



Science For A Better Life



# **Cost-effective clinical manufacturing of antibody-drug conjugates in multi-purpose facilities**

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**BioProduction Congress, 21th October 2016, Dublin**

## **Cost-effective clinical manufacturing of antibody-drug conjugates in multi-purpose facilities**

- Short introduction to Bayer Pharmaceuticals and its biotech products
- ADCs bridging large and small molecules
- Manufacture of ADCs - challenges and solutions
- Bayer's ADC production concept
- Drug product filling
- Conclusions



**116,482 employees\***

**Full year sales: €46.3 billion\*\***

**307 subsidiaries**

**R&D expenses: €4.3 billion\*\*\***

As of December 31, 2015 (including Covestro) / Employees: as of March 31, 2016 (including Covestro)

\* excluding Covestro: 100,742 employees (in full-time equivalents)

\*\* excluding Covestro: €34.3 billion \*\*\* excluding Covestro: €4.0 billion

# Our Business Areas



## Pharmaceuticals

- Prescription drugs



## Consumer Health

- Over-the-counter medicines, dietary supplements, dermatology products, foot care and sunscreen



## Crop Science

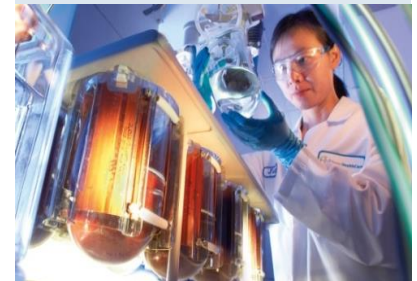
- Innovative crop protection and seeds

# Pharmaceuticals Division

One of the leading innovative companies in the healthcare industry



- **Largest division** of Bayer in terms of sales
- One of the fastest **growing pharma companies** worldwide
- **Sales of 13.7 billion Euro**
- **Pro forma sales** of 15.3 billion Euro in 2015 \*
- Global headquarter in Berlin, Germany
- **40,500 employees** worldwide in 2015 \*\*
- **Largest German** pharma company
- Focus on **prescription products**, especially for cardiology, oncology, hematology, women's healthcare, and ophthalmology
- Also markets contrast-enhanced **diagnostic imaging** equipment together with contrast agents

















# Pharmaceuticals Division

## Top 12 Products – Demonstrate the Value of Biologics



Product [ sales in € million ]		2015
 <b>Xarelto™</b> <small>rivaroxaban</small>		2,252
 <b>Eylea™</b> <small>(allergan solution for injection)</small>		1,228
 <b>Kogenate™</b> <small>Kogenate Bayer</small>		1,155
 <b>Mirena™ product family</b>		968
 <b>Nexavar™</b> <small>(sorafenib) tablets</small>		892
 <b>Betaferon™ / Betaseron™</b> <small>INTERFERON BETA-1b</small>		824
 <b>YAZ™ / Yasmin™ / Yasminelle™</b>		706
 <b>Adalat™</b>		633
 <b>Aspirin™ Cardio</b>		524
 <b>Glucobay™</b>		523
 <b>Ultravist™</b> <small>iopromide</small>		318
 <b>Gadovist™ / Gadavist™</b> <small>Gadobutrol</small>		290

# Biologics Development is the center of expertise for the CMC development of Bayer's biologics pipeline



## Biologics Development



### Berkeley, California

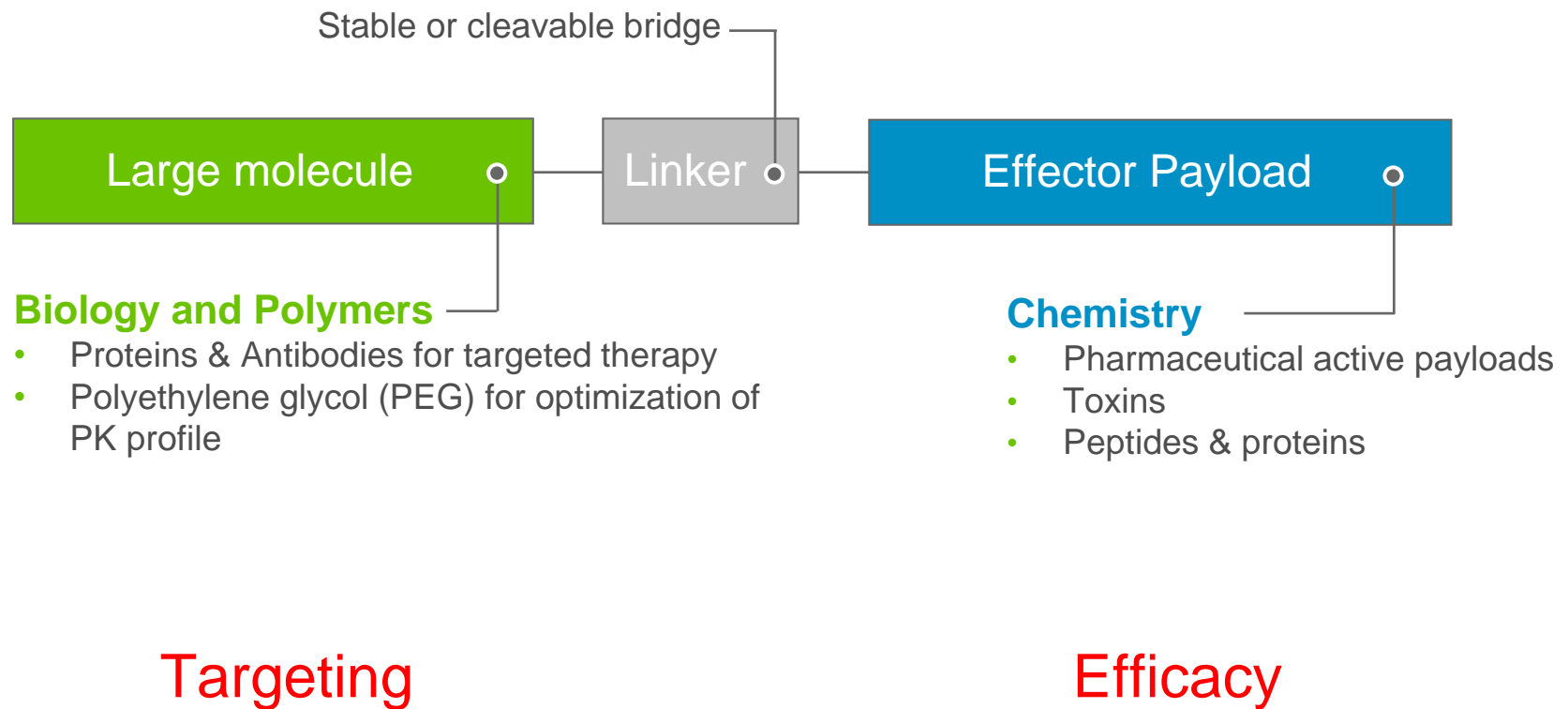
- Process development and clinical manufacture of CFS, mAbs
- Perfusion-based fermentation
- Production cell line and MCB generation



### Elberfeld, Wuppertal

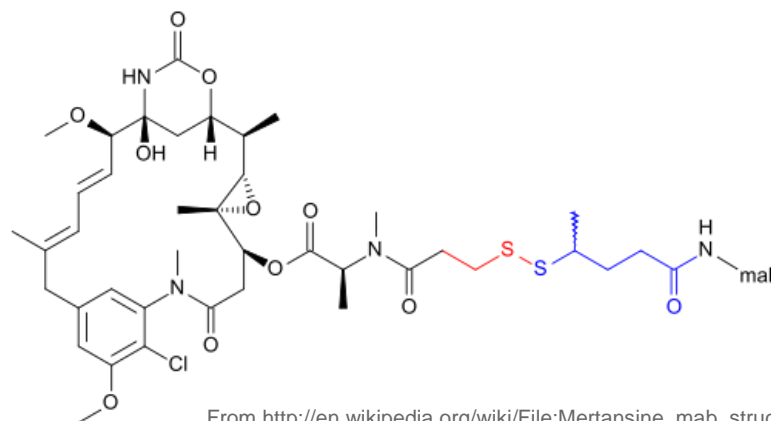
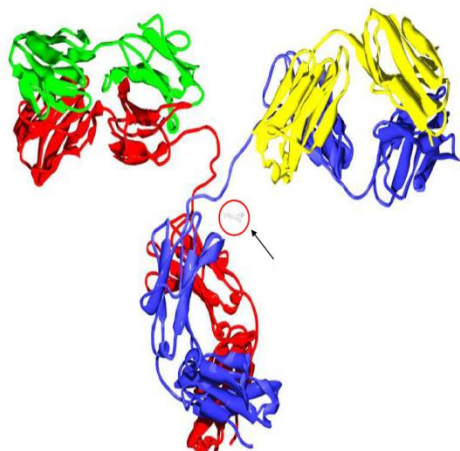
- Monoclonal antibody process development and clinical manufacture
- Batch-fed fermentation
- Microbial fermentation
- Antibody drug conjugate production

# ADCs - Bioconjugates bridging large & small molecules





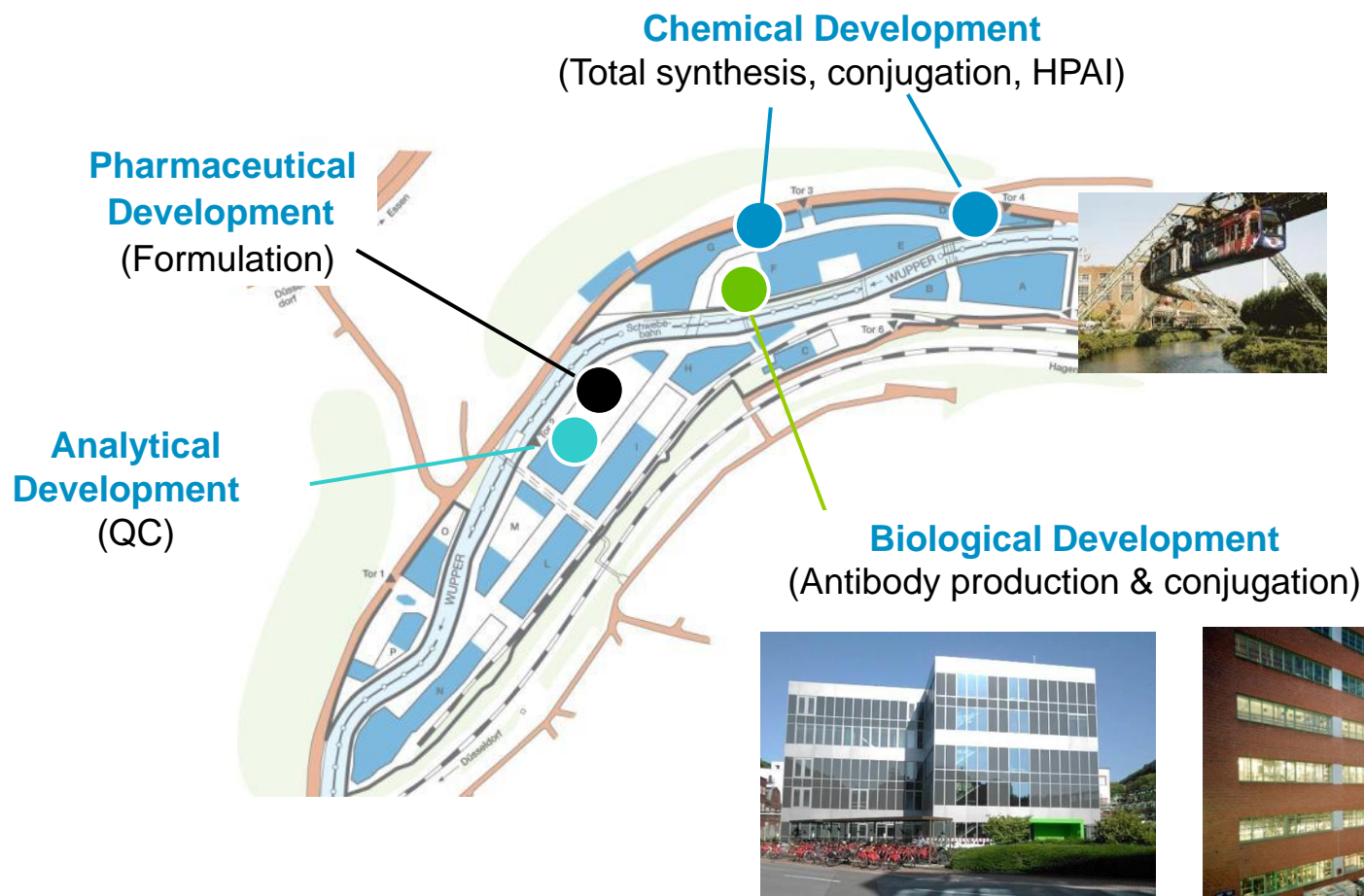
# ADCs - viewed as modified proteins, or as a toxic moiety with a protein appendix



From [http://en.wikipedia.org/wiki/File:Mertansine\\_mab\\_structure\\_coloured.svg](http://en.wikipedia.org/wiki/File:Mertansine_mab_structure_coloured.svg)

- At the typical drug-antibody ratio of 3-4, the payload accounts for <5% of MW
- Once conjugated to the antibody, it is challenging to study the toxophore selectively
- **Biologics development organizations tend to perceive ADCs as just modified proteins**
- Toxic effector is a complex and potentially labile compound in itself
- Linkers can be designed as labile or stable bridge, which at the same time effect stability/labability of the compound
- **Technical development is at risk of overlooking chemical toxophore complexity when treating ADCs as just modified proteins**

# ADC development and manufacturing at the Bayer Wuppertal site



# Bayer's Anetumab ravtansine in Phase II for 2nd line Mesothelioma



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at **Mesothelioma.com**  
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## Phase II Anetumab Ravtansine as 2nd Line Treatment for Malignant Pleural Mesothelioma (MPM)

### Brief Summary

The main purpose of the 15743 study is to assess efficacy and safety of anetumab ravtansine versus vinorelbine in progression free survival in patients with stage IV mesothelin overexpressing malignant pleural mesothelioma (MPM).

# ADC production at different scales



## **Chemical development**

- Develop and optimize process
- Weigh and fill solid toxophore
- Produce ADCs at small scale  
(up to 30 g, dedicated facility)

## **Biological development**

- Clinical manufacturing at larger scale  
(up to 500 g, multi-purpose facility)

How to produce ADCs in already existing pilot facilities ?

# Challenges



- Handling of up to 100 L toxic solution in a multi-purpose clean room
- Waste disposal
- Cross contamination risk
- How to protect the personnel ?
- How to protect working area and environment ?

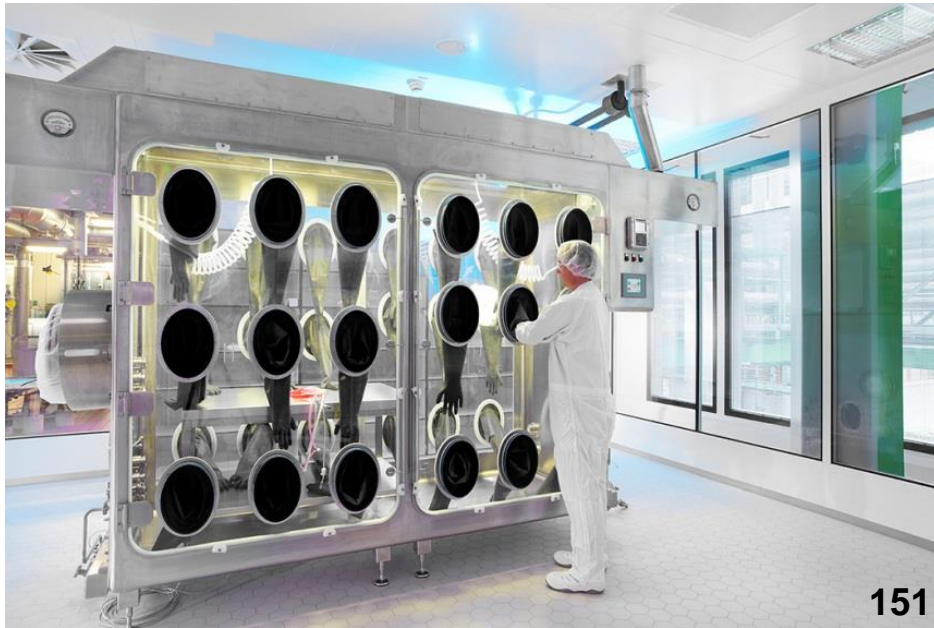
# ADC production concept



- Produce toxophore and linker by chemical synthesis
- Produce mAb in standard mammalian cell culture facility with usual segregation
- Use existing mAb pilot plants on site for conjugation. Do the 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 up to ADC filling and storage
- Produce drug product in special DP production facility



# Glove box concept – protection of personnel and working area



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# Immunoconjugation reaction is performed in a glass reactor



- Coupling of antibody, linker, and toxophor
- Monitoring of pH and temperature
- Glass reactor is used as retentate vessel for UF/DF

**Dedicated reaction vessel for each individual product**

# Concentration and buffer exchange in a closed system



## Sartoflow UF/DF system

- „Ready-To-Use“  $\gamma$ -sterilized disposable filtration system designed as self-contained unit
- Single-use sensors for pressure and flow
- Separate control unit (placed outside the glove box)
- Good connectivity to conjugation reactor and bulk drug substance bag



**Single-use flow path**  
**Closed system**

# Personnel is protected from exposition to hazardous material



- Glove box is closed
- Low pressure inside box
- Filter system retains particles and aerosols
- Complete reaction solution is retained in glove box in case of hazard





## Minimizing the risk



- Solid forms of toxophores are weighed and filled in a dedicated facility
- Liquid manufacturing steps are performed in multi-purpose facility in a glove box
- Clean rooms are dedicated to a single product during a campaign
- Equipment with product contact is designed for single-use or dedicated to one product
- Proof absence of contamination between manufacturing campaigns

# Efficient use of multi-purpose manufacturing facilities



- Integrated concept of ADC development and clinical manufacturing at one site
- Minimizing capital investments by using existing multi-purpose facilities
- Full containment: glove box and closed flow path



# Drug product filling facility



- 3 vial lines for aseptic filling and freeze drying

Filling line	Freeze dryer (m <sup>2</sup> , vial size)	FD Capacity for 30 mL vials	Current project assignments
Isolator	1.6 m <sup>2</sup> ; 2 - 50 mL	1400	Marketed & clinical products
High potent	1.6 m <sup>2</sup> ; 2 - 50 mL	1400	Clinical products
RABS	4.5. m <sup>2</sup> ; 2 - 50 mL	4000	Clinical products (biologics & small molecules)

- Single Use System (SUS) for biologics established



RABS filling line with freeze dryer

# Conclusions



- 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 investments into the construction of a dedicated ADC facility (equipment and space)
- HSEQ concept to proof absence of any contamination in the working area between manufacturing campaigns
- Realized at 2 scales for GMP production in 2 pilot plants



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Thank you!

# Forward-Looking Statements



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The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.