Antibody Drug Conjugates (ADCs)
 Agenda

- General Aspects & Organization
- Process R&D Capabilities
- Safety, Change Over and Cleaning
- Operations
- Quality Control
What makes Lonza ADCs different?

- Leader in small molecule API and monoclonal antibody (mAb) production and process development (over 25 years of know-how)

- Dedicated high-quality ADC facilities, teams, standards and safety procedures in place since 2004

- R&D labs, QC, and production all certified by SafeBridge® Consultants

- Unparalleled expertise in product scale-up
Our ADC investments have given us leading-edge facilities and experience

Overview

- Location: Visp, Switzerland
- 1st investment: 36m CHF (2006-08)
- 2nd investment: 17m CHF (2008-10)
- 1st start: 2006
- Large-scale: mid-2008 (cGMP)

Infrastructure

- Footprint: 750m²
- Total floors: Four
  (1 production, 3 for utilities/infrastructure)

SafeBridge® Certification (Dec. 2008)
Our broad manufacturing experience equates to quality ADC production

Lonza has been involved in ADCs since 2004

- Long-term chemical and biopharmaceutical experience at lab and commercial scale (2,500L) with highly potent active ingredients
- Antibodies have been manufactured at Lonza for over 25 years for our customers at pilot and commercial scale (20,000L)
- Conjugation expertise from multiple projects (e.g. CIMZIA®)
- Experience with disulfide and amide coupling chemistry
- Required infrastructure and support functions in place
- First cGMP production start mid-2007 (small-scale) and in 2008 (large-scale)
Lonza has established the ADC teams to deliver high-quality results

Dedicated, experienced ADC teams

- Dedicated teams for R&D, operations, quality control and business development
- Operators are well trained in cytotoxic handling procedures, biopharmaceutical operations and aseptic handling
- Same operators in entire development and scale-up cycle
- Familiar with facility: Operators executed IQ and OQ tests
The R&D organization brings maximum customer focus and effectiveness
The manufacturing organization is designed to ensure the highest quality.
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Procedures and laboratories for toxic and nontoxic compounds are different

Non-toxic Compounds
- Standard R&D lab
- Purification of mAb/buffer exchange
- Modification reaction (linker introduction or reduction of mAb)
- Purification of modified mAb
- Buffer preparation

Toxic Compounds
- Clean room (L-5000) for cytotoxic and ADC work
- Room classification ISO 7
- OEL 40 ng/m3
- Air locks with separated material and personal flow

ADC Laboratory Equipment
- Isolator to handle solid cytotoxic drug
- WIBO hoods (push-pull ventilation) for conjugation reaction and ADC purification
Our state-of-the-art laboratories are designed for a range of experiments

Milligram-scale Experiments
- Jacketed glass reactors (2-10 mL) with magnetic stirring
- Purification columns (e.g. NAP)
- Temperature probes (on-line)
- pH (off-line, via sampling)

Gram-scale Experiments
- Jacketed glass reactors with mechanical stirring (100-2,000L)
- Temperature, pH probes (on-line)
- Two UF skids (Sartoflow® Slice 200)
- Peristaltic pumps

Scale-up Experience
- Experience scaling up ADC processes to 50g, 100g, 150g scale
- 25 ADC cGMP batches produced with 100% batch success rate for clinical trial supply
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Our standard cleaning procedures are well-defined and well-documented

**Defined Operating Procedures for Cleaning**
- All standard cleaning records stored
- Validation Master Plan for multi-purpose ADC plants

**MAC calculation specified for product changes**

**Cleaning Validation**
- End of campaign
- Between batches
- Clean / Dirty hold time

Cleaning concept includes inactivation of the cytotoxic compound.
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Our capabilities enable us to meet your needs throughout the product life cycle

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<th>Stages</th>
<th>R&amp;D &amp; QC characterization</th>
<th>Scale-up Preclinical Phase I &amp; II</th>
<th>Engineering &amp; NDA Enabling Batches</th>
<th>Qualification Batches Process Validation Market Supply</th>
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<td>ADC (kg / batch)</td>
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Our production facilities maintain the highest quality and safety standards

Key features
- Multipurpose set-up
- Scalable equipment

Small-Scale
- 2x10 L
- 3x20 L
- 2x35 L
- 3 UF skids

Large-scale
- 1x100L (under construction)
- 1x200 L
- 2x300 L
- 2x600L
- 2 UF skids

Procedures, Equipment & Standards
- Validated cleaning procedures
- Safe-change air filters
- cGMP (biopharma standard)
- Cleaning-in-place / Steaming-in-place
- Area classification
- Gowning concept
- On-site incineration for disposables
- Aseptic operation experiences
Our small-scale ADC facility began operations in September 2007

Facility Details

- Dedicated plant to run two projects in parallel; multi-purpose concept
- Experience scaling up ADC processes to 50g, 100g, 150g
- 25 ADC cGMP batches produced with 100% batch success rate for clinical trial supply
- Low degree of automation
- Qualified equipment
- Classified clean rooms
- Cleaning validation for fix installed equipment; Easy-to-clean design
- Single use tube sets
- Scale-up factor (Small-scale : Large-scale = 1:10)

Equipment

- Reactors: 2x10L, 3x20L, 2x35L (minimal stirring volume of 2L)
- 3 UF Skids Sartorius Sartoflow Alpha with rotary lobe pump
- Laminar flow hood
- Isolator
Our large-scale ADC facility is flexible and state-of-the-art

Facility Details
- Modular set-up ensures high flexibility for new processes
- Stainless steel vessels; Most are mobile, only one fixed installation
- Integrated biosystems shell freezing system

Specifications
- Footprint: 750 m² (25m x 30m)
- Four floors total (1 production, 3 for utilities/ infrastructure)

Equipment
- Reactors: 1x200L, 2x300L, 2x600L (1x100L under construction)
- 2 Ultra- / Dia-filtration units (additional chromatography unit possible)
- USP purified water, WFI, clean steam, CIP
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Our ADC QC laboratories ensure you have the most robust product possible

Activities

- Raw material release testing for highly toxic compounds
- Method development, implementation, transfer, verification, validation
- In addition to drug substance, drug product testing
- Stability studies for drug substance and drug product
Our QC labs ensure your product meets or exceeds specifications

**Chromatography**
- HPLC
  - Agilent 1100/1200 and Waters Alliance 2695
  - UV / DAD and Fluorescence Detection
- GC
  - Agilent
  - FID

**Microbial Tests**
- Endotoxins
  - Gel Clot LAL
  - Kinetic Turbidimetric LAL
  - Kinetic Chromogenic LAL
  - PAT

**Bioburden (TAMC and TYMC)**
We use cutting-edge equipment and procedures in our QC laboratories

**Spectroscopy**
- Nephelometer (AN2100 Hach Lange)
- UV (Lambda 25 (Perkin Elmer), Cary 50 (Varian))
- Ion-Mobility Spectroscopy IMS (Smiths Detection)

**Osmolality**
- 3320 Micro-Osmometer (Advanced Instruments)

**ELISA**
- Infinite F200 (Tecan)

**Titration**
- Titration (volumetric and coulometric; Metrohm)
- potentiometry (Metrohm)
- LOD (Mettler Toledo)

**Cleaning Procedure**
- Total Organic Carbon-Analyzer with Autosampler (Sievers)
- Conductivity (Metrohm)
We also have extensive experience with bioassay development and potent APIs

- Our Winnersh (UK) and Walkersville, MD (US) sites develop and validate bioassays
- Our ADC QC lab is SafeBridge® certified for handling of highly potent APIs with OEL of ≤ 100 ng/m³
- Dedicated team for small- and large-scale production support including cleaning
- Directly connected to groups specialized in
  - spectroscopy (NMR, MS, IR), UPLC, IC, CE,
  - Microbiology (MicroSeq-Identification system) and others
ADC Back-up
PCPLS Building (Visp, Switzerland)
Isolator Suite
Production Suite
Exterior
Freeze-Thaw Skid with Cryovessel
Production Suite
Mobile Vessel
Production Suite
ADC / HAPI QC Laboratory
Solid Handling

OEL: 1-100 ng/m³
(lab operating under negative pressure)
ADC / HAPI QC Laboratory
Liquid Handling
ADC / HAPI QC Laboratory
Solid Handling

OEL: (0.1 - 10 µg/m3 (normal pressure)
ADC / HAPI QC Laboratory

Liquid Handling