Pharmaceutical manufacturers across Asia, Africa and Latin America with the technical requirements and quality standards to manufacture mRNA vaccines

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- **Why focus on mRNA vaccines?**

One year after multiple effective vaccines against Covid-19 were brought to market, we have failed to vaccinate the world. The distribution of vaccines remains highly unequal. In Portugal, a high-income country, 87% of the population has been fully vaccinated; in Nigeria, the largest country on the African continent, the corresponding figure is less than 2%. The stark differences in vaccination rates are due to supply inequities: 74% of all vaccines dispensed this year went to high and upper-middle-income countries, while less than 1% went to low-income countries[3]. An existing shortage in vaccine supply is only set to worsen with news of the Omicron variant, and the increased demand for booster shots in high-income countries[4][5].

We need to be making billions more doses in order to vaccinate the world. The most effective way to do so would be by diversifying and expanding the manufacture of mRNA vaccines. Unlike older (pre-2020) vaccine technologies which are cell-based, mRNA vaccines are made through biochemical rather than biological processes. This makes for a simpler system of production, and one that is more predictable and easier to transfer to other manufacturers than previous vaccine technologies[6]. An essential consequence of the simplicity is speed: it takes three to seven days to produce a batch of the active pharmaceutical ingredient for the Pfizer/BioNtech vaccine, as compared to one month for an equivalent batch of the AstraZeneca vaccine[7].

It should be noted that cold-chain-management of the currently approved mRNA vaccines is a challenge in developing countries; however, developers are already exploring more thermostable formulations, and it is a matter of time before we see new mRNA vaccine formulations that only require standard refrigeration.

- **Can mRNA technology diversify the existing geographical base of vaccine supply?**

The goal is to make billions more doses of mRNA vaccines as quickly as possible, and this can be achieved in a few different ways. At present, the two mRNA vaccines in use, Moderna and Pfizer/BioNtech, are being manufactured by these companies and their contractors, for the most

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2 Email for correspondence: Alain.ALSALHANI-at-paris.msf.org
3 Josh Holder, "Tracking Coronavirus vaccinations around the world", *New York Times*, 2021 <https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html>
4 Annabelle Timsit, "Coronavirus vaccine demand grows in U.S. amid omicron variant concerns, booster eligibility expansion", *Washington Post*, 2021 <https://www.washingtonpost.com/nation/2021/12/05/covid-vaccine-demand-omicron/>
5 Editorial, "Omicron: the global response is making it worse", *Nature*, 2021 <https://www.nature.com/articles/d41586-021-03616-x>
6 Technical Brief, "Sharing mRNA vaccine technologies to save lives", *Médecins Sans Frontières*, 2021 <https://msfaccess.org/sharing-mrna-vaccine-technologies-save-lives>
7 Zoltan Kis, "Process-cost modelling for producing 100 million COVID-19 mRNA vaccine doses per year at injectable medicines manufacturing sites", 2021 <https://msfaccess.org/sites/default/files/2021-09/COVID19_TechBrief_Process_cost_modelling_ENG.pdf>

part, in high-income, Western countries, with the exception of one full manufacturing license that BioNtech has with Fosun, in China[8].

We suggest that the best way to make more mRNA vaccines is to geographically diversify the manufacturing of these vaccines, a strategy that would serve us in both the short and long terms. If vaccine manufacturing could be distributed across countries, and covered all continents, that would provide security, stability and independence to large parts of the world[9].

In the past, this has been difficult to achieve, because of the restricted number of manufacturers with experience in older (pre-2020) vaccine technologies. For instance, if we were to tabulate existing vaccine manufacturers in Africa and Latin America who have been qualified by authorities in the United States, Europe, or the World Health Organization, we would be left to work with only 1 manufacturer in Africa, and 3 in Latin America[10]. However, because of the unique nature of mRNA technology, and its lack of cell-based, biological components, mRNA vaccines can be produced by a far larger number of existing pharmaceutical manufacturers, even if these manufacturers have no previous experience with vaccines. This is not a theoretical assumption; it is the working model that Moderna[11] and Pfizer/BioNtech[12] have used to successfully partner with other contract-manufacturers in order to scale up their own production.

Recent research into requirements for mRNA vaccine manufacturing from MSF and Imperial College[13] reveals that any pharmaceutical company currently manufacturing sterile injectables (a process that requires similar competencies and facilities to those required for making an mRNA vaccine) satisfies the minimum criterion to manufacture an mRNA vaccine. Applying this criterion, and adding in a stringent quality filter, returns *at least* 8 sites in Africa and 6 sites in Latin America that can make mRNA vaccines, as opposed to 1 and 3 sites respectively for older vaccine technologies. In short, choosing mRNA technology for vaccines resulted in a more than threefold increase of the potential vaccine supply base.

It is important to note that this list represents a baseline scan. Our focus here is on technical feasibility. The companies identified by us will need to conduct their own ‘gap’ analysis before venturing into mRNA technology. Not every company in this list of 120 might necessarily want to start making mRNA vaccines: there are multiple factors to take into account, such as the ability to access the required investment, the strength of the drug regulatory authority in the country of manufacture, and, finally, the prospect of a strong business case.

The logic underlying this list, however, is compelling: if a company in Spain such as Rovi, that produces sterile injectables, with no experience making either biologic drugs or vaccines, can make Moderna’s vaccine, then there is no reason why a company with a similar profile based in Morocco, South Africa, Brazil, India or Bangladesh, cannot do the same – should it receive a full technology transfer from Moderna, as Rovi did.

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8 Fill-and-finish deals are excluded here as they do not involve manufacturing the actual vaccine substance.

9 Aisling Erwin, “How COVID spurred Africa to plot a vaccines revolution”, *Nature*, 2021 <https://www.nature.com/articles/d41586-021-01048-1>

10 WHO, Pre-Qualified Vaccines, *World Health Organization* <https://extranet.who.int/pqweb/vaccines/prequalified-vaccines>

11 Reuters, Emma Pinedo & John Miller, “Spanish drugmaker Rovi to make ingredients for Moderna COVID-19 vaccine”, *Reuters*, 2021 <https://www.reuters.com/business/healthcare-pharmaceuticals/rovi-make-active-agents-moderna-covid-19-vaccine-2021-04-12/>

12 Erika Solomon, “Where the Magic Happens – inside BioNTech’s Innovative Vaccine Plant”, *Financial Times*, 2021 <https://www.ft.com/content/cf5d6113-3698-4cc7-9d5b-8f0f29fd6a35>

13 Zoltan Kis, “Process-cost modelling for producing 100 million COVID-19 mRNA vaccine doses per year at injectable medicines manufacturing sites”, 2021 <https://msfaccess.org/sites/default/files/2021-09/COVID19_TechBrief_Process_cost_modelling_ENG.pdf>

- **Why is the Omicron variant a reason to increase mRNA vaccine manufacturing?**

Scientists across the world are currently working to identify how much of a danger the Omicron variant poses, and whether the current crop of Covid-19 vaccines work against it[14]. Regardless of the eventual findings, the emergence of this new variant means that vaccinations will increase everywhere in order to protect people, as well as to curb the amount of virus in circulation, so that the chances of new mutations and variants emerging are reduced.

In the next few years, therefore, the world will need even more vaccines than we anticipated at the beginning of 2021. In high-income countries, the emergence of the Omicron variant has already resulted in a general expansion of recommendations for booster shots[15]; in low-income countries, the emergence of this variant has resulted in a renewed urgency for any vaccines at all[16].

In this regard, mRNA technology offers some distinct advantages. First, we know that the two existing mRNA vaccines – Moderna and Pfizer/BioNtech – work against the variants we have witnessed before Omicron[17]. Second, mRNA vaccines are much easier to adapt and reformulate; earlier in the year, it took Moderna 30 days to develop a version of its vaccine for trials against a new variant, whereas, by contrast, the shortest time taken to adapt an adenoviral vacccine (such as AstraZeneca or Johnson & Johnson) has been five months[18].Third, the mRNA platform has significant future potential for use against other diseases[19], which provides private and state actors a useful long-term incentive for investing in mRNA technology today.

- **How did we arrive at a list of at least 120 manufacturers with the technical requirements and quality standards to make an mRNA vaccine across Asia, Africa and Latin America?**

The methodology used to create this list is based on findings from recent research into mRNA vaccine manufacturing from MSF and Imperial College[20], to which we added additional steps with respect to geographical interest and quality assessment.

- The first step was to identify the geographical scope of the exercise, which we fixed at countries in Asia, Africa and Latin America, representing the developing world.

- The second step was to identify companies within this geographical scope who both manufactured sterile injectables and had been certified by a reputable agency or organization for good manufacturing practices (GMP) as a guarantee of adhering to the highest international quality standards.

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14 Isaac Chotiner, "How South African Researchers Identified the Omicron Variant of COVID", *The New Yorker,* 2021 <https://www.newyorker.com/news/q-and-a/how-south-african-researchers-identified-the-omicron-variant-of-covid>

15 Reuters Staff, "Factbox: Countries weigh need for booster COVID-19 shots", *Reuters,* 2021, <https://www.reuters.com/business/healthcare-pharmaceuticals/countries-weigh-need-booster-covid-19-shots-2021-09-24/>

16 UN News, "Omicron COVID variant underlines need for global 'pandemic treaty'", *United Nations,* 2021 <https://news.un.org/en/story/2021/11/1106722>

17 Apoorva Mandavilli, "Vaccines Are Effective Against the New York Variant, Studies Find", *New York Times,* 2021 <https://www.nytimes.com/2021/04/22/health/covid-ny-variant-vaccine.html>

18 Technical Brief, "Sharing mRNA vaccine technologies to save lives", *Médecins Sans Frontières,* 2021 <https://msfaccess.org/sharing-mrna-vaccine-technologies-save-lives>

19 Mike May, "After COVID-19 successes, researchers push to develop mRNA vaccines for other diseases", *Nature,* 2021 <https://www.nature.com/articles/s41591-021-01393-8>

20 Zoltan Kis, "Process-cost modelling for producing 100 million COVID-19 mRNA vaccine doses per year at injectable medicines manufacturing sites", 2021 <https://msfaccess.org/sites/default/files/2021-09/COVID19_TechBrief_Process_cost_modelling_ENG.pdf>

- In the first leg of this phase, we consulted the largest identifiable source of the cross-sectional data we were looking for (sterile injectables + certified quality) which was the European Medicines Agency's EudraGMDP database[21], where we found companies who had passed inspection of their facilities for export of a sterile pharmaceutical product to the European Union. This gave us the bulk (82%) of the companies on our list.

- In the second leg of this phase, we consulted the WHO's Pre-Qualification project for vaccines[22], as well as for biotherapeutics[23], from which we added companies on the basis of WHO approval, which is a similar standard to the EU. (All vaccines and biotherapeutics are sterile injectables, whereas the reverse is not true). The WHO search gave us 15% of the companies on our list.

- In the third leg of this phase, we searched for anecdotal instances of US Food and Drug Administration approval of sterile injectables for export to the US, which involves GMP assessment of a similar standard to the EU and WHO. The US FDA database does not list records in the detail we require (it does not distinguish between approvals for pharmaceuticals in general and sterile injectables) and as a result, we relied on a selected list of companies who self-reported US FDA approvals, which we verified with media reports. This gave us the remainder (3%) of the companies on our list.

➢ Once a draft was drawn up, we accounted for multiple facility listings of the same company, as well as mergers and acquisitions, to the extent possible[24]. Companies with multiple qualified facilities have been summarized under one listing, and in other cases, companies wholly or partially acquired by others are listed separately, unless fully merged.

➢ We let a small number of subsidiaries of Western pharmaceutical companies stay on our list since they qualify under the criteria here, even though they do not have the same flexibility or independence to venture into mRNA technology as their more locally-owned counterparts. (A total of 8 companies[25] in all, or 6% of the total, belong to this category; 3 in India and 5 in China).

- **A sample analysis of mRNA manufacturing potential across selected manufacturers**

In addition to identifying 120 companies with the technical requirements and quality standards to make mRNA vaccines, we spoke to a sample of these companies across Asia and Africa to understand their ability in more detail. The questions we asked of them, which they answered in the affirmative, were details of mRNA production, such as whether they had evaluated what they would need in terms of human resources and equipment, whether they had enough specialized space within their facilities or could build it quickly, and if they had access to the finances required to invest in the process.

Among the companies we spoke to are Sothema, Biocon and Beximco Pharma.

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21 EudraGMP Inspections Search, http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPCompliance.do

22 WHO, Pre-Qualified Vaccines, *World Health Organization* <https://extranet.who.int/pqweb/vaccines/prequalified-vaccines>

23 WHO, Pre-Qualified Biotherapeutics, *World Health Organization* <https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products>

24 The raw data, including a full list of facilities with the requisite quality assessments (which is a more comprehensive account than the list of companies) is available on request from the authors.

25 In India: Abbot, Sandoz & Sanofi. In China: Baxter, GE Healthcare, Novo Nordisk, Pfizer & Roche.

A brief profile of each of these companies follows.

Sothema is a publicly-listed Moroccan pharmaceutical corporation in operation since 1976[26]. The company's annual turnover in 2019 was US$177 million. Its subsidiaries include West Afric Pharma (WAPH) in Dakar, Senegal. Sothema has traditionally made small molecules, or chemistry-based pharmaceuticals. Beginning in 2021, during the pandemic, it ventured into "fill and finish" operations for Sinopharm's Covid-19 vaccine. In addition, the company has a 11,000 square-meter dedicated facility for sterile operations, to produce sterile injectables. It employs in the region of 10,000 people, spread across multiple production facilities. Sothema was assessed as having EU-compliant standards of GMP for the manufacture of sterile products in 2010 and 2013 (Inspecting authority: France) and in 2019 (Inspecting authority: Netherlands).

Biocon is a publicly-listed Indian bio-pharmaceutical manufacturer, founded in 1978[27]. In the financial year ending in March 2021, the company reported annual revenue of US$974 million. Among its subsidiaries is Syngene, a contract research-and-development organization. The company's revenue stream primarily comes from biologic drugs, generic bio-pharmaceuticals and research services, with 81% coming in from exports and 29% from the Indian market. It employs over 13,500 people across multiple facilities. Biocon was assessed as having EU-compliant standards of GMP for the manufacture of sterile products at a facility in India in 2018 (Inspecting authority: France) and in 2020 (Inspecting authority: Ireland), as well as at a facility in Malaysia in 2019 (Inspecting authority: Ireland). The company was assessed as having WHO-compliant standards of GMP for the manufacture of an oncology biologic drug (Trastuzumab) in 2021. Additionally, the company was assessed as having United States FDA-compliant standards of GMP for the manufacture of sterile pharmaceutical products in 2017 (for Trastuzumab), in 2018 (for Pegfilgrastim) and in 2020 (for Insulin Glargine).

Beximco Pharma is a publicly-listed pharmaceutical company in Bangladesh that was founded in 1980[28]. In the financial year ending in 2020, the company reported annual revenue of US$345 million. Beximco has traditionally made chemistry-based small molecules, in addition to other pharmaceutical products, and is now actively exploring expansion into mRNA technology both for vaccines in the pandemic, as well as for other uses, such as oncology, in the future. The company employs in the region of 4500 people, across two plants, including its main 23-acre campus with multiple self-contained production facilities. Beximco was assessed as having EU-compliant standards of GMP for the manufacture of sterile products in 2012 and 2015 (Inspecting authority: Austria), as well as in 2019 (Inspecting authority: Germany).

26 Sothema, https://sothema.com/web/
27 Biocon, https://www.biocon.com/
28 Beximco Pharma, https://beximcopharma.com/

Pharmaceutical manufacturers across Asia, Africa and Latin America with the technical requirements and quality standards to manufacture mRNA vaccines
(in alphabetical order, by country)

ASIA

1	Abbott Healthcare	India
2	Accure Labs	India
3	Ahlcon Parenterals	India
4	Aspiro Pharma	India
5	Astral SteriTech**	India
6	Aurobindo Pharma	India
7	Bharat Biotech International	India
8	Biocon	India
9	Biological E	India
10	Brooks Laboratories	India
11	Cadila Healthcare (Zydus Cadila)*	India
12	Cadila Pharmaceuticals	India
13	Caplin Point Laboratories	India
14	Cipla	India
15	Dr Reddy's Laboratories	India
16	Emcure Pharmaceuticals	India
17	Eugia Pharma Specialities Limited	India
18	Gland Pharma	India
19	Gufic Lifesciences	India
20	Haffkine Bio Pharmaceutical Corporation*	India
21	Hetero Labs	India
22	Immacule Life Sciences**	India
23	Indoco Remedies	India
24	Intas Pharmaceuticals	India
25	Jodas Expoim	India
26	Lupin	India
27	Maiva Pharmatech	India
28	Mediorals Laboratories	India
29	MSN Laboratories	India
30	Mylan Laboratories	India
31	Naprod Life Sciences	India
32	Nectar Lifesciences	India
33	Orchid Pharma	India
34	Panacea Biotech*	India
35	Reliance Life Sciences	India
36	Revacure Lifesciences	India
37	Sakar Healthcare	India

38	Samrudh Pharmaceuticals	India
39	Sandoz	India
40	Sanofi Healthcare India*	India
41	Sanzyme	India
42	Sentiss Pharma	India
43	Serum Institute of India	India
44	Shilpa Medicare	India
45	Sovereign Pharma	India
46	SP Accure Labs	India
47	Steril-Gene Life Sciences	India
48	Strides Pharma Science	India
49	Sun Pharmaceutical Industries	India
50	Swiss Parenterals	India
51	USV Private Limited	India
52	Venus Remedies	India
53	Wintac	India
54	Wockhardt**	India
55	Zeiss Pharma	India
56	Baxter Healthcare	China
57	Beijing Institute of Biological Products*	China
58	Beijing Sciecure Pharmaceutical Company	China
59	Chengdu Institute of Biological Products*	China
60	Chia Tai-Tianqing Pharmaceutical Group	China
61	Fresenius Kabi Pharmaceutical Company	China
62	GE Healthcare	China
63	Hainan Poly Pharm	China
64	Hainan Shuangcheng Pharmaceuticals	China
65	Hebei Dawn Pharmaceutical Co., Ltd.	China
66	Hebei Huari Pharmaceuticals	China
67	Hualan Biological Bacterin*	China
68	Hybio Pharmaceutical Company	China
69	Jiangsu Hansoh Pharmaceutical Group	China
70	Jiangsu Hengrui Medicine	China
71	Lilly Suzhou Pharmaceutical Company	China
72	Linyi Dongcheng Dongyuan Biological Engineering	China
73	Nanjing Kin-friend Biochemical Pharmaceutical Company	China
74	NCPC Hebei Huamin Pharmaceutical Company	China
75	Novo Nordisk	China
76	Pfizer	China
77	Qilu Pharmaceutical Company	China
78	Shandong Anxin	China

79	Shanghai Henlius Biopharmaceutical Company	China
80	Roche	China
81	Shenzhen China Resources Gosun Pharmaceuticals	China
82	Shenzhen Techdow Pharmaceutical Company	China
83	Shenzhen Zhijun Pharmaceutical Company	China
84	Sinopharm	China
85	Sinovac Biotech*	China
86	Wanbang Biopharmaceuticals	China
87	WuXi Biologics	China
88	Xiamen Innovax Biotech*	China
89	Zhuhai United Laboratories	China
90	Celltrion	S. Korea
91	EuBiologics*	S. Korea
92	Green Cross Corporation (GC Pharma)*	S. Korea
93	Il-Yang Pharmaceuticals*	S. Korea
94	JW Life Science	S. Korea
95	LG Life Sciences	S. Korea
96	Samsung Biologics	S. Korea
97	SK Bioscience	S. Korea
98	Taejoon Pharmaceutical Company	S. Korea
99	Imexpharm Corporation	Vietnam
100	Medochemie (Fast East)	Vietnam
101	Tenamyd Pharma	Vietnam
102	Pharmaniaga Lifescience	Malaysia
103	Xepa-Soul Pattinson	Malaysia
104	Beximco Pharmaceuticals	Bangladesh
105	GPO-MBP*	Thailand
106	PT Bio Farma*	Indonesia

AFRICA

107	Egyptian International Pharmaceutical Industries	Egypt
108	EVA Pharma	Egypt
109	Global Pharmaceutical Industries	Egypt
110	Laboratoires UNIMED	Tunisia
111	Les Laboratoires MédiS	Tunisia

112	Sothema	Morocco
113	Institut Pasteur de Dakar*	Senegal
114	Aspen Pharmacare**	South Africa
	LATIN AMERICA	
115	Antibióticos do Brasil	Brazil
116	Bio-Manguinhos/ Fiocruz*	Brazil
117	Instituto Butantan*	Brazil
118	Eriochem S.A.	Argentina
119	Synthon Chile	Chile
120	Centro de Ingeniería Genética y Biotecnología*	Cuba

Sources:

Europe: 98 out of the 120 manufacturers on this list (unmarked) exported a sterile pharmaceutical product to the European Union, and thereby had GMP certified by the European Medicines Agency. These records are listed on the EudraGMDP database; and publicly available here: (http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPCompliance.do)

WHO: 18 of the 120 manufacturers here (marked with one *) appear on the World Health Organization's Pre-Qualification database for vaccines, a process that includes GMP evaluation, and is publicly available here: (https://extranet.who.int/pqweb/vaccines/prequalified-vaccines). While our methodology included searching through the WHO's Pre-Qualification database for biotherapeutics, there were no new companies to add from that list.

United States: 4 of the 120 manufacturers here (marked with two **) exported a sterile pharmaceutical product to the United States, and thereby had GMP certified by the US Food and Drug Administration. These records, while available on the US FDA database, do not list the level of pharmaceutical product detail we need, and are instead taken from individual public records on the companies' own websites and confirmed by media reports.

Note: As a result of the methodology employed, some manufacturers have multiple successful quality assessments (from Europe, the WHO and/or the United States) but are reported here according to the first certification that is publicly available in the order listed above. For example, Biocon has received European, WHO *and* US approval for sterile pharmaceutical products, but is listed here as European-approved, based on the order of this list.

For the methodology behind this list, see previous pages in this document.