Biologics Discovery Development & Manufacturing
Curia – now part of a powerful global network of 3,700+

29 Global Locations
Strength in Science
+600 Chemists
+230 Biologists
+285 Senior Scientists
+435 Quality & Regulatory Specialists

DISCOVERY
Albany, NY
Buffalo, NY
Hyderabad, India
San Carlos, CA
Belmont, CA
Worcester, MA

DEVELOPMENT
Albany, NY
Hopkinton, MA
Worcester, MA
Grafton, WI
Frankfurt, Germany
San Cristóbal, Spain
Belmont, CA
Hayward, CA
San Carlos, CA
Hyderabad, India

LAB TESTING SERVICES
Albany, NY
West Lafayette, IN
Lebanon, NJ
San Carlos, CA
Hayward, CA
Valladolid, Spain
Hyderabad, India

API MANUFACTURING
Springfield, MO
Grafton, WI
Rensselaer, NY
Bon-Encontre, France
Tonneins, France
Frankfurt, Germany
Aurangabad, India
Origgio, Italy
Rozzano, Italy
Valladolid, Spain

DRUG PRODUCT
Camarillo, CA
Thousand Oaks, CA
Burlington, MA
Albuquerque, NM
Glasgow, UK
Integrated Solutions Approach for Biological Therapeutics

Our integrated solutions and capabilities bridge discovery, engineering, development, and manufacturing across sites.

- Target Discovery
- Lead Discovery
- Screening & Lead Characterization
- Engineering & Optimization
- Large scale Production & Characterization
- RCB Generation
- MCB & Testing
- Process Development
- GMP manufacturing
- IND Filing
- Phase I, II
- Phase III & Commercial Manufacturing

Technical Sites with Project/Scientific Management:

- San Carlos, CA
- Belmont, CA
- Worcester, MA
- Hayward, CA
- Hopkinton, MA
- Thousand Oaks, Camarillo, CA

GMP manufacturing for diagnostic reagents only.
Drug Substance: Antibodies and Proteins
Antibody and Protein Therapeutic Discovery Development and Manufacturing

- Antibody discovery and engineering services
- Engineered CHO cell lines
- Free of animal-derived raw materials
- Tech transfer projects accepted
- Full development services

- ISO 13485:2016 certified
- Manufacturing to support clinical development
- 200-2000 L SUBs
- Full analytics on-site for in-process testing and batch release
Antibody Discovery and Engineering

Culture facilities
- BSL2 level facilities
- Dedicated AAALAC accredited vivarium for rodent immunizations
- Comprehensive projects with consultation and upfront due diligence, followed by immunization, hybridoma generation, selection, cloning and screening validated leads as deliverables. Purified mAbs are provided for Client testing.
- IgG, scFv, Fab, VHH, and other formats

Key Features and Proprietary Technologies
- Multiple Discovery Platforms: Hybridoma, Phage Display, Yeast Display, Single B Cell
- In-line HTP Affinity Analysis and Ab Production
- PentaMice®
- Rapid immunization protocols
- XOMA human scFv and Fab libraries
Single B Cell Antibody Discovery at Curia Using Berkeley Lights Beacon® System

**Superior Mouse System**
- *PentaMice*
  - Industry leading immunological diversity
  - Optimized Immunizations and proven high titers
  - Royalty-free

**AI-Enabled B Cell Selection**
- High throughput; screen 50,000+ B cells in days
- On chip hit ID & cDNA generation
- V_H/V_L paired sequence recovery; mAb diversity & developability assessments

**Fast Gene-to-Development Candidate**
- Gene to mgs Protein in <8 weeks
- HT epitope binning & affinity determination: Carterra® system, BLI
- Humanization (or humanized mouse starting point)
- *In vitro* efficacy & safety assessments: ADCC, ADA, ADC/CS.

Hit-to-candidate in 120 days ● First-to-Human-enabling technology
Antibody & Protein Therapeutic Development and cGMP Manufacturing

GMP Overview

- Single use equipment
- 200, 500, and 2000 liter SUBs
- ISO7 post-viral and fill/finish suite
- Onsite analytics for in-process testing and batch release

Stages

- Cell Line Development
  - CHO cell line engineering, cloning, and RCB
- Master Cell Bank
  - Master Cell Bank generation and characterization
- Upstream Process Development
  - Optimize culture conditions in Ambr® and scale up to 2L through 50L SUBs
  - Batch record creation
- Downstream Process Development
  - Develop purification process
  - Batch record creation
- Engineering and Manufacturing Batches
  - Engineering run in suite and cGMP manufacturing of bulk drug substance

Total timeline 12-16 months from CLD to phase I drug substance*

*Timelines are subject to change depending on the manufacturability of the candidates
Cell Line Development - Curia CHO-GSN℠ Technology

**Highlights**

- Royalty-free, no commercial milestone payments
- CHO-K1 GS knockout with stronger GS selection, high titers
- Generational stability >80 generations demonstrated
- Established track record; multi-programs in clinical stages

**Proprietary Stable Expression Vectors**
- High expression stable expression vectors
- Bicistronic vectors for antibodies
- Monocistronic vectors for proteins
- Vectors for 3+ chain molecules available

**CHO-GSN Parental Cells**
- CHO-K1 GS knockout
- Suspension adapted
- Animal product-free culturing
- Path to commercialization

**Proprietary Stable Cell Line Generation Know-how**
- Stable pool and single clone selection
- Experience in stability and scalability
- Upstream process development
- Downstream process development
**CHO-GSN Stable Cell Line Generation**

### Stable Vector Construction
- Proprietary Stable Expression Vectors
  - Custom designed for CHO-GSN platform
  - Non-CMV promoters
  - Thorough QC & sequence confirmation

### Stable Pool Generation
- CHO-GSN Platform
  - CHO-K1 derived
  - MaxCyte Electroporation
  - MSX as high selection pressure
  - 50 mL production runs to assess titer

### Stable Clone Generation
- CHO-GSN High Titer Clone and Monoclonal Cell Line
  - Solentim™ VIPS for single cell cloning
  - Solentim™ Cell Metric for confirmation of monoclonality
  - 50 mL production runs to assess titer
  - Generational stability test

**mAb Titer Profile**

- **2-3 weeks**
- **6-7 weeks**
- **11-12 weeks**
Successful Progression from Transient to RCB

Transpeated Production

CHO-GSN Stable Pool

Clone Generation: Single Cell Cloning

2L SUB

Manufacturable antibody

Fc-fusion protein

Untagged protein

>0.5 g/L

200 mg/L

300 mg/L

>1 g/L

200 mg/L

330 mg/L, high purity

>2.5 g/L

400 mg/L

660 mg/L, high purity

>4.5 g/L

>1 g/L

>1 g/L
**CHO-GSN Research Cell Bank Characterization and Process Development**

**Final Research Cell Bank**
- High titer clones selected
- Monoclonality ensured
- Tolerance to shear force & other bioreactor conditions tested

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**RCB Characterization & Testing**
- Sterility
- Mycoplasma
- Gene Copy Number Determination

**Stability Studies**
- Cryopreservation and stability study over 80 generations
- Scalability in small scale bioreactors
- Generate sufficient stability data to support shelf-life of clinical material

**Process Development**
- Process optimization
- Scale Down/Up Models
- Formulation Development
- Analytical Assay Development
- Perfusion Method Development (proof of concept showed GSN cells can grow to $8 \times 10^6$ cells/mL)

**Scale-up Productions**
- WAVE bag production
- Medium to large scale bioreactor (up to 2000 L)
- Produce and support GMP grade Drug Substance and Drug Product
CHO-GSN Cell Lines in Preclinical and Clinical stages

- **Preclinical**
- **Phase I/II/III**
- **IND-Enabling**
Upstream Therapeutic Antibody/Protein Process Development

Preliminary Upstream Media and feed screening
Evaluate production in flasks
DoE for media and feed screening

Sartorius Ambr® 15 Microbioreactor Clone & Parameter Screening
Evaluate key parameters in Microbioreactors using Ambr® 15 system:
• Clone selection
• Evaluate select culture parameters
• Early stage process optimization

2L SUB Confirmation Run
Evaluate cell line scalability

50L SUB Scale Up
Confirm cell culture parameters in scale up production
**Downstream Therapeutic Antibody Process Development**

### Downstream Process Development Stages

**Capture Step**
- Capture produced material

**Viral Inactivation**
- Inactivates any potential enveloped viruses

**Polishing Step #1**
- Remove Aggregates or product related impurities

**Polishing Step #2**
- Remove Process Related impurities (HCP, DNA, leachate)

**Nanofiltration/UF/DF**
- Remove potential viruses
  - Buffer exchange

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**Conditioned Medium**

**Purify**

**Final Product**

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# Antibody/Protein Assays and Analytics

<table>
<thead>
<tr>
<th>Test</th>
<th>Purpose</th>
<th>Assay</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Safety, Quality</td>
<td>Visual Inspection</td>
<td>USP&lt;790&gt;</td>
</tr>
<tr>
<td>Bacterial Endotoxin</td>
<td>Safety, Quality</td>
<td>Chromogenic LAL</td>
<td>USP&lt;85&gt;</td>
</tr>
<tr>
<td>Bioburden</td>
<td>Safety/quality</td>
<td>USP&lt;61&gt;</td>
<td></td>
</tr>
<tr>
<td>Sterility (w/ BnF)</td>
<td>Safety, Quality</td>
<td>1 mL x 2 Direct Inoculation</td>
<td>USP&lt;71&gt;</td>
</tr>
<tr>
<td>pH</td>
<td>Safety, Quality</td>
<td>pH Test</td>
<td>USP&lt;791&gt;</td>
</tr>
<tr>
<td>Osmolality</td>
<td>Safety, Quality</td>
<td>Osmolality Test</td>
<td>USP&lt;785&gt;</td>
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<tr>
<td>Protein Concentration</td>
<td>Strength</td>
<td>Spectrophotometry</td>
<td>USP&lt;1057&gt;</td>
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<tr>
<td>Residual Host Cell Protein</td>
<td>Purity</td>
<td>ELISA</td>
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<tr>
<td>Residual Protein A</td>
<td>Safety, quality</td>
<td>ELISA</td>
<td></td>
</tr>
<tr>
<td>Residual Host Cell DNA</td>
<td>Purity</td>
<td>qPCR</td>
<td></td>
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<tr>
<td>Charge by IEF</td>
<td>Purity/Identity</td>
<td>Capillary Electrophoresis</td>
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</tr>
<tr>
<td>% Monomer by SEC</td>
<td>Purity</td>
<td>HPLC</td>
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<tr>
<td>RP, AEX, &amp; IEX HPLC</td>
<td>Identity/Purity</td>
<td>HPLC</td>
<td></td>
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<tr>
<td>CE-SDS</td>
<td>Purity</td>
<td>Capillary Electrophoresis</td>
<td></td>
</tr>
<tr>
<td>Endotoxin by colorimetric LAL</td>
<td>Safety/quality</td>
<td>Spectrophotometry</td>
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<td>Subvisible Particles</td>
<td>Safety</td>
<td>Subvisible particle analysis, various equipment</td>
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<tr>
<td>Stability</td>
<td>Various</td>
<td>Various assays</td>
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</tr>
<tr>
<td>Activity</td>
<td>Potency</td>
<td>Octet or cellular assay</td>
<td></td>
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Drug Substance: mRNA
Features of mRNA Development and Manufacturing Services

- DNA template engineering
- Cell-free, enzymatic synthesis
- Relatively short manufacturing timelines relative to traditional biologics
- Free of animal-derived raw materials
- Short and long RNAs
  - Self-amplifying RNA (saRNA): typically 9-16 kb
  - Non amplifying RNA: typically 3-6 kb
- ISO 13485:2016 certified
- ISO 7 RNA suite
- Manufacturing to support clinical development
- 0.1 to 8 L scale (current)
- Expanding capacity to 100 L in 2022
- Full analytics on-site for in-process testing and batch release
Curia supports mRNA Platform Development from Research to Clinic

mRNA Research and Manufacturing Services

- **Research Cell Bank Generation**: Generation of bioprocessing grade plasmid and cell bank from sequence or existing construct scale-up
- **IVT Optimization**: AOF template linearization and certification of testing of all materials suitable for mRNA production
- **Research Scale Expansion**: Assessment of capping procedure and characterization of mRNA to ensure maximal modification and potency
- **Capping Process Development**: Assessment of purification methods to optimize yield recovery and purity
- **Purification**: Core and molecule-specific testing for appearance, endotoxin, sterility, pH, and other key product attributes
- **Analytics**: Scaled production for testing and pre-GMP studies
- **Engineering**: Process refinement and optimization to enable GMP qualified production
- **GMP Operations**: Production of GMP grade bulk material at scales from 100mls to 8L
- **All GMP qualified testing and documentation required for material release**
## mRNA Analytics

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<td>Osmolality</td>
<td>Safety, Quality</td>
<td>Osmolality</td>
<td>USP&lt;785&gt;</td>
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<tr>
<td>RNA Concentration</td>
<td>Strength</td>
<td>UV A$_{260}$</td>
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<tr>
<td>RNA Identity</td>
<td>Identity</td>
<td>CE-Based (Size Confirmation)</td>
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<td>Identity (as RNA)</td>
<td>Identity</td>
<td>Enzyme Degradation and CE</td>
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</tr>
<tr>
<td>Residual protein</td>
<td>Purity</td>
<td>PAGE (silver stain) or Fluorescent</td>
<td></td>
</tr>
<tr>
<td>Residual DNA</td>
<td>Purity</td>
<td>qPCR (Thermo &quot;kan&quot; reagent)</td>
<td>Report</td>
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<tr>
<td>Residual DS RNA</td>
<td>Purity</td>
<td>Dot Blot</td>
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<tr>
<td>RNA Integrity</td>
<td>Quality</td>
<td>CE-Based</td>
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<tr>
<td>Functional Assay</td>
<td>Strength</td>
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<tr>
<td>% Cap [Optional]</td>
<td>Strength</td>
<td>R&amp;D available; GMP in development</td>
<td></td>
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</table>
Curia Bulk Drug Substance mRNA Manufacturing Capabilities

- GMP compliant, single use equipment
- Cell-free mRNA manufacturing
- Large scale production up to 8-80 grams/batch
- ISO7 suite
- Expertise in self-amplifying mRNA production
- Onsite analytics for in-process testing and batch release

Stages and Timeline

1. **RCB Generation, DNA Production and Linearization**
   - 8-10 weeks
   - Plasmid DNA template

2. **mRNA IVT Scouting**
   - 1-2 weeks
   - Small scale optimization and production level proof-of-concept

3. **Pilot Program Production**
   - 1-2 weeks
   - Target small scale deliverable / purification optimization

4. **Process Development**
   - 2-4 weeks
   - Target client specific quantity for GMP run
   - Scale-up process for analysis and downstream development
   - GMP compliant batch record creation

5. **Production Run**
   - 1-2 weeks
   - Repeat of engineering run conditions in GMP suite
   - Execution of process as developed in engineering run and deliverable of GMP grade bulk material
Drug Product: Antibodies, Proteins, and mRNA-LNP
Formulation Development

• Based on the most relevant ICH stability guidelines

• Upon the foundation of the most critical parameters:
  o Stress factors
  o Degradation products
  o Stability indicating assays
  o Formulation sweet-spot(s)

• Targeting for the most competitive presentations:
  o Liquid, lyophilized, or multidose formulations
  o Ideal container/closure systems
  o Convenient routes of administration
Process Development

• Formulation, Fill Finish, Lyophilization Process Development (disposable product contact manufacturing train available)
  • Antibodies, proteins, peptides, mRNA-LNPs
  • Specializing in First In Human manufacturing support
  • Tech Transfer
  • Engineering runs
  • Validation
  • Novel processes
## Drug Product Formulation Development and Manufacturing

### Stages and Timeline

<table>
<thead>
<tr>
<th>Stage</th>
<th>Duration</th>
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<tr>
<td>Formulation Development</td>
<td>8-10 weeks</td>
</tr>
<tr>
<td>Tech Transfer Fill/Finish</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td>Batch Records/Documentation</td>
<td>3-4 weeks</td>
</tr>
<tr>
<td>Engineering Runs</td>
<td>2-4 weeks</td>
</tr>
<tr>
<td>GMP Runs and Lot Release</td>
<td>8-12 weeks</td>
</tr>
<tr>
<td>Stability Studies</td>
<td>2 to 5 years</td>
</tr>
</tbody>
</table>

### Key Points

- **EU Grade A Environment**
- **Vial size**: 2-30cc
- **Fill Volume**: 0.2-32 mL
- **Max batch size**:
  - Liquid: 20,000 units
  - Lyophilized: 1200-5,000 (2 cc to 20 cc)
- **Onsite analytics for in-process testing and batch release**
Biomanufacturing at Curia

GMP manufacturing of biologics: single use, and flexible
• First in human manufacturing that bridges the gap between development and late-stage manufacturing
• ISO 13485:2016 certified

Integrated Solution approach for biologics development
• On-site assays and analytics for in-process testing and batch release
• Rapid advancement from process development to clinical supply
• Thought partnership and close collaboration with clients

Advantages
- Comprehensive platforms for development, manufacturing, and analytics
- Close collaboration and open communication
- On-site analytics for rapid turn-around
Thank You

Contact us for more information