Process-cost modelling for producing 100 million COVID-19 mRNA vaccine doses per year at injectable medicines manufacturing sites

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1. Executive summary

To understand how scaling up mRNA vaccine manufacturing can be accelerated, Médecins Sans Frontières (MSF) asked the Imperial College of London to analyse the suitability of injectable medicines manufacturers as prospective mRNA vaccines manufacturers and estimate the resources required to manufacture up to 100 million doses of mRNA vaccines annually at such facilities. This work is based on information obtained or estimated for the two WHO-listed mRNA vaccines, BioNTech-Pfizer's BNT162b2 vaccine (30 micrograms [μg] of mRNA per vaccine dose) and Moderna's mRNA-1273 vaccine (100 μg of mRNA per vaccine dose).

These findings, which build on previous research, indicate that injectable medicines manufacturers are well positioned to produce mRNA vaccines thanks to compatibilities in

production processes and limited additional facility space required. Certainly, there are also some gaps in injectable medicines manufacturers capacities that will require supplemental equipment, investments or training, and a more detailed gap analysis will be required on a case-by-case basis for any prospective manufacturer. However, this analysis and recent examples of mRNA vaccine technology transfer suggest that injectable medicines manufacturers meeting certain prerequisites could be able to manufacture mRNA vaccines following technology transfer (even without prior vaccine manufacturing experience).

Based on this analysis, annual production capacity of 100 million doses of mRNA vaccines can be established in an existing injectable medicines production facility with minimal additional manufacturing footprint (160-240 m^2). The estimated total cost needed for starting up mRNA vaccine manufacturing in such facilities and producing 100 million doses is US$127.1 million for the BNT162b2 vaccine and $270 million for the mRNA-1273 vaccine (**Table 1**). This estimate includes facility-related requirements, consumables, equipment, materials, labour, other resources for drug substance production and fill and finish requirements.

This analysis focuses specifically on the capabilities of injectable medicines manufacturers and additional capacity and resources needed to add mRNA production capacity to these sites. For a more detailed description of the overall mRNA production process, please see: How to Make Enough Vaccine for the World in One Year (Kis and Rizvi, 2021). ***Figure 1*** *below offers a summary of the mRNA production process.*

Table 1. Estimated total annual cost needed to start up mRNA vaccine manufacturing in injectable medicines facilities and produce 100 million doses of mRNA vaccines

Cost category	Costs for starting up and producing 100 million **mRNA-1273** doses	Costs for starting up and producing 100 million **BNT162b2** doses
Total operating costs for drug substance[a]	$241.6 million	$88.1 million
Facility-related operating costs[b]	$4.3 million	$2.5 million
Consumables and single-use equipment costs	$59.5 million	$17.5 million
Total costs of raw materials	$162.9 million	$54.2 million
Total costs of labour	$12.7 million	$11.9 million
Total operating fill and finish costs for producing 100 million doses[c]	$28.4 million	$39 million
TOTAL	**$270 million**	**$127.1 million**

[a] The total operating cost includes the annualized facility-dependent capital costs.
[b] Facility-related operating costs include the annualized capital costs, facility maintenance costs, insurance, local taxes and other factory expenses.[1]
[c] Includes the cost of the empty glass vials, however, the cost of the drug substance is not included in this estimate. This includes the annualized capital cost for the fill and finish facilities.

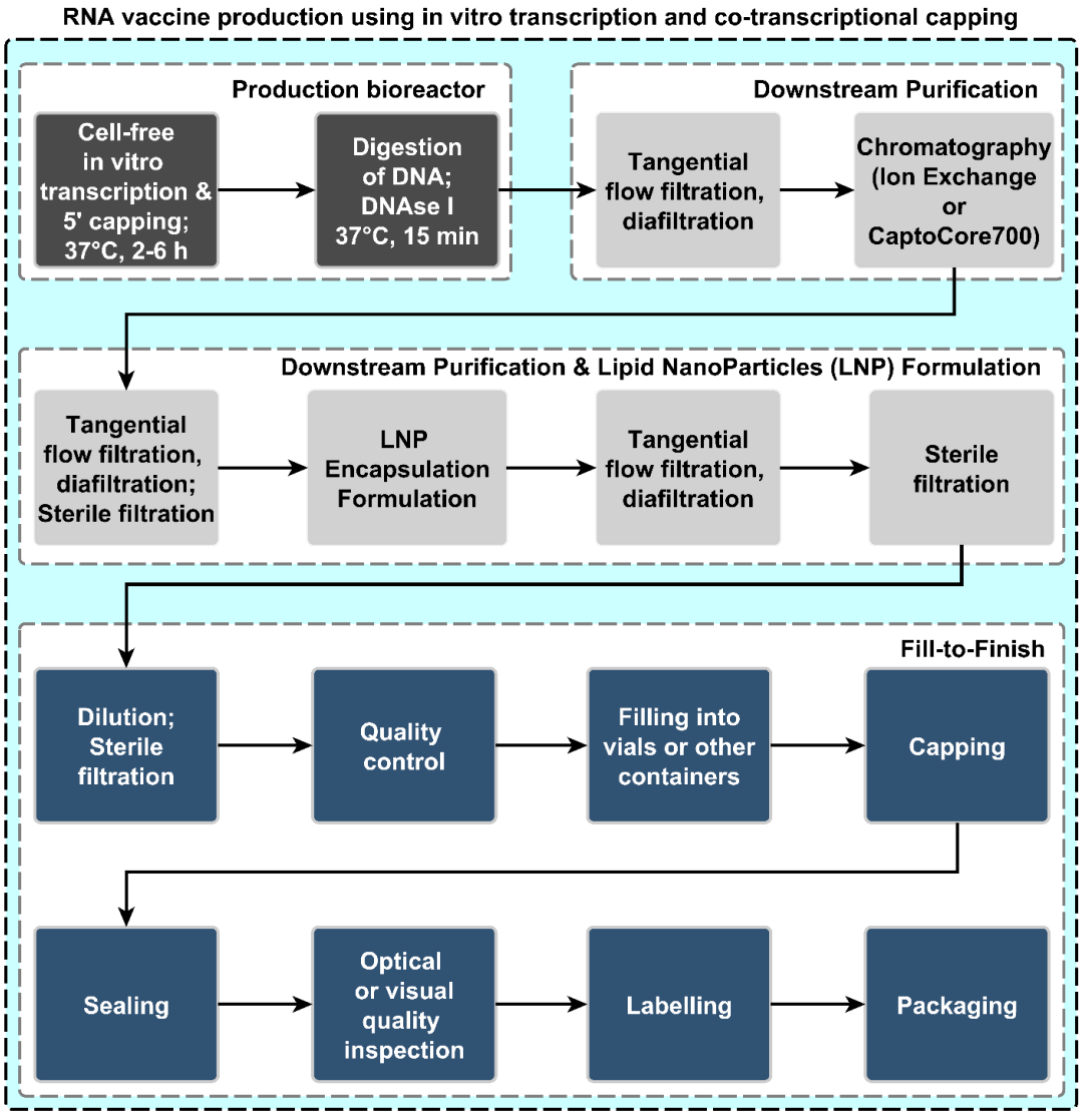

Figure 1. Process flow diagram for mRNA drug substance production[d]

Process flow diagram for mRNA drug substance production (a.k.a. active pharmaceutical ingredient production, bulk production or primary manufacturing) and drug product manufacturing (a.k.a. fill-to-finish or secondary manufacturing): The mRNA drug substance is synthesized in the production bioreactor using the in vitro transcription reaction using the T7 RNA polymerase enzyme and is 5' capped co-transcriptionally. After mRNA synthesis, the template DNA is digested using the DNAse I enzyme. Next, the downstream purification starts with tangential flow filtration (TFF) where the mRNA molecule is retained by the filter and the other, smaller components of the reaction mix flow through the TFF filter. Next, the protein enzymes can be further removed using a chromatography unit operation, such as ion exchange chromatography, oligo dT, CaptoCore 700 chromatography, or hydroxyapatite chromatography. Next, the buffer is replaced for the formulation buffer in a second TFF step and then the solution is sterile filtered. This solution then enters the lipid nanoparticle (LNP) encapsulation unit operation which is the bottleneck of mRNA drug substance production. After formulation, the LNP encapsulated mRNA solution enters a third TFF for diafiltration then an optional dilution step is carried out followed by a sterile filtration operation. The sterile LNP-encapsulated mRNA solution is then transferred to the fill-to-finish section. There, the solution can be further diluted and sterile filtered. Next, the formulated mRNA solution undergoes quality control and is filled into vials or other containers. The vials are then capped, sealed, inspected, labelled and packaged into secondary and tertiary packaging.[2-11]

[d] Figure 1 reproduced with permission from Public Citizen.

2. Suitability of injectable medicines production facilities to produce mRNA vaccine

Because mRNA vaccines are produced without using living cells, expertise in biological medicines or vaccines production is not essential for mRNA vaccine production. In fact, some mRNA vaccine developing and manufacturing companies, such as Moderna, BioNTech and CureVac did not have experience in cell-based biological production or any large-scale pharmaceutical production to that effect prior to this pandemic. Although some contract manufacturers currently producing mRNA vaccines for one of the three companies, such as Lonza, do have previous expertise in the area of biologicals manufacturing, in a recent announcement, Moderna's mRNA drug substance (or active pharmaceutical ingredient) will also be produced at Laboratorios Farmacéuticos ROVI, S.A. (ROVI) in Spain,[12] a company which has no experience in cell-based manufacturing. The only 'biological' medicine ROVI produces is enoxaparin that is chemically extracted from porcine intestinal mucosa.[13] Hence, the mRNA vaccine production process is suitable for integration in facilities that produce aseptically prepared injectable medicines based on the nature of the product and of the production process.

2.1. Product and quality testing compatibility

The quality attributes of the mRNA vaccine drug substance and drug product are evaluated using both structural and functional assays. These quality control tests combine molecular biology type assays and assays used in case of injectable medicine manufacturing.[14,15]

The personnel required to perform the molecular biology type of assays needs to receive the relevant training and qualifications. Personnel with experience in both biologics and injectable medicines manufacturing needs to be re-trained and re-qualified for mRNA vaccine manufacturing. Training of personnel can be achieved at the WHO COVID-19 mRNA Vaccine Technology Transfer Hubs for technology transfer and training, such as the Hub being launched in South Africa.[16] Alternatively, quality testing for both incoming raw materials and outgoing products can be (at least partially) outsourced to the relevant certified organisations.

2.2. Production process compatibility

The mRNA vaccine manufacturing is a synthetic biochemical process, whereby an enzyme is used to synthesise the mRNA vaccine drug substance based on a DNA template. As a consequence, the complexities associated with cell-based biologics production are not present in the mRNA vaccine drug substance production process. These complexities include maintaining cell viability, culturing cells under conditions which ensure that their gene expression regulation pathways, cell signalling pathways and all functions of the cells are optimal for producing the biologic product of interest (e.g. a recombinant protein, a virus-like particle or a virus of an inactivated viral vaccine). In addition, cell-based processes are slower, with the upstream and mid-stream section of the process taking up to a few months, and contamination from bacteria and viruses must be prevented during this longer period.

Since the mRNA vaccine production process is not a biologics production process, mRNA vaccines can also be produced in existing current Good Manufacturing Practices (cGMP)

facilities where injectable medicines are being produced. The placement of the mRNA vaccine production process into such an injectable medicine producing facility is also favourable considering the simpler, smaller scale and faster nature of the mRNA production process. In addition, the mRNA production process is predominantly established based on standard unit operations and equipment, such as tangential flow filtration and ion-exchange or oligo dT or core beads chromatography unit operations. To produce the mRNA vaccine drug substance, the injectable medicine producing facility has to be fitted with the equipment required for mRNA vaccine production, however most of this equipment (e.g. downstream purification equipment) is also available in a single-use format.

Due to the use of predominantly standard equipment, personnel operating injectable medicine producing facilities could, in principle, also operate the small-scale unit operations required for mRNA vaccine production. The only unit operation which is new is the lipid nanoparticle (LNP) formulation step whereby the mRNA is enclosed into LNPs, for increased stability and for delivery into the cells of the human body. LNP formulation has been achieved using microfluidics mixers at lab-scale, however at production scale impingement jet mixers and pressurized tanks are used.[17,18] In addition, during the production of the mRNA drug substance, RNase-free environment should be maintained to avoid the degradation of the mRNA molecule. Therefore, the personnel should be trained and qualified to operate all unit operations for the mRNA drug substance production under conditions which prevent mRNA degradation. Maintaining an RNase-free conditions in the production is also facilitated by the 'closed' nature of the mRNA drug substance production process, meaning that the production process is hermetically sealed from the environment.[18]

2.3. Facility footprint requirements

The equipment requirements for producing 100 million doses of mRNA vaccine drug substance per year have been calculated using the SuperPro Designer Version 11, Build 2 from Intelligen, Inc.'s bioprocess modelling tool.[1,19] Next, based on the equipment sizes, the facility footprint has been estimated, considering the additional space required to operate the equipment. Results are shown in **Table 2** for the BNT162b2 vaccine with 30 µg of mRNA per dose and in **Table 3** for the mRNA-1273 vaccine with 100 µg of mRNA per dose.

The size of each piece of equipment was determined based on the material balance in the production process and by allowing a maximum of 90% solution volume relative to the equipment volume, thus accounting for a minimum of 10% buffer in the equipment volume.[1] The SuperPro Designer bioprocess models for mRNA vaccine drug substance production have been updated from models from previous publications.[2,20] In the models generated for this report, the production processes have been scaled down to produce 100 million doses worth of drug substance annually. In addition, the cycle time slack (i.e. gap between subsequent batches) has been increased to 12 hours, to more accurately approximate the commercial-scale mRNA vaccine drug substance production processes; in case of BioNTech's process, batches are completed every 3-7 days.[18] In the model updated for this report, 264 batches are competed per year, when scheduling is performed in staggered mode (overlapping the upstream and downstream of subsequent batches) (**Figure 1**).

Based on these modelling results it was calculated that a process scale corresponding to 4.32 L bioreactor working volume is required to produce 100 million doses of drug substance per

year in case of the 30 µg of mRNA per dose vaccines. This scale has been rounded up to 5 L bioreactor working volume to obtain a scale which can be more easily standardised in terms of equipment and unit operations. The scale increase would result in an overproduction to account for losses that can occur during fill-and-finish operations. In case of the mRNA vaccine with 100 µg of mRNA per dose, a process scale of 14.43 L bioreactor working volume is required to produce 100 million drug substance doses per year. This scale has been rounded up to a 15 L bioreactor working volume, for the same reasons as described above.

It is estimated that in total 160-190 m^2 floor area is required for producing 100 million drug substance doses of the BNT162b2 vaccine with 30 µg of mRNA per dose. On the other hand, 200-240 m^2 floor area requirement is estimated for producing 100 million doses of drug substance doses of the mRNA-1273 vaccine with 100 µg of mRNA per dose. The facility footprint of the buffer preparation and production rooms consists of:

- 36-48% of the buffer preparation room area,
- 10-14% of the mRNA synthesis room area,
- 20-25% of the mRNA purification room area,
- 5-10% of the mRNA-LNP formulation room area,
- 11-16% of the mRNA-LNP purification room area (**Figure 2**).

It is worth noting that, in general, approximately 25% of a biopharmaceutical plant surface area is dedicated to manufacturing and approximately 75% is allocated to support areas, including offices, warehouses, quality control (QC) laboratory, and mechanical (utilities) and electrical rooms.[21] It is expected that the mRNA vaccine drug substance production suite would use existing support areas serving other manufacturing activities taking place at the receiving facility.

Table 2. List of equipment and estimate of facility footprint for producing 100 million doses of BNT162b2vaccine drug substance per year, with 30 µg of mRNA per dose, at the 5 L bioreactor working volume scale

Section/Room	Equipment Name	Equipment size [L or m^2 membrane area]	Estimated floor area [m^2]
Buffer solution preparation	Mixing & storage tank - mRNA synthesis buffer prep and storage	7 or 10 L	60-80
	Mixing & storage tank - TFF1 buffer (e.g. KCl buffer) perp and storage	1000 L	
	Mixing & storage tank - Core Beads (e.g. Capto Core 700) chromatography buffer (e.g. KCl buffer) perp and storage	500 L	
	Mixing & storage tank - TFF2 buffer (e.g. Na Citrate buffer) perp and storage	500 L	
	Mixing & storage tank - TFF3 buffer (e.g. PBS) perp and storage	1000 L	
	Laminar flow safety cabinet	N.A.	
	Laminar flow safety cabinet	N.A.	

	Laminar flow safety cabinet	N.A.	
	Mixing & storage tank - Ethanol solution with 4 lipids for LNP formulation[e]	100 L	10-12
mRNA synthesis	In vitro synthesis Bioreactor	7 or 10 L	18-22
	Storage tank	7 or 10 L	
	Laminar flow safety cabinet	N.A.	
mRNA purification	Tangential Flow Filter 1 (TFF1)	5 m^2 membrane area	35-45
	Storage tank	100 L	
	Core Beads (e.g. Capto Core 700) chromatography	0.5 L bed volume	
	Storage tank	100 L	
	Tangential Flow Filter 2 (TFF2)	4 m^2 membrane area	
	Sterile filtration (e.g. 0.2 µm)	N.A.	
	Mixing & storage tank (dilution in acetate buffer)	200 L	
mRNA-LNP formulation	Reactor - Pressurized ethanol	50[f]	10-12
mRNA-LNP purification	Mixing & storage tank (2x dilution in PBS)	800 L	20-25
	Tangential Flow Filter 3 (TFF3)	5 m^2 membrane area	
	Sterile filtration (e.g. 0.2 µm)	N.A.	
	Storage tank or bags (volume depends on concentration)	80 L	
		TOTAL facility floor area [m^2]	160-190

[e] Depending on local regulations and safety requirements, the ethanol solution might be prepared and stored in a separate dedicated room suitable for flammable substances.

[f] The size of this equipment may vary depending on how the LNP formulation unit operation was scaled up, details of this are not available publicly. Values presented here are based on BioNTech's Marburg facility where the mRNA-LNP formulation at the 5 L bioreactor working volume scale takes place in a separate room for safety reasons, this room contains one 50-L pressurized formulation tank.[18] The formulation at the Pfizer facility in Kalamazoo, MI, USA is performed using impingement jet mixers, thereby the facility footprint might be different.[17]

Table 3. List of equipment and estimate of facility footprint for producing 100 million doses of mRNA-1273 vaccines drug substance per year, with 100 µg of mRNA per dose, at the 15 L bioreactor working volume scale

Section/Room	Equipment Name	Equipment size [L or m^2 membrane area]	Estimated floor area [m^2]
Buffer solution preparation	Mixing & storage tank - mRNA synthesis buffer prep and storage	20 L	70-100
	Mixing & storage tank - TFF1 buffer (e.g. KCl buffer) perp and storage	2000 L	
	Mixing & storage tank - Core Beads (e.g. Capto Core 700) chromatography buffer (e.g. KCl buffer) perp and storage	1000 L	
	Mixing & storage tank - TFF2 buffer (e.g. Na Citrate buffer) perp and storage	1000 L	
	Mixing & storage tank - TFF3 buffer (e.g. PBS) perp and storage	2000 L	
	Laminar flow safety cabinet	N.A.	
	Laminar flow safety cabinet	N.A.	
	Laminar flow safety cabinet	N.A.	
	Mixing & storage tank - Ethanol solution with 4 lipids for LNP formulation[g]	200 L	12-15
mRNA synthesis	In vitro synthesis Bioreactor	20 L	20-25
	Storage tank	20 L	
	Laminar flow safety cabinet	N.A.	
mRNA purification	Tangential Flow Filter 1 (TFF1)	15 m^2 membrane area	45-55
	Storage tank	200 L	
	Core Beads (e.g. Capto Core 700) chromatography	1.5 L bed volume	
	Storage tank	200 L	
	Tangential Flow Filter 2 (TFF2)	12 m^2 membrane area	
	Sterile filtration (e.g. 0.2 µm)	N.A.	
	Mixing & storage tank (dilution in acetate buffer)	600 L	
mRNA-LNP	Reactor - Pressurized ethanol	50[h]	10-12

[g] Depending on local regulations and safety requirements, the ethanol solution might be prepared and stored in a separate dedicated room suitable for flammable substances.

[h] The size of this equipment may vary depending on how the LNP formulation unit operation was scaled up, details of this are not available publicly. Values presented here are based on BioNTech's Marburg facility where the mRNA-LNP formulation at the 15 L bioreactor working volume scale takes place in two separate rooms for safety reasons, each room containing one 50-L pressurized formulation tank per room.[18] The formulation at the Pfizer facility in Kalamazoo, MI, USA is performed using impingement jet mixers, thereby the facility footprint might be different.[17]

formulation	Reactor - Pressurized ethanol	50[h]	10-12
mRNA-LNP purification	Mixing & storage tank (2x dilution in PBS)	2000 L	30-35
	Tangential Flow Filter 3 (TFF3)	15 m^2 membrane area	
	Sterile filtration (e.g. 0.2 µm)	N.A.	
	Storage tank or bags (volume depends on concentration)	200 L	
		TOTAL facility floor area [m^2]	200-240

A general layout of the facility floor space is shown below in **Figure 2**.

Depending on local regulation, the unit operations involving ethanol (e.g. ethanol storage and LNP formulation) may or may not require separate rooms. In addition, the purification of the mRNA-LNP complexes following formulation can take place in the same room where the mRNA is purified.

The water for injection (WFI) requirement is approximately 2200 m^3 per year for producing 100 million doses of the BNT162b2 vaccine with 30 µg of mRNA per dose. The highest instantaneous demand is circa 2,600 kg of WFI per hour, thus the WFI throughput of the facility, where mRNA vaccines are manufactured based on the modelled process, should match this demand. The highest cumulative WFI demand over 6-hour intervals is approximately 8,000 L; this information can be useful for assessing the size of the WFI storage tank present at the existing injectable medicines producing facilities. The time-averaged WFI consumption rate over a 6-hour period is approximately 1,300 kg of WFI per hour; this information can be useful in assessing the throughput of the WFI distilling apparatus (aka still). These WFI demand values include the WFI present in raw materials, WFI used in the process (e.g. for buffer preparation), WFI used for cleaning/rinsing and water/WFI used as heat transfer agent.

For producing 100 million doses per year of an mRNA vaccine with 100 µg of mRNA per dose, which is equivalent to Moderna's mRNA-1273 COVID-19 vaccine, the annual WFI demand is 6400 m^3 per year. The highest instantaneous WFI demand is approximately 5,100 kg per hour, thus the WFI throughput of the WFI system (generally consisting of a still [reverse osmosis or membrane filtration] and a storage tank) should match this demand. The highest cumulative WFI demand over 6-hour intervals is approximately 23.5 kL; this information can be useful for assessing the size of the WFI storage tank present at the existing injectable medicines producing facilities. The time-averaged WFI consumption rate over a 6-hour period is approximately 3,900 kg of WFI per hour; this information can be useful in assessing the throughput of the still. These WFI demand values include the WFI present in raw materials, WFI used in the process (e.g. for buffer preparation), WFI used for cleaning/rinsing and water/WFI used as heat transfer agent.

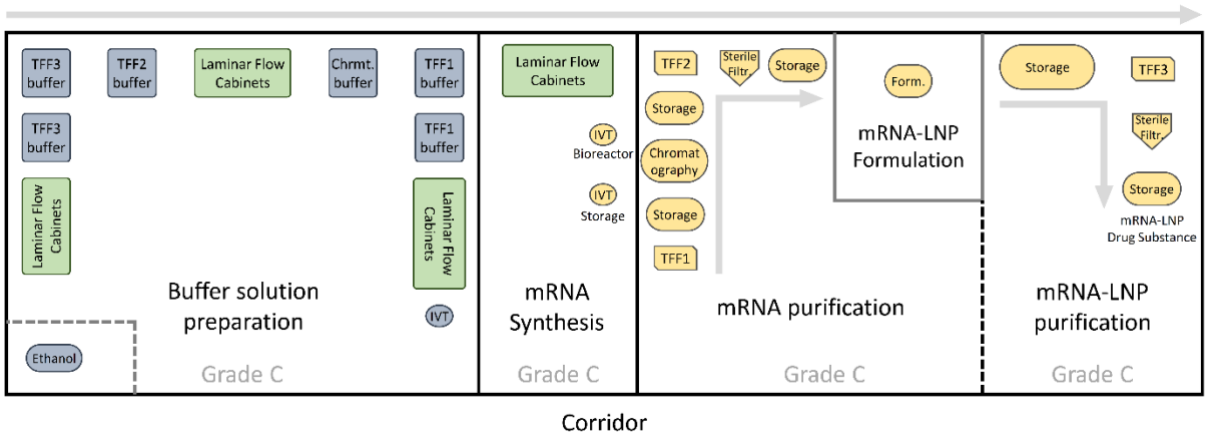

Figure 2. Generic layout of a possible mRNA-LNP vaccine drug substance production facility

*The production can take place based on a closed, sealed process housed in EU cGMP grade C rooms. The number of rooms depends on the local regulatory and safety requirements for example for handling flammable ethanol. The production rooms include the buffer preparation room, the mRNA synthesis room, the mRNA purification room, the mRNA-LNP formulation room and the mRNA-LNP purification room, as described in **Tables 2** and **3**. The mRNA purification and mRNA-LNP purification can also take place in the same room.*

Following the production of the mRNA vaccine drug substance, and also drug product, the mRNA material is stored at -80°C in order to prevent degradation. Depending on the amounts that need to be stored additional ultra-low temperature freezer capacity should also be installed. These -80°C freezers generate heat and the HVAC system should be capable to remove the excess heat generated by the -80°C freezers.[22]

2.4. Potential gaps to address for full mRNA vaccine manufacturing integration

As described above an injectable medicine producing facility can house an mRNA vaccine drug substance production process due to the similarities in terms of unit operations, overlaps in quality testing and skills of personnel, as well as in the type of on-site utilities (e.g. WFI systems).

To further enhance the integration of an mRNA vaccine drug substance production process into an injectable medicine production facility the following issues should be addressed:

- Training and qualifying the personnel to perform the mRNA-specific (molecular biology-type) quality testing;
- Training and qualifying the personnel to run the LNP formulation unit operation (and any other unit operations which are new at the tech-transfer receiving end);
- Training the personnel to work under RNase-free conditions;
- Ensuring that the required production equipment and QC equipment and facilities are available;
- Ensuring that the production facility follows the local regulatory and safety guidelines (including decontamination, biowaste handling of synthetic DNA and RNA), and if necessary placing the pressurised ethanol tank into a separate room, which is suitable for handling flammable substances;
- Ensuring that the facility has sufficient HVAC capacity to remove the excess heat generated by the ultra-low temperature freezers.

These issues should be addressed on a case-by-case basis and a detailed gap analysis should be carried out to ensure that the receiving facility will be optimally positioned to produce safe and effective mRNA-LNP vaccines.

3. Resources required for producing 100 million mRNA vaccine doses per year

The resource requirements for producing 100 million doses of mRNA vaccines were modelled using SuperPro Designer assuming batch operation mode.

The SuperPro Designer bioprocess simulation tool which performs mass balance calculations, determines the size of the equipment, calculates labour requirements, schedules the operations and procedures, and performs economic calculations both for capital costs and operating costs. SuperPro Designer is linked to databases of chemicals, consumables, equipment, and other resources. The production batches were scheduled for maximising equipment utilisation, thus maximising the number of production batches per year. However, the production process was not de-bottlenecked. The results presented in this report are based on previously published work.[2,3] The biomanufacturing models presented have been updated to include the latest developments in this rapidly evolving field.

It is assumed that the facility where the 100 million mRNA vaccine doses will be produced will rely on the supply chain of the technology originators to acquire raw materials and consumables. Thus, the technology-receiving facility/company will benefit from the advantages of the economies of scales when purchasing these components required for vaccine manufacturing. It was also assumed that the mRNA vaccine production process will be placed into existing facilities (e.g. cGMP-certified injectable medicine manufacturing facilities) and the production process will be established predominantly on single-use equipment. The results presented here are also based on the assumption that production is carried out at steady state, following the validation and ramp-up phase, thus the utilisation of the facility is maximised.

The scale of the production processes was expressed based on the working volume of the production bioreactor and the scale in this study was set to meet the target annual demand of 100 million doses for the two vaccines shown in **Table 4**. As shown therein, the amount of mRNA required to produce 100 million doses per year is different for the two vaccines due to the differences in the amount per dose. Consequently, the scale of the production process required to produce 3.16 kg of the BNT162b2 vaccine (BioNTech-Pfizer) annually is smaller compared to the production process scale needed to produce 10.53 kg of the mRNA-1273 vaccine (Moderna) annually. The total production cost for manufacturing 100 million doses per year, including both drug substance production costs and fill-and-finish costs, is $270 million per year for the mRNA-1273 vaccine and $127 million per year for the BNT162b2 vaccine, as shown below in **Table 4**.

Table 4. List of mRNA vaccines considered in this study and the amounts of mRNA required for 100 million doses

Developer	Vaccine name	mRNA per dose [μg/dose]	Doses per person	mRNA required for 100 million doses [kg][i]	Total cost for 100 million doses per year [USD/year][j]	Ref.
Moderna Inc.	mRNA-1273	100	2	10.53	$270 million	15, 23
BioNTech SE; Pfizer Inc.	BNT162b2	30	2	3.16	$127 million	24, 25

3.1. Facility-related requirements for drug substance production

Due to differences described above in the amount of mRNA required for 100 million doses, the production scales for producing these two vaccines are also different. The BNT162b2 production scale corresponds to 5 L bioreactor working volume, whereas the mRNA-1273 production scale corresponds to 15 L bioreactor working volume. In both cases, one production line would be required per facility. Due to these differences in the production scales, the facility related requirements and production costs are also different, as shown below in **Table 5**.

The facility-related operating costs amount to approximately $2.5 million per year, which is approximately 3% of the total BNT162b2 drug substance production operating costs, and to approximately $4.3 million per year which is approximately 2% of the mRNA-1273 drug substance production operating costs. It is worth noting that mRNA-1273 production was modelled based on co-transcriptional capping, however in reality this production may rely on enzymatic capping,[15] and in this case additional unit operations and equipment (e.g. bioreactors, buffer exchangers) could be required. This might slightly increase the facility-related operating costs; however, the difference is not expected to be more than 1% or maximum 2%. These very low facility-related costs are different from conventional, cell-based vaccine production technologies, whereby facility-related costs tend to represent the major operating cost component.

We performed this analysis to facilitate the implementation of the mRNA vaccine production into existing facilities (e.g. cGMP facilities with experience in injectable medicine manufacturing), hence we do not list the capital investment costs required to construct facilities. Instead, the annualised capital cost is included in the operating cost and is part of the above described $4.3 million per year (for mRNA-1273 production) or $2.5 million per year (for BNT162b2 production). The annualised capital cost corresponds to the depreciation of the fixed capital cost, calculated using the straight-line method over a 10-year period.[1] In case of both vaccines approximately 264 batches can be produced per year assuming a high 345 operating days per year for pandemic-response production and scheduling in staggered mode to maximise facility utilisation. The cost per batch was estimated at $915,000 per batch for mRNA-1273 production and at $333,600 per batch for BNT162b2 production.

[i] The amount of mRNA required for 100 million doses was calculated by multiplying the mRNA amount per dose by 100 million and by accounting for the 5% losses assumed in the fill and finish.

[j] This is the total manufacturing cost, containing the drug substance production operating costs (which in turn contains the annualized capital costs) and the fill-and-finish costs (aka. drug product manufacturing or secondary manufacturing costs).

Table 5. Facility-related requirements for producing 100 million doses of mRNA vaccine drug substance per year

Name of facility-related resource	Facility-related requirements for producing 100 million **mRNA-1273** doses	Facility-related requirements for producing 100 million **BNT162b2** doses
Scale of production line[k]	15 L bioreactor working volume	5 L bioreactor working volume
Total number of batches required	264 batches per year	264 batches per year
Total cost per batch	$915,000 per batch	$333,600 per batch
Facility-related operating costs[l]	$4.3 million per year	$2.5 million per year
Total operating costs for drug substance[m]	$241.6 million per year	$88 million per year

3.2. Consumables and equipment used in the drug substance production process

Once the suitable facility has been identified, the next step is to install the equipment required for mRNA vaccine production. mRNA vaccines can be produced using single-use, disposable equipment, which is replaced after every production batch. Single use equipment and consumables include:

- Single-use plastic bioreactor lining bags;
- Single-use plastic storage bags;
- Plastic (e.g. silicone) tubing, single-use aseptic connectors, clamps; and
- Disposable filter membranes, single-use filter assemblies and chromatography columns.

In some cases, filter membranes and certain types of chromatography resins can be re-used, helping reduce costs. However, the re-use of these components has to be validated. The single-use consumables are usually held in place by more permanent structures (e.g., a single-use plastic bioreactor lining bag is placed inside a cylindrical steel support frame which can have glass or plastic windows).

The advantage of using single-use equipment is that the process can be assembled substantially faster compared to setting up stainless steel equipment. The upfront capital investment costs for single-use equipment is lower compared to the permanent stainless-steel equipment. In addition, because the single-use based production requires substantially less cleaning, it can reduce labour costs as well as water and cleaning agent requirements, minimise cleaning validation, and increase production speeds. However, the operating costs could increase in case of single-use equipment compared to stainless steel equipment. In fact, consumables and single-use equipment represents the second-highest component of total operating costs for drug substance (after raw material costs, details in the section below), estimated at approximately 25% for mRNA-1273 production and at approximately 20% for BNT162b2 production. The cost of consumables and single-use equipment required to produce 100 million doses of the mRNA-1273 and BNT162b2 vaccines per year is estimated at $59.5 million per year and $17.5 million per year, respectively.

[k] One production line was assumed per facility.

[l] Facility-related operating costs include the annualized capital costs, facility maintenance costs, insurance, local taxes and other factory expenses.[1]

[m] The total operating cost includes the annualized facility-dependent capital costs.

The amounts of chromatography resins and tangential flow filtration (TFF) membranes were also estimated, assuming that 5 g of mRNA can be purified per one m^2 of TFF membrane, 50 g of mRNA can be purified per L of flow-through chromatography medium (e.g. Capto Core 700), 1.8 g of mRNA can be purified per L of oligo dT resin,[26] and that 5 g/L of mRNA can be purified per L of multimodal chromatography resin that combines hydrogen bonding and anion exchange chromatography (e.g. Prima S). These values were obtained from the suppliers of the consumables and from discussions with biomanufacturing experts. For TFF it also was taken into account that 3 different TFF unit operations were used in total for mRNA purification and post-formulation purification. The amount of these consumables required to produce 100 million doses is shown below in **Table 6**. It is worth noting that some of these consumables (e.g. TFF membranes, oligo dT resins, and Prima S resins) can be reused for multiple batches and this would reduce the required amounts for these consumables. However, re-using these consumables needs to be rigorously tested and validated. In this assessment it was assumed that these consumables are not reused, and the costs were calculated on this basis.

Table 6. The estimated amounts of key consumables required for producing 100 million doses of the mRNA-1273 (Moderna) and BNT162b2 (BioNTech-Pfizer) vaccines

Name of key consumables and their unit of measurement for the amount	Key consumable requirements for producing 100 million **mRNA-1273** doses	Key consumable requirements for producing 100 million **BNT162b2** doses
Tangential flow filtration membrane [m^2]	10,618	3,536
Flow through chromatography medium, e.g. Capto Core 700 [L][n]	388	129
Oligo dT chromatography resin [L][n]	5,848	1,754
Multimodal chromatography, hydrogen bonding and anion exchange chromatography, e.g. Prima S [L][n]	2,105	632

The downstream process can be implemented based on TFF and Capto Core 700 flow through chromatography alone. Oligo dT chromatography, multimodal chromatography, hydrogen bonding and anion exchange chromatography (e.g. Prima S resin) are all alternatives, which can replace or supplement the Capto Core 700 flow through chromatography. The purchase cost of the Capto Core 700 flow through chromatography was considered \$6,000/L and the purchase cost of the TFF membrane was considered \$1,000/m^2, based on information provided by suppliers and industrial partners. Therefore, the total annual cost of TFF membranes is estimated at \$10.55 million per year for producing 100 million doses of the mRNA-1273 vaccine and \$3.51 million per year for producing 100 million doses of the BNT162b2 vaccine. The total annual purchase cost of the Capto Core 700 resin is estimated at \$2.33 million per year for producing 100 million doses of the mRNA-1273 vaccine and \$0.78 million per year for producing 100 million doses of the BNT162b2 vaccine. The total consumable cost was estimated at \$59.5 million per year for producing 100 million doses of the mRNA-1273 vaccine (**Table 7**) and at \$17.5 million per year for producing 100 million

[n] Out of these three types of chromatography resins one or potentially two can be enough to purify the mRNA drug substance in combination with tangential flow filtration.

doses of the BNT162b2 vaccine (**Table 8**). The highest cost consumables can be the single-use sterile bioreactor assemblies, such as the WAVE bioreactor system, if this system is used.

Table 7. Cost of consumables for 100 million doses of mRNA-1273[o]

Consumable	Units cost ($)	Annual amount	Annual cost ($)	%
Dft Cleaning Powder	4.91	26 kg	130	0.00
UF Membrane (Biotech)	981.11	3,786 m2	3,714,535	6.24
FlexBoy Bag 1.0 L	22.00	264 items	5,808	0.01
Dft Large Bag	340.00	1,848 items	628,320	1.06
Dft DEF Cartridge	1,000.00	528 items	528,000	0.89
500 kDa membrane	1,000.00	6,832 m2	6,832,122	11.48
1 L Plastic Bag	0.20	1,129,392 items	225,878	0.38
50 L Plastic Bag	6.13	30,360 items	186,166	0.31
Flexel Bag for Mixing 1000 L	1,180.00	792 items	934,560	1.57
Large bag for storage 2000 L	850.00	264 items	224,400	0.38
Large bag for storage 4000 L	1,050.00	1,584 items	1,663,200	2.79
WAVE bag and setup	40,000.00	1,056 items	42,240,000	70.98
CaptoCore700	6,000.00	388 L	2,329,258	3.91
TOTAL			**59,512,377**	**100.00**

Table 8. Cost of consumables for 100 million doses of BNT162b2

Consumable	Units Cost ($)	Annual Amount	Annual Cost ($)	%
Dft cleaning powder	4.91	26 kg	130	0.00
UF membrane (Biotech)	981.11	1,261 m^2	1,236,817	7.08
FlexBoy bag 1.0 L	22.00	264 items	5,808	0.03
Dft large bag	340.00	1,584 items	538,560	3.08
Dft DEF cartridge	1,000.00	528 items	528,000	3.02
500 kDa membrane	1,000.00	2,275 m^2	2,274,871	13.03
1 L plastic bag	0.20	376,200 items	75,240	0.43
50 L plastic bag	6.13	10,824 items	66,372	0.38
Flexel bag for mixing 1000 L	1,180.00	528 items	623,040	3.57
Large bag for storage 2000 L	850.00	264 items	224,400	1.28
Large bag for storage 4000 L	1,050.00	528 items	554,400	3.17
WAVE bag and setup	40,000.00	264 items	10,560,000	60.47
CaptoCore700	6,000.00	129 L	775,566	4.44
TOTAL			**17,463,204**	**100.00**

There might be additional equipment required for analysing the quality of the product and this has been indirectly accounted for in Section 3.1. describing the facility-related requirements. To determine the exact equipment requirements for installing an mRNA production line into an existing facility, a gap analysis should be carried out.

[o] The Moderna COVID-19 vaccine production process was modelled assuming co-transcriptional 5' capping (i.e. capping using CleanCap AG), however this process might be implemented based on post-transcriptional (i.e. enzymatic) 5' capping.

3.3. Materials used in the drug substance production process

Raw materials represent the major cost component of mRNA vaccine drug substance production. The estimated amounts of these raw materials required for producing 100 million doses of mRNA vaccines are listed below in **Table 9**. The estimated costs of these raw materials required for producing 100 million doses of mRNA vaccines is listed below in **Table 10**.

These values were calculated using the SuperPro Designer bioprocess modelling tool. Based on process knowledge and input from other experts, we estimate that there are mRNA losses in the production process, including 30% in the downstream purification, 20% in the formulation and subsequent purification steps, and up to 5% in the processes occurring at the fill and finish sites. This translates to a total of approximately 53% losses in the entire production process. Therefore, the raw material amounts used in the production process are higher in order to account for these losses. For example, the quantity of raw materials entering the *in vitro* transcription bioreactor are nearly double the amount needed to produce the equivalent mRNA amount when not accounting for the losses.

Some of the materials used for mRNA vaccine drug substance are also new, and lack a diversified supply chain, with a limited number of suppliers providing these key materials. The key raw materials used in the *in vitro* transcription reaction that are thought to be in limited supply include the 5' cap analogue (e.g. CleanCap AG) and modified nucleotides. In addition, due to sudden increased demand suppliers might be struggling to produce sufficient quantities of the T7 RNA polymerase, the linearized template DNA, the DNase I enzyme and the RNase Inhibitor. However, the production of these components is based on well-established and scalable processes (e.g. fermentation in *Escherichia coli*). If 5' capping of the mRNA is carried out enzymatically, the amounts of capping enzymes should be considered instead of the 5' cap analogues (e.g. CleanCap AG).

Each of the two Covid-19 mRNA vaccines presented in this study is formulated in lipid nanoparticles (LNPs).[15,23-25,27,28] These LNPs are spheres composed of four different lipids with the mRNA enclosed inside.[27] The four types of lipids building up these spheres are: ionizable lipids (i.e., cationic lipids), cholesterol, phospholipids, and polyethylene glycol (PEG) lipid.[15,23-25,27,27] These classes of lipids are consistent for the two mRNA vaccines, as shown in **Tables 9** and **10**, however the individual lipids vary among these vaccines.

In case of the mRNA-1273 vaccine, the ionizable cationic lipid is heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate (SM-102); the phospholipid is 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and the PEG lipid is 1,2-dimyristoylrac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG).[15,23] In case of BNT162b2 the ionizable cationic lipid is (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315); the phospholipid is 1,2-distearoyl-sn-glycero-3-phosphocholine; and the PEG lipid is 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide.[24,25] The amounts of lipids estimated to be required per mRNA dose and for mRNA vaccine production have been previously described.[2,20] The key differentiator is the ionizable cationic lipid between these two vaccines.

Due to the lack of detailed information regarding the formulation and purification processes for the two vaccines, it was assumed that 32% of the lipids are lost during the formulation and subsequent purification steps for both vaccines. In reality, the percentage of losses might differ between these two vaccines due to differences in the formulation (e.g. microfluidics vs. macrofluidics) and subsequent purification unit operations. In addition to these costs there might also be additional licensing costs for using the lipids in the LNP formulation step, especially for the ionizable lipid.

Table 9. Estimated amounts of raw materials used in the mRNA-LNP vaccine drug substance production process based on the manufacturing process illustrated in **Figure 3**[p]

Name of pure component	Material amounts per **mRNA-1273** batch[q] [g / batch]	Material amounts per **BNT162b2** batch[r] [g / batch]	Material amount for producing 100 million **mRNA-1273** doses [g / 100 million doses]	Material amount for producing 100 million **BNT162b2** doses [g / 100 million doses]
Acetic acid	13572.41	4071.72	3,583,117	1,074,935
Adenosine-5′-triphosphate (ATP)	30.79	9.24	8,128	2,439
Calcium chloride ($CaCl_2$)	8.17	2.45	2,157	647
Cholesterol	234.85	99.91	62,000	26,375
Citric acid	1855.50	556.65	489,853	146,956
CleanCap AG	69.69	20.91	18,399	5,520
cytidine-5′-triphosphate (CTP)	29.33	8.80	7,743	2,323
Deoxyribonuclease I (DNase I)[s]	0.0383	0.0115	10	3
Disodium phosphate (Na_2HPO_4)	23422.08	7026.62	6,183,429	1,855,029
Dithiothreitol (DTT)	24.87	7.46	6,567	1,970
Ethyl alcohol (ethanol)	127223.66	38167.10	33,587,046	10,076,114
Guanosine-5′-triphosphate (GTP)	31.76	9.53	8,385	2,515
Ionizable lipid	543.56	214.96	143,500	56,750
Linear template DNA	0.759	0.228	200	60
Magnesium chloride ($MgCl_2$)	42.23	12.67	11,150	3,345
Monopotassium phosphate (KH_2PO_4)	42.58	12.78	11,242	3,373
Phospholipid	117.90	44.98	31,125	11,875
Polyethylene glycol (PEG) lipid	67.23	25.09	17,750	6,625
Potassium chloride (KCl)	41180.90	12354.27	10,871,757	3,261,527
Pyrophosphatase[s]	1.214	0.364	321	96
RNase enzyme inhibitor	0.1901	0.0570	50	15
Sodium acetate	63337.92	19001.38	16,721,211	5,016,363
Sodium chloride (NaCl)	170342.40	51102.72	44,970,392	13,491,118
Sodium citrate	9969.58	2990.87	2,631,968	789,591
Sodium hydroxide (NaOH)	12025.24	3607.57	3,174,662	952,399
Spermidine	4.41	1.32	1,164	349
Sucrose	1041.55	312.46	274,969	82,491
T7 RNA polymerase[s]	0.2529	0.0759	67	20
Tris hydrochloride (Tris HCl)	372.34	111.70	98,298	29,489
Water for injection (WFI), RNase free	24353713.06	7306113.92	6,429,380,248	2,198,814,074
1-methylpseudouridine-5′-triphosphate (mod-UTP)	29.39	8.82	7,759	2,328

[p] For calculating the material requirements for producing 100 million doses and additional 5% losses were assumed to occur in the fill and finish process. This is the list of all materials used in the production process, including materials used for cleaning.
[q] Production line at 15L bioreactor working volume scale, producing 10,406.5 grams of mRNA per year.
[r] Production line at 5L bioreactor working volume scale, producing 3,465 grams of mRNA per year.
[s] The amount of enzymes required depends on the specific activity of the enzymes and this can vary between different suppliers.

Table 10. Estimated cost of raw materials used in the mRNA-LNP vaccine drug substance production process based on the manufacturing process illustrated in **Figure 3**[t]

Name of solution or material	Material costs per **mRNA-1273** batch[u] [USD/batch]	Material costs per **BNT162b2** batch[v] [USD/batch]	Material costs for producing 100 million **mRNA-1273** doses [USD / 100 million doses]	Material costs for producing 100 million **BNT162b2** doses [USD / 100 million doses]
0.1 M $CaCl_2$ solution	0.178	0.061	47	16
0.1 M Spermidine solution	36.640	12.201	9,673	3,221
1 M DTT solution	147.542	49.125	38,951	12,969
1 M $MgCl_2$ solution	0.277	0.091	73	24
1 M NaOH solution	2.125	0.708	561	187
1 M Tris HCl solution	133.644	44.500	35,282	11,748
1 mg/ml DNA template solution	82508.299	27472.538	21,782,191	7,252,750
100 mM ATP solution	7500.723	2497.492	1,980,191	659,338
100 mM CleanCap AG solution	275550.898	91749.352	72,745,437	24,221,829
100 mM CTP solution	7485.462	2492.413	1,976,162	657,997
100 mM GTP solution	7500.723	2497.492	1,980,191	659,338
100 mM mod-UTP solution	137214.277	45687.822	36,224,569	12,061,585
250 mM KCl solution	752.856	250.674	198,754	66,178
Cholesterol	6341.004	2111.345	1,674,025	557,395
DNase I	19.955	6.644	5,268	1,754
Ethyl Alcohol	1006.038	334.977	265,594	88,434
Ionizable lipid	29352.909	9773.549	7,749,168	2,580,217
Sodium Citrate buffer	272.708	90.803	71,995	23,972
PBS solution	2537.875	845.030	669,999	223,088
PEG lipid	1448.144	482.186	382,310	127,297
Phospholipid	1908.413	635.439	503,821	167,756
Pyrophosphatase solution	19886.648	6621.598	5,250,075	1,748,102
RNase enzyme inhibitor solution	159.659	53.163	42,150	14,035
Sodium acetate	1035.962	344.939	273,494	91,064
Sucrose	5.148	1.712	1,359	452
T7 RNA polymerase solution	34080.008	11347.519	8,997,122	2,995,745
Tris-HCl 1x buffer	219.265	73.008	57,886	19,274
Water for injection (WFI), RNAse free	0.973	0.322	257	85
TOTAL	617,108	205,477	162,916,606	54,245,850

[t] For calculating the material requirements for producing 100 million doses and additional 5% losses were assumed to occur in the fill and finish process. This is the list of materials used in the production process which come in direct contact with the mRNA product, excluding auxiliary materials (e.g. materials used for cleaning).

[u] Production line at 15L bioreactor working volume scale, producing 10,406.5 grams of mRNA per year.

[v] Production line at 5L bioreactor working volume scale, producing 3465 grams of mRNA per year.

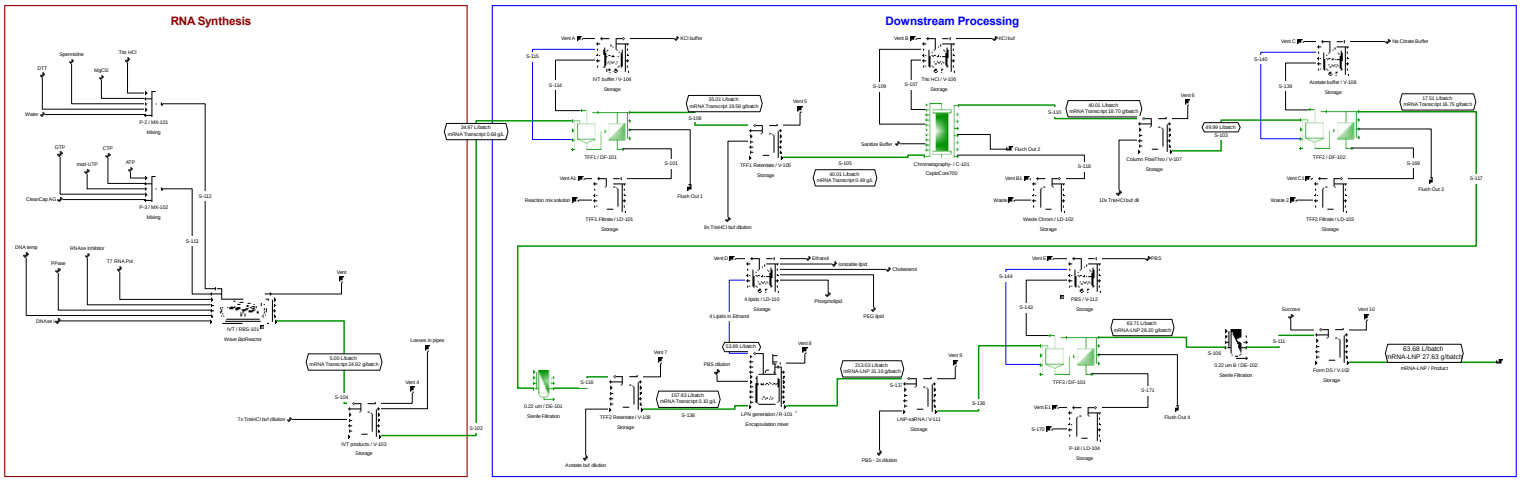

Figure 3. mRNA vaccine drug substance production process flow diagram obtained from SuperPro Designer

The production process consists of the following three key parts: 1) the in vitro transcription step, whereby the mRNA is capped co-transcriptionally using 5' cap analogues (e.g. CleanCap AG); 2) downstream purification step obtained by a series of tangential flow filtration steps and a Capto Core 700 chromatography step; 3) LNP formulation step followed by another tangential flow filtration step. The tangential flow filtration steps can perform both concentration and diafiltration of the mRNA product.

It is also worth noting that approximately 6,400 and 2,200 metric tonnes of WFI (RNase-free purified water) is required to produce 100 million mRNA-1273 and BNT162b2 vaccine doses, respectively (**Table 9**). This WFI requirement should be taken into account when selecting the facility to house the mRNA vaccine production processes.

The total estimated annual material costs for producing 100 million doses of the mRNA-1273 vaccine is $162.9 million per year, accounting for approximately 67% of the total operating costs for drug substance production. The total estimated annual purchase price of materials for producing 100 million doses of the BNT162b2 vaccine is $54.2 million per year, accounting for approximately 62% of the total drug substance production costs. For both vaccines, the purchase price of CleanCap AG is approximately 45% with respect to the total material costs. In case of enzymatic post-transcriptional capping, the purchase price of the capping enzymes is expected to drive the production costs as well.

3.4. Labour required in the drug substance production process

The availability of qualified labour/personnel represents a challenge for rapidly scaling up vaccine production for meeting the global pandemic demand. The magnitude of this challenge is even larger in case of new technologies which have not been used at commercial scale before, i.e. the mRNA vaccine platform technology. In this section the labour requirements are estimated for manufacturing 100 million mRNA vaccine doses per year.

The labour cost in the production process represents approximately 5.2% and approximately 13.5% of the total operating costs for drug substance production when producing 100 million doses of the mRNA-1273 and the BNT162b2 vaccines per year, respectively. Based on the modelling results obtained from SuperPro Designer, using the model presented in **Figure 3**,

the total annual operator labour requirement is 73,835 hours per year for the mRNA-1273 vaccine and 68,078 hours per year for the BNT162b2 vaccine. The basic labour rate for the production process operators was assumed at $25 per hour. After accounting for the benefits, supplies, supervision, and administration, the total labour cost was estimated at $57.50 per hour, as calculated in SuperPro Designer.[1]

The cost of labour can vary among the different geographical locations, countries, and continents but the cost of labour is not expected to have a substantial impact on the overall production costs. In the SuperPro Designer modelling tool, it also was assumed that 60% of the labour hours are used directly for producing the product and the remaining 40% is used for other activities.[29]

In order to calculate the number of personnel required to operate the production process, the total annual 73,835 and 68,078 labour hours required per production line were divided by the average hours that one person works per year, which is 2,760 hours. The 2,760 hours value was obtained by multiplying a high 345 working days per year per person (due to the high pandemic-induced global vaccine demand) by eight working hours per day per person. This resulted in requiring approximately 27 and 25 persons to operate the mRNA-1273 and the BNT162b2 production lines, respectively. However, Lonza reported that it required over 70 employees per production line.[30,31] The difference between the personnel requirements from Lonza and the values obtained by the model may be due to the labour required to carry out the quality control testing, warehousing for incoming and outgoing materials, logistics, and administration. To avoid underestimating the labour requirements, the calculations were updated with the assumption that 80 employees are required per mRNA-1273 production line and that 75 employees are required per BNT162b2 production line.

To produce 100 million doses of the mRNA-1273 and BNT162b2 vaccines per year, an estimated 222,000 hours and 207,000 hours are required, respectively, as shown below in **Table 11**. These values were calculated by multiplying the personnel required per production line (80 people for mRNA-1273 and 75 people for BNT162b2) with the hours that one person works per year (2,760 hours). Next, the total labour cost was calculated by multiplying the number of work hours required per year (222,000 hours for mRNA-1273 and 207,000 hours for BNT162b2) with the total labour cost of $57.50 per hour. This resulted in $12.7 million and $11.9 million for total labour costs for producing 100 million doses of the mRNA-1273 and BNT162b2 vaccines, respectively.

Table 11. Labour required for producing mRNA vaccine drug substance for 100 million doses[w]

Name	**mRNA-1273**	**BNT162b2**
Total number of hours for producing 100 million doses	220,800 hours	207,000 hours
Total number of persons for producing 100 million doses	80 persons	75 persons
Total labour costs for producing 100 million doses	$12.7 million	$11.9 million

[w] The labour required to construct, equip, validate and start-up the production process is not included in this analysis.

3.5. Other resource requirements for drug substance production

The remaining resource requirements include: 1) laboratory, quality control, and quality assurance; 2) utilities; 3) sales resources; 4) waste treatment & disposal, failed product disposal; 5) transportation and miscellaneous. In total, these were estimated to account for less than 1% of the total operating costs for drug substance production. Out of these, laboratory, quality control and quality assurance costs are the highest cost components, and these were assumed to account for 50% of the total labour costs in SuperPro Designer. In addition, assessing royalties and licensing fees for some components, including the cationic lipids (aka. ionizable lipids) used in the lipid nanoparticle formulation, was outside the scope of this report.

3.6. Fill and finish requirements

Following the production of the mRNA vaccine drug substance, this active ingredient is filled into plastic bags and shipped to the fill-and-finish facilities, where it is filled into vials using aseptic filling lines operating under cGMP guidelines. The cost of filling into vials depends mostly on the filling technology and vial or container size. The cost per dose tends to decrease as the vial size increases. The mRNA-1273 vaccine is filled into 10-dose vials, whereas the BNT162b2 vaccine is filled into 5-dose vials, which were eventually approved as 6-dose vials. The fill and finish production cost (including the cost of the vial) was estimated at $0.27 per dose and $0.37 per dose for filling into 10-dose vials and 5-dose vials, respectively. These cost estimates were obtained using the SuperPro Designer bioprocess modelling tool. Filling 100 million mRNA-1273 vaccine doses into 10-dose vials is estimated to cost $28.42 million. Filling 100 million BNT162b2 vaccine doses into 10-dose vials is estimated to cost $38.95 million, as shown below in **Table 12**.

One large-scale filling line should be able to fill 100 million vaccine doses in 2.25 months and 3.75 months in case of the mRNA-1273 and BNT162b2 vaccines, respectively. For these estimates a filling rate of 400 vials per minute and 5% losses in the fill and finish were assumed at 60% overall equipment effectiveness (OEE). The amount of empty glass vials required for 100 million vaccine doses is 10.5 million vials and 21.05 million vials for the 10-dose mRNA-1273 and 5-dose BNT162b2 vials, respectively, after accounting for the 5% losses in the fill and finish.

Table 12. Key fill and finish resource requirements for producing 100 million doses of mRNA vaccines

Name of fill and finish resource	Fill-and-finish requirements for producing **mRNA-1273** vaccines[x]	Fill-and-finish requirements for producing **BNT162b2** vaccines[x]
Doses per vial	10	6
Number of empty glass vials for producing 100 million doses, with 5% losses	10.5 million vials	21.05 million vials
Total operating fill and finish costs for producing 100 million doses[y]	$28.42 million	$38.95 million

[x] The losses during fill-and-finish were assumed at 5%, hence 5% overproduction and over-costing was considered.

[y] Includes the cost of the empty glass vials, however, the cost of the drug substance is not included in this estimate. This includes the annualized capital cost for the fill and finish facilities.

4. Maintaining outbreak-response surge manufacturing capacity based on the mRNA vaccine platform technology

As presented in the sections above and as previously described, the mRNA vaccine platform technology offers great flexibility for producing vaccines and candidate vaccines against a wide range of disease targets, including currently known viral pathogens and currently unknown viral pathogens.[2,3,8,20,32] Moreover, this technology also offers record speeds both for developing new candidate vaccines against future emerging threats and for rapidly mass-producing vaccines.[2,3,8,20,32] All of these make the mRNA vaccine platform ideal for outbreak-response vaccine production.

Importantly, as described in section 3 above, mRNA vaccine drug substance production requires low facility footprints and low capital investment costs, the facility-related operating cost is 2-3% of the total drug substance operating cost, in stark contrast with cell-based vaccine platform technologies whereby the facility-related costs tend to represent the major cost component. Hence, maintaining dedicated outbreak-response mRNA vaccine production surge capacity would be associated with low facility-related costs. Moreover, the production equipment can be single use, further reducing the investment costs and allowing for flexibility in terms of scale and choices of unit operations, allowing for upgrades/improvements in the longer term and for rapid assembly. In addition, closed system mRNA vaccine production processes are also available,[18] an advantage when it comes to maintaining the RNase-free production conditions and potentially reducing facility costs. The mRNA drug substance production cost is currently dominated by the costs of the raw materials. However, this cost component would be low when no production takes place (during periods with no outbreaks), thus the total costs related to maintaining dedicated outbreak-response surge capacity would be low. When no production takes place, the variable cost will disappear, but the fixed costs will prevail. The fixed costs comprise of facility dependent costs and labour costs. Therefore, maintaining surge capacity during times of no production, is estimated to cost $17 million per year for the mRNA-1273 vaccine and $14.4 million per year for the BNT162b2 vaccine when maintaining the 100 million dose per year production capacity.

Maintaining a trained production and quality control workforce during times when there is no demand for outbreak-response vaccine production could be a challenge. However, the personnel could be periodically involved in producing mRNA vaccines and therapeutics for clinical trials and once approved, vaccines against existing pathogens (e.g. mRNA vaccines against influenza).

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