ Configured to use Eco cassettes up to 10 L process</td>
<td>✓ Fully enclosed sterile pathway</td>
<td>✓ Gamma-Sterilized</td>
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<tr>
<td></td>
<td>✓ Configurable DCU</td>
<td>✓ 0.1 to 3.5 m²</td>
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<tr>
<td></td>
<td>✓ 5, 10, 20L Bag available</td>
<td>✓ Fully crosslinked Hydrosart membrane</td>
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<tr>
<td></td>
<td></td>
<td>✓ 10kD</td>
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<tr>
<td></td>
<td></td>
<td>✓ Integrated into disposable loop (up to 14 m²)</td>
</tr>
<tr>
<td></td>
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<td>✓ 200 cm² cassettes for PD</td>
</tr>
</tbody>
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Reduce development time and increase operator safety
Single-Use Membrane Chromatography – Sartobind®

- Removal of aggregates with Phenyl (HIC) or S membranes
  - Post-Quench or diafiltration
  - Also available with Q membrane
- Autoclavable
- Increased operator safety with contained device
- Scalable from nano scale
- Reproducible results at every scale
- Reduced time for set up and processing
- High flow rates

Sartobind® 8mm Range

QbD: conditions screening using Sartobind® 96-well plates
Chemical Compatibility

We have chemical compatibility data at

- 100% DMAc|DMSO  (1h @ room temperature)
- 10% DMAc|DMSO    (48h @ room temperature)

Extended chemical compatibility study is scheduled for early 2016
Single-use technologies are addressing all major requirements of ADC manufacturing:

**Safety:** Fully closed system protects operator and product, Cytotoxic substances are not exposed to the environment at any time

**Flexibility:** Single-Use Technology allows to share equipment for multiple products. No dedicated equipment necessary

**Cost:** Less expensive equipment can get shared for multiple products. Less waste disposal cost, leverage consumable cost

**Extractables & Leachables:** Have to be investigated for process conditions but proven not to be critical or limiting in processes being evaluated till now
Process Development Consultant Team

- **Engage Customers on the Whole Process**
  - Bring a global process platform approach to our clients’ process development groups from Upstream to Downstream

- **Help Rapidly Develop Robust Processes**
  - Think about future scale-up and manufacturability
    - Utilizing Biosolve process modeling software
  - Identify key market trends → review and make recommendations to R&D for improvements to our process platform approach

- **Global Collaboration**
  - Six members in the US
  - Three in Europe and Asia

- **Cross-functionality across business areas**
  - Including R&D, Product Managers, Sales, etc.
  - Knowledge of projects, launches, prototypes, potential issues
We would love to have your feedback!

Please stop by our booth (#11) to see some of our capabilities and to fill out our ADC Questionnaire.

Thank you for your attention!