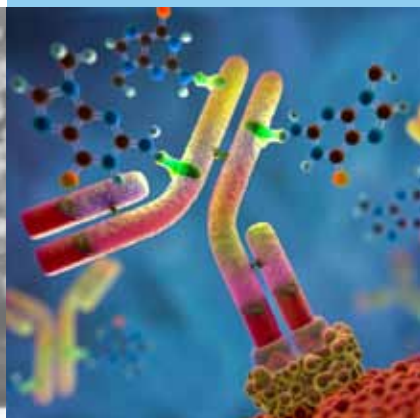
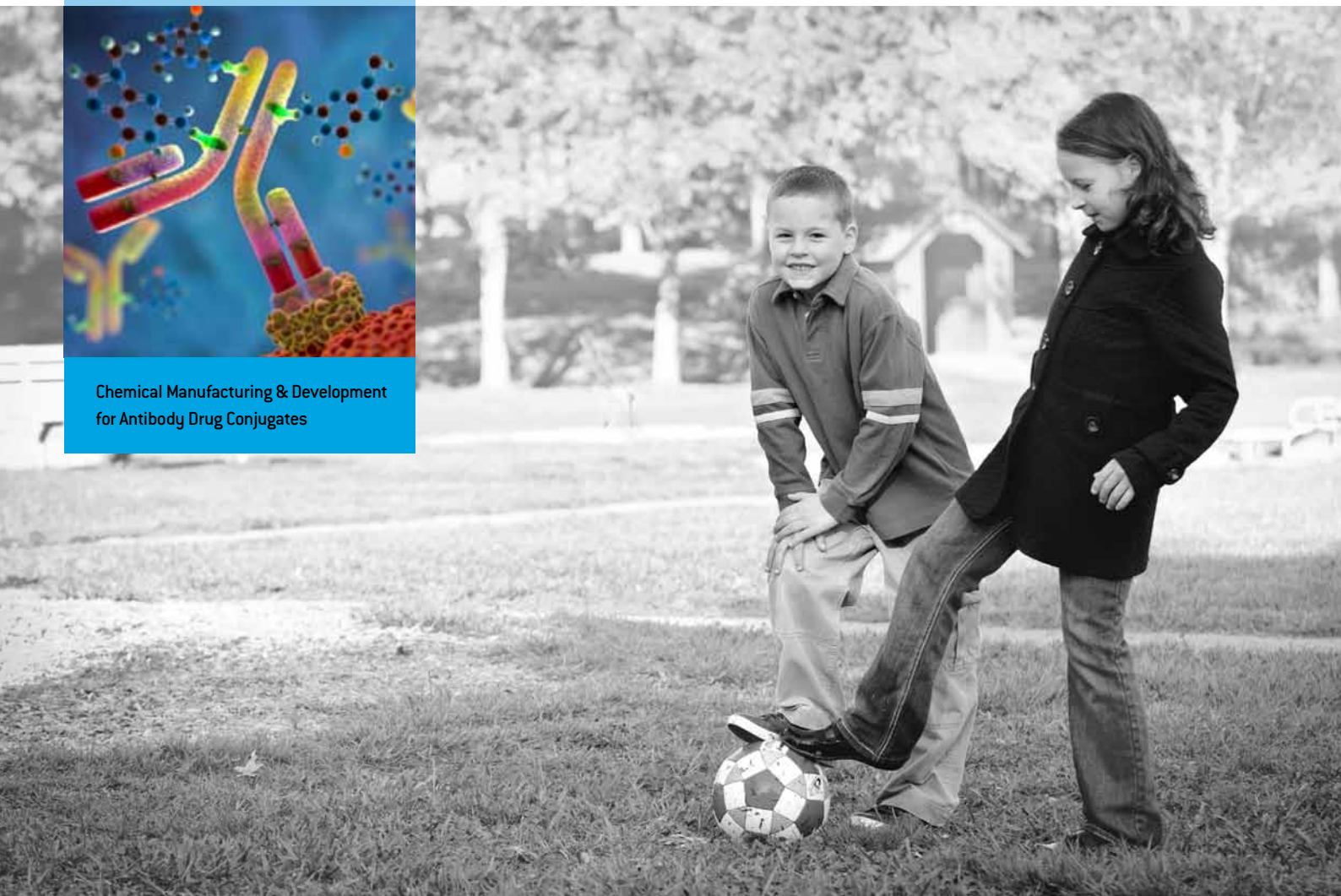


# Antibody Drug Conjugates

## The Next Generation of Pharmaceuticals



Chemical Manufacturing & Development  
for Antibody Drug Conjugates



## Lonza's Broad Set of Technologies

For nearly three decades Lonza has been one of the leading contract manufacturing organizations (CMOs) serving the pharmaceutical, biotechnology, nutrition, personal care and cosmetic industries. Today, we offer a broad set of chemical, biotechnology and hybrid manufacturing technologies and scales, a complete range of process development services, and a wide variety of bioresearch products. Whether for early development, clinical, in-market, or off-patent needs, Lonza's proven track record, industry-leading experience, dedicated project management, and innovative technologies help your products reach their full potential.

In addition to having over 110 years of standard chemical know-how, Lonza is an expert in advanced chemical synthesis and pharmaceutical process development. Not only have we been pioneers in developing innovative manufacturing pathways for active pharmaceutical ingredients (APIs), but we are also leaders in the production and development of the next generation of pharmaceuticals: highly potent APIs, which have a dosage 20 to 50 times lower than typical APIs. A specialized and even more technically challenging subset of highly potent APIs is a new type of therapy that combines innovations from biotechnology and chemistry. This new class of highly potent biopharmaceutical drugs is called antibody drug conjugates (ADCs).

## Antibody Drug Conjugates (ADCs)

Antibody drug conjugates are monoclonal antibodies (mAbs) attached to biologically active drugs by chemical linkers with labile bonds. By combining the unique targeting of mAbs with the cancer-killing ability of cytotoxic drugs, ADCs allow sensitive discrimination between healthy and diseased tissue. Advances in coupling antibodies to cytotoxic drugs permit greater control of drug pharmacokinetics and significantly improve delivery to target tissue. Potent new anticancer drugs can now be used to target cancers while minimizing exposure of healthy tissue.

### Typical ADC Characteristics

- Broader therapeutic window
- (efficacy at low dosages)
- High therapeutic activity
- Targeted delivery of potent drugs
- Reduced undesirable side-effects of chemotherapy
- Address unmet needs in cancer therapies



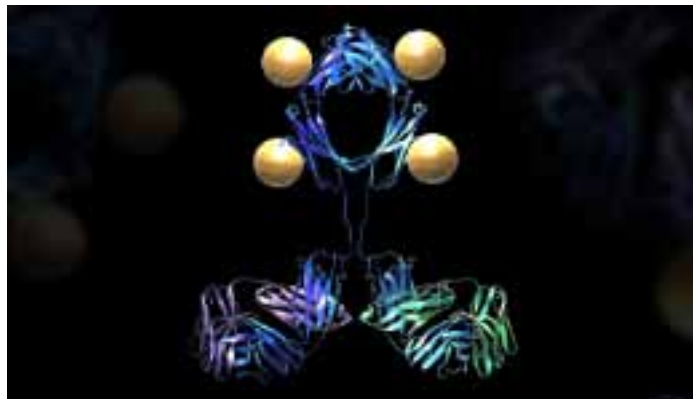
## Quality Control Capabilities

- QC team / labs dedicated to ADC production
- Method development
- Method transfer and validation
- Raw material testing
- In-process testing (24/7), PAT
- Cleaning (swab / rinse by TOC; conductivity)
- Stability testing
- Environmental monitoring
- Quality Control Methods
  - HPLC /UPLC, LC-MS, GC
  - CE
  - UV, IMS
  - Bioassay (enzyme and protein assays)
  - ELISA
  - SDS-PAGE / PAGE
  - Western blotting
  - Microbiology (Bioburden, Endotoxins)
  - Karl-Fischer titration units
  - Osmolality
  - Turbidity

## The Lonza Difference

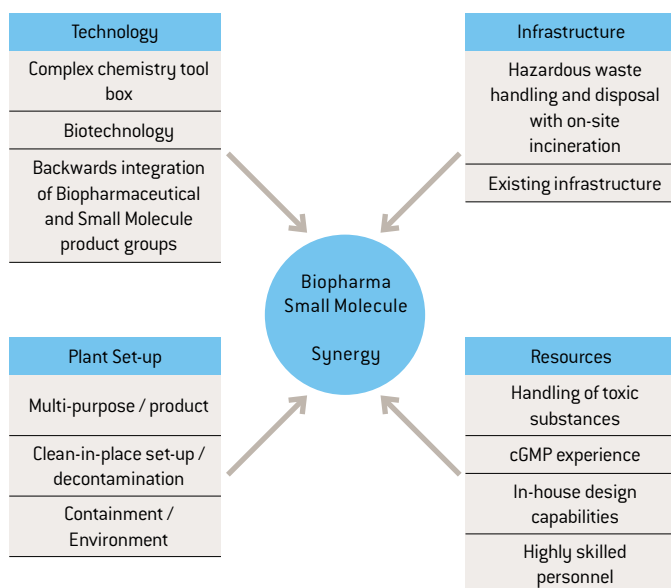
Unlike any other CMO in the industry, Lonza is in the unique position to offer complete development and manufacturing services from both mammalian cell culture and advanced chemical synthesis for the production of antibody drug conjugates.

Lonza's experience and proven track record in both fine chemicals (small molecules) and biotechnology (mammalian cell culture / proteins) vastly increases the chances of antibody drug conjugate manufacturing success. Over the last couple of years Lonza has gained substantial experience with the leading conjugation technologies. A further advantage for customers is the potential manufacture of mAbs at one of our mammalian cell culture facilities.

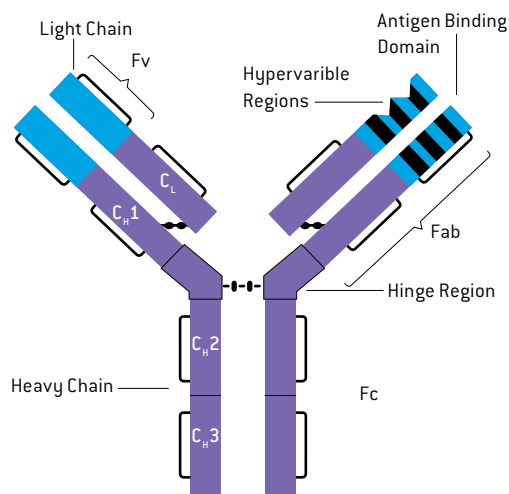
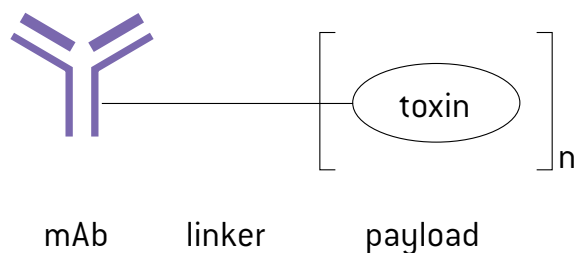


## Summary

- The ADC business leverages Lonza's experience in small molecules and biopharmaceuticals
- Experience with the key conjugation technologies
- Possibility to manufacture mAbs in-house
- Strict safety concept, procedures and training in place
- Certified by SafeBridge® for handling highly potent compounds (above industry average)
- Handling of cytotoxic drugs with OEL  $\geq 40$  ng/m<sup>3</sup> in a biopharmaceutical environment



Biotechnology + Chemistry = Antibody Drug Conjugates



## Strict Safety Standards & Procedures

Manufacturing ADCs is very demanding and completely different from either conventional organic small molecule or typical biotechnology. The traditional biological manufacturing environment must be designed to protect personnel from exposure to cytotoxic substances while maintaining an aseptic environment. Often the OEL defines the threshold that a healthy adult can be exposed to during an 8-hour work shift [g/m<sup>3</sup>]. Based on the relevant OELs, Lonza has selected the optimal containment philosophy, based on thorough studies. We are capable of handling cytotoxic drugs with an OEL of 40 ng/m<sup>3</sup> in a biopharmaceutical environment.

In October 2008, SafeBridge® Consultants, Inc. assessed Lonza's ADC facilities and procedures. Based on the certification criteria established by SafeBridge® and the assessment performed, SafeBridge® has certified that Lonza's potent compound plants in Visp, Switzerland, meet current industry standards for the safe handling of highly potent active pharmaceutical ingredients in ADC operations.



SafeBridge® certification – December 2008





## Meeting the Manufacturing Challenge

Manufacturing highly potent biopharmaceuticals presents a series of unique engineering and chemistry challenges that have resulted in Lonza designing and building a new dedicated large-scale manufacturing plant in Visp, Switzerland. By leveraging experience in both biopharmaceuticals and small molecule drug process development and scale-up, this new class of high potency biologicals can now be manufactured to support both clinical development and licensure.

### Production Capabilities

- Multipurpose cGMP plants dedicated for ADC products
- Qualified equipment
- Biopharmaceutical environment:
  - Cleaning-in-place (CIP)
  - Steaming-in-place (SIP)
  - Water for Injection (WFI)
  - Area classification
  - Gowning concept
- Dedicated and well-trained staff
- Validated cleaning procedures
- Safe-change air filters
- On-site incineration for disposables
- Aseptic operation experience
- Scalable equipment
- ADC cGMP manufacturing experience with more than 25 released GMP batches until 2008 with 100% batch success rate

### Small Scale

2x10L  
3x20L  
2x35L  
3 UF skids

### Large Scale

1x100L (under construction)  
1x200L  
2x300L  
2x 600L  
2 UF skids

### R&D Capabilities

- R&D team dedicated to ADC process development and
- tech transfer
- Clean room with isolator and push-pull ventilation cabinets
- Lab equipment for milligram- and gram-scale experiments
- Ability to flexibly cover various R&D phases based on customer needs
  - Process development
  - Scale up (milligram to gram, gram to kilogram)
  - Scale-down studies
  - Process- and product-related impurity reduction
  - Process qualification / characterization
  - Use of design of experiment (DoE)
  - Preparation of samples for toxicity studies





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