Therapeutic Manufacturing

GMP Cytokines & Growth Factors

bio-techne®

GMP PROTEINS FOR THERAPEUTIC MANUFACTURING

Immune cell therapies, stem cell therapies, and regenerative medicine offer some of the most revolutionary and exciting new approaches for treating human diseases. Since these types of therapies utilize living cells or tissues as the therapeutic, high-quality media supplements such as growth factors and cytokines are necessary for ensuring safety, efficacy, and batch-to-batch consistency. To address this need, Bio-Techne offers R&D Systems™ GMP-grade recombinant proteins.

GMP-grade proteins are manufactured under guidelines that allow for their use as ancillary materials in cell therapy manufacturing processes. They undergo extensive quality control testing and come with comprehensive documentation and full transparency and traceability of source and manufacturing system. This allows cell therapy manufacturers to be confident that they are using a consistent, safe, and traceable supply of reagents.

REGULATORY CERTIFICATIONS, SUPPORT, AND SUPPLY CHAIN CONTINUITY PROCESSES FOLLOWED TO ENSURE CONSISTENCY:

- GMP products manufactured, tested, and released under an ISO 9001:2015 and ISO 13485:2016-certified quality management system
- A full quality assurance (QA) review of all batch and bottling records before any material is shipped
- Individual specification sheets with all testing results reviewed by both our Quality Control (QC) and QA departments
- Documented processes and QA control of documentation and process changes
- Documented personnel training program
- Raw material testing, tracing, and vendor qualification/monitoring
- Fully validated equipment, processes, and test methods
- Equipment calibration schedules using a computerized calibration program
- Facility maintenance and safety programs
- Stability testing programs

GUIDELINES AND QUALITY CONTROL MEASURES FOLLOWED TO ENSURE SAFETY AND EFFICACY:

- USP Chapter <1043>, Ancillary Materials for Cell, Gene, and Tissue-Engineered Products
- Ph. Eur. General Chapter 5.2.12 , Raw Materials of Biological Origin for the Production of Cell-based and Gene Therapy Medicinal Products
- Lot-specific Certificate of Analysis
- N-terminal sequencing for the first 10 amino acids
- Defined endotoxin and purity specifications
- Validated activity testing including testing against a master lot
- Sterility testing in accordance to <USP71> guidelines
- Host cell protein and DNA testing
- Mycoplasma testing
- Formal stability testing program

ANIMAL-FREE GMP AND ANIMAL-FREE PRE-CLINICAL PROTEINS AVAILABLE FROM BIO-TECHNE

R&D Systems has a strict definition of animal-free. Animal-free proteins are produced in dedicated, controlled-access, animal-free laboratories using equipment and media that are certified as animal-free so that at no point in the production process are these proteins exposed to potential contamination by animal components or byproducts. The catalog numbers for our Animal-Free GMP Proteins and Animal-Free Pre-Clinical Proteins are listed in the table below.

All proteins labeled as animal-free are made in an *E.coli* expression system, in a dedicated animal-free area, with no animal-containing manufacturing components.

Protein (Human)	Source	Catalog # Animal-Free GMP Protein	DMF Filed for GMP	Catalog # Animal-Free Pre-Clinical Protein
Betacellulin	*E.coli*	BT-BTC-GMP		BT-BTC-AFL
BMP-4	*E.coli*	314E-GMP		AFL314E
EGF	*E.coli*	236-GMP	Yes	
FGF basic (145 aa)	*E.coli*	3718-GMP		AFL3718
Flt-3 Ligand/ FLT3L	*E.coli*	308E-GMP	Yes	AFL308E
GM-CSF	*E.coli*	215-GMP		AFL215
IFN-γ	*E.coli*	285-GMP	Yes	AFL285
IGF-I	*E.coli*	291-GMP		AFL291
IL-1β	*E.coli*	201-GMP		AFL201
IL-2	*E.coli*	BT-002-GMP	Yes	BT-002-AFL
IL-3	*E.coli*	203-GMP		AFL203
IL-4	*E.coli*	204-GMP	Yes	AFL204
IL-6	*E.coli*	206-GMP		AFL206
IL-7	*E.coli*	BT-007-GMP	Yes	BT-007-AFL
IL-10	*E.coli*	1064-GMP		

Protein (Human)	Source	Catalog # Animal-Free GMP Protein	DMF Filed for GMP	Catalog # Animal-Free Pre-Clinical Protein
IL-15	*E.coli*	BT-015-GMP	Yes	BT-015-AFL
IL-21	*E.coli*	8879-GMP	Yes	AFL8879
LR3 IGF-I	*E.coli*	8335D-GMP		
M-CSF	*E.coli*	216-GMP		AFL216
PDGF-AA	*E.coli*	221-GMP		AFL221
PDGF-BB	*E.coli*	220-GMP		AFL220
SCF/c-kit Ligand	*E.coli*	255B-GMP	Yes	AFL255
Sonic Hedgehog (C24II) N-Terminus	*E.coli*	1845-GMP		AFL1845
Sonic Hedgehog N-Terminus	*E.coli*	1314-GMP		
Thrombopoietin	*E.coli*	288E-GMP		AFL288 Coming Soon
TNF-α	*E.coli*	210-GMP		AFL210
VEGF	*E.coli*	BT-VEGF-GMP		

GMP-grade IL-2, IL-7, and IL-15 are available through our joint venture partnership with ScaleReady.

Learn more | scaleready.com/gmp-il-2

ADDITIONAL GMP PROTEINS AVAILABLE FROM BIO-TECHNE

There are some instances when a protein requires production in a eukaryotic system to maintain activity. This may be due to protein folding or post-translational modifications that can only be accomplished by making the protein in a eukaryotic cell line. These GMP-grade proteins, which are not considered to be animal-free, are listed in the table below. Whenever a GMP-grade protein cannot be produced in an animal-free process, it is always clearly indicated on our website.

Protein (Human)	Source	Catalog #	DMF Filed for GMP
Activin A	CHO	338-GMP	Yes
BMP-2	CHO	355-GMP	
GDF-8/Myostatin	NS0	788-GMP	
GDNF	NS0	212-GMP	
HGF	NS0	294-GMP	

Protein (Human)	Source	Catalog #	DMF Filed for GMP
KGF/FGF-7	*E.coli*	251-GMP	
Noggin	NS0	6057-GMP	
Noggin Fc tag	NS0	3344-GMP	
TGF-β1	CHO	240-GMP	
Wnt-3a	CHO	5036-GMP	

R&D Systems GMP proteins are intended for use as ancillary materials in GMP manufacturing of investigational or marketed clinical products, such as cell therapy, gene therapy, tissue-engineered products, combination products, or other Advanced Therapy Medicinal Products. They are not therapeutic products or excipient and are not suitable for direct administration to humans.

Learn more | bio-techne.com/gmp-products/gmp-proteins

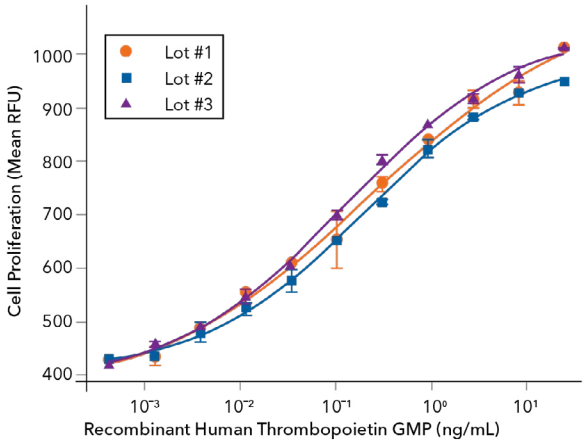
BIO-TECHNE PROVIDES AN UNPARALLELED COMBINATION OF PROTEIN AND REGULATORY EXPERIENCE

- R&D Systems, a Bio-Techne brand, has been developing and manufacturing proteins since 1985
- We have the capacity and the scientific expertise to support the large -scale production of GMP-grade proteins
- R&D Systems GMP-grade proteins are being used in numerous clinical trials
- We welcome client audits of our facilities
- If specific GMP-grade raw materials are not currently available, our custom team will work with you to develop the products that you need
- We assure your confidentiality
- We have more than 100 protein scientists dedicated to development and manufacturing
- We have more than 90 employees in quality and regulatory roles

R&D SYSTEMS GMP PROTEINS ARE RIGOROUSLY TESTED FOR PURITY, BIOACTIVITY, AND LOT-TO-LOT CONSISTENCY

Over decades of experience, R&D Systems has developed a mature quality management system and detailed protocols that allow for the manufacture of recombinant proteins with industry-leading bioactivity, purity, and consistency. Each new lot must pass stringent quality control specifications for activity in a well-defined bioassay and is tested against a master lot to control for assay variability. Lot-specific activity information can be found on each product certificate of analysis (C of A) and lot-to-lot sample data is available upon request.

A.



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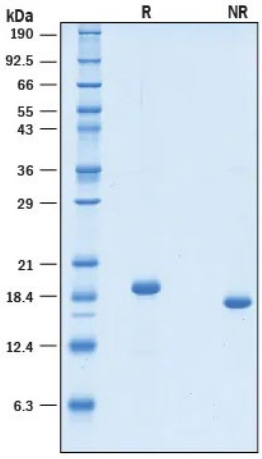
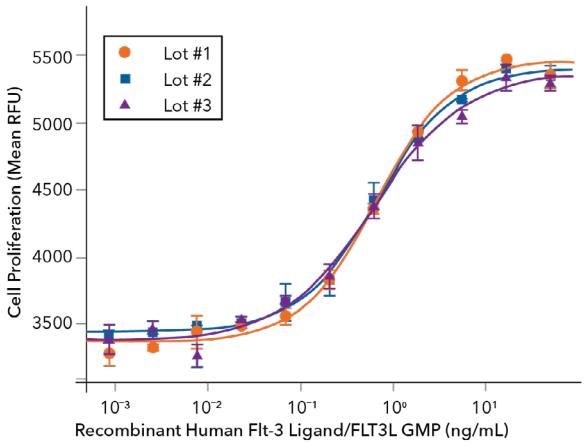


Analysis of the Activity, Purity, and Lot-to-Lot Consistency of GMP-grade Recombinant Human Thrombopoietin. (A) Three independent lots of GMP-grade Recombinant Human Thrombopoietin (R&D Systems, Catalog # 288E-GMP) were tested for their ability to stimulate proliferation of the MO7e human megakaryocytic leukemic cell line. The ED_{50} for this effect is 0.05-0.5 ng/mL. Each trace on the graph represents data obtained from GMP-grade Recombinant Human Thrombopoietin from a different manufacturing run, demonstrating the lot-to-lot consistency of the protein. **(B)** SDS-PAGE analysis of GMP-grade Recombinant Human Thrombopoietin (R&D Systems, Catalog # 288E-GMP) under reducing (R) and non-reducing (NR) conditions and visualization by Coomassie® Blue staining shows single bands at 19 kDa and 18 kDa, respectively.

A.



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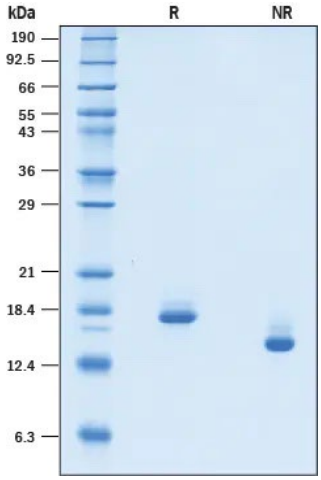


Analysis of the Activity, Purity, and Lot-to-Lot Consistency of GMP-grade Recombinant Human Flt-3 Ligand. (A) Three independent lots of GMP-grade Recombinant Human Flt-3 Ligand/FLT3L (R&D Systems, Catalog # 308E-GMP) were tested for their ability to stimulate proliferation in the BaF3 mouse pro-B cell line transfected with mouse Flt-3. The ED_{50} for this effect is 0.2-1 ng/mL. Each trace on the graph represents data obtained from GMP-grade Recombinant Human Flt-3 Ligand from a different manufacturing run, demonstrating the lot-to-lot consistency of the protein. **(B)** SDS-PAGE analysis of GMP-grade Recombinant Human Flt-3 Ligand (R&D Systems, Catalog # 308E-GMP) under reducing (R) and non-reducing (NR) conditions and visualization by Coomassie® Blue staining shows single bands at 15-17 kDa and 12-14 kDa, respectively.

CUSTOM MANUFACTURING

At times, raw materials needed for therapeutic manufacturing are only available for research use. In addition, pack sizes that would ease your manufacturing burden might not be available. We can help you navigate these hurdles by custom manufacturing proteins using GMP guidelines. Our custom development teams include dedicated project managers, regulatory experts, and world class proteins scientists to ensure the materials meet your specifications and facilitate the transition from pre-clinical to clinical applications.

PARTNERING WITH YOU TO MEET YOUR REGULATORY REQUIREMENTS

As the demand for biopharmaceuticals and the promise of cellular therapies grow, so does the need for high-quality growth factors and cytokines used for cell culture. Our experienced Quality and Manufacturing teams will partner with you to ensure we meet all of the requirements necessary to instill confidence as your reagent supplier.

ANNOUNCING THE COMMERCIAL AVAILABILITY OF GMP-GRADE PROTEINS FROM BIO-TECHNE'S NEW STATE-OF-THE-ART GMP FACILITY

CHOOSE A PARTNER THAT CAN GROW WITH YOU ON YOUR PATH TO CELL THERAPY MANUFACTURING SUCCESS

The rapidly growing number of cell therapy clinical trials worldwide and the ultimate push toward commercialization has resulted in an increased demand for larger quantities of GMP-grade animal-free proteins for clinical manufacturing. Our new 61,000 square foot animal-free GMP manufacturing facility was built to allow Bio-Techne to address this need. This facility is equipped with state-of-the-art manufacturing and quality control technologies and is backed by R&D Systems experienced manufacturing, quality, and regulatory teams. With the completion of this new facility, we now have the ability to produce larger quantities of GMP-grade proteins with lot-to-lot consistency, GMP process capabilities for patient safety, and the scalability necessary to support large clinical trials and future successful therapeutics.

"Our new facility gives us the scalability and the capacity to bring our GMP-grade protein business to the next level, providing a reliable source of the highest quality proteins to support the rapidly growing cell and gene therapy market."

– Chuck Kummeth | Bio-Techne's President and Chief Executive Officer

KEY FEATURES OF OUR NEW FACILITY

- Our new facility is completely animal-free and is dedicated solely to manufacturing GMP proteins
- Ensure supply chain through commercial phases
- No need to spend time/money requalifying lots, we can reserve an entire lot for your workflow
- Seamless transition from RUO to GMP
- Facility is optimized for scale to meet growing demand
- ISO 5/7/8 cleanrooms for the entire production process

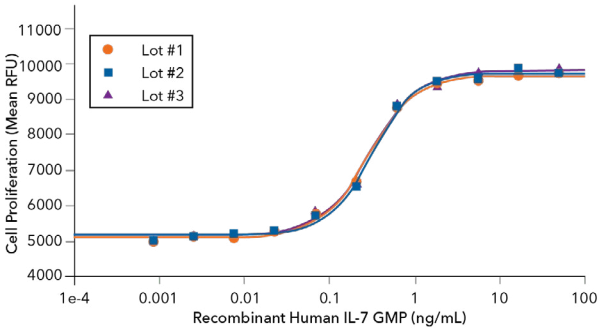
CERTIFICATIONS AND REGULATORY GUIDELINES FOLLOWED IN THE GMP MANUFACTURING FACILITY

- USP Chapter <1043>, Ancillary Materials for Cell, Gene, and Tissue-Engineered Products
- USP Chapter <92>, Growth Factors and Cytokines Used in Cell Therapy Manufacturing
- Ph. Eur. General Chapter 5.2.12 , Raw Materials of Biological Origin for the Production of Cell-based and Gene Therapy Medicinal Products

GMP-GRADE PROTEINS CURRENTLY BEING MANUFACTURED IN OUR NEW FACILITY

GMP-grade Recombinant Human IL-7 (Catalog # BT-007-GMP), GMP-grade Recombinant Human IL-10 (Catalog # 1064-GMP), and GMP-grade Recombinant Human IL-15 (Catalog # BT-015-GMP) are the first proteins that are being produced out of our new GMP facility.

A.



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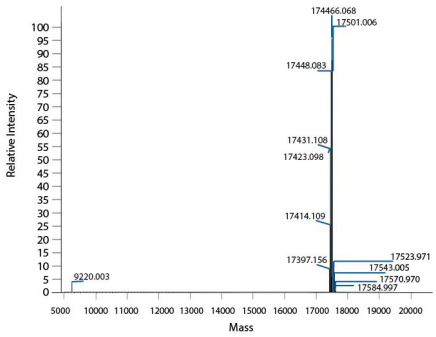

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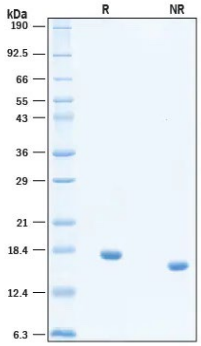
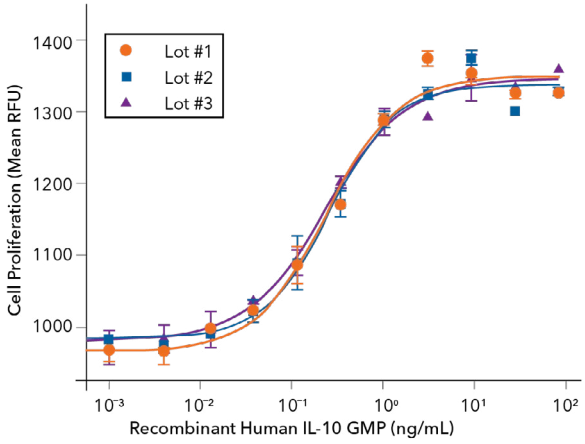


Analysis of the Activity, Purity, and Lot-to-Lot Consistency of GMP-grade Recombinant Human IL-7. (A) Three independent lots of GMP-grade Recombinant Human IL-7 (R&D Systems, Catalog # BT-007-GMP) were tested for their ability to stimulate proliferation of PHA-activated human peripheral blood lymphocytes. The ED_{50} for this effect is 0.100-0.500 ng/mL. Each trace on the graph represents data obtained from GMP-grade Recombinant Human IL-7 from a different manufacturing run, demonstrating the lot-to-lot consistency of the protein. **(B)** MALDI-TOF analysis of GMP-grade Recombinant Human IL-7 (R&D Systems, Catalog # BT-007-GMP) shows a major peak at 17501 Da. **(C)** SDS-PAGE analysis of GMP-grade Recombinant Human IL-7 (R&D Systems, Catalog # BT-007-GMP) under reducing (R) and non-reducing (NR) conditions and visualization by Coomassie® Blue staining shows a single band at 17 kDa.

A.



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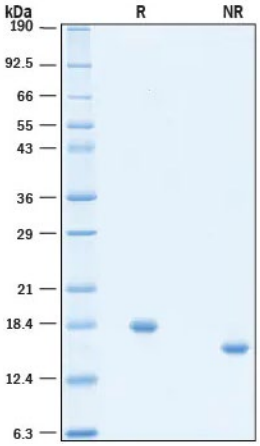
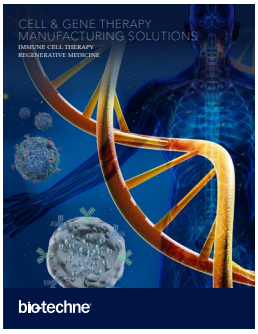
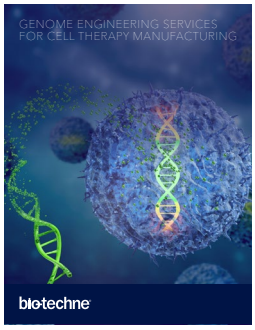


Analysis of the Activity, Purity, and Lot-to-Lot Consistency of GMP-grade Recombinant Human IL-10. (A) Three independent lots of GMP-grade Recombinant Human IL-10 (R&D Systems, Catalog # 1064-GMP) were tested for their ability to stimulate proliferation of MC/9-2 mouse mast cells. The ED_{50} for this effect is 0.0750-0.750 ng/mL. Each trace on the graph represents data obtained from GMP-grade Recombinant Human IL-10 from a different manufacturing run, demonstrating the lot-to-lot consistency of the protein. **(B)** SDS-PAGE analysis of GMP-grade Recombinant Human IL-10 (R&D Systems, Catalog # 1064-GMP) under reducing (R) and non-reducing (NR) conditions and visualization by Coomassie® Blue staining shows a single band at 18 kDa and 16 kDa, respectively.

ADDITIONAL RESOURCES FOR CELL & GENE THERAPY RESEARCHERS





Learn more | bio-techne.com/gmp-manufacturing-facility

Where Science Intersects Innovation™

Bio-Techne® | R&D Systems™ Novus Biologicals™ Tocris Bioscience™ ProteinSimple™ ACD™ ExosomeDx™ Asuragen®

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