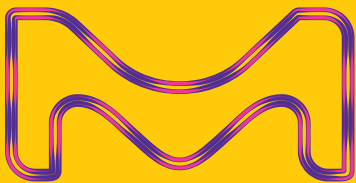


Raw Materials for Biopharmaceutical Manufacturing



The life science business
of Merck KGaA, Darmstadt,
Germany operates as
MilliporeSigma in the U.S.
and Canada.

SAFC®

Pharma & Biopharma Raw
Material Solutions

Introduction

The development of pharma and biopharma products requires materials as well as the expertise on how to use them. The SAFC portfolio of ready-to-use and customized material solutions were developed to meet the specific needs of pharma and biopharma production and backed by deep regulatory expertise.

We go beyond just the raw materials as we understand your need for safety, security and scalability to get health solutions to patients faster.

Contents

Regulatory Support

The Bioprocess	4
Regulatory Trends Related to Pharmaceutical Excipients and Process Raw Materials	5
Emprove® Program	7

Upstream Application

BioPharm Raw Materials for Upstream and Cell Culture	8
Poloxamer 188 Emprove® Expert Cell Culture Optimized	11
Benzonase® endonuclease	13

Downstream and Formulation Application

BioPharm Raw Materials for Downstream and Purification	14
BioContinuum™ Buffer Delivery Platform	17
Cleaning-in-Place	19
Hybrid Processes and CIP	20
Custom Product Offering	22
Process Raw Materials for Treatment of Process Intermediates	24

Products for Purification Processes

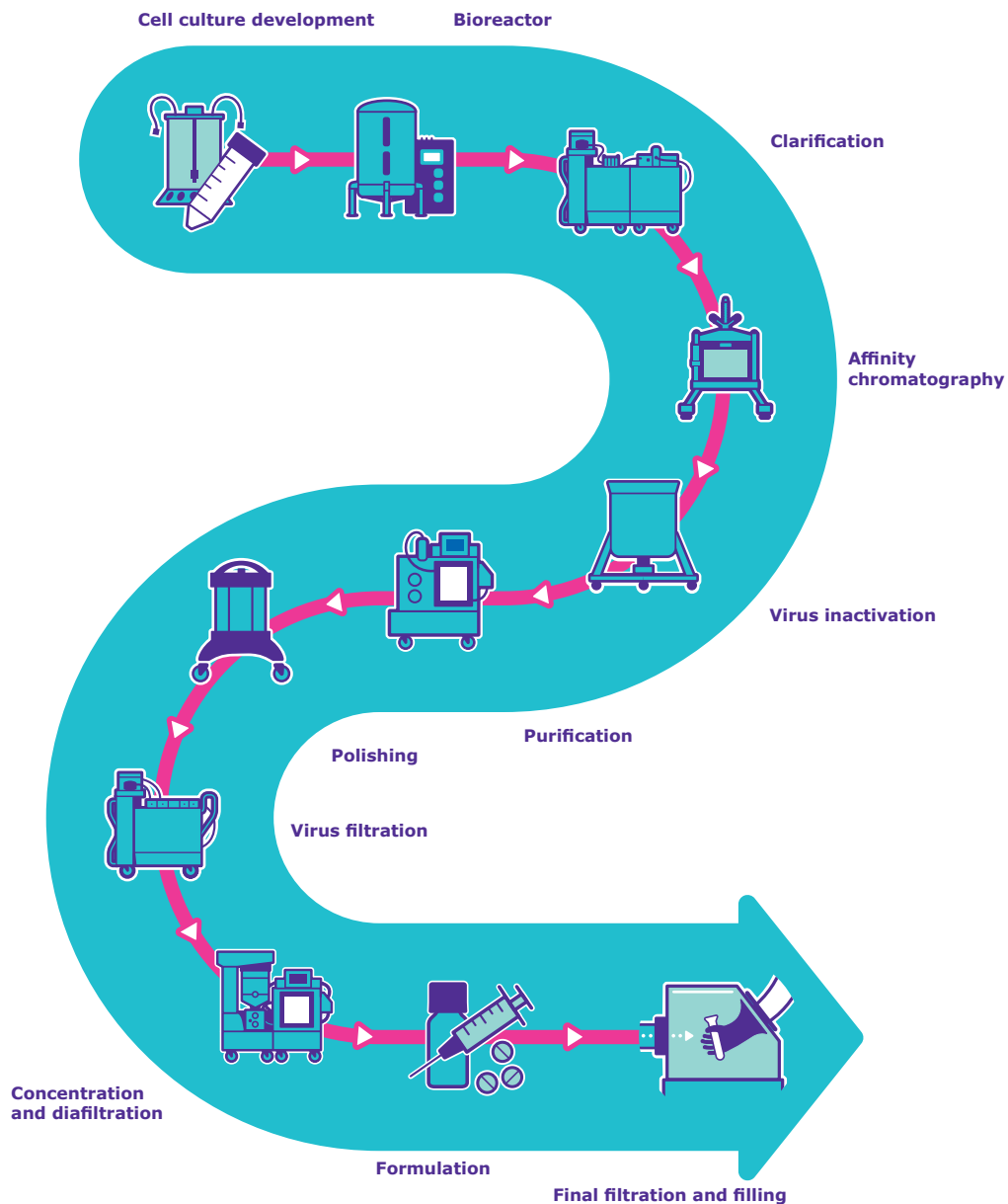
Protein A	28
Cation Exchange/Anion Exchange	29
Viral Clearance - TFF Concentration/Diafiltration	30

Regulatory Support

The Bioprocess: Our Raw Material Offering for Biopharmaceutical Production

Products that meet the highest quality and purity standards with extensive documentation and services to help speed up internal qualification procedures and accelerate your preparation of the drug approval process.

Solutions spanning every step of the process from cell culture to final formulation and everything in between.



Regulatory Trends Related to Pharmaceutical Excipients and Process Raw Materials

Risk Assessment and ICH Q3D Guideline for Elemental Impurities

The pharmaceutical industry is faced with evolving guidelines that impact the control of elemental impurities - primarily metals - for final drug products and ingredients such as active pharmaceutical ingredients (APIs) and excipients. We understand the importance of being compliant with existing and upcoming regulations.

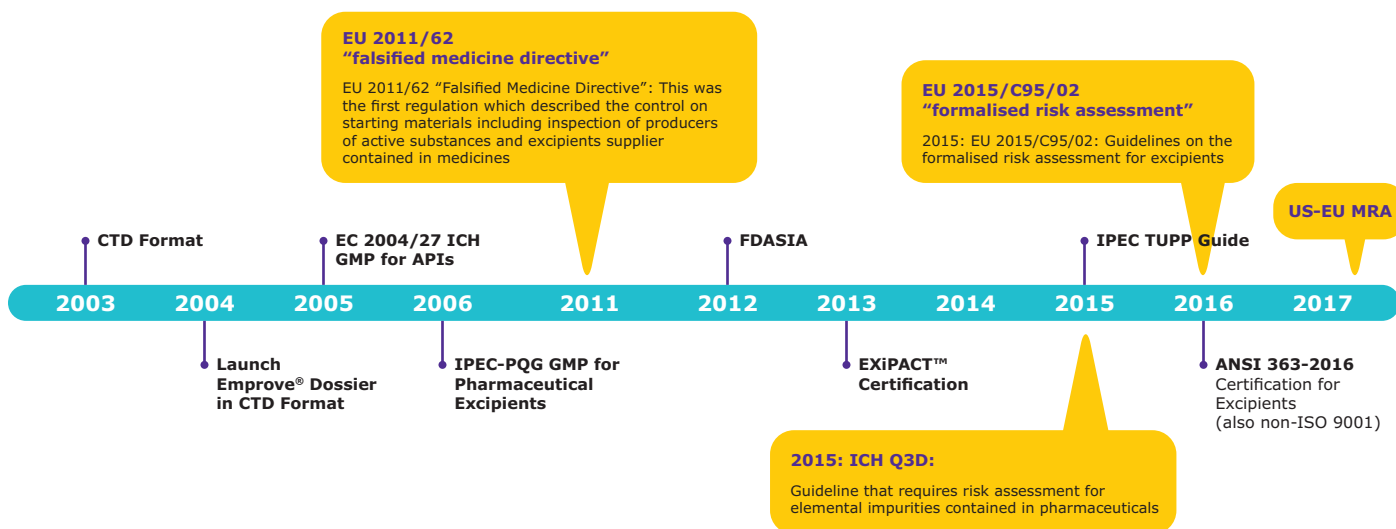
The ICH Q3D Guideline for Elemental Impurities is designed to provide a global policy for limiting elemental impurities qualitatively and quantitatively in final drug products. Proper control of elemental impurities of the ingredients plays a vital role in assessing the contamination risk in the final drug product.

Therefore, it is necessary to conduct a risk assessment for elemental impurities according to ICH Q3D Guideline for Elemental Impurities in the application for approval of new formulations. This ICH Q3D Guideline also requires risk assessment for the existing formulations.

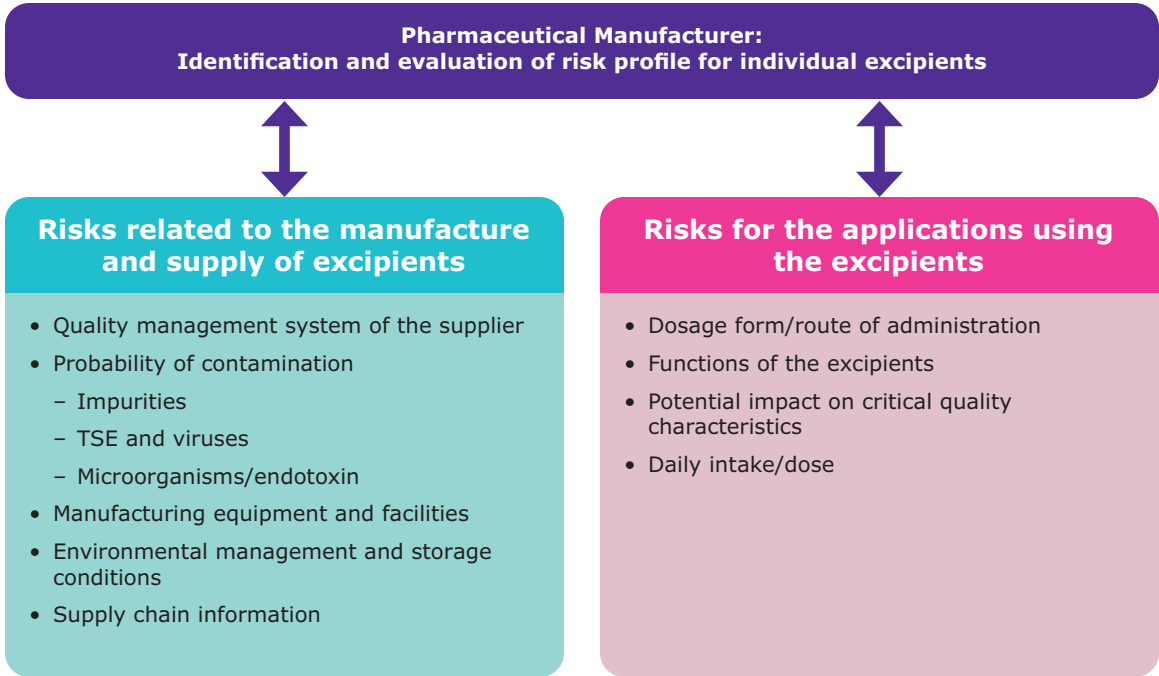
How can we help?

We have compiled supportive information in a step-by-step process for our Emprove® Chemicals to facilitate risk assessment of potential elemental impurities.

History of Regulatory Trends: Pharmaceutical Excipients and Process Raw Materials



Following 2015/C95/02, the manufacturing authorization holder is required to ensure that the excipients used in their process are suitable for use in medicinal products. The effect of these on the quality and safety of the drug must be evaluated by formalized risk assessments. In addition, excipients must be selected from appropriate suppliers who are able to meet these requirements and assessments should be performed to address the evaluated risks.



Raw materials used in downstream processing of biotechnological APIs as well as buffers in the final bulk are generally considered as “higher risk” as they may be found in or are part of the final formulation of the biopharmaceutical product. A raw material/excipient should be selected and used according to the assessed level of risk for the particular application.

Excipients/Raw Materials Used in the Manufacturing Process and Final Formulation of a Biopharmaceutical Product

Risk assessment should include the following considerations:



Regulatory Support

Emprove® Program - Regulatory Support for Bioprocessing Raw Materials

Each product portfolio is supported with Emprove® Dossiers that provide comprehensive, up-to-date documentation to help you navigate regulatory challenges, manage risks, and improve your manufacturing processes.

Emprove® Chemicals Portfolio: Raw and Starting Materials

Our Emprove® Chemicals portfolio contains over 400 pharmaceutical raw materials supported with comprehensive, up-to-date documentation to help you navigate regulatory challenges, manage risks, and improve your manufacturing processes. To address different levels of risk, and to simplify and streamline the selection process, the Emprove® Chemicals portfolio is divided into four categories:

- Emprove® Evolve
- Emprove® Essential
- Emprove® Expert
- Emprove® API



Emprove® Evolve

For early stages of biopharmaceutical manufacturing

Fills the gap between lab-grade and GMP compliant raw and starting materials. This product line provides detailed and transparent supply chain information and documentation to support risk assessments for critical raw materials used in manufacturing processes. These materials are for further manufacturing or research and development use only – not for direct use in humans or animals.

Emprove® Essential

Moderate Risk Applications

Designed for moderate risk applications, Emprove® Essential products offer compliance to IPEC-PQG GMP Guide and/or EXCiPACT™ Certification Standard, supply chain transparency and regulatory support designed to assist drug manufacturers' formalized risk assessments. They are produced according to controlled manufacturing processes. Critical parameters such as elemental impurities and residual solvents are characterized by using validated analytical techniques.

Emprove® Expert

High Risk Applications

Addresses higher risk applications where the lowest microbiological and endotoxin levels are of utmost importance. Along with the risk management features of Emprove® Essential, the Emprove® Expert line goes even further: The GMP (IPEC-PQG and/or EXCiPACT™) manufacturing processes are designed to yield products with specified low microbiological and endotoxin levels, thus supporting the overall risk mitigation strategy.

Emprove® API

Support Final Drug Product Compliance with International Standards

Manufactured in Europe, meeting the quality and regulatory requirements of active pharmaceutical ingredients, according to ICH Q7 GMP. In order to support final drug product compliance with international standards, our Regulatory Management team offers dedicated support with access to extensive documentation including DMFs, CEP and ASMF.

Emprove® Chemical Dossiers

Our Emprove® Chemicals portfolio is supported by Emprove® Dossiers. This comprehensive documentation facilitates your qualification, risk assessment and process optimization efforts.

	Material Qualification	Quality Management	Operational Excellence	DMF, ASMF, CEP
Emprove® Evolve	•	•	•	
Emprove® Essential	•	•	•	
Emprove® Expert	•	•	•	
Emprove® API				•

Upstream Application

BioPharm Raw Materials Upstream and Cell Culture

Raw materials and chemical components suitable for cell culture media formulations and upstream applications used in biopharmaceutical production.

Amino Acids

Product	Catalogue No.	Product Name	CAS No.	Pack Size
Glycine	G5417	Glycine	56-40-6	1 kg, 10 kg, 25 kg
GlycylGlycine	G0674	GlycylGlycine	556-50-3	100 gm
L-Alanine	101700	L-Alanine, Emprove® Expert, Ph Eur, JP, USP	56-41-7	1 kg, 10 kg
L-Arginine	A4474	L-Arginine	74-79-3	1 kg, 10 kg, 25 kg
L-Arginine Monohydrochloride	A4599	L-Arginine Monohydrochloride	1119-34-2	1 kg, 10 kg, 25 kg
L-Asparagine Monohydrate	101565	L-Asparagine Monohydrate, Emprove® Expert, Ph Eur	5794-13-8	1 kg, 5 kg, 10 kg
L-Asparagine Monohydrate	RES10070-A7	L-Asparagine Monohydrate, meets FCC	5794-13-8	1 kg, 10 kg
L-Aspartic Acid	100129	L-Aspartic Acid, Emprove® Essential, Ph Eur, BP, USP	56-84-8	1 kg, 25 kg
L-Cysteine	C5360	L-Cysteine	52-90-4	1 kg, 10 kg, 25 kg
L-Cysteine Hydrochloride Monohydrate	102735	L-Cysteine Hydrochloride Monohydrate, Emprove® Essential, Ph Eur, USP	7048-04-6	1 kg, 10 kg, 25 kg
L-Cysteine-S-sulfate sodium salt sesquihydrate	137116	L-Cysteine-S-sulfate sodium salt sesquihydrate, Emprove® Expert	150465-29-5	100 gm
L-Cystine	RES1520C-A7	L-Cystine	56-89-3	1 kg, 10 kg, 25 kg
L-Cystine Dihydrochloride	RES1513C-A7	L-Cystine Dihydrochloride, Non-Animal Derived	30925-07-6	10 kg
L-Glutamic Acid	101791	L-Glutamic Acid, Emprove® Expert, Ph Eur, JP	56-86-0	1 kg
L-Glutamic Acid Sodium Salt	RES5063G-A7	L-Glutamic Acid Sodium Salt, low endotoxin	6106-04-3	1 kg, 10 kg, 25 kg
L-Glutamine	100286	L-Glutamine, Emprove® Essential, DAB, USP	56-85-9	1 kg, 10 kg
L-Glutamine	G5792	L-Glutamine	56-85-9	1 kg, 10 kg, 25 kg
L-Histidine	H3911	L-Histidine	71-00-1	1 kg, 10 kg, 25 kg
L-Histidine Monohydrochloride Monohydrate	H4036	L-Histidine Monohydrochloride Monohydrate	5934-29-2	1 kg, 10 kg, 25 kg
L-Isoleucine	105357	L-Isoleucine, Emprove® Essential, Ph Eur, USP	73-32-5	1 kg, 10 kg
L-Isoleucine	I5281	L-Isoleucine	73-32-5	1 kg, 10 kg, 25 kg
L-Leucine	105020	L-Leucine, Emprove® Expert, Ph Eur, USP	61-90-5	1 kg, 10 kg
L-Lysine Monohydrochloride	105701	L-Lysine Monohydrochloride, Emprove® Essential, Ph Eur, BP, USP	657-27-2	1 kg, 5 kg, 25 kg
L-Methionine	M8439	L-Methionine	63-68-3	1 kg, 10 kg, 25 kg
L-Phenylalanine	107267	L-Phenylalanine, Emprove® Expert, Ph Eur, USP	63-91-2	1 kg, 10 kg
L-Proline	107430	L-Proline, Emprove® Expert, Ph Eur, USP	147-85-3	1 kg, 10 kg
L-Proline	P8865	L-Proline	147-85-3	1 kg, 10 kg, 25 kg
L-Threonine	T4071	L-Threonine	72-19-5	1 kg, 10 kg, 25 kg

Amino Acids

Product	Catalogue No.	Product Name	CAS No.	Pack Size
L-Tryptophan	108396	L-Tryptophan, Emprove® Expert, Ph Eur, BP, USP	73-22-3	1 kg
L-Tyrosine	108378	L-Tyrosine, Emprove® Expert, Ph Eur, JP, USP	60-18-4	1 kg, 10 kg
L-Tyrosine	T4321	L-Tyrosine	60-18-4	1 kg, 10 kg, 25 kg
L-Tyrosine Disodium Dihydrate	RES3156T-A7	L-Tyrosine Disodium Salt Dihydrate	122666-87-9	1 kg, 10 kg
L-Valine	V4638	L-Valine	72-18-4	1 kg, 10 kg, 25 kg
Phospho-L-Tyrosine Disodium Salt	137119	Phospho-L-Tyrosine Disodium Salt, Emprove® Expert	1610350-91-8	1 kg, 10 kg

Carbohydrates

Product	Catalogue No.	Product Name	CAS No.	Pack Size
D-(+)-Glucose	137048	D-(+)-Glucose anhydrous Emprove® Expert Ph Eur, BP, USP, ACS	50-99-7	1 kg, 3 kg, 5 kg, 12 kg, 25 kg, 50 kg
D(+)-Galactose	137129	D(+)-Galactose, Plant-Derived, Emprove® Expert, Ph Eur, NF	59-23-4	1 kg, 10 kg, 25 kg
N-Acetyl-D-Mannosamine	PHG0017	N-Acetyl-D-Mannosamine	7772-94-3	10 gm, 100 gm, 1 kg

Buffers

Product	Catalogue No.	Product Name	CAS No.	Pack Size
HEPES	110110	HEPES, Emprove® Expert	7365-45-9	250 gm, 1 kg, 25 kg
HEPES	PHG0001	HEPES	7365-45-9	5 kg, 10 kg, 25 kg, 50 kg
HEPES	RES6003H-B7	HEPES	7365-45-9	5 kg, 25 kg, 50 kg
HEPES Hemisodium	RES6008H-A7	HEPES Hemisodium Salt	103404-87-1	1 kg, 10 kg
HEPES Sodium	RES6007H-A7	HEPES Sodium Salt	75227-39-3	1 kg, 10 kg, 25 kg
Sodium Carbonate	137014	Sodium Carbonate Anhydrous, Emprove® Expert, Ph Eur, BP, JP, NF	497-19-8	1 kg, 5 kg, 12 kg, 25 kg
Sodium Hydrogen Carbonate	137013	Sodium Hydrogen Carbonate, Emprove® Expert, Ph Eur, BP, USP, JP	144-55-8	1 kg, 2.5 kg, 12 kg, 25 kg

Lipids

Product	Catalogue No.	Product Name	CAS No.	Pack Size
Cholesterol	C1231	Cholesterol, Plant-Derived (Synthechol®), USP/NF, Ph Eur	57-88-5	1 gm, 10 gm, 100 gm
Linoleic Acid	39269	Linoleic Acid	60-33-3	10 gm, 100 gm
Oleic Acid	91541	Oleic Acid	112-80-1	10 gm, 100 gm
Sodium Butyrate	ARK2161	Sodium Butyrate, USP/NF	156-54-7	250 gm, 1 kg, 10 kg, 30 kg
Sodium Cholate	S1702	Sodium Cholate Hydrate	206986-87-0	100 gm, 1 kg
Sodium Deoxycholate	S1827	Sodium Deoxycholate	302-95-4	100 gm, 1 kg, 10 kg
Sodium Pyruvate	105477	Sodium Pyruvate, Emprove® Essential	113-24-6	250 gm, 1 kg

Specialty Components

Product	Catalogue No.	Product Name	CAS No.	Pack Size
2-Mercaptoethanol	07604	2-Mercaptoethanol	60-24-2	100 mL
Biotin	RES1052B-A7	Biotin	58-85-5	1 gm, 10 gm, 25 gm
Cystamine Dihydrochloride	108318	Cystamine Dihydrochloride, Emprove® Essential	56-17-7	100 gm
Cysteamine Hydrochloride	53729	Cysteamine Hydrochloride	156-57-0	100 gm, 1 kg
Dextran Sulfate Sodium Salt	RES2029D-A7	Dextran Sulfate Sodium Salt	9011-18-1	10 gm, 100 gm, 1 kg
Ferric Ammonium Citrate	RES20400-A7	Ferric Ammonium Citrate	1185-57-5	1 kg, 5 kg
Ferric Citrate	RES4055F-A7	Ferric Citrate	2338-05-08	1 kg, 5 kg
Fumaric Acid	ARK2164	Fumaric Acid, USP/NF	110-17-8	1 kg, 15 kg
Hypoxanthine Sodium Salt	RES6104H-A7	Hypoxanthine Sodium Salt	45738-97-4	100 gm, 1 kg
L-Methionine Sulfoximine	104309	L-Methionine Sulfoximine, Emprove® Essential	15985-39-4	1 gm, 5 gm, 10 gm
Methotrexate	M7824	Methotrexate, Meets EP, USP	59-05-2	1 gm, 5 gm
Phenol Red	137038	Phenol Red, Emprove® Essential	143-74-8	5 gm, 100 gm
Poloxamer 188	137097	Poloxamer 188, Emprove® Expert, cell culture optimized	9003-11-6	1 kg, 10 kg, 25 kg
Spermine Tetrahydrochloride	52983	Spermine Tetrahydrochloride	306-67-2	25 gm, 100 gm
Taurine	T4571	Taurine	107-35-7	1 kg, 10 kg

Upstream Application

Poloxamer 188 Emprove® Expert Cell Culture Optimized

Predictable Protection and Performance

Poloxamer 188 is a surface-active nonionic polymer used in cell culture media as shear protectant. Recognized as a standard ingredient in cell culture media for commercial production processes, it has been shown to increase the robustness of mammalian cells to shear from sparging, which is one of the strongest contributors to the hydrodynamic stress in bioreactors.



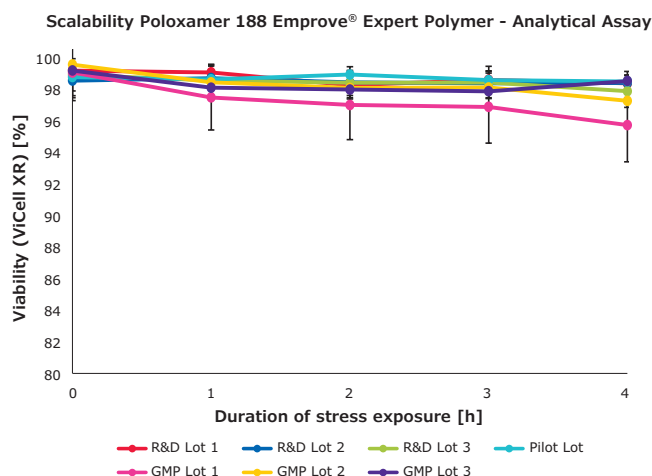
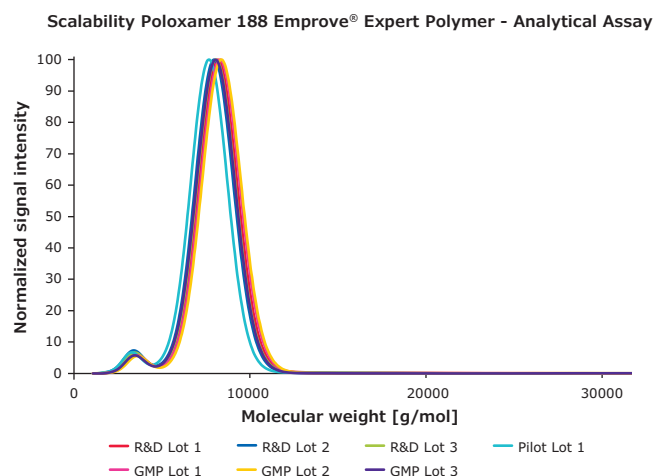
Product Information	
CAS Number	9003-11-6
Chemical Formula	$\text{HO}(\text{C}_2\text{H}_4\text{O})_n(\text{C}_3\text{H}_6\text{O})_m(\text{C}_2\text{H}_4\text{O})_n\text{H}$
HS Code	3402 13 00
Physicochemical Information	
Density	1.06 g/cm ³ (70 °C)
Flash Point	260 °C
Melting Point	52 °C
pH Value	5.0–7.5 (25 g/L, H ₂ O)
Bulk Density	1050 kg/m ³
Solubility	>100 g/L
Safety Information According to GHS	
Storage Class	10–13 Other liquids and solids
WGK	WGK 1 slightly water endangering
Disposal	3 Relatively unreactive organic reagents should be collected in container A. If halogenated, they should be collected in container B. For solid residues, use container C.

With process intensification through increasing cell densities and production in fed-batch and perfusion, issues such as unexpected loss of cell density and viability in manufacturing operations began to increase. They were correlated to lot-to-lot variation in Poloxamer 188 polymer.

Identification of critical parameters for Poloxamer 188 polymer was determined by extensive investigation into the sources of lot-to-lot variability, development and validation of proprietary analytical and biological tests, and creation of a reference library consisting of 100+ customer and supplier samples.

Our Poloxamer 188 Emprove® Expert has been developed for reliable quality and consistency and to provide shear stress protection for large-scale cell culture processes.

Our two Poloxamer grades are tailored to biopharmaceutical manufacturer's needs, depending on the compendial requirements. For the best shear protection functionality in the bioreactor, the cell culture optimized version (#137097) is recommended, if no compendial requirement is present. If a compendial product is needed, the compendial cell culture grade (#137197) provides a thoroughly tested alternative to assure performance of the cells in the bioreactor. Both Emprove® Expert grades of our Poloxamer 188 have been developed for reliable quality and consistency and to provide shear stress protection for large-scale cell culture processes.



Benefits

- Consistent quality**
 With methods developed in-house, we are able to predict the performance and ensure lot-to-lot consistency.
- Proven functionality**
 We test and certify shear protection on the Certificate of Analysis.
- Superior performance**
 Our products perform superior to lots across different suppliers, batches and quality grades.
- Reliable supply**
 Large manufacturing capacities ensure reliable supply for our customers.
- Quality / Regulatory insights**
 We provide GMP documentation with our Emprove® dossiers.

Our primary recommendation: Poloxamer 188 Emprove® Expert cell culture optimized

Product Name	Catalogue No.
Poloxamer 188 Emprove® Expert cell culture optimized - 3 x 1 kg (Sample Kit)	137097.0003
Poloxamer 188 Emprove® Expert cell culture optimized - 1 kg	137097.1000
Poloxamer 188 Emprove® Expert cell culture optimized - 10 kg	137097.9010
Poloxamer 188 Emprove® Expert cell culture optimized - 25 kg	137097.9025

Our compendial alternative: Poloxamer 188 Emprove® Expert compendial cell culture grade Ph Eur, NF

Product Name	Catalogue No.
Poloxamer 188 Emprove® Expert compendial cell culture grade Ph Eur, NF - 3 x 1kg (Sample Kit)	137197.003
Poloxamer 188 Emprove® Expert compendial cell culture grade Ph Eur, NF - 1 kg	137197.1000
Poloxamer 188 Emprove® Expert compendial cell culture grade Ph Eur, NF - 10 kg	137197.9010
Poloxamer 188 Emprove® Expert compendial cell culture grade Ph Eur, NF - 25 kg	137197.9025

Upstream Application

Benzonase® endonuclease

Benzonase® endonuclease—the smart solution for DNA removal in biopharmaceutical production has proven its value for over 30 years. Balancing efficiency and regulatory compliance by delivering reliability and high-quality due to manufacturing under GMP (ICH Q7). Benzonase® endonuclease is originated from bacteria *Serratia marcescens* and expressed in *E.coli* K12. It is nonspecific, making it highly active against all kinds of nucleic acids (DNA, RNA, circular, single or double stranded).

Benzonase® endonuclease has an exceptionally high level of specific activity for nucleic acids without any detectable proteolytic activity, making it a suitable tool for the purification of viral vaccines, viral vectors for vaccine-, cell- & gene therapy- and oncolytic applications. The use of Benzonase® endonuclease can reduce the levels of DNA by more than 100,000-fold while also decreasing viscosity and protecting downstream equipment from DNA fouling.

Benefits of using Benzonase® endonuclease in a viral manufacturing process:

- Prevents yield loss due to virus-nucleic acid complexes
- Prevents fouling of downstream equipment
- Reduces viscosity of process intermediates

Regulatory expectations and documentation for viral vaccines and vectors:

- Residual DNA considered a contaminant requiring removal (size of residual DNA no more than 100–200 bp, less than 10 ng per dose).
- FDA Bulk Biological Master File (BBMF; FDA Reg. No. BBMF 5403) and Emprove® dossiers available.



Product Name	Catalogue No.	Pack size
Benzonase® endonuclease, purity grade II (≥90%), for biotechnology	101654.0001	100,000 U/vial
Benzonase® endonuclease, purity grade II (≥90%), for biotechnology	101656.0001	500,000 U/vial
Benzonase® endonuclease, Emprove® Expert	101695.0001	100,000 U/vial
Benzonase® endonuclease, Emprove® Expert	101697.0001	500,000 U/vial
Benzonase® endonuclease, Emprove® Expert	101697.0010	5,000,000 U/vial
Benzonase® endonuclease Safety Plus Emprove® Expert (≥99.0% purity)	103773.1010	100,000 U/vial
Benzonase® endonuclease Safety Plus Emprove® Expert (≥99.0% purity)	103773.0001	500,000 U/vial
Benzonase® endonuclease Safety Plus Emprove® Expert (≥99.0% purity)	103773.0010	5,000,000 U/vial
Benzonase® endonuclease ELISA Kit II for the immunological detection of Benzonase® endonuclease	101681.0001	5 plates (8 x 12) plus reagents

Downstream and Formulation Application

BioPharm Raw Materials for Downstream and Purification

Buffers and process chemicals suitable for downstream purification processes for proteins and other biological products intended for biopharmaceutical production.

Buffers Compounds - raw materials for purification processes

In downstream purification processing, buffers are used in maintaining purification conditions to stabilize your valuable proteins and biological compounds. To ensure reproducible processes, we use only high-purity raw materials and defined processes to minimize microbiological contamination and protease/nuclease activities. We offer a range of buffer compounds supported by high quality standards, and necessary supporting documentation for biopharmaceutical production.

Biological Buffers

Product	Catalogue No.	Product Name	CAS No.	Pack Size
Tris				
Tris	108307	Tris(hydroxymethyl)aminomethane (Trometamol) (TRIS) high purity EMPROVE® Expert, Ph Eur, BP, ChP, JPC, USP, ACS	77-86-1	1 kg, 25 kg
Tris HCl	108219	TRIS((hydroxymethyl)aminomethane (Trometamol) (TRIS) hydrochloride high purity EMPROVE® Expert	1185-53-1	1 kg, 5 kg, 12 kg, 25 kg
Tris	RES3193T-A7	Tromethamine, USP, EP, JPC, BP Tested	77-86-1	5 kg, 25 kg, 50 kg
Tris HCl	RES3098T-B7	Tris hydrochloride	1185-53-1	5 kg, 25 kg, 50 kg
Tris HCl	PHG0002	Tris hydrochloride	1185-53-1	5 kg, 25 kg, 50 kg
MES				
MES	RES0113M-A7	MES	145224-94-8	5 kg, 25 kg, 50 kg
MES Sodium Salt	RES0114M-A7	MES Sodium Salt	71119-23-8	1 kg, 10 kg, 25 kg
MES	PHG0003	MES Hydrate	1266615-59-1	5 kg, 25 kg, 50 kg
MES Sodium Salt	PHG0008	MES Sodium Salt	71119-23-8	1 kg, 10 kg, 25 kg
Bis Tris				
Bis Tris	RES1161B-A7	BIS-TRIS	6976-37-0	1 kg, 10 kg, 25 kg
Bis Tris HCl	RES1164B-A7	BIS-TRIS Hydrochloride	124763-51-5	1 kg, 10 kg
Bis Tris	PHG0004	BIS-TRIS	6976-37-0	1 kg, 10 kg, 25 kg
MOPS				
MOPS	PHG0007	MOPS	1132-61-2	1 kg, 10 kg, 25 kg
MOPS, Sodium Salt	RES0197M-A7	MOPS, Sodium Salt	71119-22-7	1 kg, 10 kg
PIPES				
PIPES, Disodium Salt	RES0704P-A7	PIPES, Disodium Salt	76836-02-7	1 kg, 10 kg

Product	Catalogue No.	Product Name	CAS No.	Pack Size
Others				
Bis Tris Propane	PHG0005	BIS-TRIS Propane	64431-96-5	1 kg, 10 kg
Tricine	RES3077T-A7	Tricine	5704-4-1	1 kg, 10 kg, 25 kg

Buffers

Product	Catalogue No.	Product Name	CAS No.	Pack Size
Phosphate				
Sodium dihydrogen phosphate dihydrate	137018	Sodium dihydrogen phosphate dihydrate Emprove® Expert, Ph Eur, BP, USP, JPE	13472-35-0	1 kg, 5 kg, 12 kg, 25 kg
Disodium hydrogen phosphate dihydrate	137036	di-Sodium hydrogen phosphate dihydrate Emprove® Expert, Ph Eur, BP, USP	10028-24-7	1 kg, 5 kg, 12 kg, 25 kg
Potassium dihydrogen phosphate	137039	Potassium dihydrogen phosphate cryst. Emprove® Expert, Ph Eur, BP, JPC, NF	7778-77-0	1 kg, 5 kg, 12 kg, 25 kg
Dipotassium hydrogen phosphate	137010	di-Potassium hydrogen phosphate anhydrous Emprove® Expert, Ph Eur, BP, USP	7757-11-4	1 kg, 5 kg, 12 kg, 25 kg
Disodium hydrogen phosphate heptahydrate	137092	di-Sodium hydrogen phosphate heptahydrate Emprove® Expert, DAC, USP	7782-85-6	1 kg, 5 kg, 12 kg
Sodium dihydrogen phosphate monohydrate	137093	Sodium-dihydrogen phosphate monohydrate Emprove® Expert, BP, USP	10049-21-5	1 kg, 5 kg, 12 kg

Acetate				
Sodium acetate trihydrate	137012	Sodium acetate trihydrate suitable for biopharmaceutical production Emprove® Expert, Ph Eur, BP, JP, USP	6131-90-4	5 kg, 12 kg, 25 kg
Sodium acetate	137046	Sodium acetate anhydrous Emprove® Expert, USP	127-09-3	5 kg, 12 kg, 25 kg
Acetic acid 30%	137047	Acetic acid 30% Emprove® Expert, Ph Helv	-	2.5 L, 25 L, 950 L

Histidine				
L-Histidine	104352	L-Histidine Emprove® Expert Ph Eur, USP, JP	71-00-1	1 kg, 10 kg
L-Histidine HCl H ₂ O	104354	L-Histidine monohydrochloride monohydrate Emprove® Expert, Ph Eur, BP, JP	5934-29-2	0.5 kg, 10 kg

Citrate				
Citric acid anhydrous	137002	Citric acid anhydrous powder Emprove® Expert Ph Eur, BP, JP, USP, ACS	77-92-9	5 kg, 12 kg, 25 kg
Citric acid monohydrate	137003	Citric acid monohydrate cryst. Emprove® Expert Ph Eur, BP, JP, USP, ACS	5949-29-1	5 kg, 12 kg, 25 kg
tri-Sodium citrate dihydrate	137042	tri-Sodium citrate dihydrate cryst. Emprove® Expert, Ph Eur, BP, JP, USP, ACS	6132-04-3	5 kg, 12 kg, 25 kg

Carbonate				
Potassium Carbonate	104924	Potassium Carbonate anhydrous Emprove® Essential, Ph Eur, USP, E 501	584-08-7	1 kg, 5 kg, 25 kg
Sodium Carbonate Decahydrate	106384	Sodium Carbonate Decahydrate Emprove® Essential, Ph Eur, BP, E 500	6132-02-1	1 kg, 25 kg
Sodium Carbonate Monohydrate	106386	Sodium Carbonate Monohydrate Emprove® Essential, Ph Eur, BP, NF, E 500	5968-11-6	1 kg, 25 kg, 45 kg, 50 kg
Sodium Carbonate	106398	Sodium Carbonate anhydrous Emprove® Essential, Ph Eur, BP, JP, NF	497-19-8	1 kg, 5 kg, 12 kg, 25 kg
Sodium hydrogen carbonate	137013	Sodium hydrogen carbonate Emprove® Expert, Ph Eur, BP, JP, USP	144-55-8	2.5 kg, 12 kg, 25 g
Sodium carbonate anhydrous	137014	Sodium carbonate anhydrous Emprove® Expert, Ph Eur, BP, JP, NF	497-19-8	5 kg, 10 kg, 25 kg

Product	Catalogue No.	Product Name	CAS No.	Pack Size
Acids, Bases				
HCl fuming 37%	137007	HCl fuming 37% Emprove® Expert, Ph Eur, BP, JP, NF, ACS	-	1 L, 2.5 L, 25 L
Ortho phosphoric acid, 85%	100563	ortho-Phosphoric acid 85% Emprove® Essential, Ph Eur, BP, JPE, NF, E 338	-	1 L, 2.5 L, 5 L, 25 L, 55 L, 180 L, 950 L
Acetic acid (glacial) 100%	137000	Acetic acid (glacial) 100% Emprove® Expert, Ph Eur, BP, JP, USP	64-19-7	2.5 L, 25 L, 190 L
Sodium hydroxide	137020	Sodium hydroxide, pellets Emprove® bio, Ph Eur, BP, JP, NF	1310-73-2	5 kg, 12 kg, 25 kg, 50 kg
Potassium hydroxide	105032	Potassium hydroxide, pellets Emprove® Essential, Ph Eur, BP, JP, NF, FCC, E 525	1310-58-3	1 kg, 5 kg, 25 kg, 50 kg

Salts

Product	Catalogue No.	Product Name	CAS No.	Pack Size
Sodium chloride	137017	Sodium chloride Emprove® Expert, Ph Eur, BP, ChP, JP, USP	7647-14-5	1 kg, 5 kg, 12 kg, 25 kg
Potassium chloride	137009	Potassium chloride Emprove® Expert, Ph Eur, BP, USP, JP	7447-40-7	1 kg, 5 kg, 12 kg, 25 kg
Magnesium chloride hexahydrate	137008	Magnesium chloride hexahydrate, Emprove® Expert, Ph Eur, BP, USP, JPC, ACS	7791-18-6	5 kg, 12 kg, 25 kg
Calcium chloride dihydrate	137101	Calcium chloride dehydrate Emprove® Expert, Ph Eur, BP, JP, USP	10035-04-8	5 kg, 12 kg, 25 kg
Sodium sulfate anhydrous	137144	Sodium sulfate anhydrous Emprove® Expert, Ph Eur, USP, BP	7757-82-6	1 kg, 12 kg, 25 kg

Surfactants

Product	Catalogue No.	Product Name	CAS No.	Pack Size
Polysorbate 20 Tween® 20	817072	Tween® 20 (Polysorbate) Emprove® Essential, Ph Eur, PE, NF	9005-64-5	1 L, 2.5 L
Polysorbate 80 Tween® 80	817061	Tween® 80 (Polysorbate) Emprove® Essential, Ph Eur, JP, NF	9005-65-6	1 L, 2.5 L, 25 kg, 50 kg

Downstream Chemicals

Product	Catalogue No.	Product Name	CAS No.	Pack Size
CDAP	RES1458C-B1	CDAP	59016-56-7	100 mg, 500 mg, 1 gm
Guanidinium hydrochloride	PHG0006	Guanidinium hydrochloride	50-01-1	100 g, 5 kg, 25 kg, 50 kg
Guanidinium chloride	137037	Guanidinium chloride Emprove® Expert	50-01-1	1 kg, 3 kg, 12 kg, 25 kg
CTAB	ARK2188	Hexadecyltrimethylammonium bromide, USP/NF	57-09-0	100 g, 1 kg, 5 kg, 10 kg
Glutathione (reduced)	104090	Glutathione (reduced) Emprove® Expert Ph Eur	70-18-8	5 g, 50 g, 500 g
L-GLUTATHIONE OXIDIZED	G2299	L-Glutathione Oxidized	27025-41-8	100 g, 1 kg
Triton® X-100	108643	Triton® X-100 Emprove® Expert Ph Eur	9002-93-1	1 L, 2.5 L, 25 L, 190 L

Downstream and Formulation Application

BioContinuum™ Buffer Delivery Platform

Biomanufacturing requires large volumes of buffers for downstream processing, which can often be a bottleneck. As processes evolve and intensify, additional focus has been placed on reducing bottlenecks, footprint, and capital expenditures while delivering the right buffers at the right time and specifications.

The BioContinuum™ Buffer Delivery Platform is a configurable offering of buffer concentrates, buffer dilution system, single-use assemblies and services tailored to provide the highest level of accuracy and precision in buffer preparation and management. Whether designing a new, low-overhead facility or expanding capacity at an existing facility, the BioContinuum™ Buffer Delivery Platform delivers a competitive edge by reliably supplying process buffers from point of manufacturing to point of use, utilizing a fraction of the resources and facility space.

Benefits

- Average of 42% CAPEX reduction
- Up to 50X dilution with <1% variability
- 18% less footprint in cleanroom
- Configurable platform can be installed and ready in 16 weeks



Buffer Dilution System

Designed to streamline buffer preparation in a reduced facility footprint, our Buffer Dilution System allows you to precisely prepare accurate buffers from concentrates, reducing bottlenecks with additional flexibility that meets your timeline, specifications and quality standards.

Advanced metering pumps

The Buffer Dilution System utilizes Lewa Ecodos® metering pumps with Intellidrive® to deliver precise and accurate flow of concentrates and diluent to assure final buffer composition with minimum variability of critical quality attributes such as ionic strength, concentration, pH and conductivity. Robustness of flow control reduces in-process adjustments and facilitates validation.

Dilution factor

The advanced system design and pumps allows for dilution of low conductivity buffers up to 50:1. An accuracy of $\leq \pm 1.0\%$ and precision $\leq \pm 0.5\%$ is delivered for dilution ratio up to and including 20:1. This enables a single solution to prepare multiple, complex buffers while reducing warehouse space.

System options

Based on your buffer volume requirements, choosing a 17 L/min or 33 L/min Buffer Dilution System provides a wide range of flow rates and dilution capabilities to meet your process needs while minimizing facility footprint and reducing capital investment costs.

Downstream and Formulation Application

Cleaning-in-Place

GMP Solutions for CIP

Cleaning is a key operation in biopharmaceutical manufacturing for removal of product residues and microbial contamination. Our tailor-made, top quality cleaning-in-place (CIP) solutions save you time, money and effort. We also provide technical support regarding packaging and full regulatory documentation to simplify approval and validation procedures.



In addition to tailor-made solutions, we also provide technical support and full regulatory documentation to simplify approval and validation procedures. Since all our CIP products comply with GMP guidelines, you are well prepared for the future in this increasingly regulated segment.

Benefits of our CIP products

- Save time and money with ready to use CIP solutions
- Improved operator safety
- Easy to use
- Large variety of pack sizes and packaging types available (jerry cans, IBC's, tank containers)
- Bulk supply capabilities
- Less documentation effort

Downstream and Formulation Application

Hybrid Processes and CIP



In large stainless steel biopharmaceutical plants, CIP solutions are often supplied from a fixed tank farm with in-house or in-line dilution to the required concentration. When using single-use hybrid processes, the demand for CIP solutions is less. In these situations, our ready-to-use CIP solutions provide an ideal solution that reduces cost, improves safety (no dangerous raw material handling), and reduces infrastructure requirements.

Clean in Place Solutions

Product Name	Catalogue No.	Category	Pack Size
2-Propanol 70% Emprove® Expert	137040	Emprove® Expert	1 L (PB), 25 L (PEMD), 180 L (PEMD)
Acetic Acid 1 mol/L Emprove® Expert	137035	Emprove® Expert	2.5 L (PB), 25 L (PBC), 950 L (PIBC)
Acetic Acid 100% Emprove® Expert	137000	Emprove® Expert	2.5 L (PB), 5 L (PB), 10 L (PC), 25 L (PC), 200 L (PBC), 950 L (PIBC)
Acetic Acid 25% Emprove® Expert	137094	Emprove® Expert	1 L (GB), 10 L (PC)
Acetic Acid 30% Emprove® Expert	137047	Emprove® Expert	2.5 L (GB), 25 L (PC), 950 L (PIBC)
Acetic acid 60% Emprove® Expert	137034	Emprove® Expert	25 L (PC), 950 L (PIBC)
Acetic acid 75% Emprove® Expert	137011	Emprove® Expert	1 L (GB), 25 L (PC), 950 L (PIBC)
Acetic acid 80% Emprove® Expert	137072	Emprove® Expert	1 L (PB), 950 L (PIBC)
Acetic Acid, Glacial Emprove® Expert	137130	Emprove® Expert	New Product
Benzyl Alcohol Emprove® Expert	137043	Emprove® Expert	2.5 L (GB), 25 L (SUSD), 190 L (SUSD)
Benzyl Alcohol Emprove® Expert	137120	Emprove® Expert	New Product
Citric Acid 50% Emprove® Expert	480855	Emprove® Expert	1 L (PB), 25 L (PC), 180 L (PBC), 950 L (PIBC)
Ethanol 20% w/w Emprove® Expert	480910	Emprove® Expert	1 L (PB), 10 L (PC), 180 L (PBC), 180 L (PEMD), 950 L (PIBC)
Ethanol 20% v/v with 150 mMol/L NaCl Emprove® Expert	480940	Emprove® Expert	1 L (PB), 190 L (PEMD), 950 L (PIBC)
Ethylene Glycol Emprove® Evolve	137666	Emprove® Evolve	1 L (PB), 25 L (PC), 950 L (PIBC)
Hydrochloric Acid 1 mol/L Emprove® Expert	110165	Emprove® Expert	1 L (PB), 2.5 L (PB), 25 L (PC), 190 L (PBC), 200 L (PBC), 950 L (PIBC)
Hydrochloric Acid 10% Ph Eur, NF Emprove® Expert	480592	Emprove® Expert	200 L (PBC), 950 L (PIBC)
Hydrochloric Acid 2 mol/L Emprove® Expert	480934	Emprove® Expert	1 L (PB), 25 L (PC)
Emprove® Expert Hydrochloric Acid 25% Ph Helv	137312	Emprove® Expert	2.5 L (GB), 25 L (PC), 950 L (PIBC)
Hydrochloric Acid 3 mol/L Emprove® Expert	480680	Emprove® Expert	25 L (PC)
Hydrochloric Acid 4 mol/L Emprove® Expert	137055	Emprove® Expert	1 L (PB), 950 L (PIBC)
Hydrochloric Acid 5 mol/L Emprove® bio	480791	Emprove® bio	5 L (PB)
Hydrochloric Acid 6 mol/L Emprove® Expert	110164	Emprove® Expert	1 L (PB), 2.5 L (PB), 25 L (PC), 200 L (PBC), 950 L (PIBC)
Hydrochloric Acid Fuming 37% Emprove® Expert	137007	Emprove® Expert	1 L (GB), 2.5 L (GB), 25 L (PC)
Phosphoric acid 1 mol/L Emprove® Expert	480939	Emprove® Expert	1 L (PB), 950 L (PIBC)
Phosphoric acid 75% Emprove® Expert	100250	Emprove® Expert	10 L (PC), 950 L (PIBC)
Sodium Chloride Solution 3 M Emprove® Expert	137076	Emprove® Expert	1 L (PB), 10 L (PC)

Product Name	Catalogue No.	Category	Pack Size
Sodium Hydroxide Solution 2 mol/L Emprove® Expert	480512	Emprove® Expert	1 L (PB), 10 L (PBC), 25 L (PC), 950 L (PIBC)
Sodium Hydroxide Solution 0.1 mol/L Emprove® Expert	137058	Emprove® Expert	25 L (PC), 950 L (PIBC)
Sodium Hydroxide Solution 0.5 mol/L Emprove® Expert	137060	Emprove® Expert	1 L (PB), 25 L (PC), 200 L (PBC), 950 L (PIBC)
Sodium Hydroxide Solution 25% extra pure Emprove® Expert	480659	Emprove® Expert	25 L (PC), 950 L (PIBC)
Sodium Hydroxide Solution 0.15 mol/L Emprove® Expert	137084	Emprove® Expert	10 L (PC), 25 L (PC)
Sodium Hydroxide Solution 0.25 mol/L Emprove® Expert	100233	Emprove® Expert	25 L (PC), 950 L (PIBC)
Sodium Hydroxide Solution 1 mol/L Emprove® Expert	137031	Emprove® Expert	1 L (PB), 2.5 L (PB), 5 L (PB), 25 L (PC), 200 L (PBC), 950 L (PIBC)
Sodium Hydroxide Solution 10 mol/L Emprove® Expert	480648	Emprove® Expert	2.5 L (PB), 25 L (PC), 200 L (PBC), 950 L (PIBC)
Sodium Hydroxide Solution 10 mol/L CIP	100221		25 L (PC), 950 L (PIBC)
Sodium Hydroxide Solution 10% Emprove® Expert	100232	Emprove® Expert	25 L (PC), 950 L (PIBC)
Sodium Hydroxide Solution 20% low iron Emprove® Expert	480005	Emprove® Expert	200 L (PBC)
Sodium Hydroxide Solution 25% low iron Emprove® Expert	480659	Emprove® Expert	25 L (PC), 950 L (PIBC)
Sodium Hydroxide Solution 32% Emprove® Expert	137023	Emprove® Expert	1 L (PB), 25 L (PC), 200 L (PBC), 950 L (PIBC)
Sodium Hydroxide Solution 5 mol/L Emprove® Expert	137041	Emprove® Expert	2.5 L (PB), 25 L (PC), 200 L (PBC), 950 L (PIBC)
Sodium Hydroxide Solution 50% Emprove® Expert	100238	Emprove® Expert	25 L (PC), 950 L (PIBC)
Sodium Hydroxide Solution 50% CIP	100239		160 L (PBC), 950 L (PIBC)
Sodium Hydroxide Solution 6 mol/L Emprove® Expert	137032	Emprove® Expert	5 L (PB), 25 L (PC)
Sodium Hydroxide Solution 8 mol/L Emprove® Expert	480763	Emprove® Expert	200 L (PBC)
Sulfuric Acid 10% Emprove® Expert	480704	Emprove® Expert	1 kg (PB), 900 kg (PIBC), 950 L (PIBC)

Legend

ALB	Aluminum bottle	FD	Fibre drum	PBG	Plastic bag	SBC	Steel barrel
ALC	Aluminum can	FS	Paper sack	PC	Plastic container	SD	Steel drum
ALT	Aluminum tube	GB	Glass bottle	PD	Plastic drum	SUSBC	Stainless steel barrel
DPES	Double polyethylene sack	MC	Metal can	PEMD	Polyethylene/metal drum	SUSD	Stainless steel drum
FC	Fibre carton	PB	Plastic bottle	PIBC	Plastic intermediate bulk container	TC	Tank container
FCB	Flexible container bag	PBC	Plastic barrel	PP	Plastic peel		

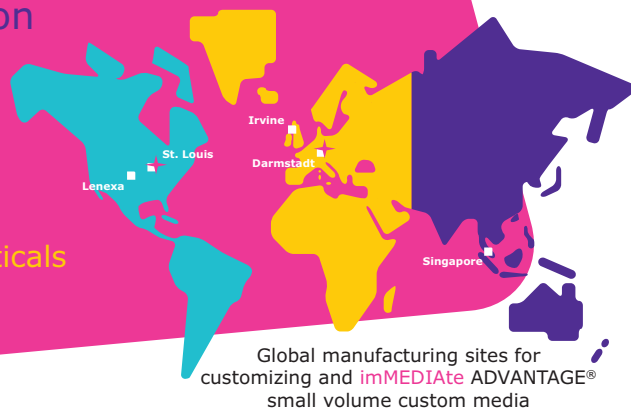
* Can't find what you need? Contact us for any CIP solution and pack sizes not listed above.

Downstream and Formulation Application

Custom Product Offering

Liquid Buffers, Custom-Order Packages

We offer custom-made products and customized solutions used for the manufacture of pharmaceuticals



Global manufacturing sites for customizing and imMEDIate ADVANTAGE® small volume custom media

Upstream

- Customized powder media
- Liquid media, liquid supplements
- Custom-packaged media

Downstream

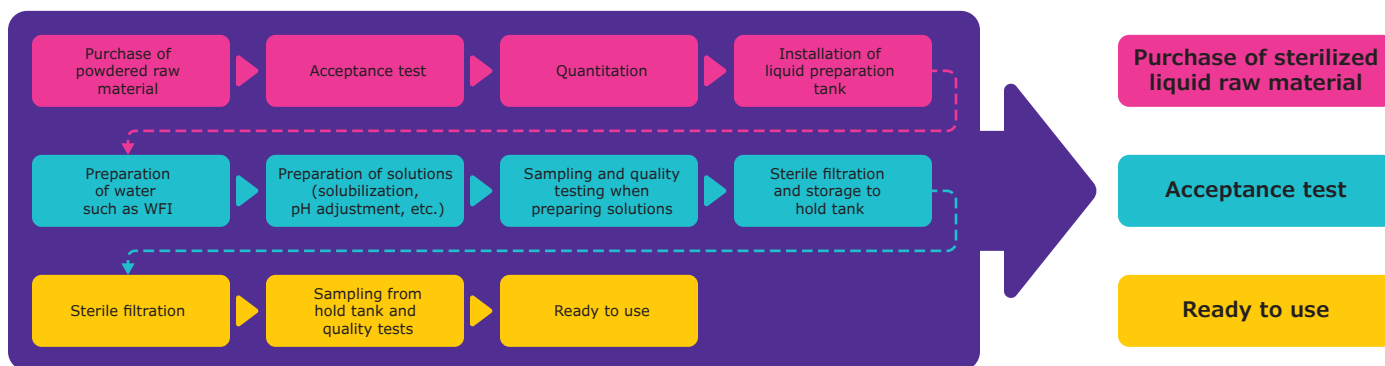
- Liquid buffers
- Custom-packaged powders
- Premix powders
- Compaction

All

- Customized product specifications

Customized production of liquid buffers and media

Preparation of liquid buffers and cell culture media can be a complex and time-consuming process. These operations can be greatly simplified by using sterile filtered pre-made solutions, which are often used in the production of biopharmaceuticals for clinical trials and vectors for cell therapy.



Sterile filtered liquid products can be delivered packed in single-use bags from 1 to 1000 L sizes.

Custom products are made according to required specifications/quality conditions and are manufactured from qualified raw materials.

Contact your representative to discuss your liquid chemical requirements.

	Description	St. Louis, MO U.S.	Irvine, U.K.
Liquid Buffers and Media Capabilities	Animal component-free/non-animal origin manufacture	Yes	Yes
	Animal component-containing manufacture (dedicated area)	Yes	No
	Batch size capability (316L SS)	50-10,000 L	50-10,000 L
	Hazardous	Yes	Yes
Flexible Packaging	PET bottles	10-2000 mL	10-2000 mL
	2D and 3D single use bags	1-500 L	1-500 L & 1000 L
	Fleet management	Policy	Policy
Qualification	Comprehensive E+L data pack	Yes	Yes
	ISTA (totes, drums, flex stations)	Yes	Yes
	Performance testing (RT stability for WAI and CCM)	Yes	Yes

Improvements in handling of powdered raw materials

As production scales increase, problems with caking (solidification) of hygroscopic raw materials and handling those with low fluidity may arise. We can provide a variety of innovative solutions to mitigate this issue and improve handling.

DRYPOUR™ Packaging System

The DRYPOUR™ packaging system minimizes caking, thus significantly reducing the time needed for material preparation. DRYPOUR™ packaging consists of a PE drum with a tamper-evident seal, a polyethylene liner with integrated desiccant bags (non-product contact) and a breathable interior Tyvek® liner. This triple protection delivers two invaluable results: dramatically reduced caking and no contamination risk from the desiccant.



Compaction of powdered raw material

Compaction is a granulation technology that is completely water- and additive-free, working with compression force only. In addition to minimizing dust formation and exposure of staff, a further advantage of our compacted materials (including media) is their fixed and stable homogeneity. Our strong expertise in milling and mixing leads to excellent powder homogeneity, which is fixed in place through the compaction process.

EZ BioPac® Pre-filled ILC Dover Transfer Bag

To provide you with a safe, convenient option for delivery powders to your processes, we can supply our products in EZ BioPac® powder transfer bags. Cell culture media and buffers can be supplied as single components, mixtures, or blends to their specified delivery weight. Bags connect directly to the hydration tank to minimize product contamination risk and increase personnel and facility safety.



ImMEDIATE ADVANTAGE® Program A non-GMP service for liquid and powder formulations

We can customize a wide variety of raw material products intended for use in pharmaceutical production and, as such, are supplied based on GMP management.

The specification, setup and lead time for custom manufacturing can be prohibitive, especially when the formulation or product specification is not yet finalized. In order to speed these up, you can evaluate a non-GMP sample for suitability and feasibility.

The imMEDIATE ADVANTAGE® program provides small volume custom media and buffers. Small volumes of customized, non-GMP upstream and downstream materials, such as cell culture media, buffers and liquid concentrates, are available to support scale-up from development to commercial production, reducing the need for expensive revalidation.

Liquid media formulations:

- 1 L – 200 L
- Single use bag: 1 - 20 L
- Bottle (for cell culture media samples): 100 - 2000 mL

Powder media formulations:

- Powder media corresponding 5 - 100 L of cell culture media sample

Downstream and Formulation Application

Process Raw Materials for Treatment of Process Intermediates

Virus inactivation in blood products

Viral risk assessment and subsequent mitigation/inactivation/removal steps are essential in biopharmaceutical processes to ensure patient safety. Virus inactivation can be achieved using technologies such as solvent/detergent (S/D) treatment or heat treatment (e.g. 60 °C), while removal can be achieved through chromatography and virus filtration steps.

We offer a wide range of raw materials suitable for GMP manufacturing, for viral inactivation and protein stabilization during processing at elevated temperatures and other processing steps.

Virus inactivation - S/D treatment

Product	Catalogue No.	Product Name	CAS No.	Pack Size
Tri-n-butyl phosphate Tributyl phosphate	100002	Tri-n-butyl phosphate Emprove® Expert, Ph Eur	126-73-8	500 mL, 2.5 L, 25 L
Triton® X-100 Octoxynol	108643	Triton® X-100 Emprove® Expert, Ph Eur	9063-19-5	1 L, 2.5 L, 25 L, 190 L
Tween® 80	817061	Tween® 80 (polysorbate) Emprove® Essential, Ph Eur, JP, NF	9005-65-6	1 L, 2.5 L, 25 L, 50 L

Virus inactivation - stabilization during heat treatment

Product	Catalogue No.	Product Name	CAS No.	Pack Size
Acetyltryptophan	112488	N-acetyl-DL-tryptophan Emprove® Expert, Ph Eur, BP	87-32-1	1 kg, 5 kg, 25 kg
Sodium caprylate	817081	Sodium caprylate Emprove® exp, Ph Eur, ChP, NF	1984-06-1	1 kg, 10 kg, 25 kg
Caprylic acid	100193	Caprylic acid (Octanoic acid) Ph Eur, NF	124-07-2	250 mL, 2.5 L, 23 L

Plasma Processing - other stabilizers

Product	Catalogue No.	Product Name	CAS No.	Pack Size
Sorbitol	111597	Parteck® SI 400 LEX (Sorbitol) Emprove® Exp, Ph Eur, BP, NF, JP (Low endotoxin Sorbitol)	50-70-4	25 kg
Sucrose	103789	Sucrose Emprove® Expert, Ph Eur, ChP, JP, NF	57-50-1	1 kg, 12 kg, 25 kg
Mannitol	137096	D(-) – Mannitol Emprove® Expert, Ph Eur, BP, USP, JP	69-65-8	12 kg, 25 kg, 50 kg
Glycine	100590	Glycine cryst. Emprove® Expert, Ph Eur, BP, ChP, JP, USP	56-40-6	1 kg, 5 kg, 25 kg, 50 kg
Granulated Glycine	103669	Glycine Granules Emprove® Expert, Ph. Eur, BP, ChP, JP, USP	56-40-6	1 kg, 5 kg, 12 kg, 25 kg, 500 kg
Maltose	105911	Maltose monohydrate Emprove® Essential	6363-53-7	1 kg, 25 kg

Protein Refolding in Microbial Systems

Proteins are the building blocks of biological systems. Some serve as nutritional sources and deliver energy, while others form frameworks for several structures of the cell. Modified and folded correctly, proteins perform highly specialized tasks in biological systems, such as enzymes, antibodies or insulin. In mammalian organisms, modification and folding takes place in cells where the functional protein takes on its critical function.

Proteins that treat certain diseases, such as antibodies or coagulation factors, can be manufactured into biotherapeutics. Many of these biotherapeutics can be produced in cell culture. The disadvantage is that those cells have high requirements to their cultivation conditions and do not provide very high yields. However, for complex biotherapeutics, it may be the only way to produce them, as the modification and refolding cannot be artificially imitated, whereas that is possible for smaller biotherapeutics, such as insulin or Fab-fragments.

One option is to use bacteria (e.g. E.coli, the workhorse of microbial manufacturing) for the production. Nevertheless, that can pose additional challenges. In general, proteins are intracellularly expressed and cell lysis (physical or chemical) is required to recover the desired biotherapeutic product. Some of these proteins are expressed as inclusion bodies (IBs), requiring further chemical solubilization and post-translational modifications (such as glycosylation and refolding), as shown in Figure 1.

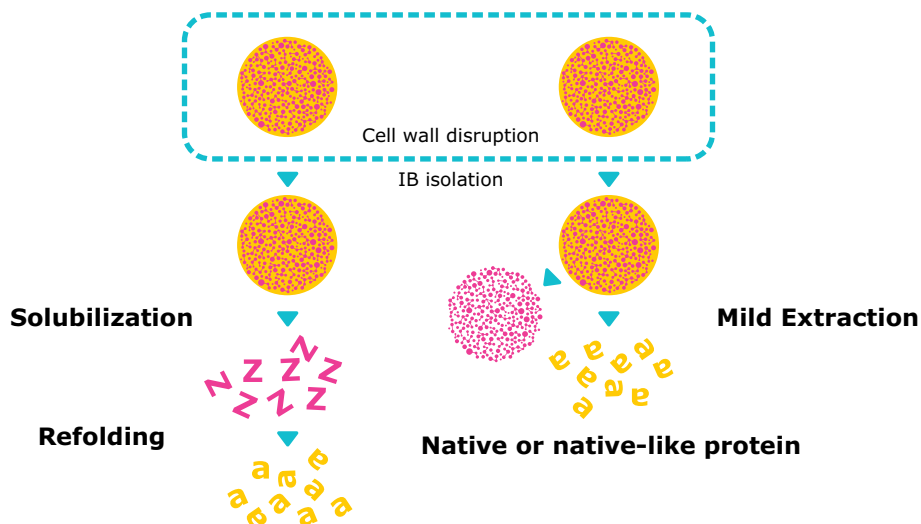


Figure 1: IBs as Raw Material for Protein Recovery Through Renaturation or Mild Extraction. Pink shapes in IBs represent the amyloid scaffold in which proteins with native-(like) conformational states are embedded (blue). The Z symbols represent solubilized unfolded polypeptides whereas a symbols represent protein in the native-(like) conformation.

Despite those challenges, the expression of recombinant proteins in bacteria or yeast has two advantages: low requirements on cultivation conditions and potentially factor higher yields, saving space, time, labor and resulting cost. We offer a portfolio, dedicated to support those challenges, enabling manufacturers to take advantage of bacterial fermentation processes.

To demonstrate the whole process of bacterial fermentation, the production process for therapeutic r insulin expressed in *E. coli* is shown. The conventional strategy for this manufacturing process encompasses the following major steps as shown in Figure 2:

- Induction of heterologous expression (A)
- Cell harvest and lysis (B)
- IB purification (C)
- IB protein extraction (D)
- Protein refolding (E)
- r insulin precursor intermediate maturation (F)
- Various chromatography steps - not covered here

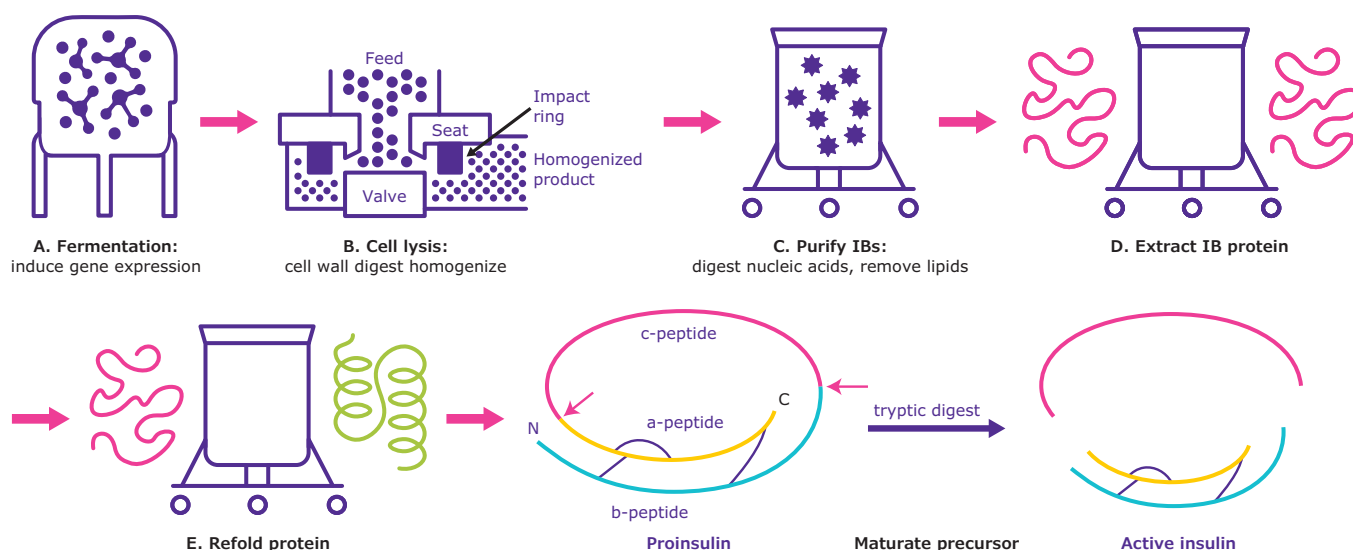


Figure 2: Manufacturing of therapeutic recombinant Insulin as a model for *E. coli* IB expressed molecules

The chemicals and recombinant enzymes that can be used in each step are listed:

Step	Catalogue No.	Product Name	Category	Function
Induce gene expression				
A	137064	Isopropyl-β-D-1-thiogalactopyranosid (IPTG)	Emprove® Expert	Induce gene expression
A	PHG0010	Isopropyl-β-D-1-thiogalactopyranosid (IPTG)		Induce gene expression
Cell lysis				
B	5501	CellPrime® r lysozyme recombinant human lysozyme		Digest murein sacculus
Purify IBs				
C	101656	Benzonase® endonuclease (≥90% purity)	-	Digest nucleic acids trapped in IBs
C	103773	Benzonase® endonuclease Safety Plus (≥99% purity)	Emprove® Expert	Digest nucleic acids trapped in IBs
C	108643	Triton® X-100 Ph. Eur	Emprove® Expert	Solubilize lipids trapped in IBs

Step	Catalogue No.	Product	Category	Function
Extract IBs				
D	PHG0006	Guanidine HCL (GuaHCL)		IB dissolution
D	137037	Guanidine HCL (GuaHCL)	Emprove® Expert	IB dissolution
D	137030	UREA crystalline	Emprove® Expert	IB dissolution
D	104166	UREA granulated	Emprove® Expert	IB dissolution
D	RES2190D	Dithiothreitol (DTT)	-	Reduce intra/ intermolecular
D	07604	2- Mercaptoethanol		Reduce intra/ intermolecular
Protein Refolding				
E	104090	Glutathione (reduced)	Emprove® Expert	Redox reagent
E	G2299	L-Glutathione oxidized		Redox reagent
E	102735	L-Cysteine HCL	Emprove® Essential	Redox reagent
E	C5360	L-Cysteine		Redox reagent
E	101587	L-Arginine	Emprove® Expert	Aggregation inhibitor
E	101544	L Arginine monohydrochloride	Emprove® Expert	Aggregation inhibitor
E	103789	Sucrose	Emprove® Expert	Protein stabilizer
E	102776	Trehalose dihydrate	Emprove® Expert	Protein stabilizer
Maturation				
F	106301	CellPrime® r Trypsin powder		Precursor maturation
F	106302	CellPrime® r Trypsin liquid		Precursor maturation
F	106353	CellPrime® r Trypsin STD powder		Precursor maturation
F	106354	CellPrime® r Trypsin STD liquid		Precursor maturation

Other Processing Raw Materials

Catalogue No.	Product	Category	Function
128218	Ammonium Sulfate	Emprove® Expert	Precipitation
100201	Phenol	Emprove® Essential	Preservative
817043	Thimerosal	Emprove® Essential	Preservative
137123	Benzalkonium chloride	Emprove® Expert	Preservative
137124	Benzalkonium chloride 50%	Emprove® Expert	Preservative

Products for Purification Processes

Protein A

Recommended chemical products suitable for chromatography and purification processes of proteins and other biological products.

Steps	Purpose	Buffers	Buffer pH	CV	Product	Catalogue No.	Category	Compendial	
Protein A Capture	Equilibration	PBS	Same as load sample	5	Sodium dihydrogen phosphate dihydrate	137018	Emprove® Expert	Ph Eur, BP, USP, JPE	
					Disodium hydrogen phosphate dehydrate	137036	Emprove® Expert	Ph Eur, BP, USP	
					Sodium chloride	137017	Emprove® Expert	Ph Eur, BP, ChP, JP, USP	
	Middle wash No.1 (Choose equilibrium buffer)		PBS	Same as load sample	5	Equilibration buffer (Choose from above materials)	--	--	--
	Middle wash No.2 (If necessary)	Option 1	Equilibration buffer and ≤ 0.5 M NaCl	Same as harvest sample	5	Sodium chloride	137017	Emprove® Expert	Ph Eur, BP, ChP, JP, USP
						Equilibration buffer (choose from above materials)	--	--	--
		Option 2	Equilibration buffer with pH changed	5.0~6.0	5	Hydrochloric acid fuming 37%	137007	Emprove® Expert	Ph Eur, BP, JP, NF, ACS
						Equilibration buffer (choose from above materials)	--	--	--
		Option 3	Elution buffer with pH changed	5.0~6.0	5	Elution buffer (Choose from below materials)	--	--	--
		Option 4	Other pH-changed buffer and ≤ 0.5 M NaCl	5.0~6.0	5	Sodium chloride	137017	Emprove® Expert	Ph Eur, BP, ChP, JP, USP
						Other buffer	--	--	--
		Option 5	Equilibration buffer with 0.1~1.0% polysorbate80	Same as harvest sample	5	Tween®80 (Polysorbate)	817061	Emprove® Essential	Ph Eur, JP, NF
						Equilibration buffer (choose from above materials)	--	--	--
		Elution	Option 1	0.1 M acetate buffer	3.0-4.0	3	Sodium acetate trihydrate	137012	Emprove® Expert
	Acetic acid (glacial) 100%						137000	Emprove® Expert	Ph Eur, BP, JP, USP
	Option 2		0.1 M citrate buffer	3.0-4.0	3	Citric acid	137002	Emprove® Expert	Ph Eur, BP, JP, USP, ACS
						Tri-Sodium citrate dehydrate cryst.	137042	Emprove® Expert	Ph Eur, BP, JP, USP, ACS
	CIP*	Option 1	150 mM phosphate acid	1.5	3	Ortho phosphoric acid 85%	100563	Emprove® Essential	Ph Eur, BP, JPE, NF, E 338
		Option 2	0.1-0.3 NaOH	13	3(~5)	Sodium hydroxide	137020	Emprove® bio	Ph Eur, BP, JP, NF
	Sanitization	Option 1	PAB Solution	--	3	PAB	480949	--	--
		Option 2	PAB Solution 120 mM phosphoric acid + 167 mM acetic acid + 2.2% benzyl alcohol	--	3	Ortho-phosphoric acid 85%	100563	Emprove® Essential	Ph Eur, BP, JPE, NF, E 338
						Acetic acid (glacial) 100%	137000	Emprove® Expert	Ph Eur, BP, JP, USP
						Benzyl alcohol	137043	Emprove® Expert	Ph Eur, BP, JP, NF, ACS
Column storage		pH 5.2±0.5 sodium acetate buffer with 1% benzyl alcohol	5.2±0.5	3	Sodium acetate trihydrate	137012	Emprove® Expert	Ph Eur, BP, JP, USP	
					Benzyl alcohol	137043	Emprove® Expert	Ph Eur, BP, JP, NF, ACS	

* Either 150 mM phosphate acid or 0.1 - 0.3N NaOH can be used if they are effective in cleaning; cleaning will be more effective if they are used in combination.

Products for Purification Processes

Cation Exchange/Anion Exchange

Steps	Purpose	Buffers	Buffer pH	CV	Product	Catalogue No.	Category	Compendial	
Cation exchange capture & elution mode chromatography	Equilibration	Neutral condition	PBS	Same as load sample	5	Sodium dihydrogen phosphate dihydrate	137018	Emprove® Expert	Ph Eur, BP, USP, JPE
						Di-sodium hydrogen phosphate dodecahydrate	106573	Emprove® Essential	Ph Eur, BP, JP, USP
						Sodium chloride	137017	Emprove® Expert	Ph Eur, BP, ChP, JP, USP
		Acid area choice 1	25 mM – 50 mM acetate buffer	Same as load sample (pH 4.5-5.5)	5	Sodium acetate trihydrate	137012	Emprove® Expert	Ph Eur, BP, JP, USP
						Acetic acid (Glacial) 100%	137000	Emprove® Expert	Ph Eur, BP, JP, USP
						Citric acid	137002	Emprove® Expert	Ph Eur, BP, JP, USP, ACS
	tri-Sodium citrate di-hydrate cryst	137042	Emprove® Expert	Ph Eur, BP, JP, USP, ACS					
	Middle wash			5	Equilibration buffer (choose from above materials)	--	--		
	Elution		Equilibration buffer + 0.5 – 1 M NaCl	Same as load sample (pH 4.5-5.5)	3	Sodium chloride	137017	Emprove® Expert	Ph Eur, BP, ChP, JP, USP
						Equilibration buffer (choose from above materials)	--	--	
	Regeneration		1-2 M NaCl or equilibrium buffer + 1-2 M NaCl		3 (-5)	Sodium chloride	137017	Emprove® Expert	Ph Eur, BP, ChP, JP, USP
	CIP		0.5 – 1.0N NaOH	13	3 (-5)	Sodium hydroxide	137020	Emprove® bio	Ph Eur, BP, JP, NF
Sanitization		0.5 – 1.0N NaOH	13	3 (-5)	Sodium hydroxide	137020	Emprove® bio	Ph Eur, BP, JP, NF	
Storage		20% ethanol + 150 mM NaCl		5	Ethanol 96%	100967	Emprove® Expert	Ph Eur, JP, USP	
					Sodium chloride	137017	Emprove® Expert	Ph Eur, BP, ChP, JP, USP	

Steps	Purpose	Buffers	Buffer pH	CV	Product	Catalogue No.	Category	Compendial	
Anion exchange flow-through mode chromatography	Equilibration	Option 1	PB	Same as load sample	5	Sodium dihydrogen phosphate dihydrate	137018	Emprove® Expert	Ph Eur, BP, USP, JPE
						Di-sodium hydrogen phosphate dodecahydrate	106573	Emprove® Essential	Ph Eur, BP, JP, USP
						Tris (Hydroxymethyl) aminomethane (Trometamol) high purity	108307	Emprove® Expert	Ph Eur, BP, JPC, USP, ACS
		Option 2	Tris-HCl buffer	Same as load sample	5	Tris (Hydroxymethyl) aminomethane hydrochloride	108219	Emprove® Expert	
						Equilibration buffer	-	-	-
						Equilibration buffer (Choose from above materials)	-	-	-
	Regeneration		1-2 M NaCl or Equilibration buffer + 1-2 M NaCl	-	3 (-5)	Sodium chloride	137017	Emprove® Expert	Ph Eur, BP, ChP, JP, USP
	CIP		0.5-1.0 N NaOH	13	3 (-5)	Sodium hydroxide	137020	Emprove® bio	Ph Eur, BP, JP, NF
	Sanitization		0.5-1.0 N NaOH	13	3 (-5)	Sodium hydroxide	137020	Emprove® bio	Ph Eur, BP, JP, NF
	Column storage		20% ethanol + 150 mM NaCl		5	Ethanol 96%	100967	Emprove® Expert	Ph Eur, JP, USP
						Sodium chloride	137017	Emprove® Expert	Ph Eur, BP, ChP, JP, USP

Products for Purification Processes

Viral Clearance TFF Concentration/Diafiltration

Steps	Purpose	Buffers	Product	Catalogue No.	Category	Compendial
Viral clearance membrane	Equilibration buffer	Phosphate buffer	Sodium dihydrogen phosphate dehydrate	137018	Emprove® Expert	Ph Eur, BP, USP, JPE
			di-Sodium hydrogen phosphate dihydrate	137036	Emprove® Expert	Ph Eur, BP, USP
		Acetate buffer	Sodium acetate trihydrate	137012	Emprove® Expert	Ph Eur, BP, JP, USP
			Acetic acid 30%	137047	Emprove® Expert	Ph Helv
			Sodium chloride	137017	Emprove® Expert	Ph Eur, BP, ChP, JP, USP
		Tris-HCl buffer	Tris(Hydroxymethyl) aminomethane (Trometamol) high purity	108307	Emprove® Expert	Ph Eur, BP, JPC, USP, ACS
			Tris(Hydroxymethyl) aminomethane hydrochloride	108219	Emprove® Expert	
	CIP	0.5N NaOH	Sodium hydroxide	137020	Emprove® bio	Ph Eur, BP, JP, NF

Steps	Purpose	Buffers	Product	Catalogue No.	Category	Compendial	
Ultrafiltration/ Concentration/ Diafiltration	Equilibrium/ Diafiltration	Phosphate buffer	Sodium dihydrogen phosphate dihydrate	137018	Emprove® Expert	Ph Eur, BP, USP, JPE	
			di-Sodium hydrogen phosphate dehydrate	137036	Emprove® Expert	Ph Eur, BP, USP	
		Acetate buffer	Sodium acetate trihydrate	137012	Emprove® Expert	Ph Eur, BP, JP, USP	
			Acetic acid 30%	137047	Emprove® Expert	Ph Helv	
			Sodium chloride	137017	Emprove® Expert	Ph Eur, BP, ChP, JP, USP	
		Citrate buffer	Citric acid, anhydrous powder	137002	Emprove® Expert	Ph Eur, BP, JP, USP, ACS	
			tri-Sodium citrate dihydrate cryst	137042	Emprove® Expert	Ph Eur, BP, JP, USP, ACS	
			Sodium chloride	137017	Emprove® Expert	Ph Eur, BP, ChP, JP, USP	
		Formulation	Histidine	L-histidine	104352	Emprove® Expert	Ph Eur, USP, JP
			Sucrose	Sucrose, low in nanoparticles	103789	Emprove® Expert	Ph Eur, ChP, JP, NF
	Trehalose dihydrate		Trehalose dihydrate	102776	Emprove® Expert	Ph, Eur, NF, JP	
	Sorbitol		Parreck® SI 400 LEX (Sorbitol)	111597	Emprove® Expert	Ph Eur, BP, NF, JP	
	Mannitol		D (-) – Mannitol	137096	Emprove® Expert	Ph, Eur, BP, USP, JP	
	CIP	0.5N NaOH	Sodium hydroxide	137020	Emprove® bio	Ph Eur, BP, JP, NF	
	Storage	0.1N NaOH	Sodium hydroxide	137020	Emprove® bio	Ph Eur, BP, JP, NF	

MilliporeSigma
400 Summit Drive
Burlington, MA 01803

sigmaaldrich.com

For additional information, please visit www.sigmaaldrich.com. To place an order or receive technical assistance, please visit www.sigmaaldrich.com/customer-service

© 2021 Merck KGaA, Darmstadt, Germany and/or its affiliates. All Rights Reserved. MilliporeSigma, the vibrant M, SAFC, Emprove, Mobius, Benzonase, CellPrime, imMEDIATE Advantage, DRYPOUR, Parreck and BioContinuum are trademarks of Merck KGaA, Darmstadt, Germany or its affiliates. All other trademarks are the property of their respective owners. Detailed information on trademarks is available via publicly accessible resources.

MS_PG6668EN Ver. 1.0

The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.

Contact us:
www.sigmaaldrich.com

