



**ThermoFisher**  
SCIENTIFIC

## Gibco Bulk Process Liquid and Buffer Capabilities

# The World Leader in Serving Science

- \$17 billion in revenues
- \$700 million spent on R&D
- 50,000 employees
- 50 countries
- 5 premier brands

**ThermoFisher**  
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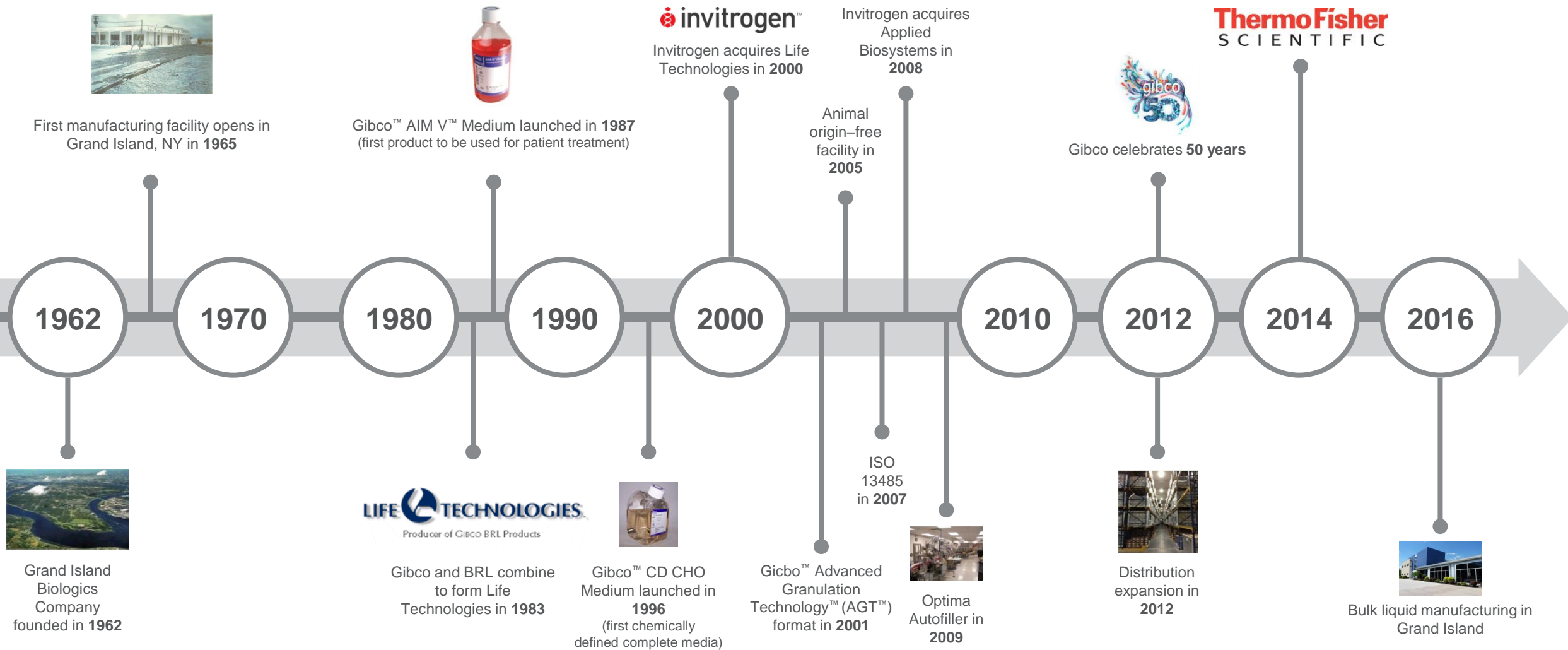
applied  
biosystems

invitrogen

 **Fisher  
Scientific**

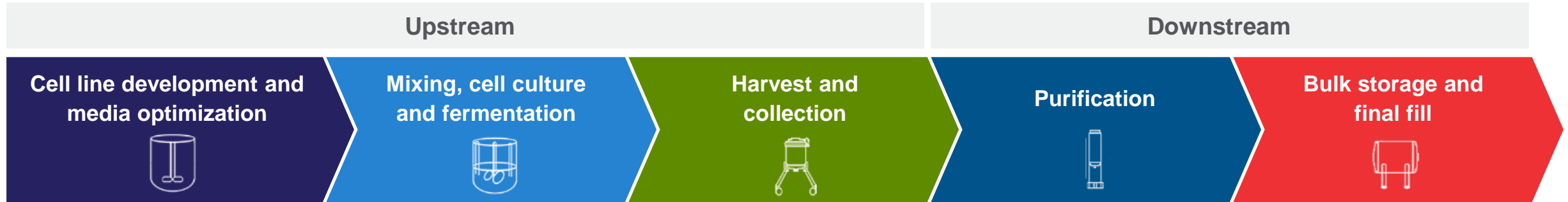
Unity Lab Services

# Cell Culture and Cell Therapy History



Growing with you at every stage **for over 50 years**

# Leading Capabilities for Every Step of the Bioprocess Workflow



- |                                                                                                                                                |                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li> CHO cell lines</li> <li> Process development services</li> <li> Media optimization services</li> </ul> | <ul style="list-style-type: none"> <li> Cell culture media, feeds and enhancers</li> <li> Single-use fermentors, bioreactors and mixers</li> <li> BioProcess Containers (BPCs)</li> <li> Integrity testing solutions</li> <li> Single-use heat exchanger</li> <li> Large-volume liquids</li> </ul> | <ul style="list-style-type: none"> <li> Harvest and separation products</li> <li> Storage and transport</li> <li> Single-use frozen handling system</li> <li> Single-use sampling system</li> </ul> | <ul style="list-style-type: none"> <li> Chromatography resins</li> <li> Affinity ligands and resins</li> <li> Transfer assemblies</li> <li> Host cell DNA, host cell protein and protein A quantitation</li> <li> Large-volume liquids</li> <li> Single-use mixers</li> </ul> | <ul style="list-style-type: none"> <li> Storage and transport</li> <li> Single-use fermentors, bioreactors and mixers</li> <li> Single-use BPCs, manifolds and containers</li> <li> Single-use filling system</li> <li> Single-use frozen handling system</li> </ul> |
|------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## 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



## 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



## 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



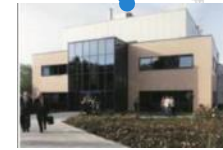
## Cramlington, UK

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



## Warrington, UK

- Analytics kits



## Naarden, the Netherlands

- Affinity ligands
- ISO 9001–certified



**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

## 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



BPC film



Chamber inspection



ASI film (Millersburg, PA)



Final assembly

# 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



Buffers and Process Liquids Stability Data												
Product Description (Concentration)	Storage Conditions	Duration	Stability Testing									
			CX5-14 BioProcess Containers Additional data points to include 18, 24, 36 and 48 months									
			Appearance	Conductivity	Endotoxin	Normality	Osmolality	pH	Sterility	Glucose	Glycine	Nitrate
Sodium Hydroxide (3M)	15-30°C	0 mo	✓	✓	✓	✓	✓	✓	✓			
		3 mo	✓	✓	✓	✓	✓	✓	✓			
		6 mo	✓	✓	✓	✓	✓	✓	✓			
		12 mo	✓	✓	✓	✓	✓	✓	✓			
EDTA (0.5M)	15-30°C	0 mo	✓		✓			✓	✓			
		3 mo	✓		✓			✓	✓			
		6 mo	✓		✓			✓	✓			
		12 mo	✓		✓			✓	✓			
Glucose (50%)	15-30°C	0 mo	✓				✓	✓	✓			
		3 mo	✓				✓	✓	✓			
		6 mo	✓				✓	✓	✓			
		12 mo	✓		✓		✓	✓	✓			
PBS (10X)	15-30°C	0 mo	✓				✓	✓	✓			
		3 mo	✓				✓	✓	✓			
		6 mo	✓				✓	✓	✓			
		12 mo	✓				✓	✓	✓			
Tris (20mM) NaCl (1.5M)	15-30°C	0 mo	✓	✓	✓		✓	✓	✓			
		3 mo	✓	✓			✓	✓	✓			
		6 mo	✓	✓			✓	✓	✓			
		12 mo	✓	✓			✓	✓	✓			
Glycine (100mM)	15-30°C	0 mo	✓	✓	✓		✓	✓	✓		✓	
		3 mo	✓	✓	✓		✓	✓	✓		✓	
		6 mo	✓	✓	✓		✓	✓	✓		✓	
		12 mo	✓	✓	✓		✓	✓	✓		✓	
WFI Quality Water	15-30°C	0 mo	✓	✓	✓		✓	✓	✓		✓	✓
		3 mo	✓	✓			✓	✓	✓		✓	✓
		6 mo	✓	✓			✓	✓	✓		✓	✓
		12 mo	✓	✓			✓	✓	✓		✓	✓
MES (50mM) NaCl (200mM)	2-8°C	0 mo	✓	✓	✓		✓	✓	✓			
		3 mo	✓	✓	✓		✓	✓	✓			
		6 mo	✓	✓	✓		✓	✓	✓			
		12 mo	✓	✓	✓		✓	✓	✓			

# 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**



## Why?

- Outsource partnership/manufacturing extension
- Pronounced synergies with vertical integration
- Existing liquid and single-use technologies expertise
- Enables cost reduction for customers

## What?

- Manufacturing capacity
- Cold warehouse space and distribution
- Support resources
- Process optimization

2014

- Launch integrated custom large-volume liquid (LVL) portfolio
- Grand Island expansion project scope

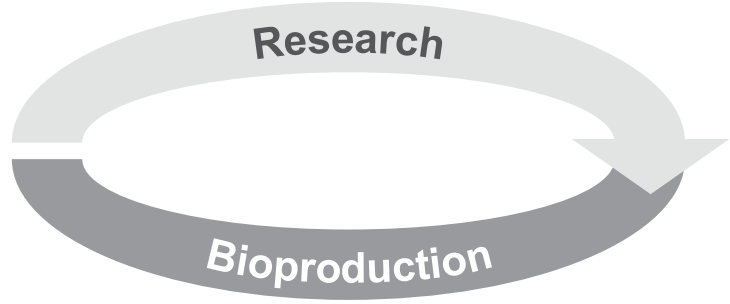
2015

- Liquid facility investments (US & EU)
- Water for injection (WFI) launch (20 & 200 L)

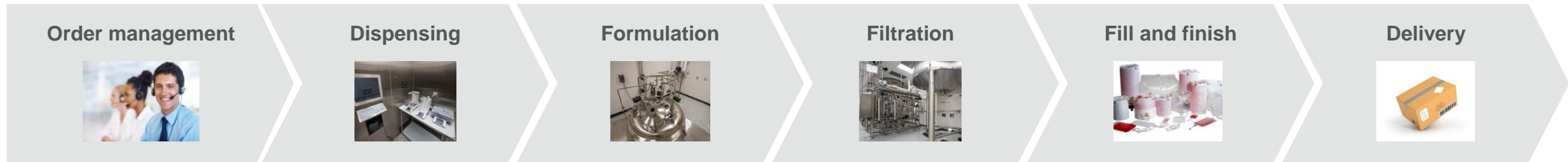
2016

- Facility / equipment implementation
- Validation

# Liquid Production Network



		Grand Island, USA	Paisley, Scotland
Bottled liquids	(10 mL–1 L)	✓	✓
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)	✓	



# Grand Island Liquid Facility Investments

## Facility footprint

- 15,000 ft<sup>2</sup> manufacturing over two floors
- 12,400 ft<sup>2</sup> 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**

# Design Criteria and Quality Standards

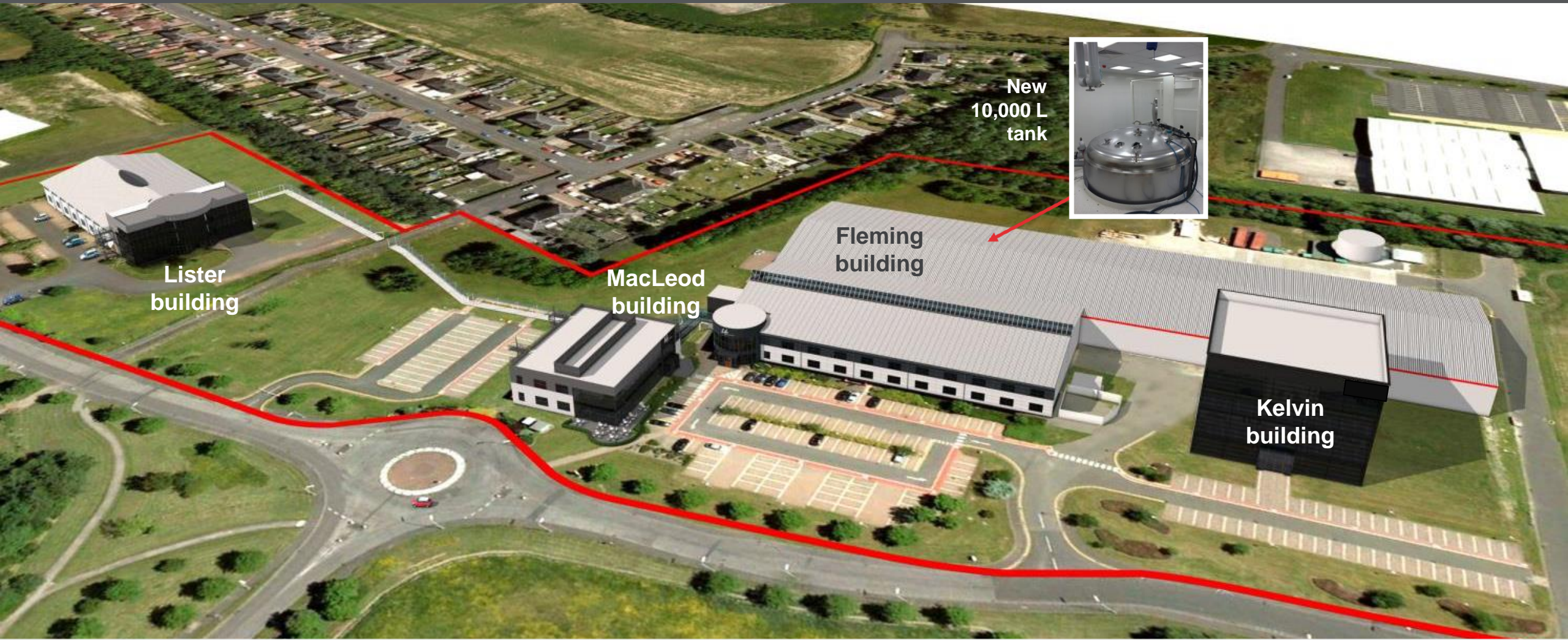


To meet current and future customer requirements for insourcing bulk liquids, **our Grand Island manufacturing facility is built to and compliant with the following standards:**

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



# Incremental Investments to Improve Liquid Capacity in Europe



New  
10,000 L  
tank



Lister  
building

MacLeod  
building

Fleming  
building

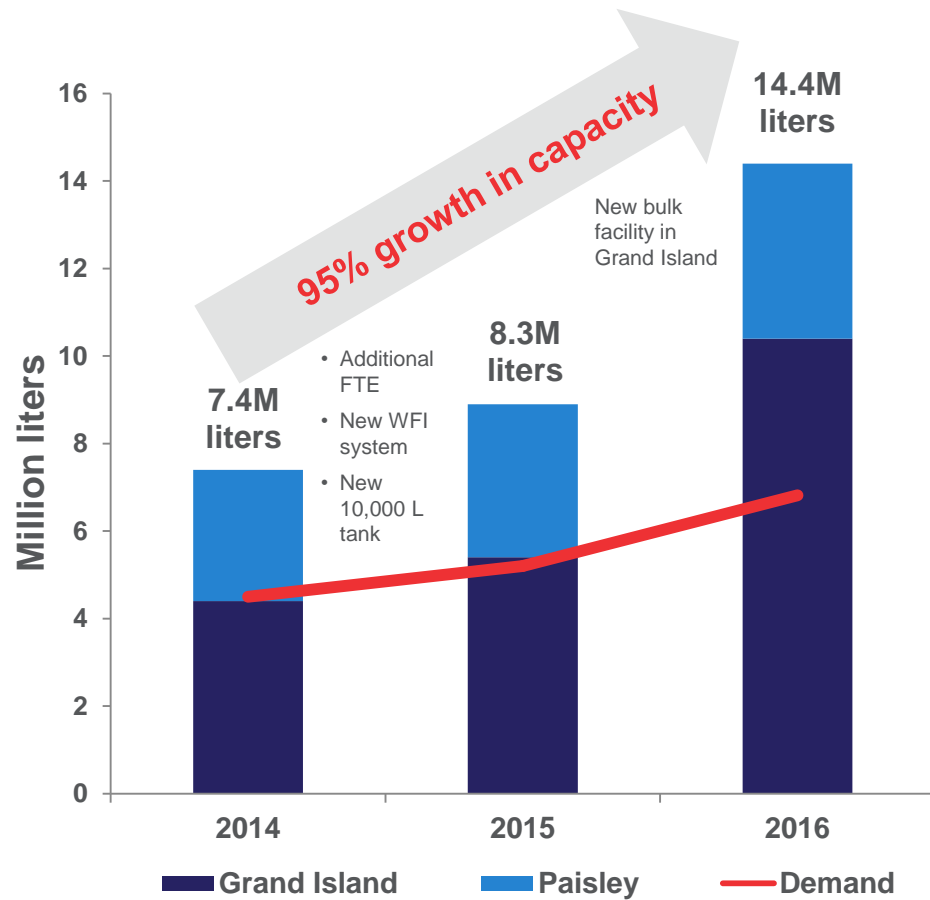
Kelvin  
building

**LSG EMEA headquarters**

**600 employees**

**In Scotland since 1970**

# Liquid Capacity Exceeds Demand



Ways to increase capacity	Capacity assumptions	Capacity variables
<ul style="list-style-type: none"> <li>• 24x7</li> <li>• Additional headcount</li> <li>• Bolt-on tankage</li> <li>• Use disposables</li> </ul>	<ul style="list-style-type: none"> <li>• 5x3 shift operation</li> <li>• Existing people</li> <li>• Tank utilization &lt;75%</li> </ul>	<ul style="list-style-type: none"> <li>• Tanks</li> <li>• Workflow (24x6, 24x7)</li> <li>• Number of people</li> </ul>

Number of tanks	400–1,000 L	1,500–2,500 L	3,000–10,000 L
Grand Island	2	5	6
Paisley	3	2	4

**Robust systems** to accommodate increased demand

# 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

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

# Outsourced Buffers Provide Cost and Time Savings

## 0.1 M NaOH buffer cost analysis

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



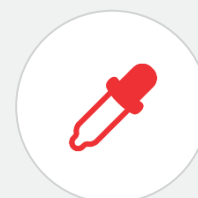
**\$90,000**

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

### Liquid format

- Process liquids for upstream and downstream applications
- Gibco media and feeds for cell culture processes
- 1X and concentrates

### Container type

- Bottles from 10 mL–1 L
- Flexible bioprocess containers from 1–1,000 L
- Custom designs and sizing available

### Film choice

- Industry-standard CX5-14 film for general applications
- Aegis5-14 film for critical applications
- Industry-standard ASI 26/77 film for general applications

### Manufacturing speed

- Non-GMP Gibco™ Media Express™ (GME) services
- Full GMP for scale-up

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

Feasibility  
assessment

Quotation  
provided

Order  
acknowledgement

Manufacturing

QC testing

COA and  
shipping

Learn more at [thermofisher.com/bioprocessliquids](https://thermofisher.com/bioprocessliquids)



**Results matter.**

**ThermoFisher**  
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