

**MERCK**

# PROCESS CHEMICALS FOR RNA DRUG MANUFACTURING

Providing high quality raw materials and services  
for mRNA manufacturing and formulation

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

**SAFC**<sup>®</sup>

Pharma & Biopharma Raw  
Material Solutions

# Join the M-Revolution

Non-viral gene delivery systems represent an efficient approach to deliver nucleic acid payloads (DNA and RNA) into the cells of interest with the aim for a temporary augmentation or knock-down of protein expression. Especially, the mRNA technology has the potential to revolutionize vaccination, protein replacement therapies, and the treatment of genetic diseases, as it is safe, simple to reproduce and lower in manufacturing cost compared to other technologies and offers a great deal of versatility.

We offer a comprehensive chemical portfolio and custom manufacturing capabilities for the entire mRNA manufacturing. Make use of our raw materials required for mRNA with an integrated offering for all process steps, from plasmid DNA (pDNA) to mRNA synthesis to final formulation.

## Main benefits and features of our offering

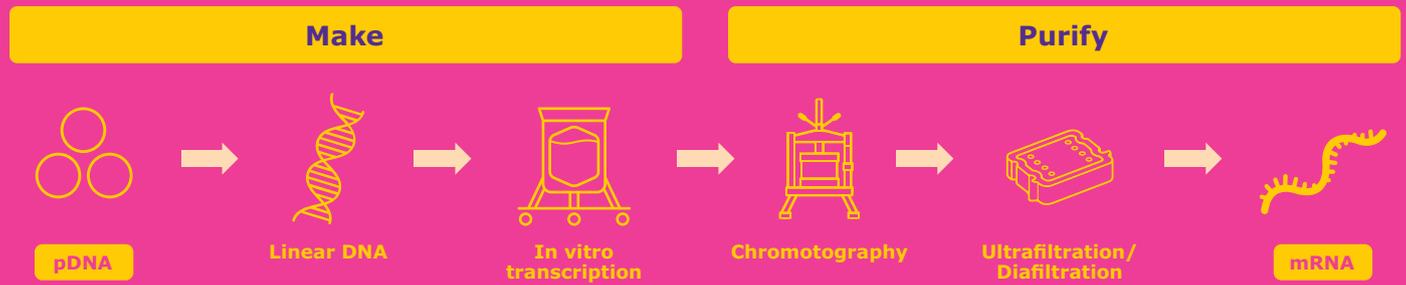
- Integrated offering of chemicals required for entire mRNA manufacturing process
- Unique mRNA custom manufacturing workflow
- CMO partner for high quality lipids
- Chemicals are tested for absence of endonucleases

## pDNA manufacturing process overview

To produce mRNA, a plasmid DNA Template is required. We offer high quality chemicals for all relevant process steps such as Alkaline Lysis, Chromatography and UF/DF to ensure a safe and stable process.



# mRNA manufacturing process overview



To ensure stable mRNA and minimize the risk of enzymatic degradation the selection of the right process chemicals is crucial, especially as the mRNA is unprotected during in vitro transcription and downstream purification. We offer a comprehensive chemicals portfolio with many of the critical products tested for the absence of endonuclease activity.

## mRNA Services

mRNA technology has the power to revolutionize how diseases are treated. mRNA therapeutics require high quality raw materials with superior performance. We are specialized in manufacturing high quality synthetic mRNA. With our unique workflow, the mRNA manufacturing is reproducible and the final product has superior activity. Some key features of our offering are listed below:

- Manufacture fully customizable sequence up to 13,000 nt
- Need for ~10,000x less plasmid DNA compared to standard mRNA manufacturing processes
- Robust and reproducible process yielding highly homogeneous poly A tail and high performing product
- Full technical and regulatory support

## Our offer of raw materials for mRNA manufacturing

| Process Step   |  |
|--|--|
|  <p>Plasmid production in E.coli DH5alpha</p>             | 599920C Antifoam, Gamma Irradiated, 1% EX-CELL®  |
|  | 137048 D(+)-Glucose anhydrous EMPROVE® EXPERT Ph Eur,BP,USP,ACS  |
|  | 137064 IPTG (Isopropyl-β-D-1thiogalactopyranoside) EMPROVE® EXPERT   |
|  | For our comprehensive portfolio of upstream chemicals, such as amino acids, vitamins and carbohydrates, and buffers please visit: <a href="http://sigmaaldrich.com/upstreamchemicals">sigmaaldrich.com/upstreamchemicals</a> |
|  <p>Alkaline Lysis</p>                                   | 137000 Acetic acid (glacial) 100% EMPROVE® EXPERT Ph Eur,BP,JP,USP   |
|  | 137101 Calcium chloride dihydrate EMPROVE® EXPERT Ph Eur,BP,JP,USP   |
|  | 5501 CellPrime® rLysozyme  |
|  | 104820 Potassium acetate extra pure EMPROVE® ESSENTIAL Ph Eur,BP,JPE,E 261   |
|  | 128205 Sodium acetate trihydrate EMPROVE® EXPERT Ph Eur,BP,ChP,JP,USP  |
|  | 817034 Sodium dodecyl sulfate EMPROVE® ESSENTIAL Ph Eur  |
|  | 137020 Sodium hydroxide pellets suitable for the biopharmaceutical production EMPROVE® bio Ph Eur,BP,JP,NF   |
|  | 137004 Titriplex® III (ethylene dinitrilo tetraacetic acid disodium salt dihydrate) EMPROVE® EXPERT Ph Eur,BP,ChP,JP,USP,ACS   |
|  | <b>108219 Tris(hydroxymethyl)aminomethane hydrochloride EMPROVE® EXPERT<sup>1</sup></b>  |
|  | 108307 Tris(hydroxymethyl)aminomethane (Trometamol) high purity EMPROVE® EXPERT Ph Eur, BP,ChP,JPC,USP,ACS   |
|  | 137008 Magnesium chloride hexahydrate cryst. EMPROVE® EXPERT Ph Eur,BP,USP,JPC,ACS   |
| 137004 Titriplex® III (ethylene dinitrilo tetraacetic acid disodium salt dihydrate) EMPROVE® EXPERT Ph Eur,BP,ChP,JP,USP,ACS               |  |
| <b>108219 Tris(hydroxymethyl)aminomethane hydrochloride EMPROVE® EXPERT<sup>1</sup></b>  |  |
| 108307 Tris(hydroxymethyl)aminomethane (Trometamol) high purity EMPROVE® EXPERT Ph Eur, BP,ChP,JPC,USP,ACS                                 |  |
|  <p>pDNA Linearization &amp; In vitro transcription</p> | <b>DTT (Dithiothreitol):</b> GMP grade available soon  |
|  | <b>Spermidine:</b> We offer GMP grade Spermidine with a standard item code coming soon. Please contact your local Sales representative for more information.   |

# Protect your RNA with our high-quality chemicals

To minimize the risk of RNase degradation during your process, many of our critical raw materials are tested for the absence of nuclease activity. Also, to control the risk of microbial and endotoxin contaminations, our Emprove® Expert products are tested for low microbial and endotoxin levels. To support you during the manufacturing process and formulation, we are expanding our portfolio of **endonuclease free products (highlighted magenta in the tables)**.

## Process Step



### Chromatography

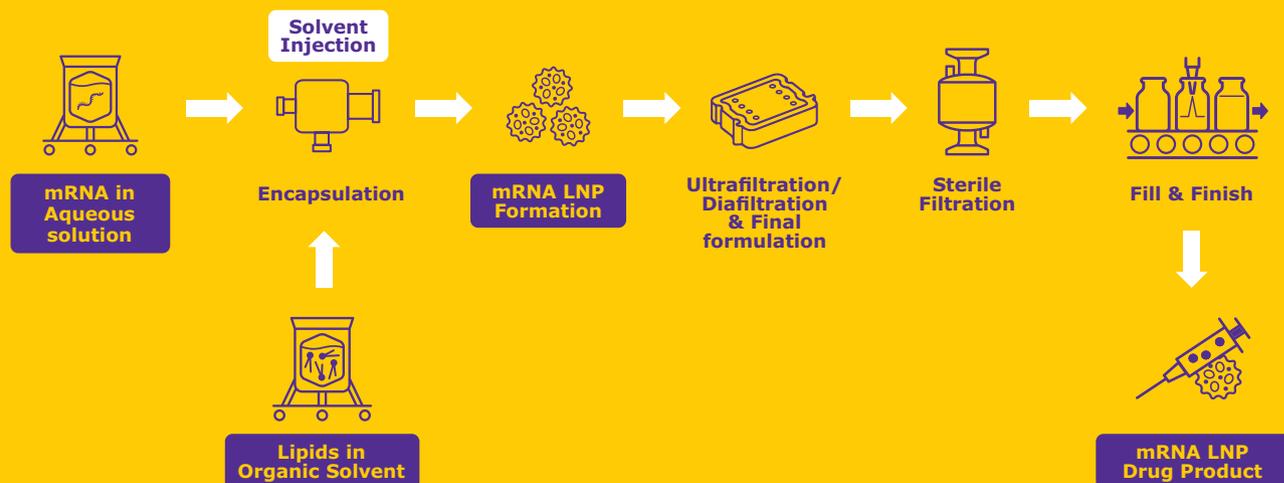
|               |   |
|---------------|---|
| 137000        | Acetic acid (glacial) 100% EMPROVE® EXPERT Ph Eur,BP,JP,USP   |
| 137134        | Acetonitrile EMPROVE® ESSENTIAL   |
| 128218        | Ammonium sulfate EMPROVE® EXPERT ChP,NF,ACS   |
| 137043        | Benzyl Alcohol EMPROVE® EXPERT  |
| <b>137036</b> | <b>di-Sodium hydrogen phosphate dihydrate EMPROVE® EXPERT Ph Eur,BP,USP<sup>1</sup></b>                               |
| <b>137092</b> | <b>di-Sodium hydrogen phosphate heptahydrate EMPROVE® EXPERT DAC,USP<sup>1</sup></b>                                  |
| 137007        | Hydrochloric Acid Fuming 37% EMPROVE® EXPERT  |
| 104820        | Potassium acetate extra pure EMPROVE® ESSENTIAL Ph Eur,BP,JPE,E 261   |
| 137009        | Potassium chloride EMPROVE® EXPERT Ph Eur,BP,USP,JP   |
| <b>137039</b> | <b>Potassium dihydrogen phosphate cryst. EMPROVE® EXPERT Ph Eur,BP,JPC,NF<sup>1</sup></b>                             |
| <b>128205</b> | <b>Sodium acetate trihydrate EMPROVE® EXPERT Ph Eur,BP,ChP,JP,USP<sup>1</sup></b>                                     |
| <b>137017</b> | <b>Sodium chloride EMPROVE® EXPERT Ph Eur,BP,ChP,JP,USP<sup>1</sup></b>   |
| <b>137018</b> | <b>Sodium dihydrogen phosphate dihydrate EMPROVE® EXPERT Ph Eur,BP,USP,JPE<sup>1</sup></b>                            |
| 137004        | Titriplex® III (ethylene dinitrilo tetraacetic acid disodium salt dihydrate) EMPROVE® EXPERT Ph Eur,BP,ChP,JP,USP,ACS |
| <b>108219</b> | <b>Tris(hydroxymethyl)aminomethane hydrochloride EMPROVE® EXPERT<sup>1</sup></b>                                      |
| 108307        | Tris(hydroxymethyl)aminomethane (Trometamol) high purity EMPROVE® EXPERT Ph Eur,BP,ChP,JPC,USP,ACS                    |
| <b>137036</b> | <b>di-Sodium hydrogen phosphate dihydrate EMPROVE® EXPERT Ph Eur,BP,USP<sup>1</sup></b>                               |
| <b>137092</b> | <b>di-Sodium hydrogen phosphate heptahydrate EMPROVE® EXPERT DAC,USP<sup>1</sup></b>                                  |
| 137009        | Potassium chloride EMPROVE® EXPERT Ph Eur,BP,USP,JP   |
| <b>137039</b> | <b>Potassium dihydrogen phosphate cryst. EMPROVE® EXPERT Ph Eur,BP,JPC,NF<sup>1</sup></b>                             |
| <b>137017</b> | <b>Sodium chloride EMPROVE® EXPERT Ph Eur,BP,ChP,JP,USP<sup>1</sup></b>   |
| <b>137018</b> | <b>Sodium dihydrogen phosphate dihydrate EMPROVE® EXPERT Ph Eur,BP,USP,JPE<sup>1</sup></b>                            |
| 137020        | Sodium hydroxide pellets suitable for the biopharmaceutical production EMPROVE® bio Ph Eur,BP,JP,NF                   |
| 137004        | Titriplex® III (ethylene dinitrilo tetraacetic acid disodium salt dihydrate) EMPROVE® EXPERT Ph Eur,BP,ChP,JP,USP,ACS |
| <b>108219</b> | <b>Tris(hydroxymethyl)aminomethane hydrochloride EMPROVE® EXPERT<sup>1</sup></b>                                      |
| 108307        | Tris(hydroxymethyl)aminomethane (Trometamol) high purity EMPROVE® EXPERT Ph Eur,BP,ChP,JPC,USP,ACS                    |



### Ultrafiltration/ Diafiltration

<sup>1</sup>Endonuclease free products

# mRNA formulation process overview



Naked mRNA is unstable and drug delivery systems are necessary to deliver mRNA first into the human body and then into the cells. Encapsulation is a crucial step and selecting the right quality of excipients and lipids is essential.

Lipid nanoparticles (LNP) are commonly used for mRNA delivery; each lipid nanoparticle consists of four different lipids allowing the mRNA to be carried in it and protected from degradation. We offer custom and portfolio lipids to be able to create stable LNP.

Several critical aspects must be considered when selecting lipids. Lipid type, source and quality have a direct impact on the impurity profile and properties such as the particle characteristics, stability and release profile in the final formulation. To achieve reproducible results with the final formulation, consistent quality of lipids is required. This is dependent on the quality of the raw materials used to synthesize the lipids and appropriate material characteristics of the lipid itself.

If you are interested in mRNA or lipids custom manufacturing services please contact:  
[MerckMillipore.com/contactPS](https://www.MerckMillipore.com/contactPS)

# Our offer of raw materials for mRNA formulation

## Process Step



mRNA in aqueous solution

|        |   |
|--------|---|
| 137000 | Acetic acid (glacial) 100 % EMPROVE® EXPERT Ph Eur,BP,JP,USP  |
| 137002 | Citric acid anhydrous powder EMPROVE® EXPERT Ph Eur,BP,JP,USP,ACS                                   |
| 137003 | Citric acid monohydrate cryst. EMPROVE® EXPERT Ph Eur,BP,JP,USP,ACS                                 |
| 137007 | Hydrochloric acid fuming 37 % EMPROVE® EXPERT Ph Eur,BP,JP,NF,ACS                                   |
| 137046 | Sodium acetate anhydrous EMPROVE® EXPERT USP  |
| 128205 | Sodium acetate trihydrate EMPROVE® EXPERT Ph Eur,BP,ChP,JP,USP                                      |
| 137020 | Sodium hydroxide pellets suitable for the biopharmaceutical production EMPROVE® bio Ph Eur,BP,JP,NF |
| 100713 | Sulfuric acid 95 – 98 % EMPROVE® ESSENTIAL Ph Eur,BP,JPE,NF   |
| 137042 | tri-Sodium citrate dihydrate cryst. EMPROVE® EXPERT Ph Eur,BP,JP,USP,ACS                            |



Lipids in organic solvent

|            |   |
|------------|---|
| 137040     | 2-Propanol 70 % (v/v) EMPROVE® EXPERT USP                   |
| 100013     | Acetone EMPROVE® ESSENTIAL Ph Eur,BP,JPE,NF                 |
| 5786322900 | DMG PEG 2000  |
| 5002602900 | DOPE  |
| CH2900013  | DOPC  |
| CH2900047  | DPPC  |
| 5724952900 | DSG PEG 2000  |
| W2660      | DSPC  |
| 100967     | Ethanol 96 % EMPROVE® EXPERT Ph Eur,JP,USP                  |
| 100986     | Ethanol absolute EMPROVE® EXPERT Ph Eur,BP,JP,USP           |
| ARK2210    | Ethanol API   |
| 106008     | Methanol EMPROVE® ESSENTIAL Ph Eur,BP,JPE,NF                |
| 5002442900 | (R)-DODMA   |
| CH2900029  | (R)-DOTAP Cl  |
| 5002492900 | (R)-DOTMA Cl  |
| CH2900014  | (R,S)-DOTAP Cl  |
| CH2900030  | (S)-DOTAP Cl  |
| W004591    | Synthetic Cholesterol                                       |
| 104672     | Synthetic Cholesterol, extra pure, powdered Ph Eur,BP,JP,NF |



Ultrafiltration/  
Diafiltration &  
Final formulation

|               |  |
|---------------|--|
| <b>137036</b> | <b>di-Sodium hydrogen phosphate dihydrate EMPROVE® EXPERT Ph Eur,BP,USP<sup>1</sup></b>            |
| <b>137092</b> | <b>di-Sodium hydrogen phosphate heptahydrate EMPROVE® EXPERT DAC,USP<sup>1</sup></b>               |
| <b>137017</b> | <b>Sodium chloride EMPROVE® EXPERT Ph Eur,BP,JP,USP<sup>1</sup></b>                                |
| <b>137018</b> | <b>Sodium dihydrogen phosphate dihydrate EMPROVE® EXPERT Ph Eur,BP,USP,JPE<sup>1</sup></b>         |
| <b>137093</b> | <b>Sodium dihydrogen phosphate monohydrate EMPROVE® EXPERT BP,USP<sup>1</sup></b>                  |
| 103789        | Sucrose EMPROVE® EXPERT Ph Eur,ChP,JP,NF   |
| <b>108219</b> | <b>Tris(hydroxymethyl)aminomethane hydrochloride EMPROVE® EXPERT<sup>1</sup></b>                   |
| 108307        | Tris(hydroxymethyl)aminomethane (Trometamol) high purity EMPROVE® EXPERT Ph Eur,BP,ChP,JPC,USP,ACS |

<sup>1</sup>Endonuclease free products

# SAFC®

Pharma & Biopharma Raw  
Material Solutions

## The Emprove® Program Your fast track through regulatory challenges.

Ensuring the compliance of your pharma and biopharma products involves the compilation of a vast amount of data, which can be time and resource intensive. Our Emprove® Program provides comprehensive and up-to-date documentation to help you navigate regulatory challenges, manage risks, and improve your manufacturing processes.

Our Emprove® Chemicals portfolio contains over 400 pharmaceutical raw and starting materials. To address different levels of risk, and to simplify and streamline the selection process, the portfolio is divided into four categories: Emprove® Evolve, Essential, Expert and API. The Emprove® Expert category addresses higher risk applications where the lowest microbiological and endotoxin levels are of utmost importance.

The Emprove® Program also covers filter and single-use components, as well as selected chromatography resins and cell culture media. Each product portfolio is supported with Emprove® Dossiers.

Find out more at:  
[MerckMillipore.com/emprove](https://www.MerckMillipore.com/emprove)

The typical technical data above serve to generally characterize the product. These values are not meant as specifications and they do not have binding character. The product specification is available separately at: [MerckMillipore.com](https://www.MerckMillipore.com)

We provide information and advice to our customers on application technologies and regulatory matters to the best of our knowledge and ability, but without obligation or liability. Existing laws and regulations are to be observed in all cases by our customers. This also applies in respect to any rights of third parties. Our information and advice do not relieve our customers of their own responsibility for checking the suitability of our products for the envisaged purpose.

For additional information, please visit [MerckMillipore.com](https://www.MerckMillipore.com)  
To place an order or receive technical assistance, please visit [MerckMillipore.com/contactPS](https://www.MerckMillipore.com/contactPS)

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