CBG MEB | MEDICINES EVALUATION BOARD

Regulatory Considerations on mRNA Products in Cancer Therapy

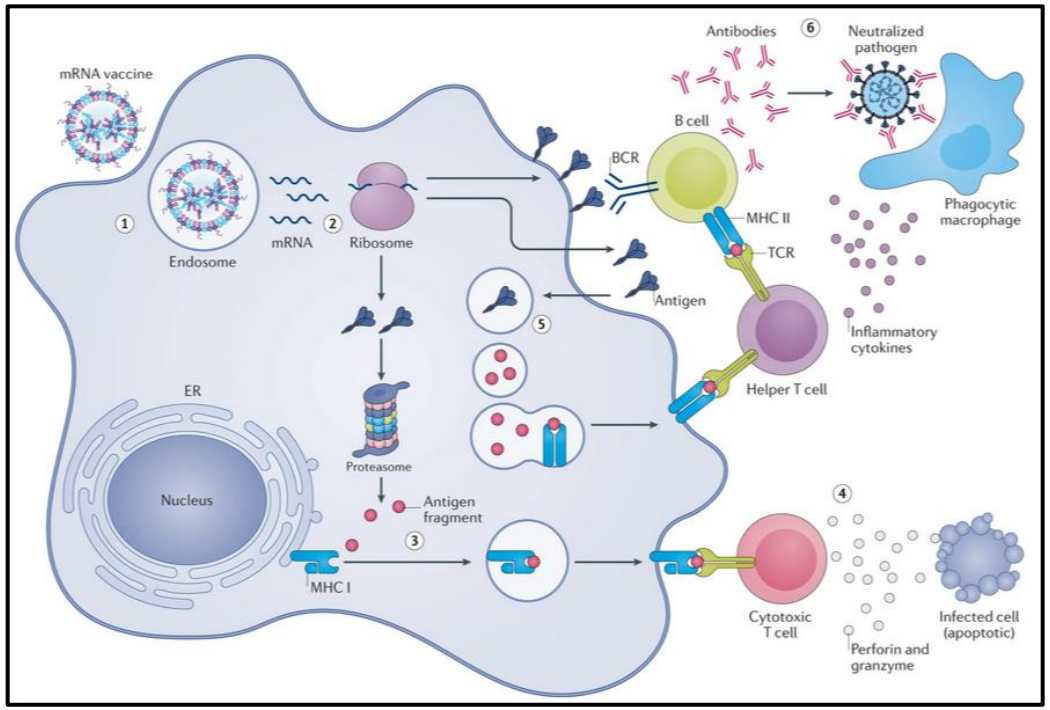
Marcel Hoefnagel
Senior Assessor Biopharmaceuticals, MEB

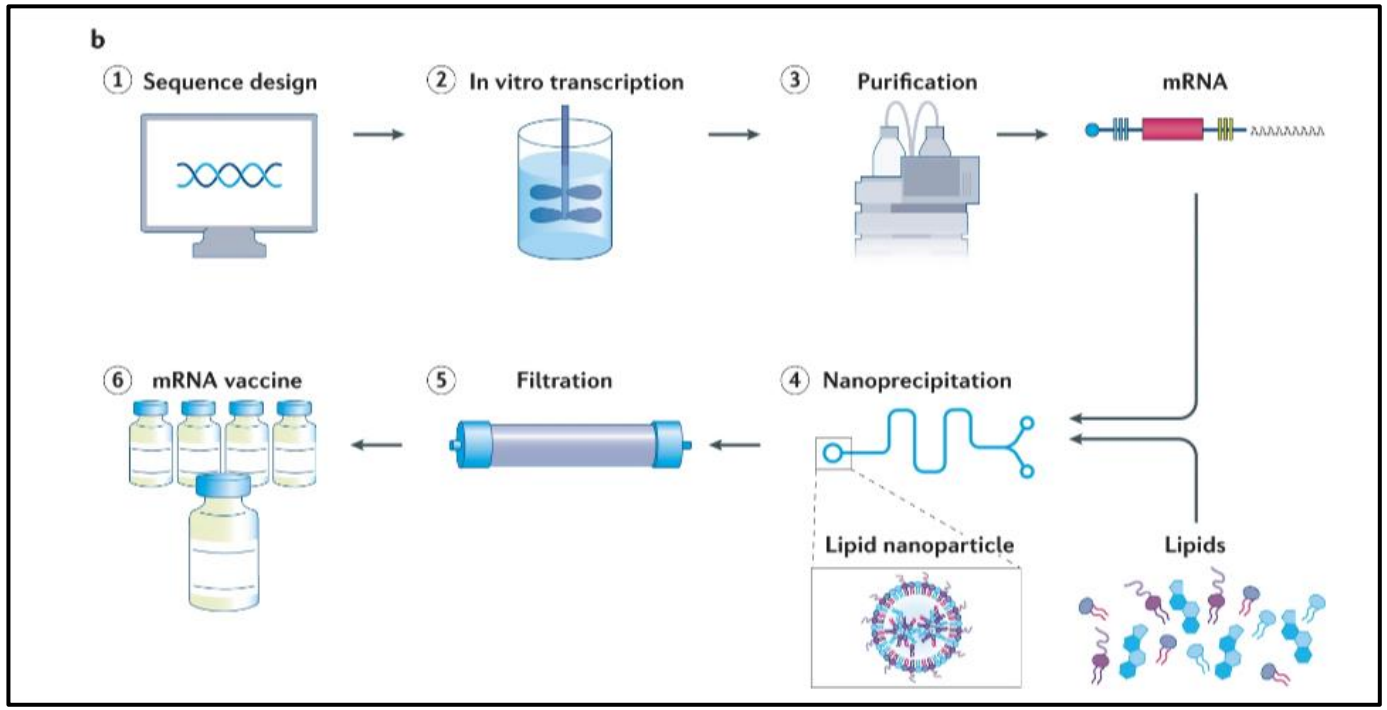
GOOD MEDICINES USED BETTER

DISCLAIMER: Personal views only, meant to initiate further discussion; may not necessarily reflect views/opinions of MEB, EMA or EDQM.

Outline

- General considerations
- mRNA Drug Substance manufacturing and testing
- mRNA Final Product manufacturing and testing

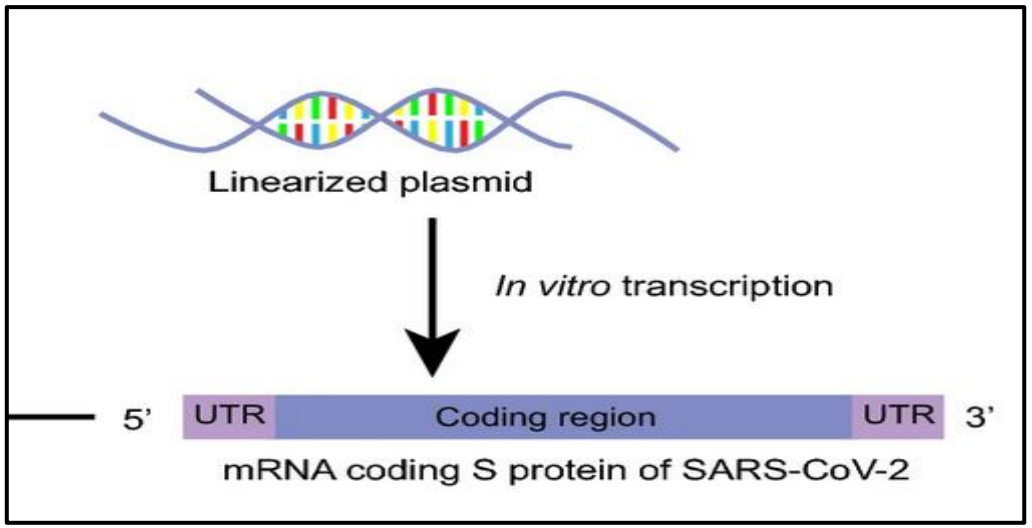




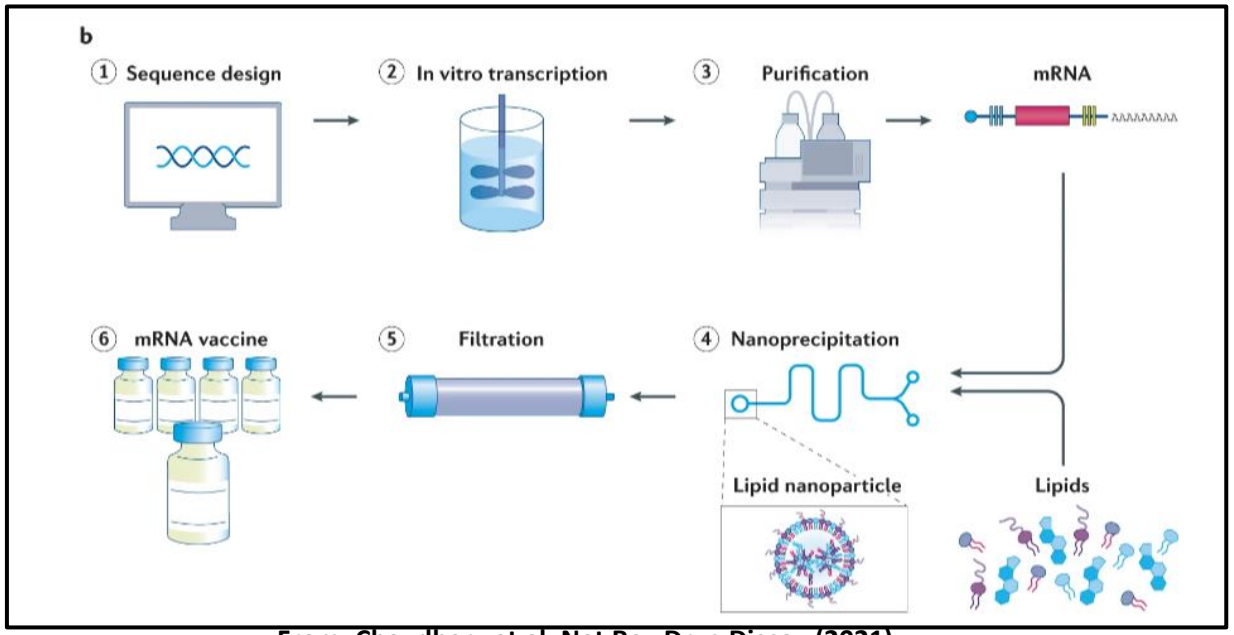
From: Chaudhary et al. Nat Rev Drug Discov (2021). https://doi.org/10.1038/s41573-021-00283-5

General considerations

- mRNA Products in Cancer therapy are Immunotherapy Products
- mRNA vaccines and therapeutics are regulated as biologicals
- Adequate control of materials, excipients, manufacturing process & final product equally important
- Covid-19 mRNA vaccines rapid & extensive regulatory experience
- mRNA therapeutics several mRNA encoding different antigens



From: Yi, Cet al, J Virol. Sin. 35, (2020).
https://doi.org/10.1007/s12250-020-00243-0



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Starting materials, Drug Substance definitions

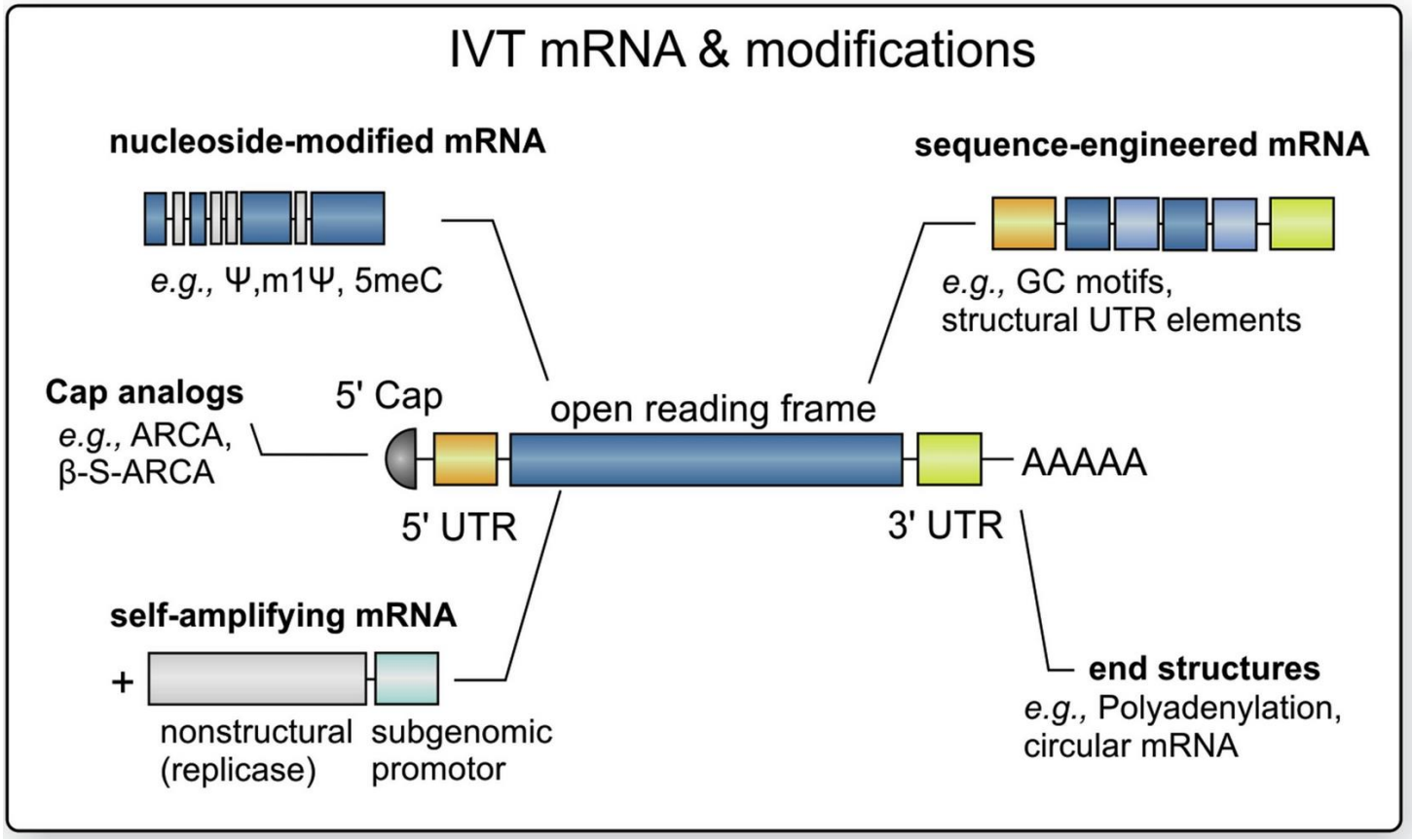
Drug Substance

- mRNA (incl. CAP, poly A tail)

Starting materials

- Linearised DNA plasmid (template)
- (Modified) Nucleotides
- Cap (analogs)
- Manufactured according to principles of GMP*

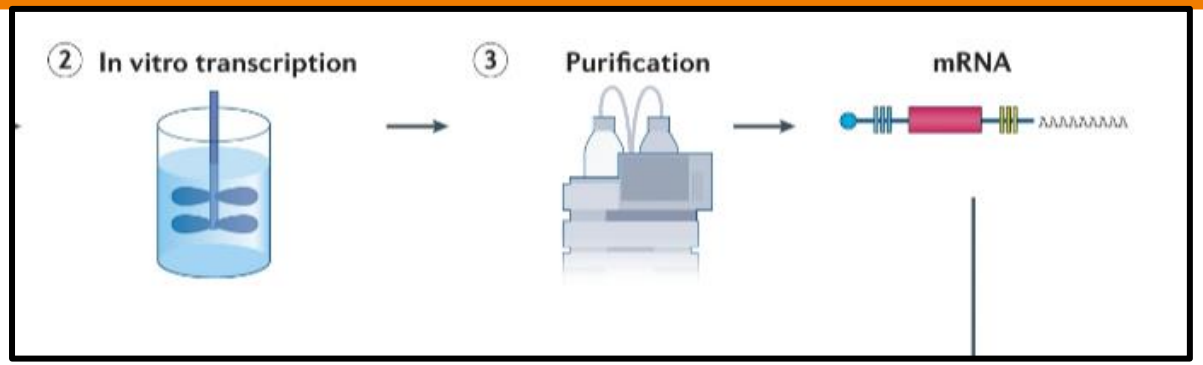
*Q&A in EMA/246400/2021

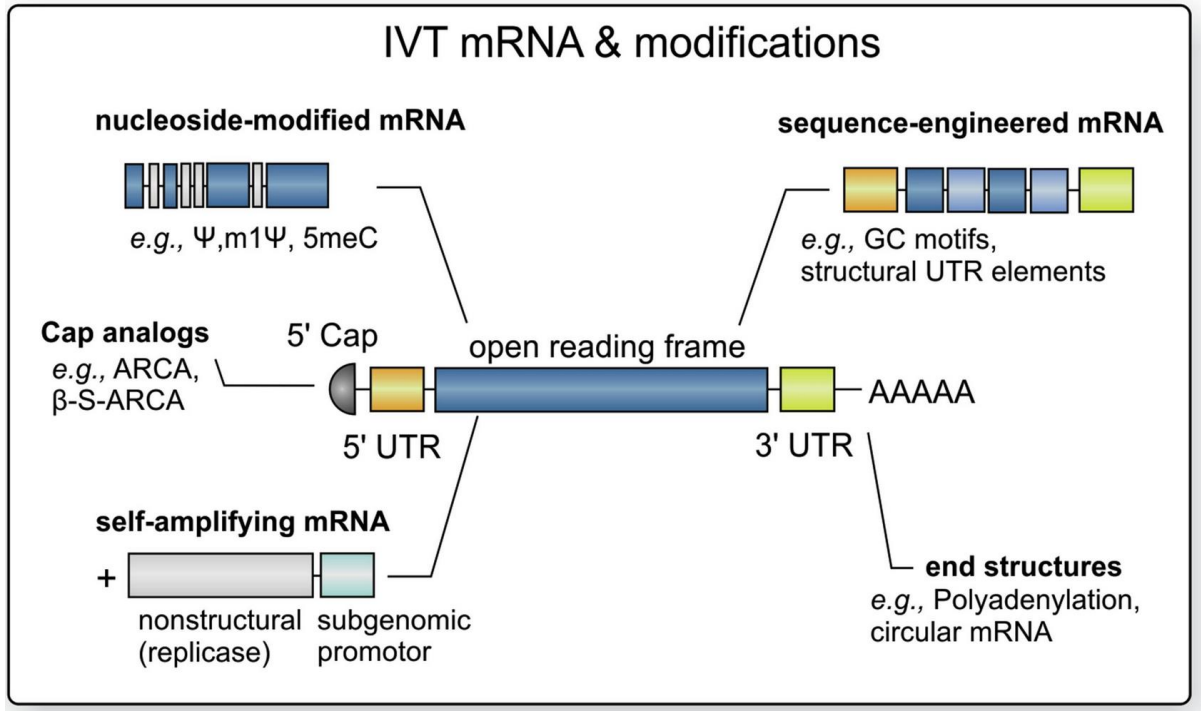


From Schoenmaker et al. https://doi.org/10.1016/j.ijpharm.2021.120586

Drug Substance manufacturing, characterisation & release

Attribute	Parameter	Method
Content	RNA concentration	Photometry/UV absorption
Identity	mRNA Identity	Sequencing/RT-PCR
Purity	mRNA Integrity (Full length, truncated, CAP, PolyA)	HPLC
	Capping efficiency	e.g. RP-HPLC, LC-MS
	Poly A tail length	
Impurities	Residual NTP	HPLC
	Residual CAP	HPLC
	Residual DNA template	
	Presence of dsRNA	
	Residual protein	
	Other impurities DTT, Ca2+ etc.	
Potency & purity	Expression Transcription fidelity	In-vitro translation assay NGS sequencing





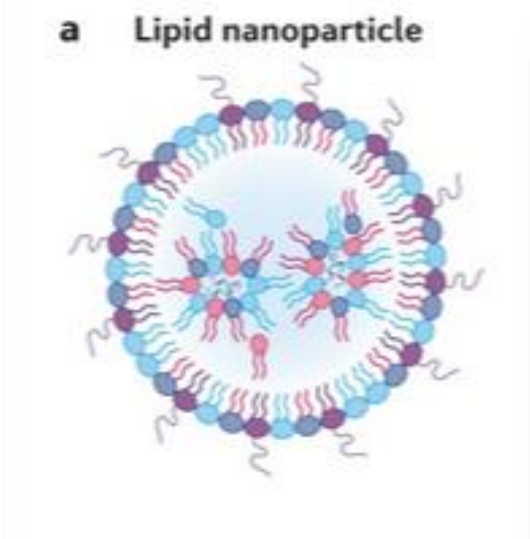
Final Product definitions & considerations

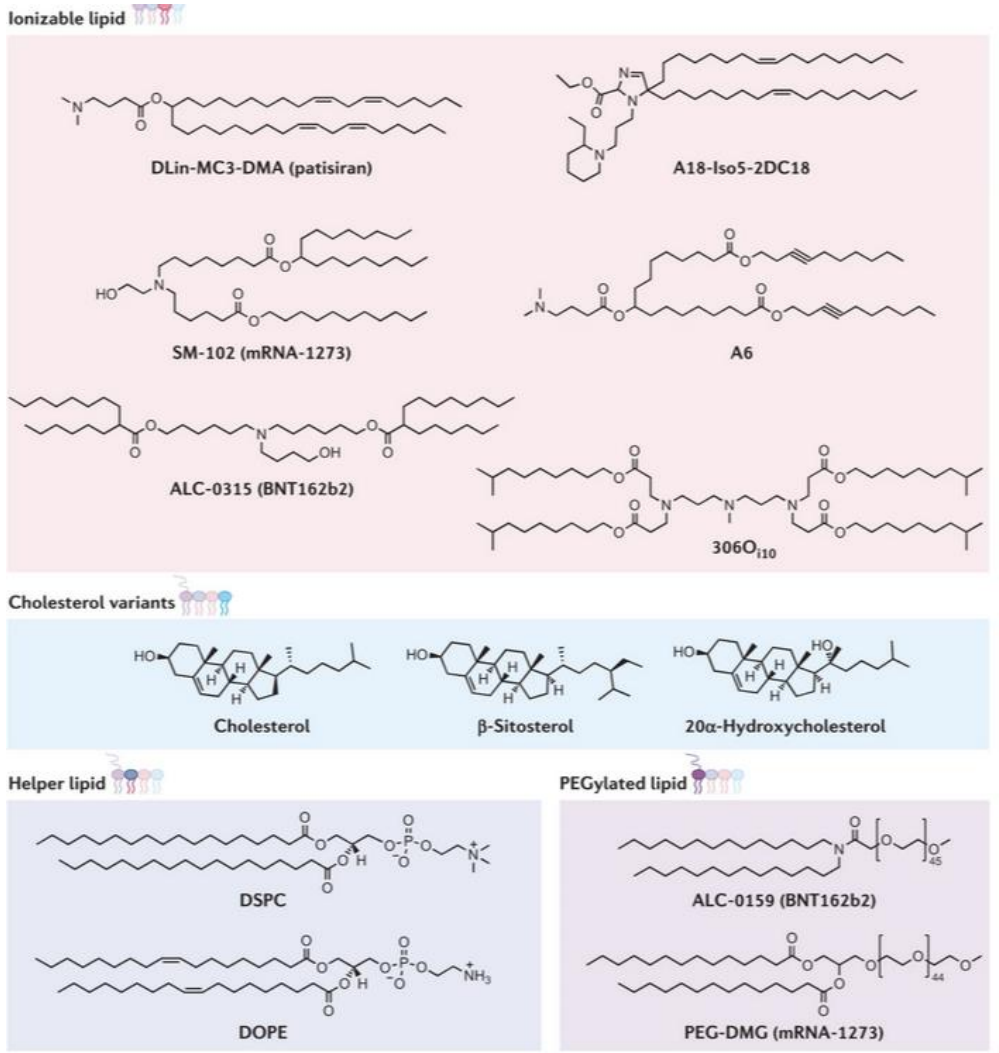
Final Product

- mRNA(s) in Lipid NanoParticles (LNP)
- Each mRNA (per antigen) formulated separately or combined
- Platform approach (process validation/stability)

Excipients

- Lipids
- Novel excipient?
- Quality: Impurities (lipid & solvents)
- Ensure comparability if >1 supplier
- If LNP pre-formulated: DP intermediate





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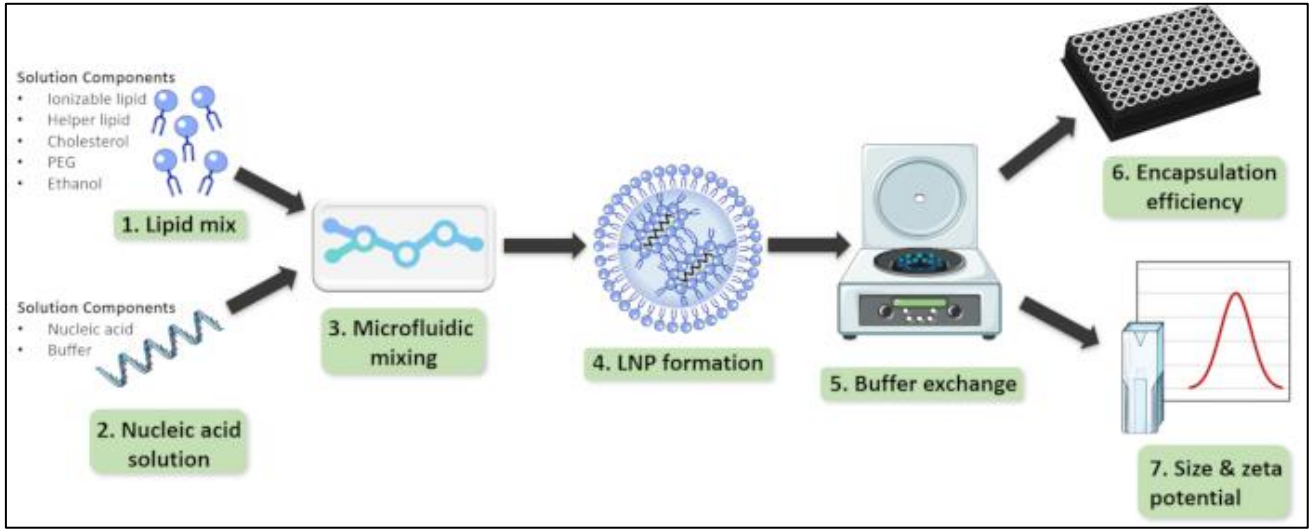
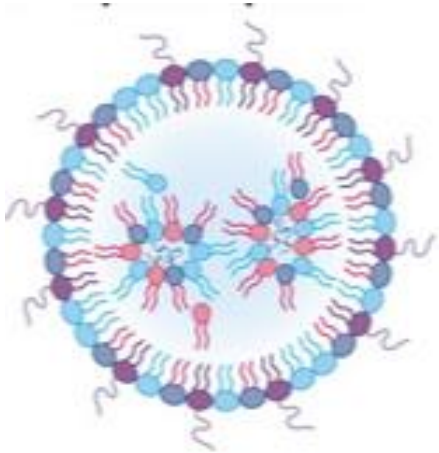
Final Product manufacturing, characterisation & Release testing

Attribute	Parameter	Method
Identity	RNA identity/identities	
Content	RNA content (of each mRNA)	
Composition & Strength	Particle Size Polydispersity Zeta potential	
	Lipid quantity/content	
	RNA/Particle Ratio	
Purity	RNA integrity (Size, CAP, PolyA)	
Impurities	Free RNA	
	Lipid degradation Residual solvents	
Potency	Transfection efficiency	Cell based assay PCR
	mRNA translation	Cell based assay LC-MS
	Expression efficiency	Cell based assay



From Bailey-Hytholt et al. Bioengineering 2021 doi: 10.3791/62226



Concluding remarks

- mRNA therapeutics are regulated as biologicals
- Quality requirements in line with mRNA vaccines
- Transcription fidelity
- Quality of Excipients (constituents LNP)
- LNP control (Particle size, Polydispersity)
- Stability & Storage Conditions