Gibco Bulk Process Liquid and Buffer Capabilities
• $17 billion in revenues
• $700 million spent on R&D
• 50,000 employees
• 50 countries
• 5 premier brands
Cell Culture and Cell Therapy History

- **1962**: Grand Island Biologics Company founded in 1962
- **1965**: First manufacturing facility opens in Grand Island, NY
- **1967**: Gibco™ AIM V™ Medium launched in 1987 (first product to be used for patient treatment)
- **1983**: Gibco and BRL combine to form Life Technologies in 1983
- **1996**: Gibco™ CD CHO Medium launched in 1996 (first chemically defined complete media)
- **2000**: Invitrogen acquires Life Technologies in 2000
- **2001**: Gibco™ Advanced Granulation Technology™ (AGT™) format in 2001
- **2005**: Animal origin-free facility in 2005
- **2007**: ISO 13485 in 2007
- **2008**: Invitrogen acquires Applied Biosystems in 2008
- **2009**: Optima Autofiller in 2009
- **2012**: Distribution expansion in 2012
- **2014**: Bulk liquid manufacturing in Grand Island
- **2016**: Gibco celebrates 50 years

Growing with you at every stage for over 50 years
Leading Capabilities for Every Step of the Bioprocess Workflow

Upstream

- Cell line development and media optimization
  - CHO cell lines
  - Process development services
  - Media optimization services

Mixing, cell culture and fermentation

- Cell culture media, feeds and enhancers
- Single-use fermentors, bioreactors and mixers
- BioProcess Containers (BPCs)
- Integrity testing solutions
- Single-use heat exchanger
- Large-volume liquids

Harvest and collection

- Harvest and separation products
- Storage and transport
- Single-use frozen handling system
- Single-use sampling system

Purification

- Chromatography resins
- Affinity ligands and resins
- Transfer assemblies
- Single-use BPCs, manifolds and containers
- Host cell DNA, host cell protein and protein A quantitation
- Large-volume liquids
- Single-use mixers

Bulk storage and final fill

- Storage and transport
- Single-use fermentors, bioreactors and mixers
- Single-use BPCs, manifolds and containers
- Single-use filling system
- Single-use frozen handling system

QC and analytics

- Mycoplasma and viral detection
- Microbial identification
- Glycan analytics
- Analytical columns
- Automation solutions for nucleic acid sample preparation
Global BioProduction Manufacturing Facilities

- **Millersburg, PA**
  - BioProcess Containers
  - Single-use technologies
  - ISO 13485
  - cGMP standards

- **Logan, Utah**
  - BioProcess Containers
  - Single-use technologies
  - Class 10,000/ISO 7 clean room

- **Matamoros, Mexico**
  - BioProcess Containers
  - Single-use technologies
  - ISO 13485
  - cGMP standards

- **Bedford and Framingham, MA**
  - Chromatography resins
  - ISO 13485

- **Grand Island, NY**
  - Cell culture media, reagents
  - Sera
  - ISO 13485
  - GMP 21 CFR 820

- **Paisley, Scotland**
  - Cell culture media, reagents
  - ISO 13485
  - GMP 21 CFR 820

- **Lillestrom and Oslo, Norway**
  - Invitrogen™ Dynabeads™ Magnetic Beads
  - ISO 9001– and ISO 13485–certified

- **Auckland and Christchurch, New Zealand; Newcastle, Australia**
  - Sera
  - Protein products
  - GMP 21 CFR 820

- **Naarden, the Netherlands**
  - Affinity ligands
  - ISO 9001–certified

- **Cramlington, UK**
  - Bioprocess containers
  - Single-use technologies
  - Class 10,000/ISO 7 clean room

- **Warrington, UK**
  - Analytics kits

- **Lillestrom and Oslo, Norway**
  - Invitrogen™ Dynabeads™ Magnetic Beads
  - ISO 9001– and ISO 13485–certified
Gibco Media Network

**US manufacturing**
Grand Island, New York

**EMEA manufacturing**
Paisley, Scotland

- **Dry powder media**
- **AGT media**
- **1X media/buffer**
- **Concentrated media/buffers**

Serving over **110 commercial therapies** worldwide
Reliably Serving Customers with Operational Excellence

Assurance of supply
- Redundant manufacturing facilities
- Persistent facility and capability investment
- Supply chain and supplier development
- Multilevel safety stock management
- Continuous investment in business continuity planning

Quality
- Robust, defined, and proven quality management systems
- Dedicated animal origin–free manufacturing capabilities
- Highly specific analytical methods to reduce risk of contamination
- Testing of raw materials and in-process/finished goods
- Fully integrated serum sourcing and manufacturing in country of origin

Process control and improvement
- Documented and controlled manufacturing procedures
- Process validation and statistical process control (SPC)
- High-functioning process and continuous improvement (PPI)
- Formalized system of customer interactions and priorities
Benefits to Outsourcing Bioprocess Liquid Manufacturing

Advantages

- Better product consistency
- Improved cell culture performance
- Suppliers of liquids are more knowledgeable and experienced
- Fewer contamination risks
- Eliminate need for mixing tanks
- Time and labor-intensive steps eliminated:
  - QC of salts, liquid preparation, filtration, quarantine, finished good testing, documentation, procedures, validation
- Improved safety due to less handling
- Just-in-time logistics solutions
  - Doe & Ingalls cGMP warehousing (in US)

Customer benefit

- Decreased capital and operating costs
- Improved quality and compliance
- Increased productivity
Multiple Film Offerings for BPCs

Proven history

• Extensive liquid handling experience
• Over 20 years’ experience customizing single-use assemblies
• Over 1 million BPCs produced yearly

Custom products optimized

• For the application
• For specific operating parameters
• Using qualified components
• To meet time and cost requirements

Film choices for liquids

• BPCs with Thermo Scientific™ CX5-14 and Aegis™ films are validated for liquid fills and shipments from Grand Island and Paisley
• Thermo Scientific™ ASI™ 26/77 film qualification for fill and shipment (Grand Island and Paisley) initiated in 2016
• Continuing to support legacy films
Critical Attributes Help Ensure Product Integrity and Performance

Characteristics that determine whether a flexible container will maintain product integrity and perform as expected during specific bioprocess operations:

- Biological compatibility
- Tensile properties
- Puncture resistance
- Glass transition temperature
- Transportability
- Clarity
- Permeability
- pH stability
- Extractable profile
- Cell culture growth performance
- Stability
Expanded Choice of Secondary Packaging

5, 10, and 20 L bioprocess containers
- Corrugate cases
- Returnable plastic crates

50, 100, and 200 L bioprocess containers
- Option to ship in different drum designs
- Top-emptying
- Bottom-emptying
- Nestable
- Single-trip
- Hazardous material handling

100, 200, 500, and 1,000 L bioprocess containers
- ALLpaQ (Arca/Auer) plastic returnable systems
- Bottom- or top-emptying
- 100 and 200 L returnable containers only available in EU
Extension of your **supply chain management** and **finished goods distribution**

**Mitigate risk**
- Quality compliance and raw material traceability
- On-time delivery and backorder management
- Change notice and corrective action management

**Increase productivity**
- Dedicated account management team
- Raw material handling services
- Supplier management
- Document management

**Reduce costs**
- cGMP chemical storage
- Inventory solutions
- Increased lots and consolidated shipments

* Available only in the US.
Aspiration: Best-in-Class Bulk Liquid Manufacturing

Bulk process liquids and buffers increase **biopharmaceutical process efficiency** and reduce risk by **simplifying and standardizing workflows**

<table>
<thead>
<tr>
<th>Why?</th>
<th>What?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Outsource partnership/manufacturing extension</td>
<td>• Manufacturing capacity</td>
</tr>
<tr>
<td>• Pronounced synergies with vertical integration</td>
<td>• Cold warehouse space and distribution</td>
</tr>
<tr>
<td>• Existing liquid and single-use technologies expertise</td>
<td>• Support resources</td>
</tr>
<tr>
<td>• Enables cost reduction for customers</td>
<td>• Process optimization</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Launch integrated custom large-volume liquid (LVL) portfolio</td>
<td>• Liquid facility investments (US &amp; EU)</td>
<td>• Facility / equipment implementation</td>
</tr>
<tr>
<td>• Grand Island expansion project scope</td>
<td>• Water for injection (WFI) launch (20 &amp; 200 L)</td>
<td>• Validation</td>
</tr>
</tbody>
</table>
## Liquid Production Network

### Research

### Bioproduction

<table>
<thead>
<tr>
<th>Bottled liquids</th>
<th>Grand Island, USA</th>
<th>Paisley, Scotland</th>
</tr>
</thead>
<tbody>
<tr>
<td>(10 mL–1 L)</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

| Bagged liquids           |                   |                   |
| (1–1,000 L)              | ✓                 | ✓                 |

| Batch sizes              |                   |                   |
| (10–10,000 L)            | ✓                 | ✓                 |

| Corrosive solutions      |                   |                   |
| (5,000 L polypropylene tank) | ✓                  | ✓                 |

| Alcohols (up to 20% v/v ethanol) (750–2,500 L) |                   |                   |
|                                           | ✓                 |                   |

### Order management

### Dispensing

### Formulation

### Filtration

### Fill and finish

### Delivery

---

**Formulation**

**Filtration**

**Fill and finish**

**Delivery**

---

**Grand Island, USA**

**Paisley, Scotland**

---

**Thermo Fisher Scientific**
### Grand Island Liquid Facility Investments

#### Facility footprint
- 15,000 ft² manufacturing over two floors
- 12,400 ft² finished goods warehouse space
- Clean room, gowning, storage, formulation, staging

#### Equipment deployed
- Multiple 10,000 liter tanks
- 5,000 liter tank
- 2,500 liter tank

#### Support systems
- WFI still
- HVAC
- Clean steam generation
- Electronic batch records

$21.8M investment to increase liquid manufacturing (5 million liters)

Additional capabilities added to include an **alcohol suite** to manage hazardous solutions

---

**Grand Island facility expansion for bulk liquids Q4 2016**
To meet current and future customer requirements for insourcing bulk liquids, our Grand Island manufacturing facility is built to and compliant with the following standards:

<table>
<thead>
<tr>
<th>Design criteria</th>
<th>Value</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO 13485</td>
<td>Internationally recognized standard on the requirements for a quality management system for medical devices</td>
<td>Industry standard</td>
</tr>
<tr>
<td>21 CFR 820–compliant</td>
<td>FDA current Good Manufacturing Practice (cGMP) quality system regulation for medical devices</td>
<td>Industry standard</td>
</tr>
<tr>
<td>Annex 1 standard</td>
<td>cGMP guidelines to harmonize US/EU controls and procedures to manufacture sterile medicinal products</td>
<td>Differentiator</td>
</tr>
<tr>
<td>Animal origin–free (AOF)</td>
<td>All raw materials are free of animal-derived components; dedicated AOF equipment</td>
<td>Differentiator</td>
</tr>
<tr>
<td>Grade C and grade D controlled spaces</td>
<td>Monitored and controlled temperature, pressure, air change rate for formulation and filtration</td>
<td>Differentiator</td>
</tr>
<tr>
<td>Single material flow</td>
<td>One-way raw material flow with no return to inventory; dedicated AO/AOF raw materials for manufacturing</td>
<td>Differentiator</td>
</tr>
<tr>
<td>Proximity to raw material and finished goods warehouse</td>
<td>Segregated AO/AOF raw material sampling booths; close proximity to manufacturing and distribution</td>
<td>Differentiator</td>
</tr>
<tr>
<td>2nd floor formulation</td>
<td>Gravity transfer to fill and filtration for ergonomic workflow; separate formulation suites for each tank</td>
<td>Differentiator</td>
</tr>
<tr>
<td>Manifold filling</td>
<td>Semiautomated closed manifold system</td>
<td>Differentiator</td>
</tr>
</tbody>
</table>
Incremental Investments to Improve Liquid Capacity in Europe

LSG EMEA headquarters

600 employees

In Scotland since 1970
Liquid Capacity Exceeds Demand

Robust systems to accommodate increased demand

<table>
<thead>
<tr>
<th>Ways to increase capacity</th>
<th>Capacity assumptions</th>
<th>Capacity variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 24x7</td>
<td>• 5x3 shift operation</td>
<td>• Tanks</td>
</tr>
<tr>
<td>• Additional headcount</td>
<td>• Existing people</td>
<td>• Workflow (24x6, 24x7)</td>
</tr>
<tr>
<td>• Bolt-on tankage</td>
<td>• Tank utilization &lt;75%</td>
<td>• Number of people</td>
</tr>
<tr>
<td>• Use disposables</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of tanks</th>
<th>400–1,000 L</th>
<th>1,500–2,500 L</th>
<th>3,000–10,000 L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grand Island</td>
<td>2</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Paisley</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
Examples of Customer Liquid Projects

Total liquid volume in 2015
- 8.3M liters of catalog and custom liquids
- 2.0M liters in bioprocess containers
- 6.3M liters in bottles

Gibco BioProduction services
- Media / buffer / concentrate development
- Process development
- Scale-up / technology transfer

<table>
<thead>
<tr>
<th>Liquid type</th>
<th>Gibco™ product and annual volume examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell culture media</td>
<td>GMEM: [66,000 L] 330 x 200 L bag</td>
</tr>
<tr>
<td></td>
<td>Custom media formulation: [462,500 L] 925 x 500 L bag</td>
</tr>
<tr>
<td></td>
<td>AIM V T cell Medium: 15,000 x 1 L bag</td>
</tr>
<tr>
<td>Feeds and additives</td>
<td>10% antifoam: [13,000 L] 2,600 x 5 L bag</td>
</tr>
<tr>
<td></td>
<td>CHO CD EfficientFeed™ A supplement: [3,800 L] 760 x 5 L bag</td>
</tr>
<tr>
<td></td>
<td>BME: 8,130 x 1 L bottle</td>
</tr>
<tr>
<td>Bioprocess liquids</td>
<td>Sodium citrate: [90,000 L] 450 x 200 L bag</td>
</tr>
<tr>
<td></td>
<td>PBS: [32,000 L] 1,600 x 20 L bag</td>
</tr>
<tr>
<td></td>
<td>WFI: [28,000 L] 2,800 x 10 L bag</td>
</tr>
<tr>
<td>Concentrates</td>
<td>CD CHO concentrate: [296, 400 L] 1,800 x 150 L bag + 1,320 x 20 L bag</td>
</tr>
<tr>
<td></td>
<td>1,000X CD lipids: [3,900 L] 1,950 x 2 L bottle</td>
</tr>
</tbody>
</table>
## 0.1 M NaOH buffer cost analysis

<table>
<thead>
<tr>
<th></th>
<th>In-house</th>
<th>ThermoFisher Scientific</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Batch size</strong></td>
<td>2,000 L</td>
<td>10,000 L</td>
</tr>
<tr>
<td><strong>Batches per year</strong></td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td><strong>QC releases</strong></td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td><strong>Prep time (2,000 L)</strong></td>
<td>4 hours</td>
<td>1 hour</td>
</tr>
<tr>
<td><strong>Annual prep time</strong></td>
<td>10 days</td>
<td>2.5 days</td>
</tr>
<tr>
<td><strong>Total batch cost</strong></td>
<td>$11,500</td>
<td>$35,000</td>
</tr>
<tr>
<td><strong>Per liter cost</strong></td>
<td>$5.75</td>
<td>$3.50</td>
</tr>
<tr>
<td><strong>Annual prep time</strong></td>
<td>$230,000</td>
<td>$140,000</td>
</tr>
</tbody>
</table>

- **$90,000 annual savings**
- **75% reduction in prep time**
- **80% reduction in lot testing**
# More Choice and Control Through Manufacturing Flexibility

The right liquid format, container, and manufacturing process for each product

<table>
<thead>
<tr>
<th><strong>Liquid format</strong></th>
<th><strong>Container type</strong></th>
<th><strong>Film choice</strong></th>
<th><strong>Manufacturing speed</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Process liquids for upstream and downstream applications</td>
<td>• Bottles from 10 mL–1 L</td>
<td>• Industry-standard CX5-14 film for general applications</td>
<td>• Non-GMP Gibco™ Media Express™ (GME) services</td>
</tr>
<tr>
<td>• Gibco media and feeds for cell culture processes</td>
<td>• Flexible bioprocess containers from 1–1,000 L</td>
<td>• Aegis5-14 film for critical applications</td>
<td>• Full GMP for scale-up</td>
</tr>
<tr>
<td>• 1X and concentrates</td>
<td>• Custom designs and sizing available</td>
<td>• Industry-standard ASI 26/77 film for general applications</td>
<td></td>
</tr>
</tbody>
</table>

Streamlined management of order, manufacturing, testing, storage, and delivery

1. Feasibility assessment
2. Quotation provided
3. Order acknowledgement
4. Manufacturing
5. QC testing
6. COA and shipping

Learn more at [thermofisher.com/bioprocessliquids](http://thermofisher.com/bioprocessliquids)
Results matter.

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