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Sustainable Vaccines Manufacturing in Africa

Business case simulation for Fill & Finish Contract Manufacturing Organization in Africa to cover the demand for human vaccines on the continent

Implemented by

giz Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH

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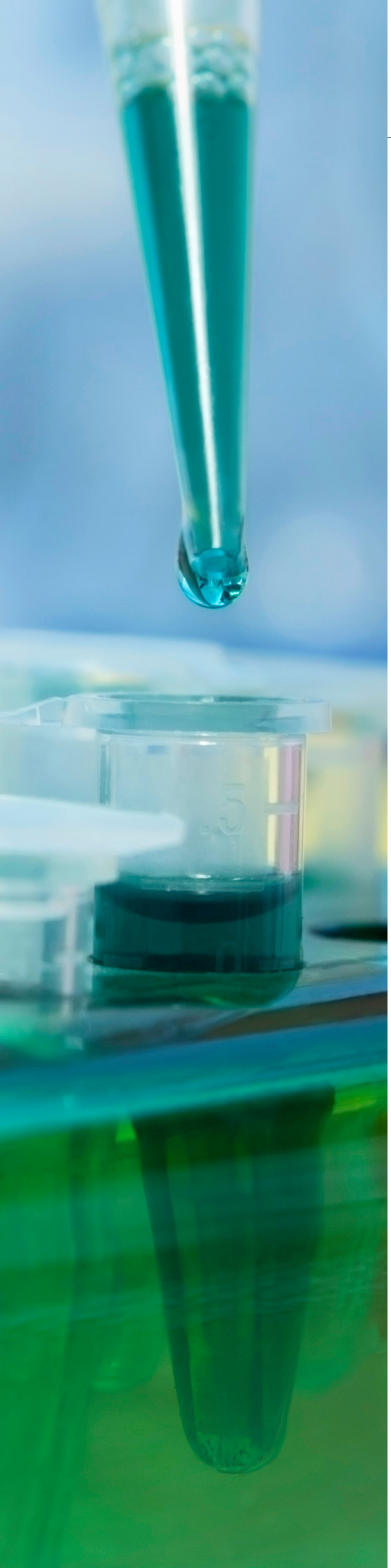


Commissioned Service Provider: Unizima

About Unizima

Unizima

Unizima is a biomanufacturing services and technology provider, delivering the expertise and technology needed to enable geographically diversified manufacturing of biologics such as vaccines, monoclonal antibodies and insulins. We are part of the Univercells Group and share its ground-breaking technology and engineering innovations.

We provide a full suite of solutions that includes strategy, product licensing, design and build of facilities and workforce development, allowing clients to accelerate the implementation and operations of their facilities and projects. Our team has extensive global experience in manufacturing strategy, investment profitability analysis, engineering, biologics manufacturing, GMP and Quality Assurance, Regulatory Affairs, supply chain, logistics management, training and recruitment.

Since our inception in 2020, we have served as a trusted partner for biopharma manufacturers, governments and global health agencies to make sustainable biologics production in low- and middle-income countries (LMICs) and emerging markets a reality. We are driven by the end goal of delivering life-changing biologics to people who would otherwise lack access to them.

Learn more: www.unizima.com

1. Executive Summary

Today, Africa almost entirely depends on the importation of vaccines from South Asia and Europe. Localizing vaccine manufacturing will improve the resilience of the continent's healthcare system and can help to provide faster access to vaccines in a future pandemic. The Partnerships for African Vaccine Manufacturing vision is to produce 60% of routine vaccines on the continent by 2040.

Transferring Fill/Finish (F/F) operations of established commercial vaccines to contract manufacturing organizations (CMO's) in Africa is a realistic first step to localize manufacturing, achievable within a reasonable time period. The owners of commercial vaccines will – however – only consider a product transfer, if a CMO has credible quality standards and is reliable, strong continuous support is provided by governments and incentives are provided to make the investment financially attractive.

The present report has been commissioned by BACKUP Health, a global programme of the Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH, commissioned by the German Federal Ministry for Economic Cooperation and Development. A concept for a vaccine Fill/Finish CMO network in Africa has been elaborated. A flexible costing simulation has been developed to enable the assessment of the financial viability of such an investment and to compare the cost of manufacturing in Africa versus importing the products.

Africa will need 2.1 billion doses of vaccines in 2040. With product presentations not changing versus today this represents 280 million containers comprising multi- and single dose glass vials, vials with freeze-dried vaccines, and BFS tubes for oral vaccines and diluents. A network of at least 5 factories would be required to leverage economy of scale and limit risks due to complexity. A standard factory would have 2 liquid vial filling lines, one freeze-drying line and one BFS tube line. The factories should be located across the continent in countries where adequate infrastructure and skilled workforce are available. The wider regions around the factories could be directly supplied outside of the factories, simplifying shipments.

A conceptual design and operational mode for a standard factory have been elaborated. Setting up a factory would require a capital investment of 89 mio EUR and an associated project expense of 35 mio EUR. The time to first commercial production is estimated at 5 to 6 years.

A flexible financial model has been developed to allow the assessment of profitability of the investment and how it is impacted by various parameters. The investment can be profitable with adequate product mix, high-capacity utilization, and smooth and timely execution of the project. Profitability is strongly influenced by capacity utilization, raw materials cost (mainly filling raw materials such as vials and stoppers) and the local salary and energy costs.

Detailed analysis has shown that substantial cost savings can be achieved by replacing the shipment of finished products by the shipment of vaccine bulk concentrates. The Fill/Finish costs of routine vaccines in Africa are higher than in India, where most of the vaccines currently used on the continent are manufactured. However, higher costs in Africa can partially or entirely be compensated by shipping cost savings.

The development of alternative containers can provide substantial incremental benefits. The replacement of multi-dose glass vials for injectable vaccines by multi-dose blow-fill-seal (BFS) containers would reduce the Fill/Finish cost by 45%. Prototypes are available but need further development. BFS technology would also allow the transition from multi-dose to single-dose presentations in Africa while limiting the cost increase.

The African vaccine F/F facilities can be used to manufacture additional products to use spare capacity and generate additional revenue. Their design allows to switch from routine vaccines to the production of pandemic vaccines within a short lead time of several months only.

Multiple challenges would need to be overcome to achieve fully functioning and sustainable contract manufacturing of vaccines in Africa. A CMO must demonstrate high quality standards and reliability, ideally certified through WHO prequalification. Vaccine license holders will require this assurance to accept liability for their products partially manufactured by a contractor in Africa. This reliability can only be achieved with a strong and continuous political willingness and ability to provide support, develop the required infrastructure and capability. Incentives such as advance purchase agreements will be required to compensate for any financial disadvantages.

The study has shown a pathway to overcome today's challenges and establish sustainable Fill/Finish contract operations for vaccines in Africa.

2. Background and Objectives

African countries almost exclusively rely on the import of vaccines. Today less than 1% of the vaccine volumes needed on the continent are locally manufactured. During the COVID-19 pandemic, this dependance on importation resulted in substantially delayed access to vaccines. While many wealthy countries were offering their citizens doses for revaccination hundreds of millions of people in low-income countries were still waiting for their first dose. A key contributor for this inequality is the lack of vaccine manufacturing capacity on the African continent[1] .

It is – however – unrealistic that vaccine production can only be ramped up during a pandemic. Continuously operating robust facilities are required on the African continent. Between pandemics the local vaccine industry could create greater supply resilience for a broad range of vaccines and other pharmaceutical products. Such operations must be economically viable and be embedded in a well-functioning infrastructure and support network to be sustainable.

The Partnership for African Vaccine Manufacturing (PAVM) has set the goal that by 2040 the African vaccine manufacturing industry shall produce and supply 60% of the continent's total routine vaccine doses.

The study provides a business case simulation for Fill/Finish Contract Manufacturing of vaccines in Africa.

In this context the Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH commissioned a study for a business case simulation for Fill/Finish (F/F) Contract Manufacturing Operations in Africa. Companies holding licenses for vaccines used in Africa would have formulation, filling and packaging of their vaccines done by newly established local contract manufacturing organizations. This business model would be made attractive through appropriate incentives. This could be the fastest pathway to the establishment of sustainable vaccine manufacturing capacity in Africa.

This business case simulation is based on an assessment of the projected demand of vaccines in Africa. It includes a manufacturing concept with optimized facility and process designs. This enables a realistic assessment of investment and operational cost, and it allows for the evaluation of the impact of various parameters on the financial feasibility. The tool can be used for the assessment of future business opportunities.

'The African vaccine manufacturing ecosystem: supply landscape and expansion plans'. Published by Clinton Health Access Initiative, Inc. in December 2022

3. Methodology

The volume of vaccine demand for African countries was estimated based on data published by GAVI[2], and complemented by estimates from Unizima and data from the PAVM Framework for Action[3]. Container volumes were calculated on a dose-per-vial basis, for the most procured vial size, as set out in the Market Information for Access to Vaccines[4] (M4iA) database, published by the WHO.
The containers assumed are as follows: liquid vaccines in glass vials; oral vaccines and diluents in Blow-Fill-Seal (BFS) plastic tubes; and freeze-dried vaccines in glass vials.

Total volume figures were further broken down into demand estimates by region: Central, East, South, North and West Africa, based on disease prevalence. Compound Annual Growth Rate (CAGR) between 2025 to 2040 was also based on data from GAVI.

The study focused on formulation, filling, and packaging, including associated quality control activities. Options for establishing an African vaccine manufacturing network have been elaborated to reach a total capacity of 60% of the estimated demand for routine vaccines in 2040. Generic manufacturing and quality control (QC) process flows for different types of vaccines have also been prepared. Based on these assumptions, a generic facility design has been developed to meet current GMP requirements and industry standards. A flexible operational mode of such a facility with detailed staffing plans allows for adaptation to variable demand. The model also includes a fully integrated supply chain, from incoming raw and starting materials, to outgoing product shipments.

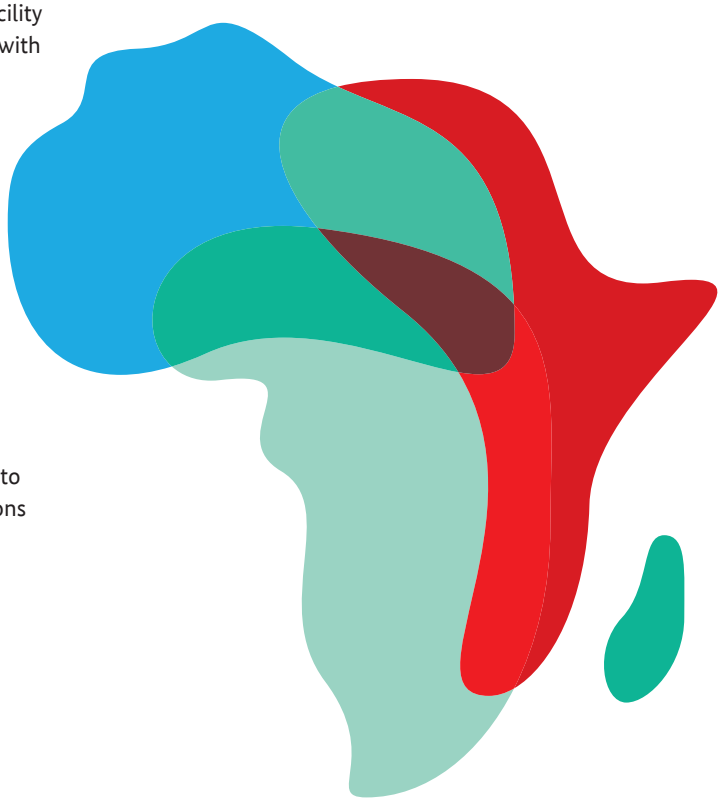
Cost estimates and timelines for the construction of the facility and startup are based on experience from similar projects, with updated quotations for major equipment from renowned European suppliers. Similarly, the cost of main raw materials has been estimated based on information from European and Asian suppliers. Shipment cost estimates are derived from information provided by logistics companies. Salary estimates take variations between African regions into account.

In this model, a F/F factory in the African network can be designed and adapted to meet varying capacity needs, by modifying generic design and operational plans. It is assumed that such a factory would operate as a contract manufacturer, providing manufacturing services to companies holding vaccine licenses. In the initial phase, to facilitate start-up and ensure robust operations, key positions would be held by highly experienced expatriates.

A network of facilities has been designed to meet 60% of the projected routine vaccine demand in 2040.

To enable the evaluation of the economic feasibility of such investments in African vaccine F/F facilities, a financial model was created which is designed to be flexible. It allows the assessment of varying parameters such as different levels of build-out of the generic facility design, different levels of capacity utilization, and raw material costs. The model also allows for an estimation of the F/F costs, and the profitability of the investment.

Options to improve profitability were assessed. This includes the development and implementation of alternative containers, namely using the BFS technology. Additional sources of revenue such as the production of non-vaccine products are presented.



[2] Expanding Sustainable Vaccines Manufacturing in Africa, GAVI (2022).
[3] PAVM Framework for Action (2022).
[4] Market Information for Access to Vaccines, WHO (2022)

4. Input/approach for local manufacturing

Table 1 - Total annual dose volumes for each prioritized vaccine (million - 2040).
Note that diluent volumes are not included in the figures below

		Vaccine Information				Total Container Volumes (excluding diluent)			
Category	**No.**	**Vaccine**	**Formulation**	**Dosing[3]**	**Number of doses per child[4]**	**GAVI Sustainable Mfg report Total doses - Millions (2040)[1]**	**PAVM Framework for Action Total dose volumes (base case) - Millions (2040)[2]**	**Unizima estimates Total doses -Millions (2040)**	**Notes**
Legacy Routine	1	Pentavalent (Diphtheria, Tetanus, Pertussis, Hepatitis B, HiB)	Liquid or freeze-dried injectable	6, 10, 14 weeks plus booster	4	166	246,67	N/A	Gavi estimates used
	2	Bacille Calmette-Guérin (Tuberculosis)	Freeze-dried injectable	Birth	1	N/A	140	N/A	PAVM estimates used
	3	Measles-Rubella	Freeze-dried injectable	9, 18 months	2	213	240	N/A	Gavi estimates used
	4	Yellow Fever	Freeze-dried injectable	9 months	1	53	50	N/A	Gavi estimates used
	5	Oral Cholera Vaccine	Liquid oral	1 year	2	23	30	N/A	Gavi estimates used
	6	Typhoid	Liquid Injectable	9-12 months	1	33	20	N/A	Gavi estimates used
	7	Meningococcus A conjugate	Freeze-dried injectable	9-18 months	1	53	60	N/A	Gavi estimates used
	9	Polio (IPV)	Liquid Injectable	6, 10, 14 weeks	3	103	150	N/A	Gavi estimates used
	9	Tetanus Diptheria	Liquid Injectable	Older children	2	83	N/A	N/A	Assume 1/3 of Gavi volume estimates for pentavalent needed for 2 boosters
	Total container volumes - Legacy Routine (Millions - 2040)					727	140		
Expanding	10	Human Papillomavirus	Liqud injectable	9 years	2	36	30	N/A	Gavi estimates used
	11	Pneumococcal conjugate vaccine	Liquid injectable	6, 10, 14 week	3	142	140	N/A	Gavi estimates used
	12	Rotavirus	Liquid oral	6, 10 weeks	3	125	120	N/A	Gavi estimates used
	13	Malaria	Liquid injectable	5 months	4	72	120	N/A	Gavi estimates used
	14	HIV	TBD	TBD	TBD	N/A	110	N/A	PAVM estimates used
	15	Multivalent meningococcal Vx (e.g MenACWY)	Liquid or freeze-dried injectable	Adolescents	1	53	N/A	N/A	Gavi MenA estimates used as proxy - could be overestimation
Outbeak	16	Ebola	Liquid injectable	Outbreak	1	0,3	1	N/A	Gavi estimates used
	17	Influenza	Liquid injectable	Outbreak	Varies	N/A	10	N/A	PAVM estimates used
	18	Chikungunya	TBD	Outbreak	TBD	N/A	1	N/A	PAVM estimates used
	19	Rift Valley	TBD	Outbreak	TBD	N/A	1	N/A	PAVM estimates used
	20	Lassa Fever	TBD	Outbreak	TBD	N/A	1	N/A	PAVM estimates used
	21	Disease X	TBD	Outbreak	TBD	N/A	N/A	N/A	Not included
	22	COVID-19	Freeze-dried Injectable	Outbreak	Varies	N/A	710	N/A	PAVM estimates used
	Total container volumes - Outbreak (Millions - 2040)					0,3	723		
Additional	23	Rabies	Freeze-dried Injectable	Varies	3	N/A	0	7	Unizima estimates used
	24	Dengue	Freeze-dried injectable	Varies	1	N/A	N/A	9	Unizima estimates used
	25	Varicella	Freeze-dried injectable	Varies	1	N/A	N.A	3,6	Unizima estimates used
	Total container volumes - Additional (Millions - 2040)				**19,6**				
	Total container volumes - All categories (Millions - 2040)				**2.147,9**				

Indicates Pipeline Vx
Indicates Unizima addition on top of PAVM priority diseases

[1] Gavi: Expanding Sustainable Vaccine Manufacturing in Africa Report 2022. Figure 15 Global and African demand for potential priority antigens, p. 21
[2] PAVM: Framework for Action Report. 22 Priority Diseases, Exhibit 11, p. 35
[3] Most commonly purchased vial image from WHO M4IA 2022 Vaccine Purchase database

Note that diluent volumes are not included in the figure above.

Refer to Annex 01 for detailed vaccines market demand

A capacity to fill 280 million containers annually is required to meet the PAVM goal.

4.1. Market data, products presentation and capacity needs

4.1.1. Vaccines identification and prioritization

In order to calculate how many F/F facilities would be needed across Africa, we first set out to identify which diseases and vaccines should be included in the analysis, to establish a baseline volume demand for 2025-2040. Vaccines that had been identified as priorities in the PAVM Framework for Action, and by GAVI, were used as a starting point, with a focus on those which come under the "Legacy Routine", "Expanding" and "Outbreak" categories. "Additional" vaccines that could become more routine in the coming decades have been added, based on public health needs across Africa.

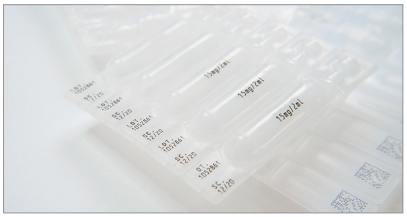
Demand projections

Demand projections, including CAGRs for 2025-2040, were also based on information in the PAVM and GAVI source documents, with the exception of the annual volumes for "Additional" vaccines, which were estimated. Accordingly, it's estimated that a total of 2.1 billion vaccines doses would be required annually by 2040, across all four categories identified above, to meet demand in Africa.

Total container volumes The F/F factories will be equipped to process three different container types, each with different sizes as per the number of doses filled per container:

a) *liquid vaccines in glass vials;*

b) *oral vaccines and diluents in BFS plastic tubes;*



c) the freeze-dried vaccines in glass vials.

Building on annual doses' volumes from Table 1, annual containers' volumes were calculated as shown in Table 2. While diluents for freeze-dried products were added to overall containers' volumes, outbreak vaccines were excluded to avoid building idle capacity into the system. It was assumed that the demand for outbreak vaccines would be fulfilled by temporarily pausing F/F operation of routine vaccines and redirecting capacity in case of an outbreak.

Table 2 - Breakdown of container type and total container volume assumptions used to calculate F/F capacity needed across vaccine types

Category	Container volumes (Million - 2040)			
	Total liquid vaccines in glass vials	Total BFS + diluent in plastic tubes	Total lyophilization in glass vials	Total container volumes
Legacy Routine	42	62	39	143
Expanding	171	125	0	296
Outbreak	0	0	0	0
Additional	0	11.5	11.5	23
Total (100% demand)	213	199	50	**462**
Total (60% demand)	128	119	30	**277**

Capacity Needs

Overall Network

The above assumptions lead to a total demand of 462 million containers in 2040. The manufacturing network proposed in this report is designed to meet 60% of this demand, in line with PAVM's vision, which equates to 280 million containers in 2040.

Regional Demand

Overall containers' volumes were broken down by five regions – North, South, East, West, Central –using attributable demand based on relative proportion of population.

Table 3 - Attribuable demand estimates used for regional breakdown using relative population per region as a proxy

Region	Number of countries	Attributable demand (%)[5]
Central	9	15.4
East	13	30.6
North	6	13
South	11	10.5
West	15	30.5
Total	54	100

Adjustments were also made to ensure that only regionally relevant vaccines/diseases were included in the facility capacity in each region.

Table 4 - Assumptions on regional relevance of vaccines in focus

Category	No.	Vaccines	Relevance by region				
			Central Africa	East Africa	North Africa	South Africa	West Africa
Legacy Routine	1	Pentavalent (Diphtheria, Tetanus, Pertus Hepatitis B, HiB)	✔	✔	✔	✔	✔
	2	Bacille Calmette-Guérin (Tuberculosis)	✔	✔	✔	✔	✔
	3	Measles-Rubella	✔	✔	✔	✔	✔
	4	Yellow Fever	✔	✔		✔	✔
	5	Oral Cholera Vaccine	✔	✔	✔	✔	✔
	6	Typhoid	✔	✔			✔
	7	Meningococcus A conjugate	✔	✔	✔	✔	✔
	8	Polio (IPV)	✔	✔	✔	✔	✔
	9	Tetanus Diphteria	✔	✔	✔	✔	✔
Expanding	10	Human Papillomavirus	✔	✔	✔	✔	✔
	11	Pneumococcal conjugate vaccine	✔	✔	✔	✔	✔
	12	Rotavirus	✔	✔	✔	✔	✔
	13	Malaria	✔	✔			✔
	14	HIV	✔	✔	✔	✔	✔
	15	Multivalent meningococcal Vx (e.g MenACWY)	✔	✔	✔	✔	✔
Outbreak	16	Ebola	✔	✔	✔	✔	✔
	17	Influenza		✔			✔
	18	Chikungunya	✔	✔	✔	✔	✔

Indicates Pipeline Vx
Indicates Unizima addition on top of PAVM priority deseases

[5] UN population division. World population prospects 2022, Online Ed.

4.2. Primary packaging technologies (BFS and glass containers)

Most of today's vaccines are filled in **glass vials**, and in Africa, multi-dose vials are the most common. Compared to single-dose containers this enables substantially lower manufacturing cost mainly driven by savings on raw materials and reduced shipping volumes. To maintain sterility after the withdrawal of a proportion of the content, preservatives are added, which is a concern in many countries due to the risk of potential long term side effects. It is often not possible to use the entire content of a multi-dose vial during its in-use shelf life, which leads to substantial waste. These disadvantages of multi-dose containers might trigger a move to the use of single-dose containers in African countries in the future, as it happened in many other regions before.

Blow-fill-seal (BFS) technology could help to reduce the cost of local vaccine production in Africa. BFS is a manufacturing process and packaging platform that has been used to produce aseptic pharmaceuticals since the late 1960's. It is less frequently used for injectable drugs, but such products are available. BFS technology uses a plastic container which is formed by LDPE resine' injection into a mold at high temperature and is then immediately filled with the vaccine. There are currently only two commercial vaccines available in BFS, both are oral vaccines against Rotavirus. Feasibility studies for different injectable vaccines have been carried out. Data accessible in the public domain indicate that BFS is technically feasible for a broad range of liquid vaccines including classical inactivated or live vaccines, recombinant proteins or RNA/DNA. However, the amount of published data on this topic is limited.

Multi-dose BFS presentations for vaccines are currently unavailable. The main technical challenge is to extract up to 10 doses of an injectable vaccine one after the other from a BFS tube and maintain sterility up to the last dose extracted. A classic BFS tube remains open after the first extraction of product. Technical solutions have been developed to enable sterile conditions during multiple extractions from a BFS tube: A rubber stopper (Figure 4) – similar to the one used for multidose glass vials - or a connector for syringes can be inserted on the top of the BFS tube.

To proceed with such development, a vaccine producer who is supportive of developing and registering an existing vaccine in a new BFS presentation must collaborate and provide materials and information or own and execute the development. Competent health authorities and stakeholders such as, the WHO, and GAVI should be involved in, and supportive of such a development project, to ensure later approval and the launch of such injectable vaccines developed using BFS technology. *Refer to Annex 02 for details.*

Feasibility studies are required for each vaccine to confirm that all technical risks - such as temporary exposure to higher temperatures, higher permeability of the container wall, and potential contamination – can be controlled. Substantial longer-term stability studies must be carried out prior to approval of the new product. Furthermore, the optimum design of the BFS presentation and its use under routine conditions must be verified by field studies by future users of the product.

Figure 4 - Rubber stopper at the top of the BFS vial

The total development cost of an injectable vaccine in BFS is estimated at 1.5 million EUR per vaccine, the time to launch at about three to four years.

The local manufacturing of liquid injectable vaccines in Africa using multi-dose BFS containers would offer the opportunity to reduce the F/F costs by an estimated half compared to multi-dose glass vials. This would make local manufacturing competitive versus product in glass containers manufactured in India. Cost simulations indicate that filling in mono-dose BFS containers would be substantially less expensive than filling into mono-dose glass vials, however the cost is still approximately 2.5 times higher than for a dose in a multi-dose glass vial.

The move to multi-dose BFS presentations would drastically reduce Fill/Finish cost

4.3. Investment considerations

4.3.1. Regional capacity considerations (Facility network/mapping)

- The baseline objective is to develop F/F capacities to meet 60% of the market demand i.e. 280 million containers by Y2040. Therefore, the baseline proposal is to set-up five multi-products regional F/F factories as follows:

  (a) three medium-sized F/F factories will each have annual F/F capacities of around 80 million containers, comprising liquid glass vials, freeze-dried glass vials and BFS tubes. They will be located close to their respective markets i.e., in East Africa, West Africa and again West Africa to cover the Central African demand (the industries in Central African countries are not sufficiently developed to host such large pharma investment project).

  (b) two smaller F/F factories will be located in North Africa and South Africa, assuming that existing F/F capacities can be leveraged; additional capacities would be installed in these locations for liquid vaccines in glass vials and freeze-dried vaccines in glass vials with total annual F/F capacities of about 20 million containers each.

- For the three medium-sized F/F factories (named West nr1, East and West nr2), the following locations are assumed, for the purpose of the model: Nigeria, Kenya and Ghana. An alternative option could be Mozambique instead of Kenya to leverage the private project initiated by the company Mozambique Holding and Senegal instead of Ghana or Nigeria to leverage the IPD existing and future F/F facilities.

- For the two smaller factories (named North and South), the following locations are preferred: Egypt and South Africa; an alternative option could be Algeria or Morocco to leverage the Sensyo Pharmatech project.

- The proposals for the above countries are preliminary and illustrative for the purpose of supporting discussions with stakeholders. They have been selected based on six basic criteria: (a) the country geographical position and its demography (b) the country eco-system and market dynamic (c) the country skills and educational system (d) the country financial strength and political stability and (e) the country support to project(s) for vaccines bulk(s) manufacturing and/or Fill/Finish (f) the country easy export logistics to the region. *Refer to the Annex 03 for the detailed selection criteria.*

A network of 5 regional factories is proposed.

Figure 5 - Proposal of factories locations on the african continent

- Financing five F/F factories represents a substantial CapEx investment which has been estimated at approximately 332 million EUR; the investment per factory has been estimated as follows:

Table 5 - CapEx investment summary

F/F factories Estimated investment CapEx – EUR	West nr1 F/F factory	East F/F factory	North F/F factory	South F/F factory	West nr2 F/F factory	Total Five F/F factories
CapEx per F/F factory – EUR	89.347.804	89.347.804	32.037.915	32.037 915	89.347.804	332.119.242

- Such a significant investment could be considered high-risk and is therefore unlikely to receive either financial support from investors, or sponsorship from all key stakeholders. Therefore, recommendation is made to invest in one large multi-products regional F/F factory to start with. This “pilot” F/F factory would be based either in East or West regions which have high vaccines demands.

4.3.2. Vaccine demand allocation per F/F factory

- As per the regional relevance of vaccines described in chapter 4.1, almost all vaccines are demanded in the five regions; therefore, proposal is made that each F/F factory will fulfill the vaccines demand of the region where it is located. Nevertheless, two exceptions are to be introduced, the first for the only three vaccines classified as "regional", the second for the low volumes' vaccines.
- The three "Regional" vaccines are Malaria, Meningitis A and Dengue. The demand for Malaria vaccine is concentrated in East, West and Central Africa regions; as of today, small volumes of vaccines are produced (the first from GSK/Bharat Biotech companies and the second in clinical trials from Serum Institute of India); proposal is made to fill that vaccine in two F/F factories located in West and South regions; they would install their additional liquid F/F lines when the market demand would be confirmed.

  The Meningitis A vaccine low demand is concentrated in East and West regions; proposal is made to fill that vaccine in one F/F factory located in West region. Dengue vaccine is the third regional vaccine with low demand concentrated in East and West Africa.
- Three vaccines have low demand making the Tech Transfer to various F/F factories not time and cost effective. Demand for the Typhoid vaccine is estimated at 4 million vials per year; proposal is made to limit its Tech Transfer to two F/F factories, in West and South Africa. Similarly, demand for Varicella and Yellow Fever vaccines is capped at 5.3 million; proposal is made to fill and freeze-dry them in one F/F factory in West Africa.
- In conclusion, the vaccines demand allocation among the five F/F factories is driven purely by F/F capacities optimization, and not by the specific medical needs in one or the other region.

  Refer to Annex 04 for details about the F/F factories capacities and utilization rate.

4.4. Operational costs considerations F/F factory

4.4.1. Operational model and process flow chart for a F/F factory

- The F/F factory will operate as per the following CMO principles:

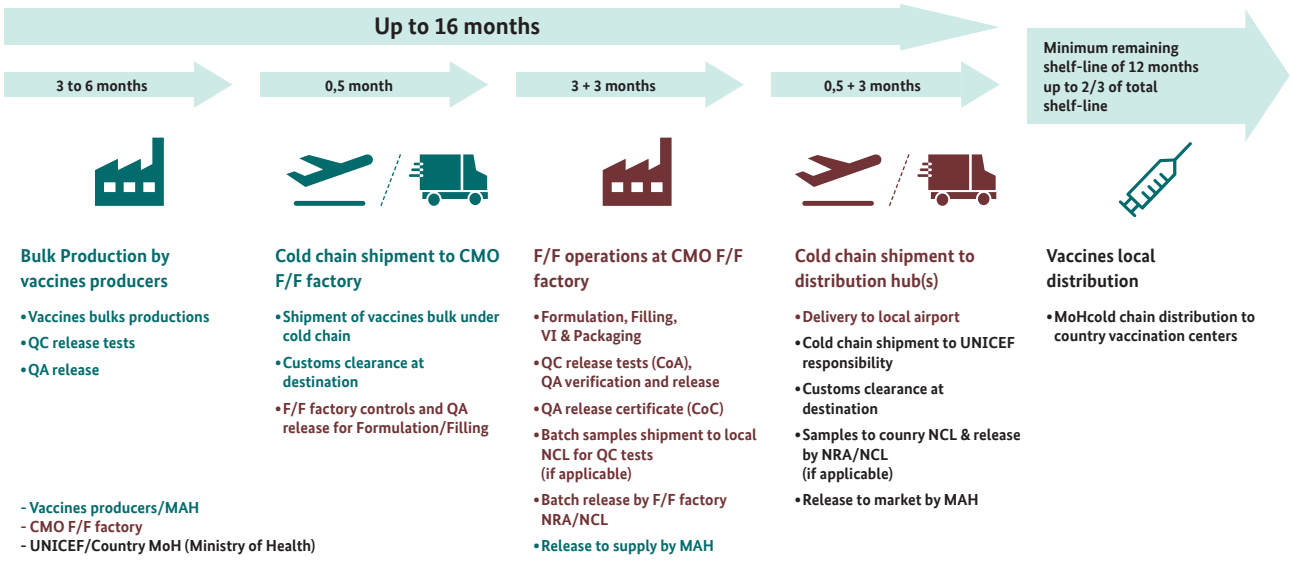
(a) The F/F factory will sign CMO agreement(s) with the vaccines bulks producer(s); the agreement(s) will include the vaccines F/F operations' Tech Transfer(s) to the CMO F/F factory;

(b) The F/F factory will import the vaccines' bulks which will remain the property of the bulks producer(s); it will execute the F/F operations (i.e., the Formulation, Filling, Packaging, QC release tests) and will be liable for those operations only;

(c) The vaccine bulk producer(s) will be liable for releasing the finished packed vaccines on the markets; they will remain the Marketing Authorization Holder (MAH) and will be responsible for the vaccine's registrations in the various markets, the supply to Unicef and the pharmacovigilance.

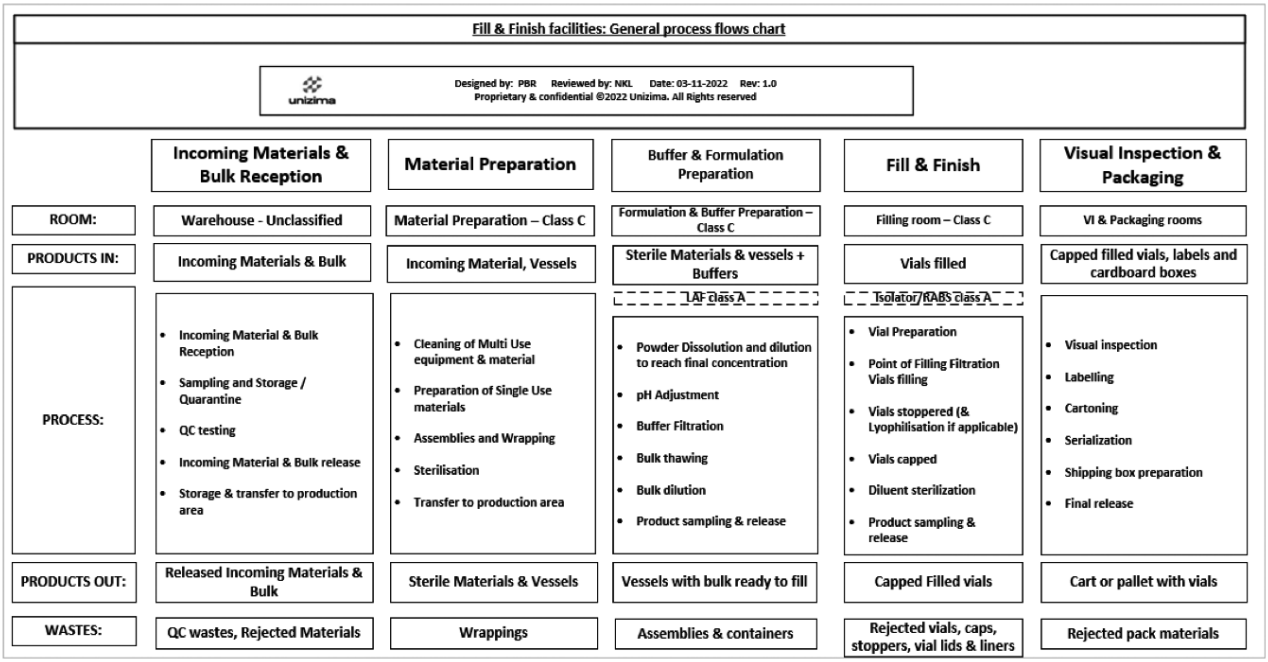
- The F/F factory' CMO operational mode defined as per below generic scheme.

Figure 6 - Generic F/F CMO model



- The F/F factory operations are summarized in below generic flows chart; it may be subject to adaptations due to vaccines' F/F process specificities. Each production step is subject to a QA release before moving to the next step.

Figure 7 - General F/F factory process flow chart



- *The specific flows chart for each F/F production step are described in the Annex 05.*

4.4.2. F/F factory GMP standards, Tech Transfer & registration aspects

- It is assumed that the vaccines considered in the F/F factory have a valid marketing authorization in the country of origin and are WHO "Pre-Qualified". The vaccines manufactured by the F/F factory are expected to be supplied in the F/F factory' country and regional countries under UNICEF' procurement and supply programs.
- The F/F factory must comply with applicable GMP and regulatory requirements, namely WHO requirements, which are similar to EU GMP and regulatory standards; meaning the F/F factory must also be WHO "Pre-Qualified". The national regulatory agency (NRA) in the country where the F/F factory is located should have a Maturity Level 3 (ML3) or higher. To date the list of NRAs operating at ML3 as benchmarked against WHO Global Benchmarking Tool (GBT) on the African continent are 5 countries. Three countries (Ghana, Nigeria and United Republic of Tanzania) are non-producing for vaccines and two countries (Egypt and South Africa) are producing vaccines.
- The F/F factory manufacturing and QC facilities as well as their Quality Systems must meet WHO GMP standards. By the time the factory is in situ, the African Medicines Agency (AMA) might be operational and hence the F/F factory will have to comply with AMA standards.
- The F/F factory needs to be fully qualified. The F/F manufacturing process would need to be transferred in a systematic, well-documented manner. Comparability of the vaccines manufactured at the F/F factory with the vaccines manufactured at the originally licensed sites needs to be demonstrated. This includes not just standard product release parameters, but also critical process parameters. The consistency of the F/F operations must be demonstrated, usually through three consecutive full scale manufacturing runs. Stability of the vaccines manufactured at the F/F factory needs to be tested. If there are no critical changes to the vaccines' configuration (e.g. container type) and no evidence of adverse stability trends, at submission six months real time stability data are typically required with the commitment to submit further data on an ongoing basis.
- In general, the role of NRA's is to oversee pharmaceutical manufacturing in their country to ensure adequate quality of the products made there, and to authorize products for use domestically. As it is assumed that the vaccines transferred are already licensed in the country of origin and will be used more widely, the regulatory authorities in the country of origin and WHO will play a critical role in the process of technology transfer.
- The F/F factory will require a general manufacturing license, which is typically issued by the NRA. The process and timing for obtaining such a license differs between countries. In light of the regulatory harmonization currently taking place in Africa, it is possible that vaccines could receive regional

marketing. authorizations and maybe even a continent-wide approval through the African Medicines Agency which is currently being established in Rwanda.

- The addition of a manufacturing site for an approved vaccine requires the submission of a variation, which is classified as 'major'. The review of such applications typically takes 4 to 12 months, depending on complexity and quality of the data/dossier. Prior to approval, an inspection of the new F/F factory will be carried out. In this case this might be a joint inspection of NRA and the WHO, who would issue the Pre-Qualification (WHO PQ) of the F/F factory.
- The F/F CMO factory is required to fully comply with the rigorous WHO GMP standards. This requires a high-level of maturity of the organization, which can only be obtained through thorough training and with strong support from experts.

4.4.3. F/F factory layout

- A conceptual Site Master Plan for the F/F factory is proposed below. The F/F factory buildings will be developed on a site of a minimum of 7500 m² to accommodate parking, trucks roads, future extensions, and green areas. It incorporates the F/F factory building, the QC animals house (for the in-vivo QC release tests), and the utilities building. The main building has an estimated surface of +/- 3700 m².

  The importation of animals to execute the in-vivo tests might be complex; a small farm for animals breeding might have to be constructed on the site.

The F/F factory building would consist of: (a) the Central Services (offices, canteen, QC laboratories), (b) the Packaging rooms and Stores, all extensible as per the F/F volumes and (c) the Filling lines aligned in a row with the possibility to extend their numbers as per the F/F volumes and types of containers. A concept for the F/F factory lay-out is proposed in Annex 06 as per the latest cGMP standards; it will be detailed and further optimized during engineering design studies.

- The F/F factory design is based on the below cGMP manufacturing principles:

a) The Filling lines installed (in a row) between a clean corridor and a dirty corridor to segregate the materials flows in from the materials flows out;

b) The glass vials Filling lines under isolator, in rooms grade C, dedicated to all liquid vaccines filling, without cross-contamination risks because either viral inactivated/ recombinant or bacterial conjugated/toxoid vaccines are processed;

c) The glass vials Filling line under isolator with two freeze-dryers, in C-grade rooms (with BSL1), dedicated to all freeze-dried vaccines filling, without cross-contamination risks because they would be dedicated to life-attenuated vaccines;

d) The BFS Filling line under isolator, in C-grade rooms (with BSL1), would be dedicated to filling two oral vaccines, without cross-contamination risks because both would be life-attenuated vaccines; the conveyors from the filling line to the freeze-dryers (and back) under isolators, would consist of an automatic loading system into the freeze-dryers;

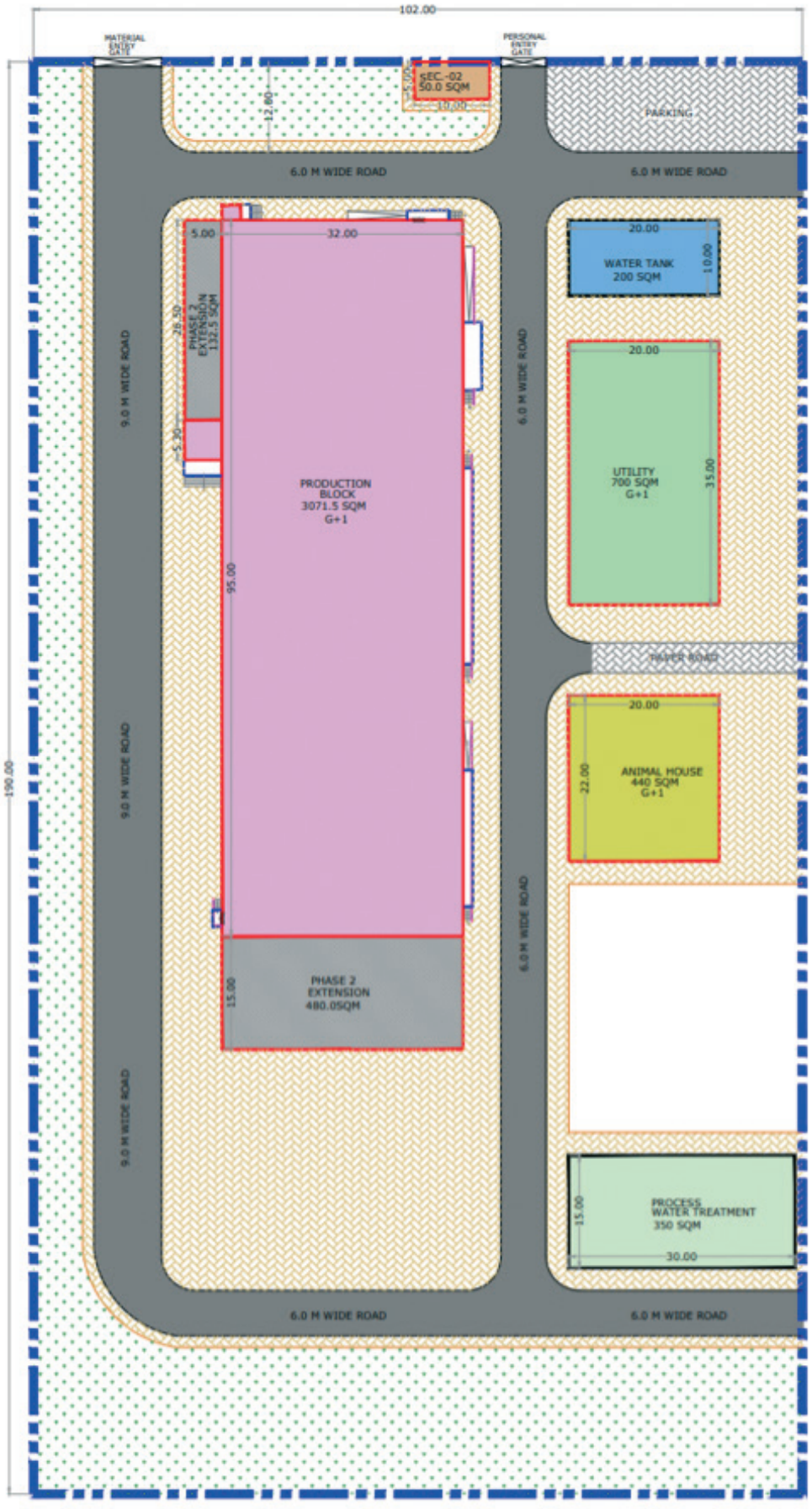
e) Filling diluents would occur on the same BFS filling line, with terminal sterilization in autoclave;

f) The Materials Preparation/Sterilization operations as well as the Media Preparation and Formulation operations for all liquid vaccines would occur in C-grade rooms, which would be duplicated for freeze-dried and oral vaccines but with BSL1;

g) The glass vials and BFS Filling lines would be with medium (approximately 200 units per minute) rather than high capacities to avoid the complexity of running larger machines and increasing the potential for any associated quality risk;

h) Additional cGMP characteristics of the F/F factory design can be seen in Annex 06.

Figure 8 - High level factory layout



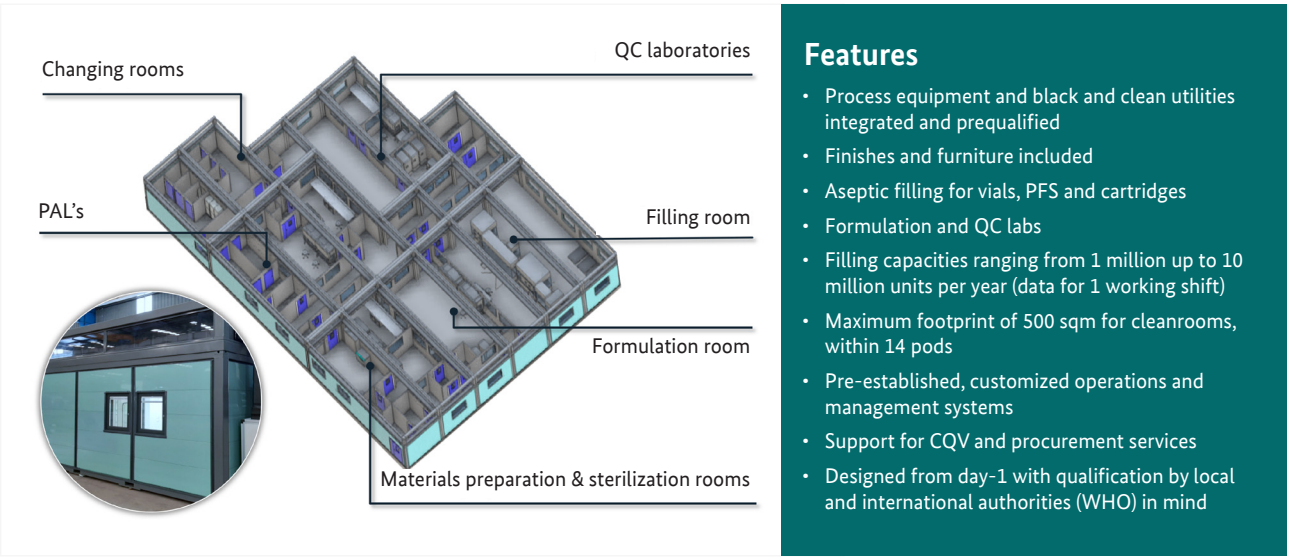
Master site plan

4.4.4. F/F factory with a modular approach

- The F/F factory can be made of PODs or modules constructed abroad with all the clean utilities and process equipment integrated and pre-qualified (FAT, SAT and pre-IQ validations). The POD's will integrate the Materials Preparation/Sterilization rooms, the Formulation rooms and the PALs/MALs, all in grade C; as well as the QC laboratories in grade D & CNC. Practically, the pre-qualified POD's are shipped to the F/F factory and integrated into its structure built in advance.

Figure 9 - Principles of modular facilities

We can deliver a rapidly deployed, modularized facility that is pre-designed and pre-qualified and customized to your needs



Features

- Process equipment and black and clean utilities integrated and prequalified
- Finishes and furniture included
- Aseptic filling for vials, PFS and cartridges
- Formulation and QC labs
- Filling capacities ranging from 1 million up to 10 million units per year (data for 1 working shift)
- Maximum footprint of 500 sqm for cleanrooms, within 14 pods
- Pre-established, customized operations and management systems
- Support for CQV and procurement services
- Designed from day-1 with qualification by local and international authorities (WHO) in mind

- The complexity of installing and qualifying all clean rooms, clean utilities and process equipment on the spot will be transferred "upwards" to the PODs producer hence it reduces all technical and quality risks at the level of the F/F factory. It brings time savings for the design and construction.

It simplifies the installation, qualification and start-up of an aseptic F/F factory. It avoids delays, for example in the clean utilities and process equipment installations and validations (usually done by European technicians flying abroad).

Figure 10 - Advantages of modular facilities

The facility is designed to remove complexity, reduce risk and time-to-market while building in flexibility to meet your future needs

Simplicity

Our in-house experts and preferred partners deliver a pre-assembled, prequalified cGMP facility for easy and quick on-site installation, reducing the need for on site experts.
Designed by biomanufacturers for biomanufacturers.

Rapid access

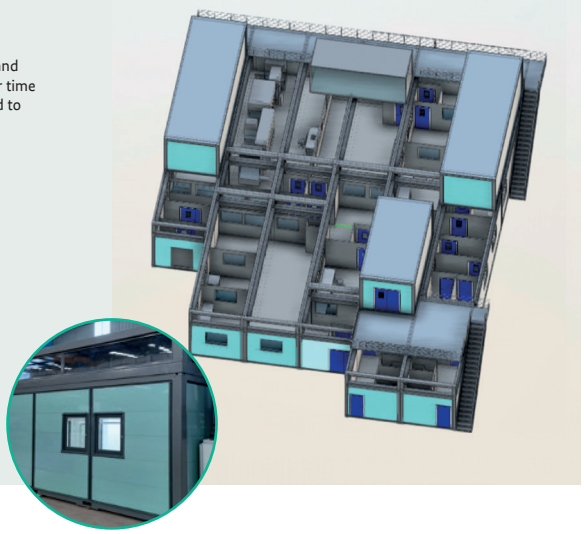
Our standardized design and operating and management systems allow for a shorter time to market by 6 up to 9 months compared to more traditional solutions.

Flexibility

- Pick the modules that you need
- Add additional modules to increase capacity or extend the production process
- Change product line as your project evolves
- Construct a "greenfield project" or connect the facility or specific modules thereof to your existing building ("brownfield project")
- Install the facility outside or inside a shell building.

Lower CapEx investment

Our modular solution helps you save about 20% on capital expenditure and avoid budget creep.



- Annex 07 elaborates on the technical details for a modular F/F factory.

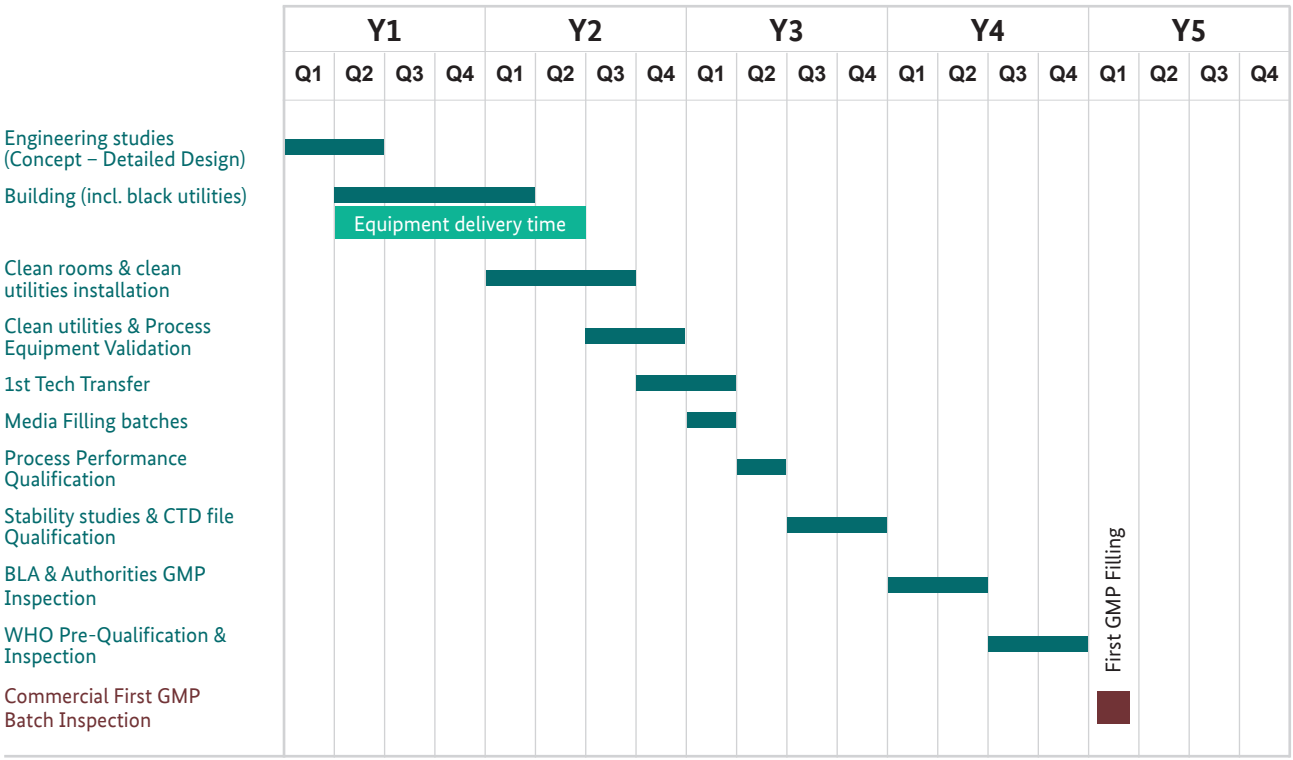
4.4.5. F/F factory organization chart

- The F/F factory will require a workforce of approximately 238 headcounts, working in two shifts, to run the factory with up to four F/F lines. The headcount consists of a 60%-40% split between those who are direct and indirect personnel respectively. The factory management team would be recruited from day 1, and would be part of the investment Project Management team; indirect employees and direct operational employees will be recruited gradually from the factory construction end, keeping pace with the installation of F/F lines and qualifications; however all employees would need to be in place for the Process Performance Quality (PPQ) validations. Direct employees for the second working shifts would be recruited as the F/F volumes increases. *Details of the financial model can be seen in the document titled "FiveFactories-Baseline", tab "3.1 OrgChart".*
- The salaries costs have been estimated based on the average salaries' grid inserted in that tab. Advise is given that at least seven critical positions to be held by expatriates for at least up to the first two to three years of the F/F factory commercial operations.

4.4.6. F/F factory raw materials

- Filling operations for liquid and freeze-dried vaccines would be executed with Ready to Use (RTU) glass vials (type 1); a full description can be found in Annex 08. Oral vaccines and diluents would be filled in BFS plastic tubes made with pharmaceutical grade Low-Density Polyethylene (LDPE).
- The various F/F operations can be executed with SUS (Single Use Systems); they are described in Annex 09.
- Specific assumptions related to the raw materials are detailed in chapter 5 related to the financial model.

Figure 11 - High level generic timeline – F/F facility



The development of a fill & finish facility in Africa is a complex project that requires careful planning and execution. The following is an overview of the different phases that the project is likely to go through, along with the estimated duration:

Business case and funding:
before project starting, a detailed project plan is developed; this involves the factory conceptual design and the preparation of a comprehensive business case; funding is done usually in parallel.

Engineering studies, 3 to 6 months:
engineering studies (conceptual and detailed design) with soil and geotechnical studies are performed; all process equipment are selected and ordered at that time.

Building & black utilities, 1 year:
construction of the building and installation of the black utilities (such as the power, water system, compressed air, HVAC system and chiller, ...) is done.

Clean rooms & clean utilities installation, 9 months:
installation of the clean rooms panels and all cGMP furnitures and accessories is done followed by the clean utilities (such as the clean compressed air, the purified water system, the WFI system, ...); delivery and installation of the first process equipment is executed.

Clean utilities & Process equipment validations, 6 months:
the IQ (Installation Qualification) and OQ (Operational Qualification) of all clean utilities, systems and process equipment are executed.

Tech Transfer, 6 months:
the transfer of the first vaccine' production process is executed as well as the transfer of its analytical QC tests methods.

Media Formulation & Filling batches, 3 months:
once all IQ/OQ validations are approved, three consecutive media batches are executed.

Process Performance Qualification, 3 months:
the PPQ is executed for the first vaccine with three consecutive Consistency production batches.

Stability studies & CTD file preparation, 6 to 9 months:
the samples from the Consistency batches are QC tested at different time points during the minimum 6 months stability studies, accelerated studies are executed in parallel; it's followed by the preparation of the CTD (Common Technical Dossier) for submission to the regulatory authorities and later to the WHO.

Certain assumptions are taken beneath this optimistic high-level timeline:

1. Six months real time stability studies are accepted by local GMP authorities;
2. The file review by the local & product owner countries will last only 6 months;
3. The WHO Pre-Qualification process will last only 6 months.

Refer to the Annex 10 for details about the registration process.

5. Financial modeling for local manufacturing

5.1. Presentation of the financial model

5.1.1. What the financial model is calculating

The financial model calculates four main profitability parameters to help the investors in the F/F factory to assess the potential investment returns and the risks.

1) The estimated **Net Present Value (NPV)** is the first and most common parameter. It is used to assess the current value of future earnings using a specific discount rate known as the Weighted Average Cost of Capital, or WACC. If the NPV is positive then the project is seen as potentially profitable, and probably sustainable.

2) The next financial parameter is the estimated **Internal Rate of Return (IRR).** This is the discount rate that makes the NPV of a project equal zero. To show a value above zero, a project must have an IRR higher than the discount rate or assumed WACC.

3) The estimated **cumulated Free Cash Flow (FCF)** is the third parameter and is the sum of all free cash flows calculated throughout the years of the financial model. The cumulated FCF not only enables to see what the total cash need is after having raised debt and equity but also to see when the project will be cash positive (when cumulated FCF are higher than 0).

4) The **payback period** is the fourth parameter and is related to the cumulated FCF. This is the year the F/F factory's cash position becomes positive i.e., the year in which the revenues start to cover all expenses. The model considers the minimum volume with the estimated F/F costs or absorption cost per container/dose for the different Stock Keeping Units (SKUs), to show the minimum positive NPV.

5.1.2. What are the model baseline assumptions ?

5.1.2.1. Assumptions of F/F factory volumes

The consolidated F/F volumes for the Y2040 correspond to 60% of the African demand for routine vaccines and represents about 280 million containers.

The F/F factory would be of medium size - with four F/F lines and an option for a fifth one to reach 100% of the market demand - which can be easily managed and would manufacture the vaccines for the region in which it is located.

The factory will have F/F capacities of around 80 million containers. Annual filling capacities for liquid vaccines would reach about 32 million glass vials (with 90% used per market demand); for freeze-dried vaccines, capacities would reach about 9.3 million glass vials (with 90% used); and for the BFS vaccines and diluents, capacities would reach about 41 million plastic tubes (with 50% used).

Further information can be found in the baseline financial model, "Five Factories-Baseline", tab "3.1 F/F Volumes".

5.1.2.2. Capital Expenditure (CapEx) assumptions for F/F factory' investment

The baseline investment CapEx for a medium-sized F/F factory is estimated at EUR 89.3 million with process equipment supplied by renowned European companies. The CapEx related to factory buildings is depreciated over 20 years and over 10 years for the equipment. The estimated expenses to execute the investment Project Management and the F/F Tech Transfer of the vaccines are "capitalized" over 4 years.

Further information can be found in the baseline financial model, "Five Factories Baseline", tab "3.2 CAPEX".

5.1.2.3. F/F factory baseline investment CapEx phasing

Investment in a medium-sized F/F factory will occur in a phased manner, as demand for the vaccines evolves. The factory building and clean facilities will be constructed, equipped, and validated with the first liquid vaccines F/F line, the first freeze-dried vaccines F/F line with its first freeze-dryer and the BFS F/F line. The second liquid vaccines F/F line will be installed only if the capacities of the first are fully utilized in two shifts; the second freeze-dryer will be installed in a second stage, after increases in vaccine demand have been confirmed.

Further information can be found in the baseline financial model, "Five Factories Baseline", tab "3.2 CAPEX".

5.1.2.4. F/F factory baseline Project Management & Tech Transfer costs

In addition to the CapEx, the investment in a F/F factory, needs to cover various expenses such as: (a) the investment project team and external experts who execute Project Management and oversee the Engineering, Construction and CQ&V works (b) costs for the management systems set-up, recruitment and QA/GMP training; (c) the PPQ and Tech Transfer costs, including vaccines F/F process transfers, and the transfer of QC analytical test methods, with support from external experts on aseptic vaccine filling; (d) costs for the Media Formulation/ Filling batches and Consistency batches; (e) stability tests costs; and (f) registration costs with external experts' support for preparing the Common Technical Documents (CTD) dossier.

The Project Management and Tech Transfers support are one off costs, variable as per the maturity level of the F/F factory teams; it includes the external experts, the F/F factory project team (from project start) and the operational teams recruited gradually; total costs are estimated at 20 million EUR spread over four years. On top, the Tech Transfer consumables costs (also one off) are variable based on the number of F/F lines and vaccines transferred; total costs are estimated at 15 million EUR for 14 vaccines and 2 diluents, large part made of the bulks for the Consistency batches; those costs would be spread over a period of about five years i.e., when all vaccines have been transferred.

Further information can be found in the baseline financial model, "Five Factories Baseline, tab "3.5 PM&TT support", and tab "3.6 TT Opex".

5.1.2.5. F/F factory baseline OpEx and raw materials costs assumptions

The financial model uses estimated operational costs to run the F/F factories as follows:

a) direct labour costs;

b) raw materials (excluding vaccines bulks);

c) indirect labour costs;

d) general and administration (G&A) expenses including energy, maintenance, insurance, security, and administration costs.

For our assumptions, we have used Kenya as the "reference" country, where the salaries are assumed to be 10% higher than those in West Africa. Kenya has also been used as the basis for estimating energy costs, as it is assumed to be at the high end (compared to other African regions), with a rate of US$ 0.146 per KW.

Baseline raw materials costs have been estimated based on:

(1) the average costs of the vaccines' Formulation Media and excipients procured from European suppliers;

(2) the average costs of filling raw materials e.g., RTU glass vials and rubber stoppers, procured from Indian suppliers;

(3) costs of consumable materials, mostly the SU assemblies for Media Preparation, Formulation and Filling operations, supplied by companies such as Merck (Europe);

(4) packaging materials procured locally or from Indian suppliers;

(5) average costs of the raw materials for the QC tests, procured from European suppliers.

The above costs are based on budget quotations received or have been estimated. It is important to note that the raw material costs depend much on the worldwide energy costs and are variable as per the quantities ordered.

Further information can be found in the baseline financial model, "Five Factories-Baseline", tab "3.3 RawMat", tab "3.4 OrgChart", tab "3.7 Energy costs" and tab "Pilot sheet details (section G&A Expenses of each F/F factory).

5.1.2.6. Estimations of F/F factory revenues

The financial model estimates the revenues of the F/F factory from the CMO F/F services it offers to vaccine producers. The revenues are estimated by multiplying the quantities of containers manufactured annually by the F/F costs per vial (or absorption costs) + a margin. A bottom-up approach has been used to estimate the F/F production costs and a markup has been added to establish the total absorption costs. The assumed F/F costs are not based on current costs for similar services in Europe or India, nor are they based on any negotiations with vaccine producers. The model estimates the F/F cost of a specific vaccine by computing all the direct and indirect costs and by applying a volume ratio, when necessary, i.e. to calculate the amount of CapEx in a F/F line allocated to a specific vaccine.

Further information can be found in the baseline financial model "Five Factories-Baseline", tab "2.1 FinPlan".

5.1.2.7. F/F factory baseline financial assumptions

The financing structure (equity, debt and cost related) for both short and long-term financing products are summarized in the WACC, which is the average cost of capital of a company weighted according to the relative weight of both sources of financing – equity and debt. In other words, it is the average annual rate of return expected by shareholders and creditors.

The WACC has been defined at 11.3% using data from the Damodaran education platform which has been aggregated based on the parameters below. It can vary with the international financial conditions, the investors' risk profiles and expectations about the return on the investment.

The model calculates a short-term cash need, based on years where Earnings Before Interests and Taxes (EBIT) is lower than zero. The EBIT is equal to the difference between the revenues and all expenses related to the realization of this revenue, except financing and taxes. Nonetheless, cash is still negative in some years due to the non-financing of some elements.

The Terminal Value (TV) is calculated by applying a multiple of 6 on the Earnings Before Interests, Taxes, Depreciations & Amortization (EBITDA). The EBITDA is the difference between revenues (absorption costs multiplied by the F/F volumes) minus all the operational expenses, i.e., the expenses incurred to generate the revenues. It is also sometimes referred to as the 'operational cash flow'.

Further information can be found in the baseline financial model "Five Factories-Baseline", tab "2.1 FinPlan".

5.1.2.8. F/F factory import duties and other baseline assumptions

- The import duties on the equipment and the vaccines' raw materials are assumed at 0%.
  Refer to Annex 11 for details.
- The inflation rate is assumed at 0%, considering that any inflation on the F/F factory costs will be transferred automatically to the absorption costs i.e., its revenues. Similarly, the VAT, the withholding taxes and taxes on the F/F factory profits are assumed at 0% considering that all countries will bring incentives to attract new biotech investments.

A flexible financial model allows to assess the feasibility of potential investments.

5.1.3. User' instructions for the financial model simulations

- The baseline financial model ("FiveFactories-Baseline") is made of several tabs clubbed in three chapters after the introduction tabs.
- The tab "1.1 Pilot sheet" summarizes:

  (1) the number of F/F factories and F/F lines,

  (2) the F/F capacities.

- The tab "1.2 Pilot sheet details" summarizes, per F/F factory and per F/F line, the key factory parameters:

  (1 to 7) the F/F absorption costs per SKU, the F/F volumes, the direct employee's costs and the consumables costs,

  (8) the indirect expenses,

  (9) the G&A expenses,

  (10) the CapEx,

  (11) the Tech Transfer costs,

  (12) the financing parameters.

- The tab "2.1 FinPlan" brings the results on the four main financial parameters: NPV, IRR, Cumulated Free Cashflow and payback period.
- The tab "2.2 F/F costs per SKU" summarizes the F/F absorption costs for Y2030, Y2035, Y2040 for each SKU.
- The tabs 5.1 to 5.7 are inputs tabs with the calculations data and figures for the (3.1) F/F Volumes, (3.2) CapEx, (3.3) Raw Materials, (3.4) Organization Charts, (3.5) Project Management & Tech Transfer support, (3.6) Tech Transfer OpEx, (3.7) Energy costs.

Further instructions can be found in the baseline financial model "Five Factories-Baseline", on top of each tab, identified by "instructions to user"; or refer to Annex 12 with a compilation of the user' instructions.

5.2. Simulations

5.2.1. F/F factories geographics: East or West

- The investment in the five F/F factories shows a baseline NPV estimated at + EUR 15.6 million, with total F/F volumes of 280 million containers, representing the minimum annual F/F volumes needed to break even. The investment payback period is estimated at 15 years.
- Should the investment be limited to one medium-sized F/F factory based in East Africa, the NPV would reach +EUR 449K, with annual F/F volumes of around 80 million containers.

  Should the same medium-sized F/F Factory be based in West Africa, the NPV would be higher at + EUR 14.3 million, due to lower salaries and energy costs.

Table 6 - Key financial parameters – Baseline F/F factories

	Vaccines F/F factories Key financial parameters	Baseline
		5 factories: 332m EUR CapEx, 280m containers - 1 factory: 89m EUR CapEx, 80m containers
5 factories	NPV (6x EBITDA) - K EUR	28.028
East		449
West nr2		14.301
5 factories	Profitable from - Year	2.031
East		2.031
West nr2		2.029
5 factories	Cumulated free cash flow in Y2040 - K EUR	204.161
East		42.249
West nr2		75.595
5 factories	TV	321.432
East		89.075
West nr2		106.534
5 factories	IRR - %	14,48%
East		11,48%
West nr2		17,44%
5 factories	Pay-back period - Years	15
East		16
West nr2		13

- Detail results can be found in the baseline financial model "Five Factories-Baseline", select in tab "1.1 Pilot sheet" the East or the West factory.
- In conclusion: based on the assumptions defined in chapter 5.1, investing in all five F/F factories would be profitable; investing in a F/F factory in West Africa would be more profitable than investing in a similar F/F factory based in East Africa.

5.2.2. F/F factory' types: single products vs multi products

- The F/F factory operations are based on the CMO model, meaning its F/F services charged per container are similar (per each SKU) regardless of the type of vaccines that are processed. The question is whether or not the F/F factory will process all three vaccines presentations (liquid, freeze-dried and oral).
- The F/F factory is executing the F/F operations for all vaccines at the baseline. Should the F/F factory execute only liquid and oral vaccine F/F representing total annual volumes of around 72 million vials (on three F/F lines), the investment profitability would improve with a NPV of 58 million EUR. This suggests that the freeze-dried vaccines are not driving the investment profitability; and it can be explained by higher CapEx (than for liquid vaccines), with a comparatively lower output.
- Note: details can be found in the financial model "Five-Factories-Simulation3-NoLyoVaccines". To execute this simulation, refer to tab "1.2 Pilot sheet details", instructions to user for the simulation; or refer to Annex 13.
- On the contrary, should the F/F factory specialize in freeze-dried vaccines and their diluents as well as oral vaccines, annual volumes would drop to about 9 million vials and the investment would not be profitable.
- In conclusion: a F/F factory should (as a baseline) process all liquid vaccines, and adding oral vaccines improves profitability, while adding freeze-dried vaccines will decrease it. Nevertheless, over and above the financial criteria, one should also consider meeting the market demand for all vaccines.

Table 7 - Key financial parameters – Simulation 3: only liquids and BFS vaccines

	Vaccines F/F factories Key financial parameters	Baseline 5 factories: 332m EUR CapEx, 280m containers 1 factory: 89m EUR CapEx, 80m containers	Simulation 3 No freeze-dried vaccines 5 factories: 261m EUR CapEx, 250m containers 1 factory: 75m EUR CapEx, 72m containers
5 factories	NPV (6x EBITDA) - K EUR	28.028	31.395
East		449	3.736
West nr2		14.301	13.376
5 factories	Profitable from - Year	2.031	2.031
East		2.031	2.031
West nr2		2.029	2.029
5 factories	Cumulated free cash flow in Y2040 - K EUR	204.161	174.765
East		42.249	41.237
West nr2		75.595	66.241
5 factories	TV	321.432	335.970
East		89.075	92.352
West nr2		106.534	109.501
5 factories	IRR - %	14,48%	15,75%
East		11,48%	12,85%
West nr2		17,44%	18,79%
5 factories	Pay-back period - Years	15	14
East		16	15
West nr2		13	13

5.2.3. F/F containers: glass vs BFS

- The total African F/F demand is estimated to be about 280 million containers in 2040. Among them, 120 million are BFS tubes for oral vaccines (Cholera, Rotavirus), and the diluents and 30 million containers are glass vials for freeze-dried vaccines. The balance is about 129 million glass vials for nine liquid vaccines.
- Of these nine, three can be disregarded at this stage because they are either yet to be developed/registered (HIV vaccine), or have limited efficacy (Malaria vaccine), or have low annual demand (Typhoid vaccine).
  In conclusion, the shortlist of liquid vaccines which could be filled in BFS tubes is reduced to six vaccines with a total of 96 million containers in Y2040.
- Each F/F factory would keep the same footprint with the same number of F/F lines to process a total of 80 million containers. The two glass vials liquid vaccines F/F lines would be replaced by two new BFS F/F lines. The F/F factory CapEx would increase by about 6 million EUR up to 95 million EUR because a BFS filling line is costlier.
- The investments expenses for the start-up of the F/F factory would be similar. The direct salaries costs would be reduced slightly because the BFS technology requires less manpower; the indirect costs would be similar; the filling raw materials costs would be reduced substantially because LDPE is way cheaper than glass; the other raw materials costs would remain similar.

Table 8 - Key financial parameters - Simulation 8: multi-dose BFS

	Vaccines F/F factories Key financial parameters	Baseline	Simulation 8 Liquid injectable vaccines in multi-doses BFS tubes
		5 factories: 332m EUR CapEx, 280m containers 1 factory: 89m EUR CapEx, 80m containers	5 factories: 357m EUR CapEx, 240m containers 1 factory: 97m EUR CapEx, 80m containers
5 factories	NPV (6x EBITDA) - K EUR	28.028	35.905
East		449	3.078
West nr2		14.301	17.386
5 factories	Profitable from - Year	2.031	2.031
East		2.031	2.031
West nr2		2.029	2.029
5 factories	Cumulated free cash flow in Y2040 - K EUR	204.161	219.437
East		42.249	47.518
West nr2		75.595	83.766
5 factories	IRR - %	14,48%	15,47%
East		11,48%	12,33%
West nr2		17,44%	18,94%
5 factories	Pay-back period - Years	15	14
East		16	15
West nr2		13	13

- Note: details can be found in the financial model "Five-Factories-Simulation8-newBFS". To execute this simulation, refer to tab "1.2 Pilot sheet details", instructions to user for the simulation; or refer to Annex 13.
- In conclusion: a F/F factory investment with most of the liquid injectable vaccines filled in multi-doses BFS would reduce by about two the F/F costs vs multi-doses glass vials and would increase substantially the investment profitability to about 36 million EUR.

5.2.4. NPV sensitivity analysis

- From the baseline financial model, 8 simulations can be done to assess the NPV' impacts. Two have already been analyzed in the above chapter; the next are described below. More simulations can be created.
- **Simulation nr1:** the overall volumes for liquid vaccines are reduced by one third because (for example) no HIV vaccine registered and no demand for the Meningitis CWY (i.e., vaccine demand for the freeze-dried component A only). The new F/F volumes would reach 240 million vials or about 50% of the total African demand. The F/F factory CapEx will remain un-changed but the F/F lines capacities utilization will be reduced.

Table 9 - Key financial parameters - Simulation 1: lower vaccine demand

	Vaccines F/F factories Key financial parameters	Baseline	Simulation 1
			Vaccines volumes down by about 18% (no HIV and MenCWY)
		5 factories: 332m EUR CapEx, 280m containers 1 factory: 89m EUR CapEx, 80m containers	5 factories: 332m EUR CapEx, 240m containers 1 factory: 89m EUR CapEx, 68m containers
5 factories	NPV (6x EBITDA) - K EUR	28.028	(19.134)
East		449	(13.590)
West nr2		14.301	2.673
5 factories	Profitable from - Year	2.031	2.031
East		2.031	2.032
West nr2		2.029	2.031
5 factories	Cumulated free cash flow in Y2040 - K EUR	204.161	64.010
East		42.249	1.028
West nr2		75.595	45.580
5 factories	IRR - %	14,48%	9,31%
East		11,48%	6,51%
West nr2		17,44%	12,95%
5 factories	Pay-back period - Years	15	17
East		16	18
West nr2		13	15

- Note: details can be found in the financial model "Five-Factories-Simulation1-Vaccines-38%".
To execute this simulation, refer to tab "1.2 Pilot sheet details", instructions to user for the simulation; or refer to Annex 13.

- **Simulation nr2:** the project implementation is extended by one year due to (for example) delays in PPQ batches' execution and/or longer WHO PQ timing than expected. The first vaccines commercial batches would be starting one year later in Y2028 and last up to Y2031.

Table 10 - Key financial parameters - Simulation 2: project delayed by one year

	Vaccines F/F factories Key financial parameters	Baseline	Simulation 2 Project implementation extended by one year
		5 factories: 332m EUR CapEx, 280m containers 1 factory: 89m EUR CapEx, 80m containers	same as baseline
5 factories	NPV (6x EBITDA) - K EUR	28.028	1.880
East		449	(6.078)
West nr2		14.301	7.713
5 factories	Profitable from - Year	2.031	2.031
East		2.031	2.031
West nr2		2.029	2.029
5 factories	Cumulated free cash flow in Y2040 - K EUR	204.161	148.312
East		42.249	27.272
West nr2		75.595	63.819
5 factories	IRR - %	14,48%	11,67%
East		11,48%	9,36%
West nr2		17,44%	14,52%
5 factories	Pay-back period - Years	15	16
East		16	17
West nr2		13	14

- Note: details can be found in the financial model "Five-Factories-Simulation2-OneYearDelay".

To execute this simulation, refer to tab "1.2 Pilot sheet details", instructions to user for the simulation; or refer to Annex 13.

- **Simulation nr4:** the HC and/or salary costs are increased by +20% because either additional expatriates are recruited and/or salaries of local employees are increased to attract scarce talented profiles.

Table 11 -Key financial parameters - Simulation 4: headcount and/or salary costs increased by 20%

	Vaccines F/F factories Key financial parameters	Baseline	Simulation 4 HC and/or salaries costs increased by 20%
		5 factories: 332m EUR CapEx, 280m containers 1 factory: 89m EUR CapEx, 80m containers	same as baseline
5 factories	NPV (6x EBITDA) - K EUR	28.028	(3.892)
East		449	(9.737)
West nr2		14.301	6.685
5 factories	Profitable from - Year	2.031	2.031
East		2.031	2.031
West nr2		2.029	2.030
5 factories	Cumulated free cash flow in Y2040 - K EUR	204.161	132.283
East		42.249	19.238
West nr2		75.595	63.118
5 factories	IRR - %	14,48%	11,12%
East		11,48%	8,42%
West nr2		17,44%	14,16%
5 factories	Pay-back period - Years	15	16
East		16	17
West nr2		13	14

- Note: details can be found in the financial model "Five-Factories-Simulation4-Salaries+20%".

To execute this simulation, refer to tab "1.2 Pilot sheet details", instructions to user for the simulation; or refer to Annex 13.

- **Simulation nr5**: the energy costs (power) are increased by +50% because impacted by the energy costs increasing worldwide and/or because of governmental prices' incentives reduced.

Table 12 - Key financial parameters -Simulation 5: Energy costs increased by 50%

	Vaccines F/F factories Key financial parameters	Baseline	Simulation 5 Energy costs increased by +50%
		5 factories: 332m EUR CapEx, 280m containers 1 factory: 89m EUR CapEx, 80m containers	same as baseline
5 factories	NPV (6x EBITDA) - K EUR	28.028	17.828
East		449	(3.993)
West nr2		14.301	13.172
5 factories	Profitable from - Year	2.031	2.031
East		2.031	2.031
West nr2		2.029	2.030
5 factories	Cumulated free cash flow in Y2040 - K EUR	204.161	177.620
East		42.249	30.864
West nr2		75.595	74.706
5 factories	IRR - %	14,48%	13,36%
East		11,48%	10,06%
West nr2		17,44%	16,91%
5 factories	Pay-back period - Years	15	15
East		16	16
West nr2		13	13

- Note: details can be found in the financial model "Five-Factories-Simulation5-Energy+50%".

To execute this simulation, refer to tab "1.2 Pilot sheet details", instructions to user for the simulation; or refer to Annex 13.

- **Simulation nr6: the filling raw materials costs are decreased by 10%** thanks to better prices negotiated with the suppliers via global purchase contracts made with the five F/F factories together.

Table 13 - Key financial parameters - Simulation 6: Filling raw materials costs decreased by 10%

	Vaccines F/F factories Key financial parameters	Baseline	Simulation 6 vials filling raw materials costs decreased by -10%
		5 factories: 332m EUR CapEx, 280m containers 1 factory: 89m EUR CapEx, 80m containers	same as baseline
5 factories	NPV (6x EBITDA) - K EUR	28.028	62.367
East		449	9.849
West nr2		14.301	23.695
5 factories	Profitable from - Year	2.031	2.030
East		2.031	2.030
West nr2		2.029	2.029
5 factories	Cumulated free cash flow in Y2040 - K EUR	204.161	278.034
East		42.249	64.045
West nr2		75.595	101.521
5 factories	IRR - %	14,48%	18,26%
East		11,48%	14,48%
West nr2		17,44%	21,07%
5 factories	Pay-back period - Years	15	13
East		16	14
West nr2		13	12

- Note: details can be found in the financial model "Five-Factories-Simulation6-FillRawMat-10%".

To execute this simulation, refer to tab "1.2 Pilot sheet details", instructions to user for the simulation; or refer to Annex 13.

- **Simulation nr7: the process equipment investment CapEx is reduced by -15%** thanks to global purchase contracts negotiated for the five F/F factories together.

Table 14 - Key financial parameters - Simulation 7: Process equipment costs decreased by 15%

	Vaccines F/F factories Key financial parameters	Baseline	Simulation 7 Process equipment costs down by 15%
		5 factories: 332m EUR CapEx, 280m containers 1 factory: 89m EUR CapEx, 80m containers	5 factories: 296m EUR CapEx, 280m containers 1 factory: 80m EUR CapEx, 80m containers
5 factories	NPV (6x EBITDA) - K EUR	28.028	38.702
East		449	3.689
West nr2		14.301	16.898
5 factories	Profitable from - Year	2.031	2.031
East		2.031	2.031
West nr2		2.029	2.029
5 factories	Cumulated free cash flow in Y2040 - K EUR	204.161	214.657
East		42.249	47.976
West nr2		75.595	80.146
5 factories	IRR - %	14,48%	15,94%
East		11,48%	12,58%
West nr2		17,44%	18,85%
5 factories	Pay-back period - Years	15	14
East		16	15
West nr2		13	13

- Note: details can be found in the financial model "Five-Factories-Simulation7-Capex-15%".

To execute this simulation, refer to tab "1.2 Pilot sheet details", instructions to user for the simulation; or refer to Annex 13.

All above simulations are compared in the summary table from Annex 13. From those simulations, the following conclusions can be drawn. The F/F volumes are the first parameter impacting the investment profitability; with reduced volumes hence revenues, the NPV would become negative, and the F/F costs (the absorption costs) would have to be increased to bring it back to positive but to the detriment of the F/F services' competitiveness.

- The operational costs and mostly the raw materials are the second parameters impacting the investment profitability; with reduced operational and consumables costs, the NPV would improve, and the F/F costs could be decreased to improve the F/F services' competitiveness.
- The third impacting parameter is the CapEx; the lower the CapEx, the higher the investment profitability. Additionally, the salaries impact should not be neglected. Finally, the financial parameters combined into the WACC also have a major impact on the investment profitability.

6. F/F cost structure and comparison with imported products

6.1. F/F costs per container/dose

6.1.1. Baseline F/F costs

The vaccines manufactured in the F/F factory are clubbed into nine SKU's or vaccine presentations, from mono-dose glass vials to 10-dose glass vials (liquid and freeze-dried), and from mono-dose BFS tubes to 10-dose BFS tubes.

The cost structure for each SKU F/F includes five main cost items: raw materials (excluding vaccine bulks), depreciation, direct salary costs, indirect costs (salaries, energy, external services, ...) and financial interest costs on loans.

The F/F costs have been estimated with the assumption that the F/F capacities are used at 90% for glass vials, and 50% for BFS tubes.

The nine SKU's F/F costs per container range from EUR 0.985 to EUR 1.535 for liquid vaccines in glass vials, from EUR 1.076 to 1.583 for freeze-dried vaccines in glass vials, and from EUR 0.333 to 0.493 for BFS tubes. Further information can be found in the financial model, "Five Factories-Baseline", tab "2.2 FF costs per SKU".

6.1.2. F/F costs sensitivity analysis

Analysis of the F/F costs for glass vials reveals that about 85% consists of raw material costs, about 50% for the glass vial, stopper and cap only, and about 15% made up of indirect and debt costs. Depreciation impacts the F/F costs during the first 10 years, and then becomes negligeable.

Should the first costs item, i.e., the glass vial and stopper, increase due to higher raw material prices and/or higher freight charges, the F/F costs of all vaccines (in glass vials) would be directly hit by a corresponding percentage. The market would be unable to bear this unless the vaccines' producer (subcontracting the F/F operations to the African F/F factory) has negotiated an inflation clause in its supply contract with UNICEF.

Should the indirect costs increase, the vaccines F/F costs would increase as well but in a lower proportion. Should there be a reduction in the F/F factory's annual volumes, all the fixed costs would remain unchanged but allocated to lower volumes, negatively impacting the F/F costs per container. The market would be unable to bear such cost increases, and an inflation clause in the UNICEF supply contract could absorb a portion of them.

6.1.3. F/F costs savings

However, savings can be made on the F/F costs, starting with filling raw materials. Their costs have been estimated with the assumption that supplies will be drawn from Indian producers. They could be further reduced if prices are negotiated with a global purchase agreement, combining the demand from all African F/F factories. A long- term partnership with a glass vial supplier would be another way to secure attractive prices.

The use of RTU vials could be questioned because its price is about 40% higher than a classical vial. But the RTU vial has some advantages which offset its higher price, including lower CapEx because vials washing machines and sterilization tunnels will not be required, implying lower operational costs and reduced validations/maintenance costs. There will also be fewer QA risks related to Water For Injection (WFI) monitoring, and fewer defects/vial rejections linked to 'glass-to-glass' or 'glass-to-metal' contacts.

Another saving on the F/F costs could be achieved in relation to packaging raw materials, which have also been estimated based on Indian suppliers. They could be further reduced if attractive prices can be achieved through a global purchase agreement with local paper manufacturers, combining the demand from all African F/F factories and avoiding higher shipping costs from India. The Vaccine Vial Monitor (VVM) label supplied from the US company Temptime® (WHO qualified) represents one third of the packaging costs. Developing a local producer could reduce its price and avoid high shipping costs (at -25°c). Last but not least, the cold-chain shipping boxes, cold packs, and monitoring tools, are imported from Europe or India, and are thus expensive. Developing local producers would reduce their costs.

The baseline NPV & F/F cost calculations were undertaken based on the assumption that the FF/lines will only reach 65% of their theoretical unconstrained capacity. This estimate is based on the experience that – particularly with new lines and new teams – substantial proportions of the capacity are consumed to address technical or quality challenges. By reducing the down time, deviations, and wastage, the F/F lines' capacity utilization would increase, higher vaccine volumes would be processed, and thus F/F costs per container would be reduced.

The duration of freeze-drying cycles also has a substantial impact on costs. However, there are opportunities to shorten cycles even with existing technology and there may be further opportunities available in future associated with new technology, such as microwave assisted freeze-drying.

Furthermore, a strong culture of Continuous Improvement is highly recommended, and the associated tools and systems that are well established across the industry, should be applied. Efforts should also be made to minimize product loss, e.g., due to residual volumes in tanks and tubing.

Finally, lower investment costs will reduce the depreciation impact on the F/F costs during the first 10 years and will mostly have a positive impact on the NPV, because of lower working capital.

Higher manufacturing cost in Africa can be compensated by shipping cost savings

6.2. F/F costs glass vial vs BFS tube

F/F costs per BFS tube are substantially lower than those per glass vial. Our analysis of the filling raw materials cost per BFS tube reveals that it is approximately 20 times lower than that of a glass vial, because of extremely low LDPE prices. Nevertheless, the total raw materials costs remain the most expensive item for the BFS tube, at about 60% to 73%, followed by the indirect costs and debt costs representing about 24% to 35%. Further details can be found in the financial model, "Five Factories-Baseline", tab "2.2 FF costs per SKU".

Assuming injectable vaccines can be developed and registered in BFS tubes, the F/F costs of a 10 doses BFS tube would be around EUR 0.884, while the F/F costs for a 10 doses glass vial are around EUR 1.542, i.e., almost a factor of two.

In terms of BFS F/F costs, they are more impacted by salaries, energy, and debt cost increases (because with higher percentages in the total costs), than the F/F costs of glass vials. The savings mentioned for the glass vials, apart from the vial's price, are applicable to the BFS F/F costs.

6.3. F/F costs of imported vaccines

The underlying premise of this study is that local African F/F factories will offer their CMO services to vaccines producers from Europe and/or India, who would then transfer their F/F operations to the African factories. The transfer would only be attractive if the African factories are able to operate with the same level of quality, and at attractive costs.

Precise data about vaccine F/F costs from European and Indian vaccines producers are not available in the public domain for obvious reasons. Nevertheless, some figures have been deduced based on UNICEF's vaccine prices, and the estimated percentage of the F/F cost component within them.

Table 15 - Tentative estimation of vaccines F/F costs from european and indian vaccines producers

	Tentative estimation of vaccines F/F costs from European/Indian vaccines producers - EUR		Liquid vaccines in glass vial		Freeze-dried vaccine in glass vial		Oral vaccine in BFS
			Cost per dose, 4 or 5 doses vial - EUR	Cost per dose, 10 doses vial - per dose - EUR	Cost per dose, 10 doses vial - EUR	Cost per dose, 10 doses ampoule - EUR	Cost per 1 dose BFS - EUR
Ref 1	PCV vaccine: Unicef price 2022 at 2,9 EUR per dose (ref US company), assuming 10% to 15% for F/F costs	min	0,290				
		max	0,435				
Ref 2	PCV vaccine: Unicef price 2022 at 2,9 EUR per dose (ref Indian company), F/F costs based on Penta 10 doses	min	0,217				
		max	0,291				
Ref 3	Penta vaccine: Unicef price 2022 at 0,81 EUR per dose (ref Indian company), assuming 15% to 20% for F/F costs	min		0,122			
		max		0,162			
Ref 4	Rotavirus vaccine: Unicef price 2021 at 1,88 EUR per dose (ref European company), assuming 15% to 20% for F/F costs	min					0,282
		max					0,376
Ref 5	Rotavirus vaccine: Unicef price 2023 at 0,95 EUR per dose (ref Indian company), assuming 15% to 20% for F/F costs	min					0,143
		max					0,190
Ref 6	MMR vaccine: Unicef price 2015 at 1,98 EUR per dose (ref European company), assuming 15% to 20% for F/F costs	min			0,153	0,085	
		max			0,200	0,098	
Ref 7	MMR vaccine: Unicef price 2023 at 1,70 EUR per dose (ref Indian company), assuming 15% to 20% for F/F costs	min			0,139	0,065	
		max			0,180	0,075	

Disclaimers: the above F/F costs are rough estimates based on estimated percentages of the F/F costs, using UNICEF's vaccines prices in 2022. F/F factory costs vary based on their capacity utilization; the remaining depreciation; the filling batch sizes, and several other technical, quality and logistical parameters. Additionally, high inflation rates may lead to a substantial price increase on many raw materials with a significant impact on the F/F costs.

The above estimated F/F costs do not include 'hidden' costs (from reducing/halting F/F operations in some of the European/ Indian factories), that the vaccine producers will have to absorb if they decide to sub-contract their operations to the African CMO factory. These hidden costs are, for example, the factories' ongoing depreciation costs, their overhead costs which would have to be allocated across lower F/F volumes, and the social impact of reducing their F/F operations.

6.4. Comparison F/F factory F/F costs vs imported vaccines F/F costs

The F/F factories could offer attractive CMO F/F costs to European vaccine producers. For example, the F/F costs of the PCV 4 or 5 dose-vial are estimated at between EUR 0.281 and 0.311 per dose (including 5% CMO profit margin), being lower than the (assumed) big pharma companies' F/F costs of between EUR 0.290 to 0.435 per dose. The drawback is that currently, none of the major European vaccine producers plans to transfer F/F operations to Africa. However, this could be encouraged through procurement incentives provided by national or supranational organizations.

The F/F factories could offer CMO F/F services to Indian vaccine producers, but the costs would not be attractive. For example, the F/F cost of the Penta 10 dose-vial is estimated at between EUR 0.153 and 0.166 per dose (including 5% CMO profit margin), compared to the India company (assumed) F/F costs of EUR 0.122 to 0.162 per dose. The PCV 4 or 5-dose vial is estimated at between EUR 0.281 and 0.311 per dose, compared to the Indian (assumed) F/F costs of EUR 0.217 to 0.291.

The drawback is that currently, more than 75% of the EPI vaccines supplied to Africa are produced by major Indian players, who would only be attracted by local F/F CMO if it enabled them to gain access to new markets.

For a more precise comparison, the inbound shipping costs of the finished packed vaccines imported from India vs the cost for importing vaccines bulks concentrate must be incorporated in order to compare the landed costs charged to UNICEF in both cases.

The shipping costs for the finished packed vaccines have been estimated for three vaccines, based on a quotation received from a freight forwarder (see Annex 14), itself based on current freight costs and oil prices, assuming the use of a passive cold-chain shipping pallet, and considering an insurance premium at 1.25% of the vaccines' value.
The finished packed shipping costs range from 13 EUR cents (PCV vaccine) per dose to 46 EUR cents (Rotavirus vaccine) per dose at a minimum.

Table 16 - Tentative estimation of finished packed vaccines air shipping costs from India to Africa

A	**GIZ project - F/F factory - Finished packed vaccines - Estimation of +2+8 °C cold chain air shipping costs from India to Africa**							**Estimated shipping costs - EUR**	
	Liquid & freeze-dried vaccines - 10 doses vials (6R)		Vials per box	Estimated weight	Estimation dimensions			East Africa	
				(gr)	L (cm)	l (cm)	H (cm)		
	Vial 6R - 22 mm diameter - 40 mm high			8,30	2,40	2,40	4,00		
	Multi vials box (with filled vials)	6 boxes per shipping box level, 10 levels	25	357,5	12,00	12,00	4,50	Costs per pallet	
	Corrugated shipping box		1.500	21.450	36,00	24,00	45,00	Min	Max
	Cold chain shipping pallet	10 ship boxes per level, 2 levels per pallet	30.000	429.000	120,00	80,00	143,000	16.894	21.118
		MMr vials + diluent vials	15.000						
		Rota BFS tubes (25% smaller)	37.500						
		PCV vials	30.000						
	Insurance for MMR vaccine (1,25% premium on estimated value of 1,55 Eur per dose)			Nbr of MMR dose per vial: 10				2.906	2.906
	Insurance for Rota vaccine (1,25% premium on estimated value of 0,95 Eur per dose)			Nbr of Rota dose per BFS: 1				445	445
	Insurance for PCV vaccine (1,25% premium on estimated value of 2,9 Eur per dose)			Nbr of Rota dose per vial: 5				5.438	5.438

		Costs per MMR vial - EUR		Costs per Rotavirus tube - EUR				Costs per PCV vial - EUR			
		Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
	Finished packed vaccines - Estimated total shipping costs (incl insurance) per vial	1,320	1,602	0,462	0,719	0,659	0,820	0,744	0,885	0,825	0,986
	per dose	0,132	0,160	0,462	0,719	0,659	0,820	0,149	0,089	0,083	0,099

Disclaimer: the above cold-chain shipping costs are tentative estimations based on a quote received from one company only. They would also vary based on oil prices and other logistical parameters.

The vaccine bulks' shipping costs have been estimated for the same vaccines as above, based on a similar quotation (Annex 15), including: (i) current freight costs and oil prices; (ii) assumptions on the use of a passive freezing shipping pallet; (iii) the same insurance premium; and (iv) the number of bulks and their concentrations per dose. The bulks' shipping costs are substantially cheaper for the Rotavirus vaccine, twice as cheap as the MMR vaccine, and are similar in the case of PCV.

Table 17 - Tentative estimation of bulk products air shipping costs from India to Africa

GIZ project - F/F factory - Bulk vaccines Estimation of -25°C cold chain air shipping costs India to Africa Passive cooling pallet -25°C with 24 bottles			Estimated shipping costs - EUR					
			Vaccine with 3 valences such as MMR - 3 bulks		Vaccine with 1 valence such as Rotavirus - 1 bulk		Vaccine with 12 valences such as PCV - 12 bulks	
Bulk concentration (average)			East Africa 30%		East Africa 5%		East Africa 35%	
Filling batch size	number of doses	218.400						
Formulated vaccine with 20% overfill	ml per dose		0,60		2,00		0,60	
Concentrated vaccine, 12 bulks							0,21	
Concentrated vaccine, 3 bulks	ml per dose		0,18					
Concentrated vaccine, 1 bulk	ml per dose		0,06		0,10		0,02	
Bottles of 7 L, with bulk nr1	number of doses		933.333		1.680.000		800.000	
Bottles of 7 L, with bulk nr2			933.333				800.000	
Bottles of 7 L, with last bulk			933.333				800.000	
Total shipping pallet with 6 bottles per level on 4 levels			Costs per pallet - EUR Min	Max	Costs per pallet - EUR Min	Max	Costs per pallet - EUR Min	Max
Estimated shipping costs per pallet			16.894	21.118	16.894	21.118	16.894	21.118
Insurance (1,25% premium on value per dose)			18.083	18.083	19.950	19.950	29.000	29.000
Bulks vaccines - Estimated total shipping costs (incl insurance) per dose			Costs per dose - EUR		Costs per dose - EUR		Costs per dose - EUR	
			0,037	0,042	0,022	0,024	0,057	0,063

Disclaimer: the above cold-chain shipping costs are tentative estimations based on a quote received from one company only, which would vary based on oil prices and other logistical parameters.

The comparison of the vaccine landed costs in option A (F/F by the Indian vaccine producer) vs option B (F/F by the African CMO F/F factory), shows that the CMO higher F/F costs per dose are offset by the savings in shipping costs.

Table 18 - Tentative vaccines landed costs comparison between indian producer and local african CMO

Tentative vaccines landed costs' comparison: F/F costs from Indian producer vs F/F costs from East CMO F/F factory - EUR			PCV liquid vaccine in glass vial	MMR freeze-dried vaccine in glass vial	Rotavirus oral vaccine in BFS
A	With F/F executed by Indian vaccines producer		Cost per dose, 4 or 5 doses vial - sales price = 2,9 EUR	Cost per dose, 10 doses vial - EUR - sales price = 1,55 EUR	Cost per dose, 1 dose BFS - EUR - sales price = 2,5 EUR
1	Indian bulks costs, assuming 10% to 15% (of sales price) for bulks costs	min max	2,522 2,636	1,411 1,370	0,808 0,760
2	Indian F/F costs per dose, estimations	min max	0,217 0,291	0,139 0,180	0,143 0,190
3	Indian finished packed vaccines cold chain shipping costs from India to Africa, estimations	min max	0,149 0,089	0,132 0,160	0,462 0,719
1 to 3	Indian vaccine landed costs to UNICEF, estimations	min max	2,888 3,016	1,747 1,785	1,412 1,669
B	With F/F done by African CMO F/F factory				
1	Indian bulks costs, assuming 10% to 15% (of sales price) for bulks costs	min max	2,522 2,636	1,411 1,370	0,808 0,760
2	Indian bulks vaccines cold chain shipping costs from India to Africa, estimation	min max	0,057 0,063	0,037 0,042	0,022 0,024
3	East CMO F/F costs per dose, estimations from financial model	min max	0,281 0,311	0,167 0,189	0,398 0,476
1 to 3	Indian vaccine landed costs to UNICEF, estimations	min max	2,861 3,010	1,662 1,669	1,227 1,260
A vs B	Landed cost savings to UNICEF - per dose - EUR min	EUR %	-0,027 -0,94%	-0,085 -4,87%	-0,185 -13,10%
	max	EUR %	-0,006 -0,21%	-0,116 -6,51%	-0,409 -24,49%

Disclaimers: the above F/F costs are tentative, based on estimated percentages of the F/F costs of UNICEF vaccine prices in 2022. The F/F costs vary based on the factories' capacities and their utilization; the remaining depreciation, the filling batch sizes, and several other technical, quality and logistical parameters. Additionally, the current high inflation on many raw materials has a significant impact on the F/F costs. UNICEF's vaccines prices can also vary.

The above F/F cost comparison presents a double conclusion. From UNICEF's perspective, the vaccines' landed costs with F/F operations executed by the African CMO F/F factory, would bring costs savings ranging from 1% to 13% as a minimum, depending on the vaccine type. This is achieved thanks to the lower shipping costs of the bulks vaccines.

From the Indian vaccine producers' viewpoint, the picture is less positive because the costs of the African CMO F/F factory would be 25% (for glass vials) to 270% higher (for BFS). This points to an important observation: local political authorities must create incentives to support investment in, and operations of these F/F factories, through the sponsorship of healthcare, national and supranational procurement organizations (such as GAVI and UNICEF), and public and philanthropic support. Effective incentives could include financial support to reduce investment and working capital costs, which in turn would affect the F/F costs per vial/dose. Another form of incentive could be via local healthcare authorities offering a price premium on the vaccines they procure from the vaccine producers, in order to cover the extra local F/F costs.

From UNICEF's perspective, the vaccines' landed costs with F/F operations executed by the African CMO F/F factory, would bring costs savings ranging from 1% to 13% as a minimum, depending on the vaccine type. This is achieved thanks to the lower shipping costs of the bulk vaccines

7. Exploring potential additional sources of revenues

Expanding the product mix to be manufactured in the F/F factory could provide additional revenue streams and have an overall positive impact on the factory profitability. In the following sections, we explore four main other types of products that could potentially complement the vaccines F/F revenues in the proposed F/F factory including biotherapeutics, insulins, small volume parenterals and pandemic readiness vaccines. For each product type, we highlight (i) the rationale for the inclusion of such product type, (ii) the estimated F/F volumes and capacity impact, (iii) the estimated impact on CapEx and OpEx (iv) the expected impact on the revenues and F/F factory profitability.

7.1. F/F of Biotherapeutics

7.1.1. Rationale

Several biotherapeutics currently in existence have proven exceptionally successful in managing and reducing inflammation in multiple autoimmune diseases such as rheumatoid arthritis, psoriasis, Crohn's disease and ankylosing spondylitis (e.g., adalimumab and infliximab). mAbs therapies have become essential tools in oncology, with trastuzumab, bevacizumab and rituximab ranking as some of the most successful and effective therapies for a broad range of cancers. Other biotherapeutics such as human erythropoietin alpha (EPO) and PEG filgrastim support patients' recovery following chemotherapy, by stimulating the production of red and white blood cells respectively.

7.1.2. Estimated F/F volumes and F/F capacity' impact

Most biotherapeutics are filled in glass vials or glass syringes (Pre-Filled Syringes – PFS). Most are in liquid formulations, while some (e.g. trastuzumab and rituximab) are in freeze-dried formulations.

The medium-sized F/F factory has an annual liquid filling capacity of 35 million vials on two filling lines, with each working in two shifts. The demand for liquid vaccines will occupy about 90% of capacity.

Annual freeze-dried capacities reach 9 million vials with two freeze-dryers; out of which 90% are occupied as per the freeze-dried vaccines' demand.

There is free capacity of around 5 million vials annually, which could be allocated to filling and/or freeze-drying of biosimilars/mAbs. The F/F lines installed for vaccines can be used for biosimilars/mAbs with no risk of cross-contamination. This free capacity is dependent on the filling volumes per container, which can be higher for mono-dose biosimilars/mAbs (usually from 1ml to 15ml) than for vaccines.

7.1.3. Estimated CapEx and OpEx' impacts

Except for new change parts for existing filling machines and certain technology transfer-related costs for each new product, no additional major capital expenditure would be required to include most types of biotherapeutics in the product mix. Similar equipment can also be used in the QC laboratories for biotherapeutics testing.

There would be no incremental headcount or operational costs to execute the F/F of these additional biotherapeutics. The raw materials costs per container will be probably slightly higher than those of vaccines because of larger glass vials.

7.1.4. Expected F/F revenues' impact

F/F factory revenues would increase by 5 million units, multiplied by the absorption cost (assumed to be slightly higher than the highest vaccine' F/F cost). NPV will increase accordingly.

7.2. F/F of Insulins and Insulin analogs

7.2.1. Rationale

An estimated 24 million people suffer from diabetes in Africa – a figure that is expected to more than double in the next 20 years. Preventable deaths from diabetes are also higher in the region compared to the global average, due to challenges with diagnosis and management. Insulin supply and affordability continues to be challenging in most countries in Sub-Saharan Africa, highlighting the unmet medical need. Much of Africa relies on insulin imports, leading to high costs of transportation, storage, import and dispensing fees, all of which contribute to further increasing the price of insulin for the end user. However, recent changes in awareness and the fact that analogues like insulin glargine have been incorporated into the WHO's essential medicines list, are likely to catalyze the adoption of insulin analogs in these markets, making them an important product to consider from a local manufacturing perspective.

7.2.2. Estimated F/F volumes and F/F capacity' impact

Insulins (human or analogs) are filled in glass vials, glass PFS or glass cartridges. Filling volumes per container typically range from 1ml to 10ml. The vials F/F lines installed for vaccines can be used for insulins without risk of cross-contamination.

The F/F factory's liquid-filling capacities would be fully utilized with the vaccines and biosimilars/mAbs. Insulins could be filled instead of vaccines, assuming, for example, that the demand for some vaccines drops.

7.2.3. Estimated CapEx and OpEx' impacts

No additional major capital expenditure is required to include insulin in the product mix, other than new change parts for existing filling machines and technology transfer-related costs for each new product. Similar equipment can also be used in the QC laboratories for insulins testing.

There would be no incremental headcount or operational costs to execute the F/F of these additional biotherapeutics. The raw material costs per container will be probably slightly higher than those of vaccines because of larger glass vials.

Should insulin be filled over and above all vaccines and biosimilars/mAbs, an additional F/F line would need to be installed; this would also add CapEx, headcounts, and operational costs.

7.2.4. Expected F/F revenues' impact

F/F factory revenues would remain similar or slightly higher because insulin volumes would replace vaccine volumes and the insulin F/F absorption costs are assumed to be slightly higher than the highest vaccine' F/F cost. NPV will increase accordingly.

7.3. F/F of Small volume parenterals

7.3.1. Rationale

Many small volume parenterals (SVPs) are aseptically filled in plastic tubes, usually with volumes up to 10 ml, making them a perfect fit for BFS technology. Some common SVPs include sodium chloride, lidocaine, novocaine, potassium chloride, calcium gluconate, heparin, gentamicin, chloroquine, furosemide, diazepam, pentazocine, tramadol, diclofenac, metoclopramide, and betamethasone.

While African market demand for these SVPs has not been evaluated in the present study, nevertheless, their volumes are expressed in several millions per year. The BFS F/F line installed for oral vaccines and diluents can be used for SVPs with no risk of cross-contamination.

7.3.2. Estimated F/F volumes and F/F capacity' impact

The medium-sized F/F factory has BFS filling capacities of 43 million tubes with one batch per week (estimated to last three days), matching the demand for annual oral vaccines and diluents.

A second batch per week can be organized on the same BFS filling machine, offering capacity of up to 43 million per year for SVPs. Practically, working in campaigns with six months dedicated to the vaccines and diluents and the next six months for SVPs, with a properly validated inter-campaign would be a more efficient solution.

7.3.3. Estimated CapEx and OpEx' impacts

No additional major capital expenditure would be required to include SVPs in the product mix, other than new change parts for existing BFS machines and technology transfer-related costs for each new product. Similar equipment can also be used in the QC laboratories for SVPs testing.

There would be about 10 incremental direct headcounts and minor incremental operational costs to manage the second batch.

7.3.4. Expected F/F revenues' impact

The F/F factory revenues could increase by up to 43 million BFS tubes multiplied by the absorption cost (assumed equivalent to that of the oral vaccines); NPV will increase accordingly.

7.4. Pandemic readiness

One of the drivers for establishing an African vaccines F/F network is the need to enable faster and broader access to pandemic vaccines. Pandemic preparedness requires that the technologies needed for manufacturing pandemic vaccines should already be established and should be in use during inter-pandemic periods.

Below table shows the key vaccine platforms and F/F technologies that have been used in past pandemics, and that are likely to play a key role in a future pandemic.

Table 19 - F/F technologies used in pandemic vaccine platforms*

Vaccine Platform	Formulation	Filling	Inspection/ Packaging	Product Release	Storage/ Shipment
Inactivated micro-organism/ purified antigen	Dilution, sterile filtration. Mix withadjuvant (if applicable) or extemporaneous addition of adjuvant	Liquid product filled in vials or BFS	Automated, semi-automated or manual visual inspection. Labelling and packaging country specific	QC release panel including potency, sterility, purity and impurity assays	2-8°C
Recombinant protein					
Live-attenuated	Dilution, sterile filtration				2-8°C or frozen
Viral vector					
mRNA	LNP formulation. Dilution, sterile filtration				

**Modified from Rockman, S. et al., Global Pandemic Preparedness: Optimizing Our Capabilities and Influenza Experience. Vaccines 2022, 10, 589.*

The proposed F/F network uses these technologies, except for LNP formulation, which could be carried out at other specialized sites, as occurred during the COVID-19 pandemic. During inter-pandemic periods, storage and shipment under frozen conditions is foreseen to be used for bulk only, while for pandemic vaccines, these conditions might also be required for the finished product. Accordingly, ultra-cold-chain capacities would need to be created in the F/F factory and expanded substantially.

From this, we conclude that the proposed F/F factories network is equipped and capable of manufacturing pandemic vaccines within a lead time of several months only.

This would offer additional commercial and well as public health benefits. Therefore, in the event of a future, large-scale, global health crisis, F/F capacity could be re-allocated from routine to pandemic vaccines.

The vaccine factories are capable of manufacturing additional biopharmaceutical products generating incremental revenue and improving profitability of the investment. With a lead time of few months they could switch to the production of pandemic vaccines.

7.5. Summary

The additional sources of revenues for the F/F factory can be summarized in the below table.

Table 20 - Summary of additional sources of revenues for the F/F factory

	Estimated market demand	F/F factory capacity impact	F/F factory CapEx impact	F/F factory OpEx impact		Overall attractiveness
Biotherapeutics	Low	Low: use of free F/F capacities, +/- 5 million vials	New change parts on existing F/F line(s) Products' Tech Transfer costs	No additional HC Higher raw mat costs	Revenues ++ NPV ++	
Insulins	High	High: vaccines volumes to be reduced	New change parts on existing F/F line(s) Products' Tech Transfer costs	No additional HC Higher raw mat costs	Revenues = NPV =	
Insulin analogs	Low	Low: use of free F/F capacities			Revenues ++ NPV ++	
Small Volume Parenterals	High	Low: use of free F/F capacities, +/- 43 million BFS	New mold(s) on existing F/F line Products' Tech Transfer costs	10 additional HC	Revenues + NPV+	
Pandemic readiness vaccine	Very high but rare	High: vaccines F/F to be stopped	Product' Tech Transfer costs	High temporarily	Revenues = NPV =	

8. Risks assessment and mitigation

There are several risks that need to be taken into account when assessing the feasibility of setting up a F/F factory for vaccines in Africa.

8.1. Develop a robust CMO reputation to attract vaccines producers

A strong business model is a prerequisite for the establishment of vaccine manufacturing in Africa. Companies who own vaccine licenses need to have an incentive to provide drug substances, and to localize drug product manufacturing. Local CMOs require credibility, and need to compete against their international, well-established counterparts. They also need to have a track record of competence and reliability. Renowned international manufacturing organizations might operate a newly created African CMO in the early phase, or partner with them.

Companies holding and selling the vaccine license are fully liable and must assure adequate quality of the product. This includes accountability for any manufacturing undertaken by a CMO on their behalf. WHO prequalification serves as an important tool for assessing and certifying quality standards and is considered a mandatory requirement by most organizations buying vaccines for Africa.

Experience shows that the path to establishing these quality standards, gaining credibility and achieving WHO prequalification, is long.

8.2. Access to finance and financial sustainability

Access to finance and financial sustainability are major concerns. Substantial upfront investments are required to setup vaccine manufacturing. High interest rates and short payback periods are unsustainable, but these barriers could be overcome by donations or incentives such as tax credits or land giveaways.

The cost of local vaccine manufacturing in Africa will be higher than in countries such as India, from where large volumes of products are imported. Governments and sponsors must be willing to cover such extra costs through adequate pricing, and advance purchase commitments are crucial to unlock funding.

8.3. Technical risks

Vaccines are complex and setting up new manufacturing facilities is associated with substantial technical risks. This is linked to the installation and start-up of the facility, the transfer of the process and the associated control assays. Such challenges have often substantially delayed projects, increased costs, and even led to the failure of a transfer. Realistic upfront planning, thorough process knowledge and technical competence are crucial factors for success. A close and transparent collaboration with the developers of the process and the sending site are needed.

The transfer of a manufacturing process may require clinical bridging trials to demonstrate comparability. This would substantially delay a transfer and increase the associated costs.

Manufacturers must comply with strict quality standards and policies. The personnel need to have a strong quality mindset and must operate with a state-of-the art quality system. Most African countries lack adequately trained and experienced talent in the pharmaceutical manufacturing area, largely due to insufficient educational programs and practical learning opportunities in the region. While external competence (e.g., expatriates), could be brought into a new organization in the early phase, it is crucial to secure access to local talent in the medium to long term. Therefore, training programs need to be established, supported by academic partnerships, and complemented by scholarships. Practical experience can be gained through local and global secondments. Attempts should be made to attract experienced people back to their home countries.

To date, regulatory agencies in most African countries lack the maturity to be recognized as competent authorities in the field of vaccines. The absence of harmonized requirements from one African country to the next, and inefficiencies in the approval process can increase complexity, delay approval, or even block partnerships with global organizations. Efforts to harmonize regulatory standards and to strengthen the capability of regulators must be accelerated across Africa. More established government authorities from the Global North, and globally acting manufacturers can provide support to build this critical capability and infrastructure.

The success of local vaccine manufacturing depends on a reliable and efficient supply of equipment and raw materials. Currently, these are imported at great expense, and with long lead times. Duty exemptions could help lower these costs, and the creation of a local ecosystem of raw materials manufacturers could enable substantial cost reductions in the long run.

Efforts need to be made to close gaps in transportation networks, and to improve cold-chain logistics.

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Efforts need to be made to close gaps in transportation networks, and to improve cold-chain logistics.

8.4. Political buy-in

A crucial requirement is that the political environment and leading government actors must have both the willingness and the ability to enable and support the establishment of local vaccine manufacturing. National and regional strategies need to be aligned across the continent, to avoid overlaps and ensure efficiency.

9. Main findings & recommendations

1) To meet PAVM's ambition of manufacturing 60% of Africa's vaccine demand on the continent by 2040, a network of five F/F factories is proposed. This represents the best compromise between economies of scale, proximity to the vaccines' point of use, and the need to limit complexity and risk. The capital investment for a medium-sized factory is estimated at 89 million EUR with an associated expense of 35 million EUR. It is estimated that it will take five years from project initiation to the start of GMP production.
2) Operational costs are driven largely by raw materials, with vials, stoppers and caps representing approximately 50% of the total F/F costs. Options to reduce the cost of these items should be pursued with the highest priority. Indirect costs (including salaries/costs and depreciation) amount to 15%.
3) The F/F costs of locally manufactured vaccines have been calculated based on a detailed manufacturing concept, a F/F factory conceptual lay-out and quotes for the main CapEx items (refer to Annexes 05 & 06 and the financial model). The conversion costs per container range from EUR 0.985 to EUR 1.535 for liquid vaccines in glass vials, from EUR 1.076 to 1.583 for freeze-dried vaccines in glass vials, and from EUR 0.331 to 0.493 for BFS tubes.
   They are believed to be significantly higher than the cost of corresponding activities in India. However, while shipping contributes substantially to the total cost, significant savings could be achieved by shipping concentrated drug substance bulks instead of finished products. These savings compensate for the higher cost of local production in Africa versus India. It is therefore crucial that in future business assessments, the end-to-end cost is assessed, and not only the cost of F/F operations.
4) To limit complexity and risk it is preferable to first invest in one single medium-sized factory. The financial model shows that the investment can be profitable when conditions are adequate. A capacity utilization above 85% is crucial. Liquid products provide a stronger contribution to profitability than freeze-dried vaccines. Energy and personnel costs are more favorable in West Africa than elsewhere.
5) The vaccine F/F facilities should be equipped to manufacture additional products needed in African countries, and hence generate additional revenues. They would also be able to manufacture pandemic vaccines within a short lead time.
6) Blow-fill-seal (BFS) technology could help to reduce the cost of local production in Africa. To enable this, engaging in the development of multidose BFS presentations for injectable vaccines would be needed. The technology would also enable the transition from multi-dose to single-dose presentations, with the lowest cost impact.

Multiple challenges would need to be overcome to achieve fully functioning and sustainable contract vaccine manufacturing in Africa. A CMO must demonstrate high quality standards and reliability, certified through WHO prequalification. Vaccine license holders will require this assurance before accepting liability for the partial manufacture of their products by a contractor in Africa.

This reliability can only be achieved with strong and continuous political will, the ability to provide support, and to develop the required infrastructure and capability. Incentives such as vaccines advanced purchase agreements from the MOH will be required to compensate for any financial disadvantages.

This study has shown a pathway to overcome existing challenges, and to establish sustainable Fill/Finish contract operations for vaccines in Africa.

Multiple challenges would need to be overcome to achieve fully functioning and sustainable contract manufacturing of vaccines in Africa.

10. Disclaimer

This report has been prepared in accordance with Unizima's contract with GIZ for a study on Sustainable Vaccines Manufacturing in Africa – Business Case Simulation for Fill & Finish Contract Manufacturing Operations (Project reference: 20.2155.8-015.00).

The study had the following objectives only:

(1) CapEx and OpEx of a CMO Vx Formulation, Fill & Finish (F&F) facility for both glass and BFS vials.

(2) Costing simulation tool to assess financial viability and compare local production to imports.

(3) Provide recommendations and strategic advice for sustainable CMO plants across Africa.

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11. Abbreviations

AfCFTA: African Continental Free Trade Area
AMA: African Medicines Agency
AU: African Union
BFS: Blow Fill Seal
BLA: Biologics License Application
BMGF: Bill & Melinda Gates Foundation
BSL: Biosafety Level
CAGR: Compound Annual Growth Rate
CAPEX: Capital Expenditure
CCS: Contamination Control Strategy
CNC: Controlled Non-Classified
CTD: Common Technical Document
(c)GMP: (current) Good Manufacturing Practices
C(D)MO: Contract (Development and) Manufacturing Organization
CoGS: Cost of Goods Sold
CQ(&)V: Commissioning, Qualification and Validation
CTC: Cost to Company
DNA: Deoxyribonucleic Acid
DP: Drug product
DTP: Diphteria, Tetanus, Polio
E&L: Extractables & Leachables
EBIT: Earnings Before Interest and Taxes
EBITDA: Earnings Before Interest, Taxes, Depreciation and Amortization
EHS: Environment, Health and Safety
EPO: Erythropoietin (EPO)
EU: European Union
EUR: Euro
FDA: Food & Drug Administration
F/F: Fill & Finish
FAT: Factory Acceptance Tests
FcF: Free Cash Flow
FS: Fill-Seal
G&A: General and Administrative Expenses
GBT: Global Benchmarking Tool
GIZ: Deutsche Gesellschaft für Internationale Zusammenarbeit
GMP: Good Manufacturing Practices
HC: Head Count
HPV: Human Papilloma Virus
HIV: Human Immunodeficiency Virus
HVAC: Heating, Ventilation and Air Conditionning
ICH: International Conference on Harmonization
IPV: Inactivated Polio Vaccine
IRR: Internal Return Rate
IQ: Installation Qualification
kW: Kilowatt
LDPE: Low Density Polyethylene
LMIC: Low and Middle Income country
LNP: Lipid Nanoparticles
MAH: Marketing Authorization Holder
MAL: Material AirLock
ML: Maturity Level
MOH: Ministry of Health
mRNA: messenger RiboNucleic Acid
NC: Non-Classified
NPV: Net Present Value
NRA: National Regulatory Authority
OPEX: Operational Expenditure
OPV: Oral Polio Vaccine
OQ: Operational Qualification
PAL: Personal AirLock
PAVM: Partnership for African Vaccines Manufacturing
PCR: Polymeric Chain Reaction
PCV: Pneumococcal Conjugate Vaccine
PFS: Prefilled Syringe
PoC: Proof of Concept
PQ: Performance Qualification
QA: Quality Affairs/Assurance
QC: Quality Control
QMS: Quality Management System
RA: Regulatory Affairs
RNA: Ribonucleic Acid
RTU: Ready to Use
SAT: Site Acceptance Tests
SKU: Stock Keeping Unit
SS: Stainless Steel
SU(S): Single-Use (System)
Td: Tetanus diphteria
ToRs: Terms of References
TV: Total Value
VI: Visual Inspection
VVM: Vaccine Vial Monitor
WACC: Weighted Average Cost of Capital
WFI: Water for Injection
WHO: World Health Organization
WHO PQ: WHO Prequalification
YF: Yellow Fever

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  Available at: 20220825_gmp-an1_en_0.pdf (europa.eu) Annex 1: Manufacture of Sterile Medicinal Products (new version)

13. Annexes

13.1. Annex 01 – detailed African vaccines market demand in Y2040

Table 21 - Detailed african vaccines market demand per region in 2040

		Vaccine Information				Container information			
Category	No.	Vaccine[1]	Formulation	Dosing[2]	Number of doses per child[3]	Doses per containe[r4]	Type of container	ml per dose	ml per container
Legacy Routine	1	Pentavalent (Diphtheria, Tetanus, Pertussis, Hepatitis B, HiB)	Liquid or freeze-dried injectable	6, 10, 14 weeks plus booster	4	10	Glass vial	0,5	5,00
	2	Bacille Calmette-Guérin (Tuberculosis)	Freeze-dried injectable	Birth	1	20	Glass vial	0,05	1,00
	3	Measles-Rubella	Freeze-dried injectable	9, 18 months	2	10	Glass vial	0,5	5,00
	4	Yellow Fever	Freeze-dried injectable	9 months	1	10	Glass vial	0,5	5,00
	5	Oral Cholera Vaccine	Liquid oral	1 year	2	1	BFS	3	3,00
	6	Typhoid	Liquid Injectable	9-12 months	1	5	Glass vial	0,5	2,50
	7	Meningococcus A conjugate	Freeze-dried injectable	9-18 months	1	10	Glass vial	0,5	5,00
	8	Polio (IPV)	Liquid Injectable	6, 10, 14 weeks	3	10	Glass vial	0,5	5,00
	9	Tetanus Diptheria	Liquid Injectable	Older children	2	10	Glass vial	0,5	5,00
	Total container volumes - Legacy Routine (Millions - 2040)								
Expanding	10	Human Papillomavirus	Liqud injectable	9 years	2	1	Glass vial	0,5	0,50
	11	Pneumococcal conjugate vaccine	Liquid injectable	6, 10, 14 week	3	4	Glass vial	0,5	2,00
	12	Rotavirus	Liquid oral	6, 10 weeks	3	1	BFS	1,5	1,50
	13	Malaria	Liquid injectable	5 months	4	2	Glass vial	0,5	1,00
	14	HIV	TBD	TBD	TBD	10	TBD	TBD	TBD
	15	Multivalent meningococcal Vx (e.g MenACWY)	Liquid or freeze-dried injectable	Adolescents	1	1	Glass vial	0,5	0,50
	Total container volumes - Expanding (Millions - 2040)								
Outbreak	16	Ebola	Liquid injectable	Outbreak	1	1	Glass vial	1	1,00
	17	Influenza	Liquid injectable	Outbreak	Varies	1	Glass vial	0,5	0,50
	18	Chikungunya	TBD	Outbreak	TBD	1	TBD	TBD	TBD
	19	Rift Valley	TBD	Outbreak	TBD	1	TBD	TBD	TBD
	20	Lassa Fever	TBD	Outbreak	TBD	1	TBD	TBD	TBD
	21	Disease X	TBD	Outbreak	TBD	1	TBD	TBD	TBD
	22	COVID-19	Freeze-dried Injectable	Outbreak	Varies	10	Glass vial	0,3	3,00
	Total container volumes - Legacy Routine (Millions - 2040)								
Additional	23	Rabies	Freeze-dried Injectable	Varies	3	1	Glass vial	1	1,00
	24	Dengue	Freeze-dried Injectable	Varies	1	10	Glass vial	0,50	5,00
	25	Varicella	Freeze-dried injectable	Varies	1	1	Glass vial	0,50	0,50
	Total container volumes - Additional (Millions - 2040)								
	Total dose volumes (millions) - 2040								
	Total container volumes - All categories (Millions - 2040)								

Indicates Pipeline Vx

Indicates Unizima addition on top of PAVM priority diseases

[1] PAVM: Framework for Action Report. 22 Priority Diseases, Exhibit 13, p. 27 as starting point

[2,3] WHO Immunization Data portal

[4] Most commonly purchased vial image from WHO M4IA 2022 Vaccine Purchase database

Table 22 - Studies undertaken on vaccines in BFS (information kindly provided by Rommelag Engineering)

	African markets demand in Y2040 - Volumes allocation to the five F/F factories assuming 60% - million containers		Central Africa market with West region factory nr1		East Africa market with East region factory		North Africa market with North region factory		South Africa market with South region factory		West Africa market with West region factory nr2		Factory future		Total Africa	
1	Demand liquid vaccines		at 60%	at 100%	at 60%	at 100%	at 60%	at 100%	at 60%	at 100%	at 60%	at 100%			at 60%	at 100%
	Base legacy Routine vaccines	Penta - 10 doses vial	1,49	2,49	3,09	5,15	1,29	2,16	1,10	1,83	3,09	5,15			10,06	16,77
		IPV - 10 doses vial	0,93	1,55	1,92	3,19	0,80	1,34	0,68	1,13	1,92	3,19			6,24	10,40
		TD - 10 doses vial	0,75	1,25	1,54	2,57	0,65	1,08	0,55	0,91	1,54	2,57			5,03	8,38
	Base Expanding vaccines	PCV - 4 doses vial	3,20	5,33	6,60	11,01	2,77	4,62	2,34	3,91	6,60	11,01			21,51	35,86
		HIV - 10 doses vial	0,99	1,65	2,05	3,41	0,86	1,43	0,73	1,21	2,05	3,41			6,67	11,11
		HPV - 1 dose vial	3,24	5,40	6,70	11,16	2,81	4,68	2,38	3,96	6,70	11,16			21,82	36,36
		MenCWY - 1 dose vial	4,77	7,95	9,86	16,43	4,13	6,89	3,50	5,83	9,86	16,43			32,12	53,53
	Regional Legacy Routine vaccines	Typhoid - 5 doses vial	0,59	0,99	1,23	2,05	0,51	0,86	0,44	0,73	1,23	2,05			4,00	6,67
	Regional Expanding vaccines	Malaria - 2 doses vial	4,32	7,20	8,64	14,40	0,00	0,00	0,00	0,00	8,64	14,40			21,60	36,00
	Regional Additional vaccines															0,00
	Total liquid vaccines demand		20,28	33,80	20,28	20,28	20,28	20,28	20,28	20,28	20,28	20,28	0,00	0,00	20,28	20,28
2	Demand freeze-dried vaccines		at 60%	at 100%	at 60%	at 100%	at 60%	at 100%	at 60%	at 100%	at 60%	at 100%			at 60%	at 100%
	Base Legacy Routine vaccines	BCG - 20 doses vial	0,63	1,05	1,30	2,17	0,55	0,91	0,46	0,77	1,30	2,17			4,24	7,07
		MR - 10 doses vial	1,92	3,20	3,96	6,60	1,66	2,77	1,41	2,34	3,96	6,60			12,91	21,51
	Base Additional vaccine	Rabies - 1 dose vial	0,63	1,05	1,30	2,17	0,55	0,91	0,46	0,77	1,30	2,17			4,24	7,07
		Varicella - 1 dose vial	0,32	0,54	0,67	1,12	0,28	0,47	0,24	0,40	0,67	1,12			2,18	3,64
	Regional Legacy Routine vaccines	YF - 10 doses vial	0,48	0,80	0,99	1,64	0,00	0,00	0,48	0,80	1,27	2,12			3,21	5,35
		MenA - 10 doses vial	0,00	0,00	1,59	2,65	0,00	0,00	0,00	0,00	1,59	2,65			3,18	5,30
	Regional Additional vaccines	Dengue - 10 doses vial	0,00		0,27	0,45	0,00	0,00	0,00	0,00	0,27	0,45			0,54	0,90
	Total freeze-dried vaccines demand		3,98	6,63	10,08	16,80	3,03	5,06	3,04	5,07	10,37	17,28	0,00	0,00	30,51	50,84
3	Demand BFS oral vaccines and diluents		at 60%	at 100%	at 60%	at 100%	at 60%	at 100%	at 60%	at 100%	at 60%	at 100%			at 60%	at 100%
	Base Legacy Routine vaccines															
	Base Expanding vaccines	Rota - 1 dose BFS tube	11,25	18,75	23,25	38,75	9,75	16,25	8,25	13,75	23,25	38,75			75,75	
	Regional Legacy Routine vaccines	Cholera - 1 dose BFS tube	1,38	2,30	5,52	9,20	0,00	0,00	1,38	2,30	5,52	9,20			13,80	23,00
	Diluents	Diluent 20/10 doses BFS tube	7,62	12,70	5,84	9,73	3,96	6,59			7,37	12,28	3,27	5,46	24,78	41,30
		Diluent 1 dose BFS tube (Rabies/Varicella)	0,95	1,59	1,97	3,29	0,83	1,38			1,97	3,29			5,72	9,54
	Total BFS vaccines + diluents demand		3,98	6,63	10,08	16,80	3,03	5,06	3,04	5,07	10,37	17,28	3,27	5,46	30,51	50,84
	Total F/F demand per factory		77,64	129,40	80,37	133,95	18,10	30,16	21,57	35,95	81,93	136,55	3,27	5,46	279,60	466,01

13.2. Annex 02 – F/F factory, development of Blow-Fill-Seal (BFS) packaging presentations for African vaccine markets

There are currently two commercial oral vaccines available in BFS, both against Rotavirus.
Table 1 shows the feasibility studies for vaccines that have been carried out with positive outcomes.

Table 23 - Studies undertaken on vaccines in BFS (information kindly provided by Rommelag Engineering)

Vaccine	Vaccine Type	Companies	Status
Rotavirus	Live attenuated, oral	GSK and others	Commercialized
Influenza	Live attenuated, nasal	MedImmune	Feasibility demonstrated
Human Papillomavirus	Protein subunit	Not disclosed	Feasibility demonstrated
Pneumococcus	Protein subunit	BMFB/Global Good	Feasibility demonstrated
Respiratory syncytial virus	Virus-like particle	Novavax	Feasibility demonstrated

Figure 12
Rubber stopper at the top of the BFS tube
(kindly provided by Rommelag Engineering)

Figure 20
BFS tube with a syringe connector (luer lock), and screw cap
(kindly provided by Rommelag Engineering)

Further research is being done on other vaccines, including mRNA vaccines with lipid nanoparticles, but data are not yet available or accessible.

The data demonstrate that BFS technology can be successfully applied to different types of vaccines. However, as vaccines have variable characteristics, confirmatory feasibility studies for each vaccine would need to be carried out before a major investment decision is taken.

Suitable multi-dose BFS presentations for vaccines are currently not available. The main technical challenge is to extract up to 10 doses of an injectable sterile vaccine one after the other from a BFS tube, while maintaining sterility up to the extract of the last dose. Although a classic tube remains open after the first dose extraction, two technical solutions have been developed to enable sterile conditions during multiple extractions.

The first solution is to insert a rubber stopper at the top of the BFS tube (Figure 12), while it is being sealed in the BFS machine. As this approach is comparable to glass multidose containers and uses similar stoppers, it can be assumed that it will ensure aseptic conditions in the same way.

The second solution is to equip the top of the BFS tube with a syringe connector (e.g., Luer lock) as seen in Figure 20. The product would be extracted with a syringe adapted to the connector. Between extractions, a cap could be screwed on to the top of the BFS tube to close it and protect the contents.

The BFS technology is associated with several technical challenges that are linked to the typical characteristics of vaccines. These need to be addressed in the development:

Most vaccines are heat-sensitive and therefore exposure to high temperatures must be minimized during the filling process. ‘Cool BFS’ technology has been shown to be able to control this risk.

Several products such as aluminum-adjuvanted vaccines are suspensions which tend to create sediments, and this can lead to inhomogeneity during the filling process. The same challenge applies to filling glass containers. This risk can be controlled through recirculation loops and the rejection of a sufficient number of units following interruptions to the filling process.

The appearance of the vaccine in each container is typically checked during the visual inspection process. Most BFS containers are not transparent, making this impossible. However, with adequate process validation and random sample testing, sufficient evidence should be available to ensure consistent product quality.

BFS tubes typically have a higher gas and water permeability than glass.

It has been demonstrated that this can have an impact on the product. The main effect is a partial loss of volume due to water evaporation. For oral vaccines that have a high dose volume (e.g., 2 ml), this is much less relevant than for injectable vaccines with small volumes (e.g., 0.5 ml). For single-dose injectable vaccines in BFS, volume loss might represent a substantial challenge. This could be addressed by choosing less permeable plastic resins, or by wrapping BFS containers. However, the latter will increase the volume of the container moderately.

Labelling needs to take the permeability of the BFS container into account, as components of the glue could permeate into the product. The label must either not be attached to the body of the container, or a resin with low permeability must be chosen.

Vaccines are often highly complex mixtures of different compounds. Testing critical attributes (such as potency) during stability studies is often difficult and is sometimes associated with the inherently limited precision of analytical methods. However, we cannot exclude the possibility that critical attributes may be impacted by changes to the container (for example through absorption, permeability). Therefore, long-term, comprehensive stability studies – with sufficient data points – must be conducted for each vaccine in BFS, as part of feasibility studies.

Presentation in a BFS container instead of a glass vial will be unusual for the product's users. They must be comfortable with its characteristics and handling; therefore, it is therefore crucial that any new BFS design for a vaccine must be extensively tested by users, to confirm acceptability.

The development of a BFS presentation could be jointly executed by a company specializing in this technology, and the product owner or product license holder. Such specialized companies typically have manufacturing units at both small and large scale available, to carry out development work. The product license holder could provide vaccine bulks and should oversee or support the development work.

Table 22 provides an outline of the development work. The total development cost of an injectable vaccine in BFS is estimated at EUR 1.5 million per vaccine, with the time to launch projected to be about three to four years.

In conclusion, BFS technology offers multiple benefits for vaccines intended for the African market. There is still substantial development work required to enable its application to a broad range of vaccines, particularly injectable vaccines. Multinational organizations could coordinate efforts and provide support, including financial support. The development of BFS containers could be jointly executed by companies who specialize in this technology and the vaccines' license holders who are interested in exploring this opportunity.

Table 24 - Development of a BFS presentation for a vaccine

Development steps	Main activities
Preparation	Detailed planning Contractual arrangements
BFS design	Development, production and qualification of machine mold Preparation of prototypes User acceptance studies to confirm design
Feasibility studies	Filling of product at small scale into proposed containers Comparison of standard with wrapped containers (if needed) Extractable and leachable studie Stability studies
Validation	Transfer process to commercial scale Filling of consistency batches Stability studies
Regulatory approval	Submission as a variation to an approved product license. Likely substantial real time stability studies are required pre-approval.

13.3. Annex 03 – F/F factory, criteria for African countries' selection

The table below shows the criteria that have been used to select the F/F factories' host countries

Table 25 - Criteria used for teh selection of the F/F factories's host countries

Markets	F/F factory name	F/F factory country	Criteria	Comments
Central Africa	West nr1 (medium-sized F/F factory)	Nigeria	- Large market, regional economic hub - Significant pharma experience and skills - High levels of foreign investments - Government established (Biovaccines Institute) - NAFDAC (Regulatory authority) at ML3 - Hub for distribution across West Africa	Ongoing discussions with government on vaccine-related investments (PIA-Biofarma, ...)
East Africa	East (medium-sized F/F factory)	Kenya Rwanda	- Large sophisticated market - Significant pharma sector - Government established Biovax Institute - Good pharma skills base - Academia and R&D centres - Attractive for foreign investment - Hub for distribution across East Africa	- Large mRNA DS investment announced by Moderna - Aga Khan (IPS) identified by WHO for "mRNA hub & spokes" program - Private initiatives for insulins/ biosimilars F/F
North Africa	North (smaller F/F factory)	Egypt	- Several Vx facilities in operation - Government commitment - Skilled labour available - Strong academia and industry collaboration	BioNTech commitment for mRNA DS manufacturing in Rwanda
Southern Africa	South (smaller F/F factory)	South Africa	- Two vaccines facilities in operation - Government commitment (Biovac established a PPP) - Significant R&D skills - Hub for distribution across sub-Saharan Africa	- DTP combo F/F Tech Transfer done at Vacsera for local tenders - Eva Pharma selected by WHO for "mRNA hub & spokes"program - Private initiatives for insulins/biosimilars F/F
West Africa	West nr (medium-sized F/F factory)	Ghana	- Highly committed government attracting foreign investments - Growing local pharma sector - Skilled workforce - Good R&D facilities - Regulatory agency has achieved ML 3	- Vaccine Tech Transfers with Aspen - Afrigen selected by WHO for "mRNA hub & spokes"program

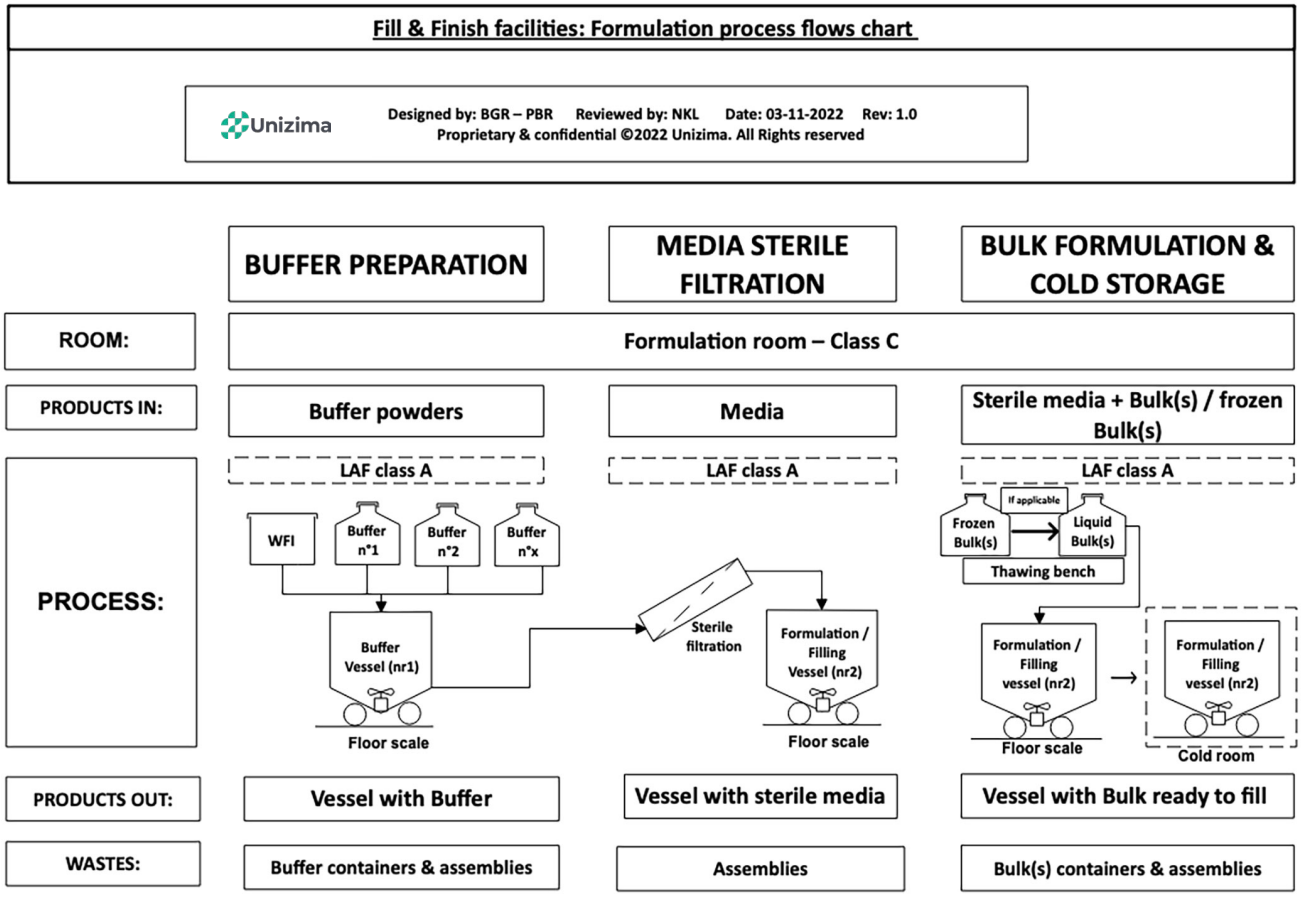
13.4. Annex 04 - Details about the F/F factories capacities and utilization rate

Table 26 - Details about the F/F factories capacities and utilization rate

	African markets demand in Y2040 - Volumes allocation to the five F/F factories assuming 60% - million containers		Central Africa market with West region factory nr1	East Africa market with East region factory	North Africa market with North region factory	South Africa market with South region factory	West Africa market with West region factory nr2	Total Africa
1	**Demand liquid vaccines**		at 60%	at 60%	at 60%	at 60%	at 60%	at 60%
	Base Legacy Routine vaccines	Penta - 10 doses vial	1,49	3,09	1,29	1,10	3,09	10,06
		IPV - 10 doses vial	0,93	1,92	0,80	0,68	1,92	6,24
		TD - 10 doses vial	0,75	1,54	0,65	0,55	1,54	5,03
	Base Expanding vaccines	PCV - 4 doses vial	3,20	6,60	2,77	2,34	6,60	21,51
		HIV - 10 doses vial	0,99	2,05	0,86	0,73	2,05	6,67
		HPV - 1 dose vial	3,24	6,70	2,81	2,38	6,70	21,82
		MenCWY - 1 dose vial	4,77	9,86	4,13	3,50	9,86	32,12
	Regional Legacy Routine vaccines	Typhoid - 5 doses vial	0,59	1,23	0,51	0,44	1,23	4,00
	Regional Expanding vaccines	Malaria - 2 doses vial	4,32	8,64	0,00	0,00	8,64	21,60
	Regional Additional vaccines							
		Total liquid vaccines demand	**20,28**	**41,62**	**13,83**	**11,70**	**41,62**	**129,04**
	Demand allocation per factory	Penta - 10 doses vial	1,49	3,09	1,29	1,10	3,09	10,06
		IPV - 10 doses vial	0,93	1,92	0,80	0,68	1,92	6,24
		TD - 10 doses vial	0,75	1,54	0,65	0,55	1,54	5,03
		PCV - 4 doses vial	3,20	6,60	2,77	2,34	6,60	21,51
		HIV - 10 doses vial	0,99	2,05	0,86	0,73	2,05	6,67
		HPV - 1 dose vial	3,24	6,70	2,81	2,38	6,70	21,82
		MenCWY - 1 dose vial	4,77	9,86	4,13	3,50	9,86	32,12
		Typhoid - 5 doses vial	2,34			1,66		4,00
		Malaria - 2 doses vial	12,96			8,64		21,60
		Checks	30,66	31,75	13,31	21,57	31,75	129,04
		Total liquid vaccines demand allocated per factory	**30,66**	**31,75**	**13,31**	**21,57**	**31,75**	**129,04**
	Fill line nr1 - liquid vials - 2 shifts	17,47	17,47	17,47	17,47	17,47	17,47	87,36
	Fill line nr2 - liquid vials - 1st shift	8,74	8,74	8,74		8,74	8,74	34,94
	2nd shift	8,74	8,74	8,74			8,74	26,21
	Fill line nr3 - liquid vials - 1st shift	8,74						
	2nd shift	8,74						
		Fill lines capacities (-) gap (+) under-utilized	**4,28**	**3,19**	**4,16**	**4,64**	**3,19**	**19,47**
2	**Demand freeze-dried vaccines**		at 60%	at 60%	at 60%	at 60%	at 60%	at 60%
	Base Legacy Routine vaccines	BCG - 20 doses vial	0,63	1,30	0,55	0,46	1,30	4,24
		MR - 10 doses vial	1,92	3,96	1,66	1,41	3,96	12,91
	Base Additional vaccines	Rabies - 1 dose vial	0,63	1,30	0,55	0,46	1,30	4,24
		Varicella - 1 dose vial	0,32	0,67	0,28	0,24	0,67	2,18
	Regional Legacy Routine vaccines	YF - 10 doses vial	0,48	0,99	0,00	0,48	1,27	3,21
		MenA - 10 doses vial	0,00	1,59	0,00	0,00	1,59	3,18
	Regional Additional vaccines	Dengue - 10 doses vial	0,00	0,27	0,00	0,00	0,27	0,54
		Total freeze-dried vaccines demand	**3,98**	**10,08**	**3,03**	**3,04**	**10,37**	**30,51**
	Demand allocation per factory	BCG - 20 doses vial		1,93			2,31	4,24
		MR - 10 doses vial		5,88			7,03	12,91
		Rabies - 1 dose vial			4,24			4,24
		Varicella - 1 dose vial	2,18					2,18
		YF - 10 doses vial	3,21					3,21
		MenA - 10 doses vial	3,18					3,18
		Dengue - 10 doses vial			0,54			0,54
		Total freeze-dried vaccines demand allocated per factory	**8,57**	**7,81**	**4,78**		**9,34**	**30,51**
	Fill line nr1 - lyo vaccine - 1st freeze-dryer	4,68	4,68	4,68	4,68		4,68	18,72
	2nd freeze-dryer	4,68	4,68	4,68			4,68	14,04
	3rd freeze-dryer	4,68						0,00
		Fill lines capacities (-) gap (+) under-utilized	**0,79**	**1,55**	**-0,10**	**0,00**	**0,02**	**2,25**
3	**Demand BFS oral vaccines and diluents**		at 60%	at 60%	at 60%	at 60%	at 60%	at 60%
	Base Legacy Routine vaccines							
	Base Expanding vaccines	Rota - 1 dose BFS tube	11,25	23,25	9,75	8,25	23,25	75,75
	Regional Legacy Routine vaccines	Cholera - 1 dose BFS tube	1,38	5,52	0,00	1,38	5,52	13,80
	Diluents	Diluent 20/10 doses BFS tube	7,62	5,84	3,96		7,37	24,78
		Diluent 1 dose BFS tube (Rabies/Varicella)	0,95	1,97	0,83		1,97	5,72
		Total BFS vaccines + diluents demand	**21,20**	**36,58**	**14,53**	**9,63**	**38,11**	**120,06**
	Demand allocation per factory	Rota - 1 dose BFS tube	11,25	33,00			31,50	75,75
		Cholera - 1 dose BFS tube	13,80					13,80
		Diluent 20/10 doses BFS tube	11,57	5,84			7,37	24,78
		Diluent 1 dose BFS tube (Rabies/Varicella)	1,78	1,97			1,97	5,72
		Total BFS vaccines demand allocated per factory	**38,41**	**40,81**			**40,84**	**120,06**
	Fill line nr1 - BFS medium speed - 1st batch	42,53	42,53					42,53
		Fill lines capacities (-) gap (+) under-utilized	4,12					-77,53
		Total F/F demand per factory	**77,64**	**80,37**	**18,10**	**21,57**	**81,93**	**279,60**

13.5. Annex 05 – F/F factory, detailed F/F process flows charts

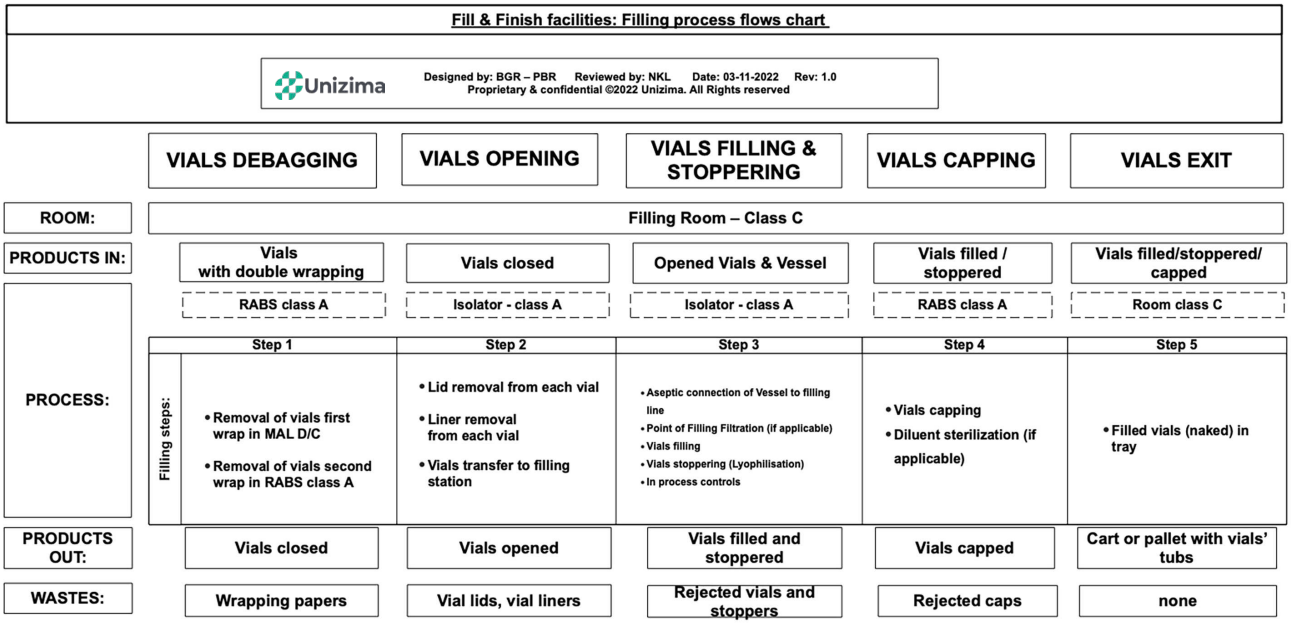
13.5.1. Media Preparation & Formulation process flow chart (generic)



Note 1: The formulation process varies from one vaccine to another with: (a) different media/excipients to be used; (b) different batch sizes; and (c) different storage conditions of the vessel or bag containing the diluted bulks (mostly +2 +8°C, but sometimes frozen for mRNA vaccines).

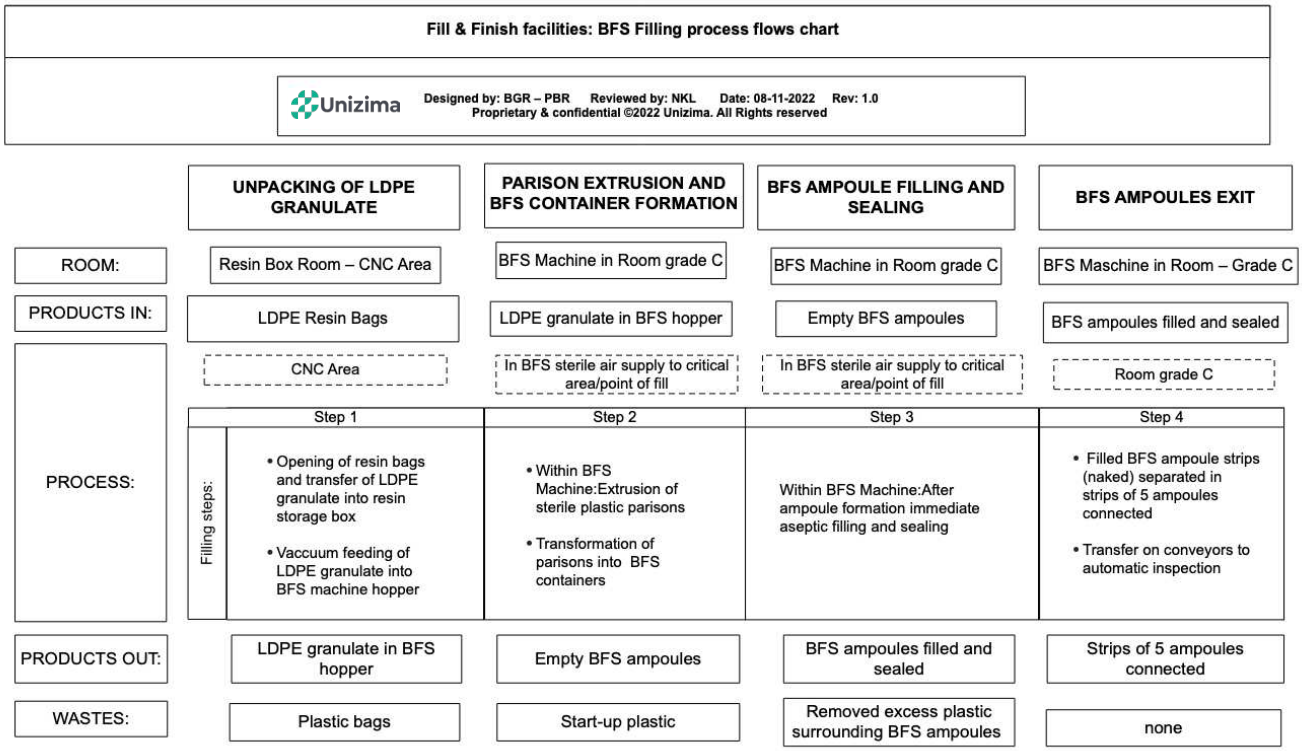
Note 2: The diluted bulks are stored either in sterile stainless-steel vessels (equipped with a mixer), or in large plastic bags. The choice of the container is made based on: (a) the vaccines' formulation process developed/registered by the vaccines producer(s); (b) the stability data and Extractables & Leachables studies of the vaccines in plastic bags; and (c) the possibility of mixing the vaccines.

13.5.2. Liquid & freeze-dried vaccines Filling process flow chart (generic)

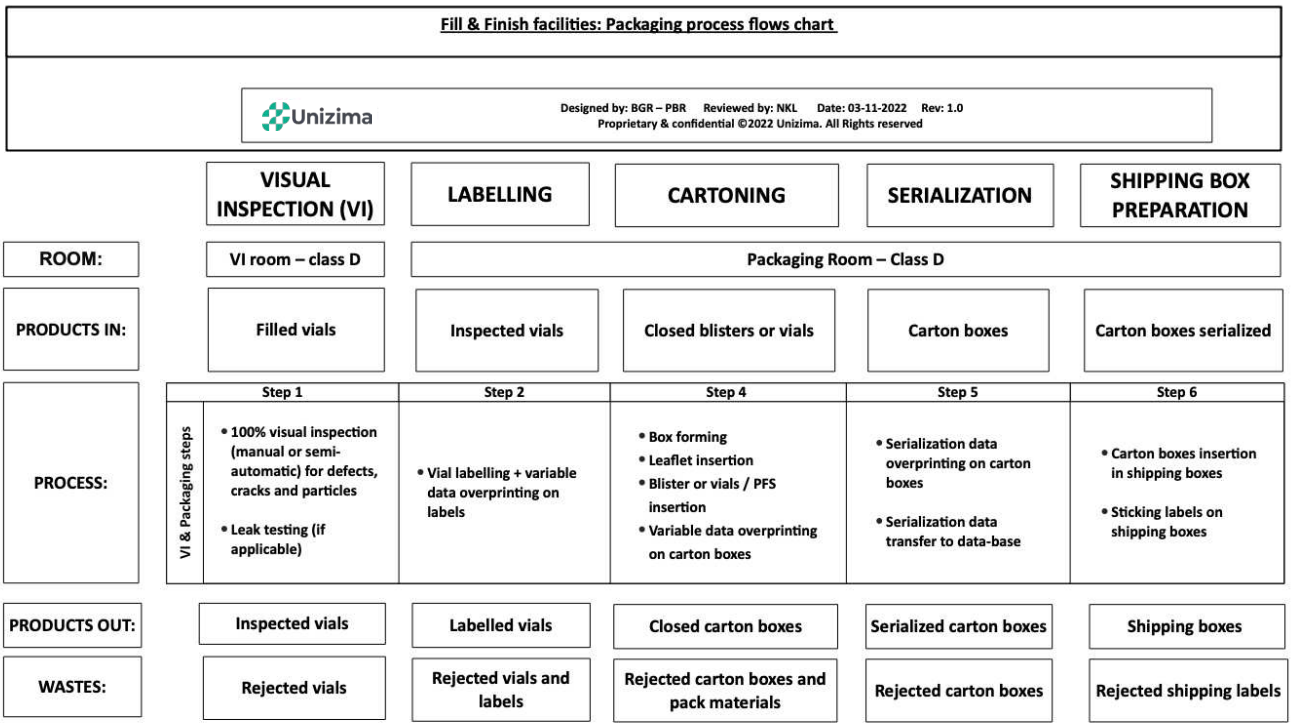


Note: the above process flow chart is applicable to Ready to Use (RTU) vials

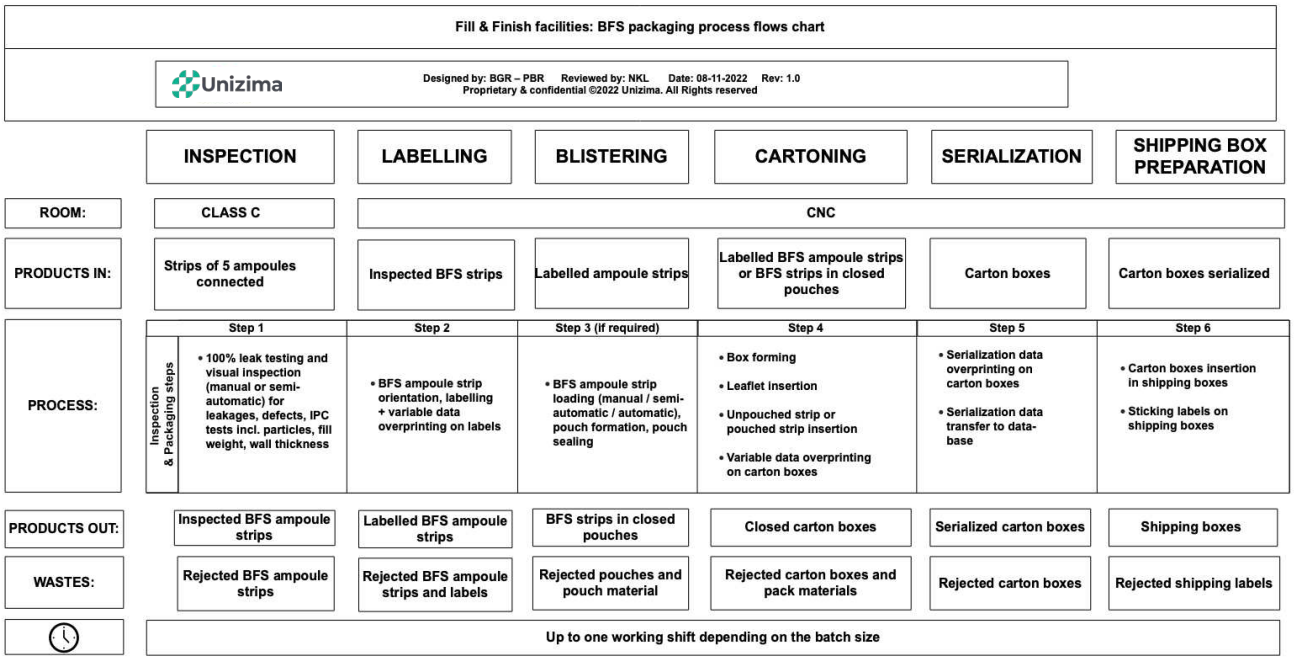
13.5.3. Oral vaccines & diluents' Filling process flow chart (generic)



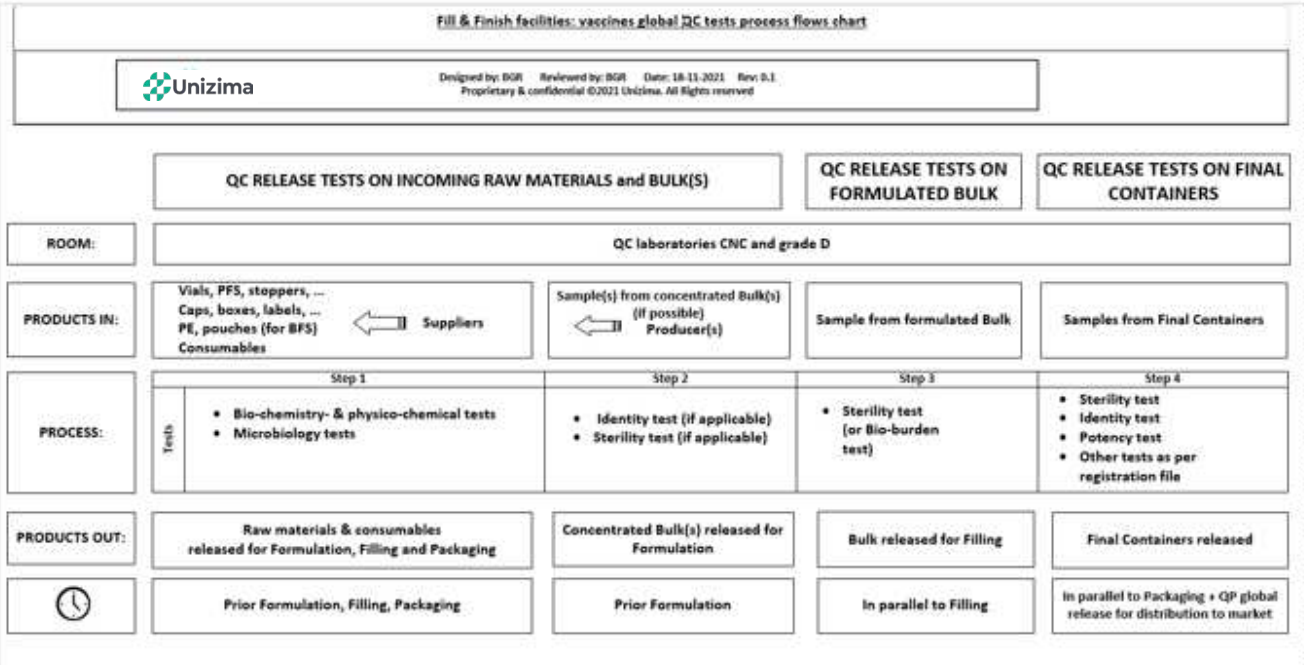
13.5.4. Liquid & freeze-dried vaccines' Visual Inspection & Packaging process flow charts (generic)

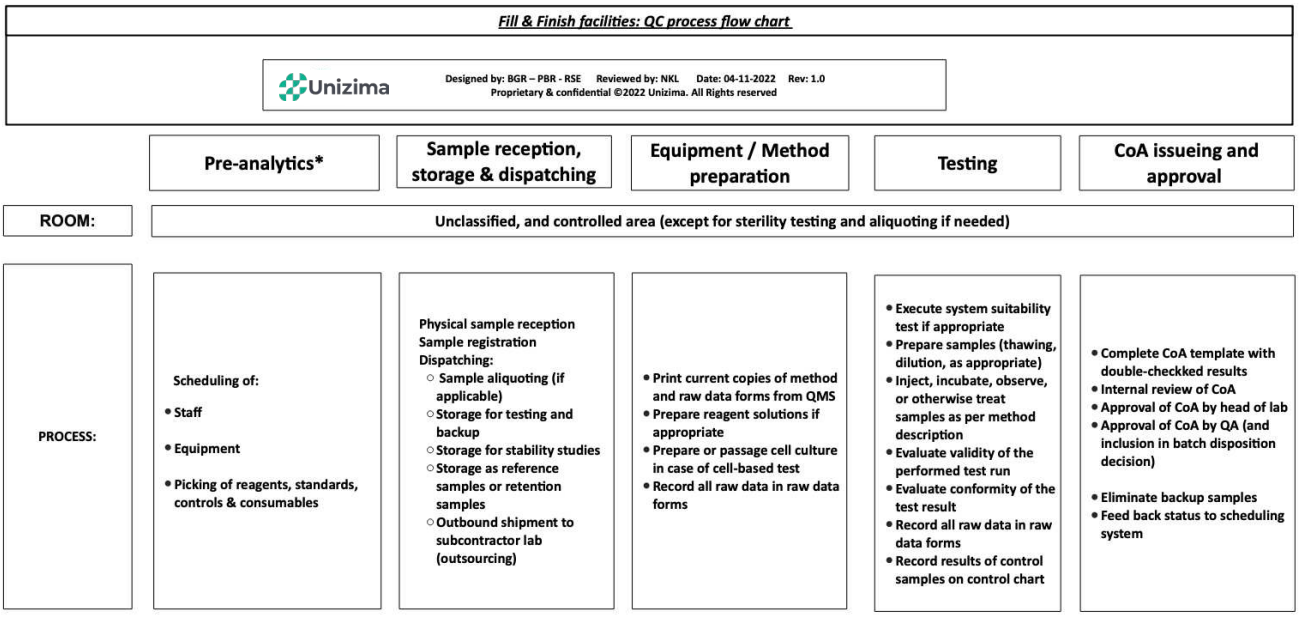


13.5.5. Oral vaccines & diluents' Visual Inspection & Packaging process flow chart (generic)



13.5.6. Vaccines' QC release tests flow charts (generic)





Note 1: All incoming raw materials and incoming bulks are also subject to QC release tests based on specific monographies.

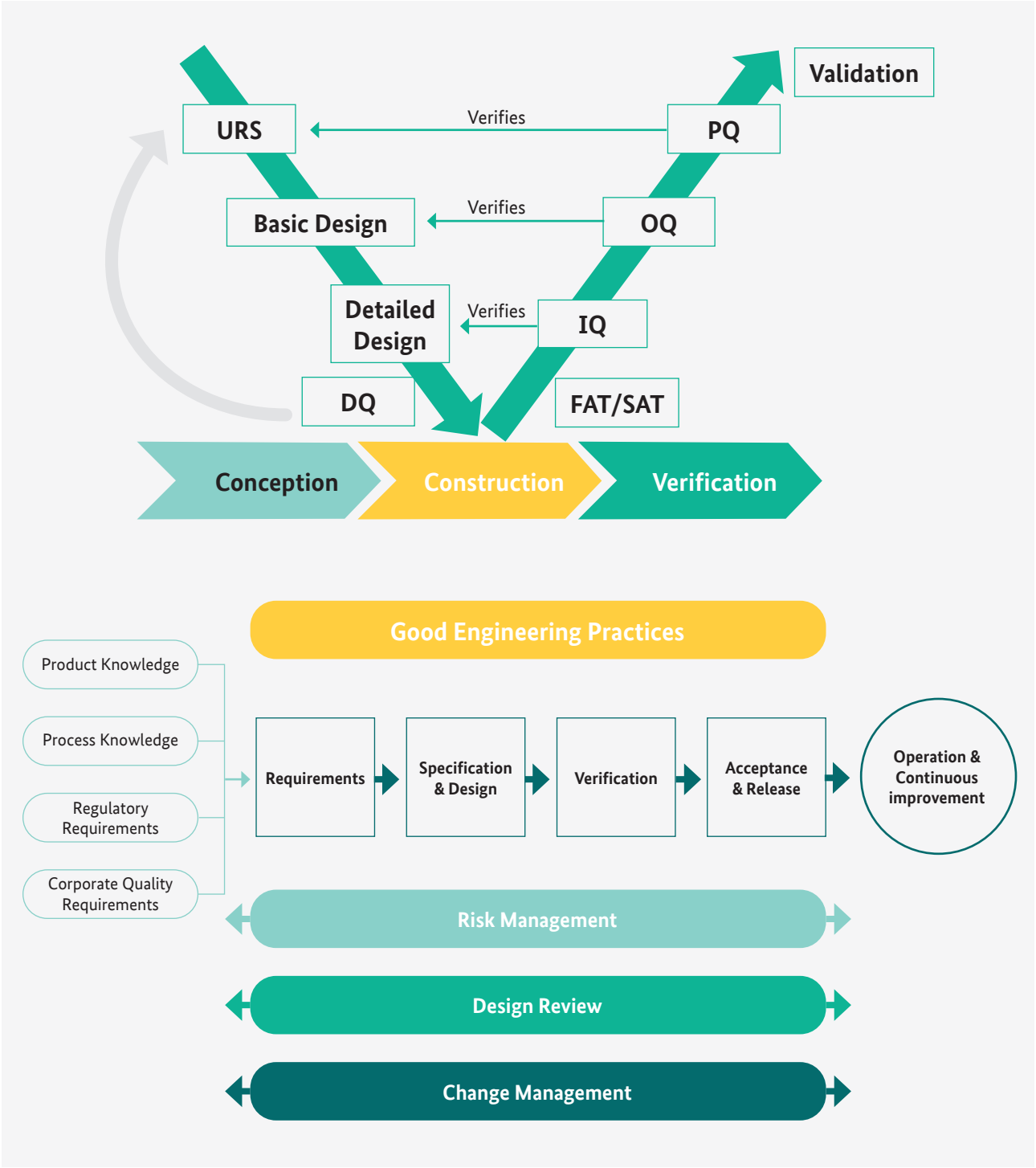
Note 2: The samples from all clean utilities (WFI, Purified Water, Clean Compressed Air, etc), and from the Environmental Monitoring are subject to QC release tests based on specific monographies.

Note 3: QC tests are executed during initial equipment/process validation activities, but also during routine re-validation activities.

13.5.7. F/F factory support departments: the Commissioning, Qualification and Validation (CQV) department

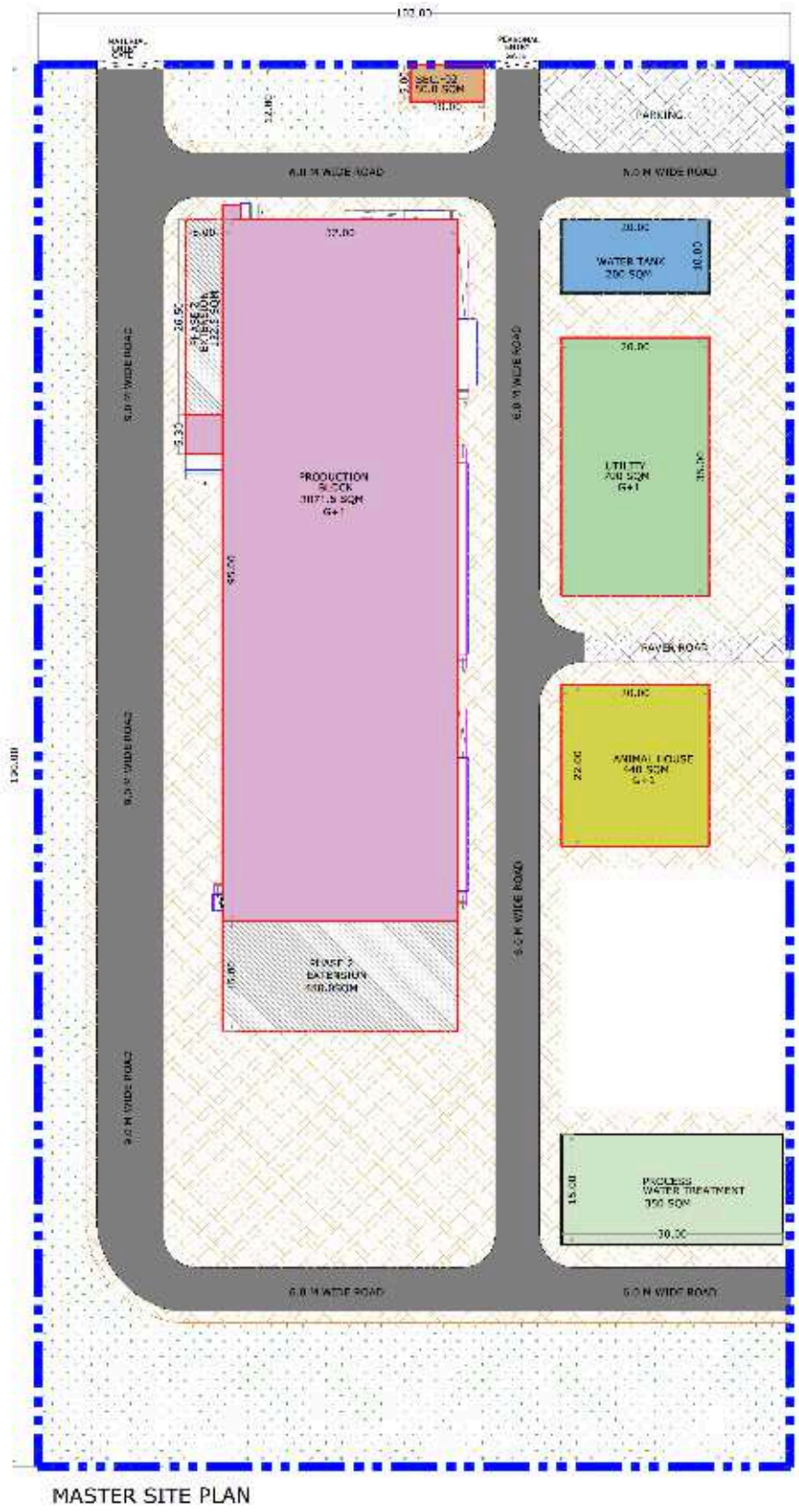
The CQV department is responsible for defining a detailed and science-based process for the specification, design, and verification of new equipment, systems, and processes. The CQV systems are developed in accordance with several regulatory guidelines, such as the Food and Drug Administration 's "Process Validation: General Principles and Practices", and "Quality Risk Management" published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH Q9). The CQV activities are defined through a Validation Plan, as presented below.

The traditional and most common approach for the qualification and validation steps is named the "V-cycle model", and the Risk-Based Approach (ASTM E2500).



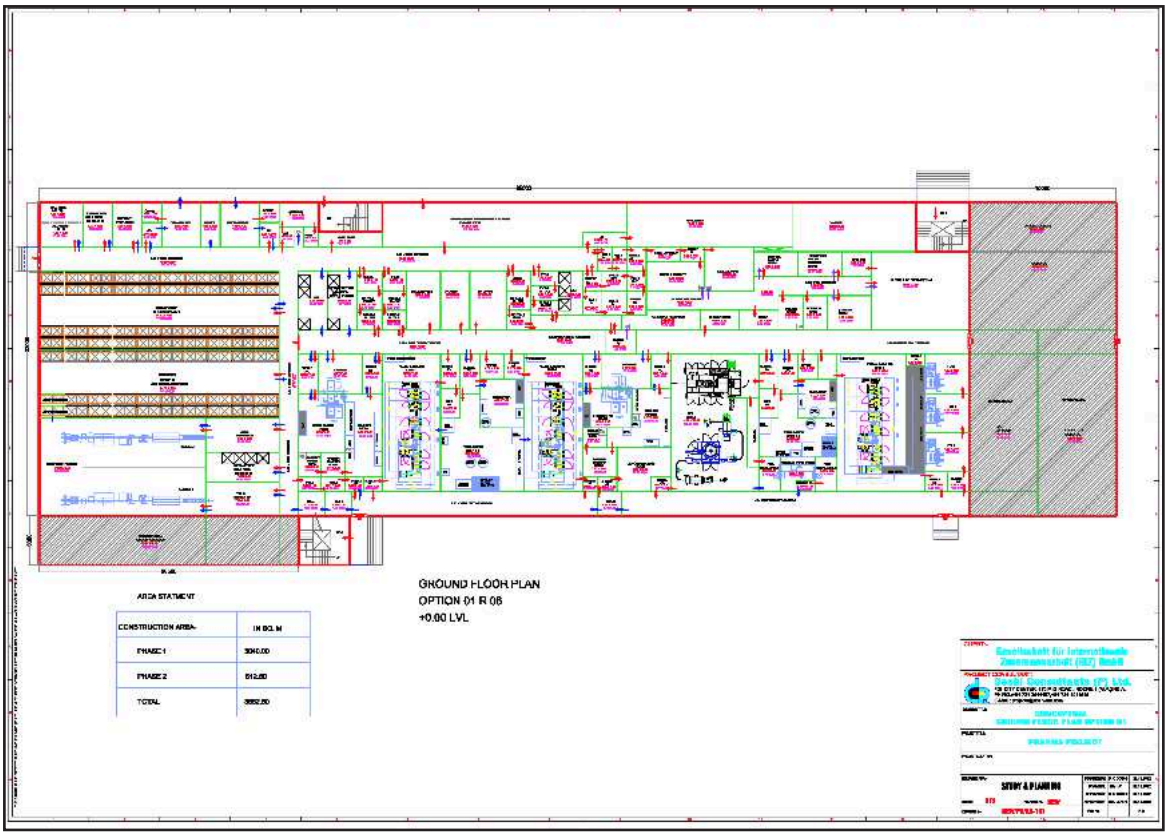
13.6. Annex 06 – Medium-sized F/F factory conceptual layouts

a. F/F factory, Site Master Plan

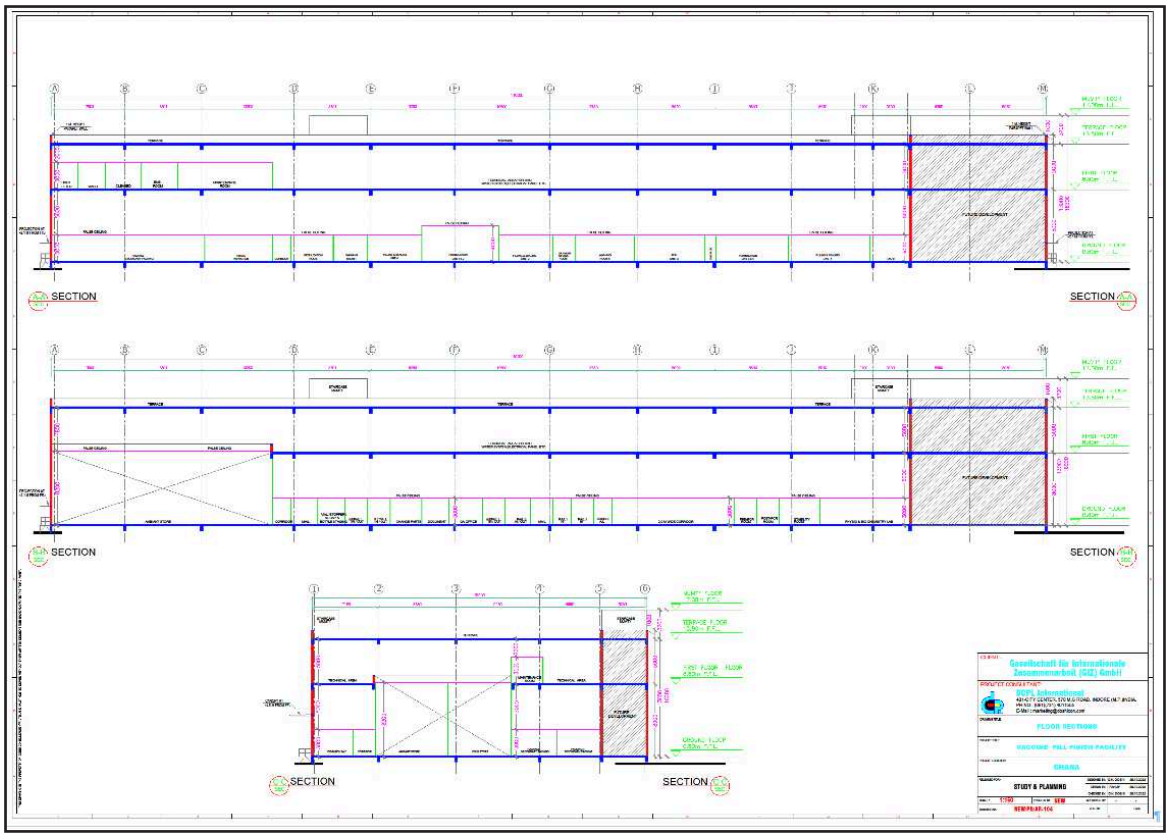


MASTER SITE PLAN

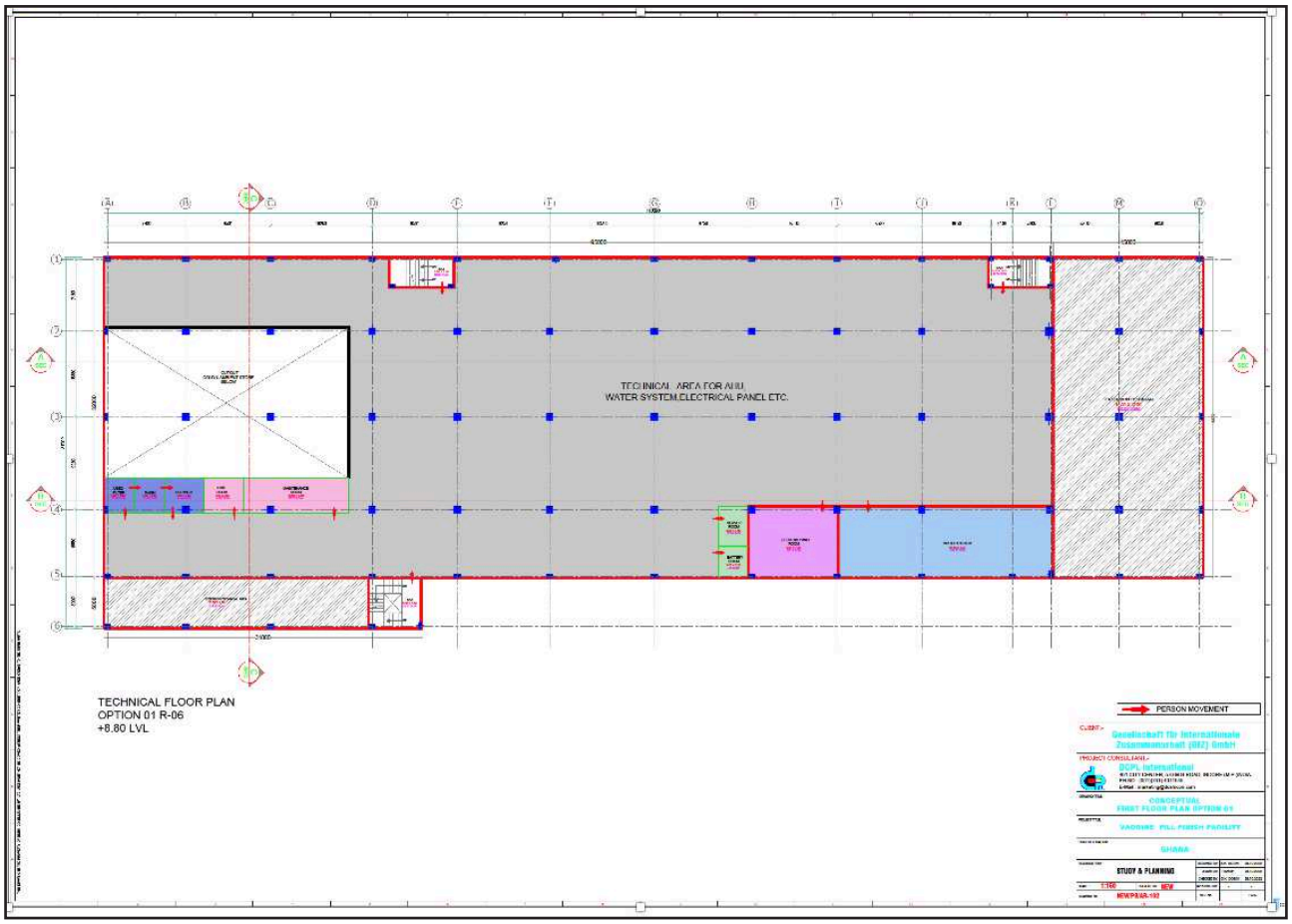
b. F/F factory, ground floor lay-out



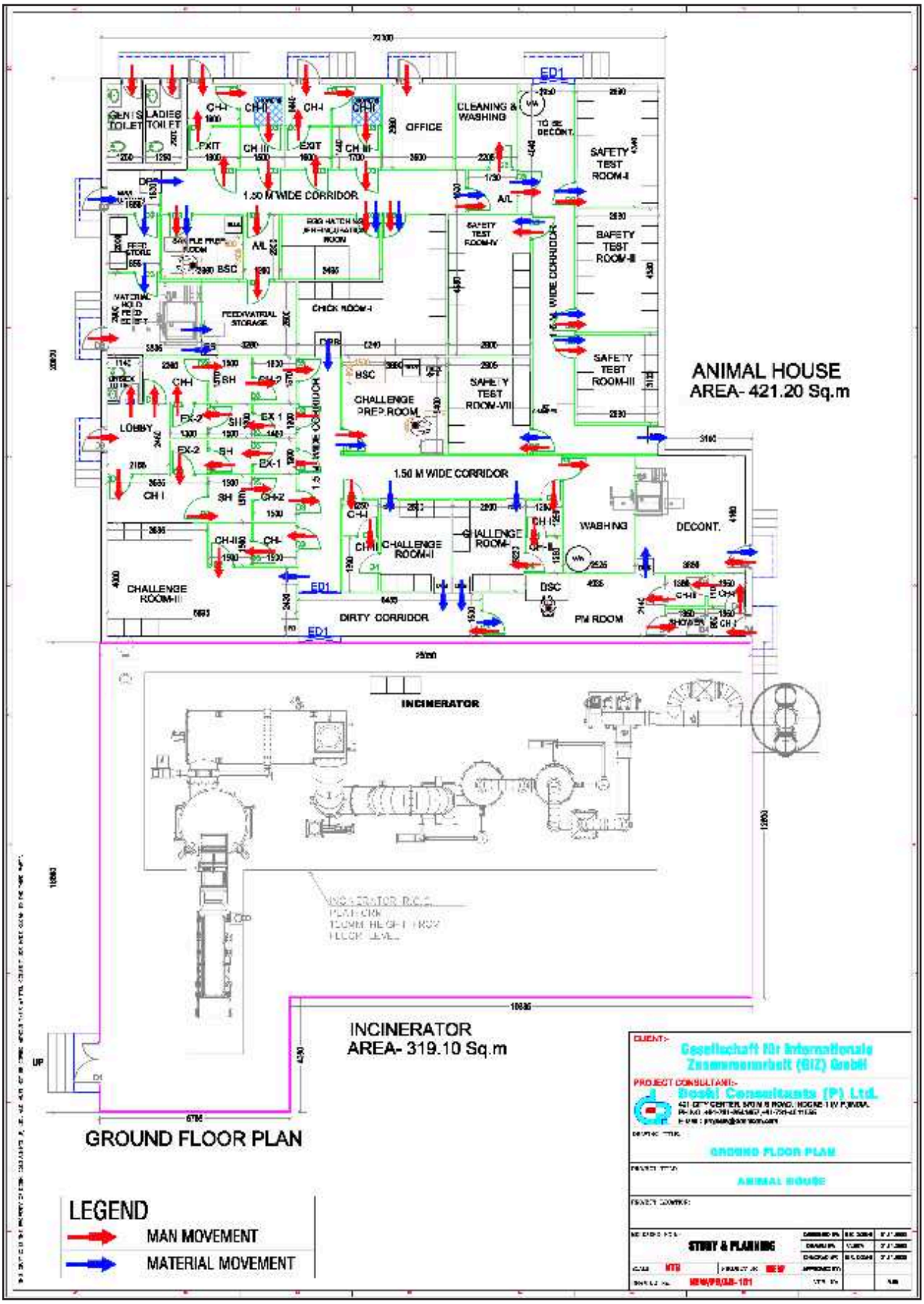
c. F/F factory, section lay-out



d. F/F factory, technical floor



e. F/F factory, animals house



13.7. Annex 07 – F/F factory, modular concept

Example of a modular F/F factory

Univercells group successfully built state of the art R&D and manufacturing scale modular & stick-built facilities in record times, over-achieving on quality, cost and rapid delivery

Univercells Biologics for all

exothera

Quantoom Biosciences

Univercells:
Built compact cGMP R&D labs in Belgium

Exothera:
Built large state of the art CDMO in Belgium in only 19 months from idea to GMP certification

Quantoom:
Built its disruptive mRNA production technology in purpose-built pods. This allowed record time R&D during the pandemic to develop and commercialize Quantoom production platform

Scenario example 1: modular factory for vaccines Fill & Finish

1 Investments assumptions

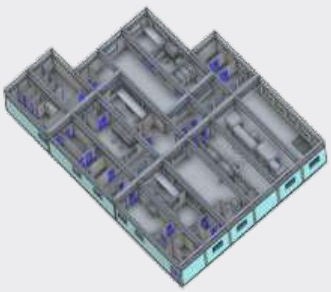
- "Green field" project with POD's under/in a building - POD's for Formulation, Filling, QC labs - VI, Pack, stores in building
- Liquid vaccines (1 dose vial); annual volumes: **10 million units** (one shift), **20 million units** (two shifts)
- One Filling line (200 units/min) under isolator
- POD's designed in Switzerland, built in Asia – Building locally constructed
- Process equipment from reputable European suppliers

2 Investment CapEx & OpEx (excluding inflation, VAT, taxes, ...*)

- Investment CapEx, estimated: between 20 to 24 million Eur
- Investment OpEx, variable as per the services required from Unizima and the number of vaccines: project Definition & Design, products In-Licensing, Training, Tech Transfer, PM, ...

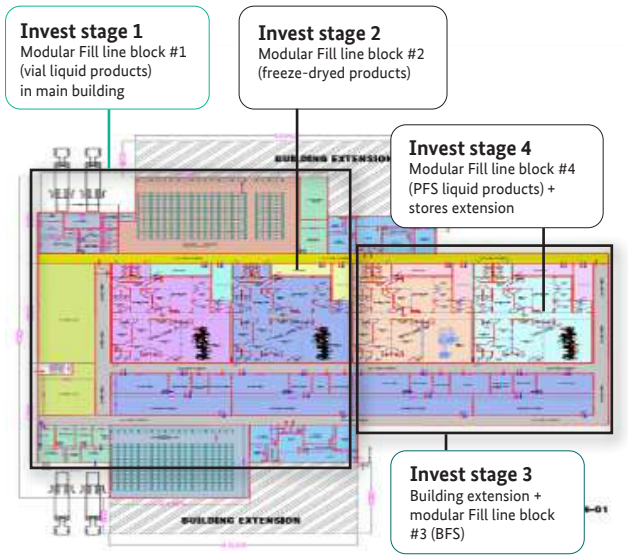
3 Estimated CoGS and profitability

- To be calculated as per client' precise business assumptions in the frame of a tailored made Feasibility study

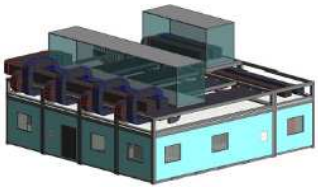


Our modular solution gives you the flexibility to adapt the facility to your specific needs

Build your "greenfield POD's facility" in different stages...



...or connect specific PODs to your existing building inside or outside your building



Our modules allow you **to increase production capacity, extend the production process or add new products line** as your project evolves

Scenario example 2: modular factory for vaccines Fill & Finish

1 Investments assumptions

- "Brown field" project with POD's in/out a building - POD's for Formulation, Filling, QC labs - VI, Pack, stores already in a building
- Liquid biosimilars (1 dose vial or cartridge); annual volumes: **2,5 million units** (one shift), 5 million units (two shifts)
- One Filling line **(50 units/min)** under isolator
- POD's designed in Switzerland, built in Asia
- Process equipment from reputable European suppliers

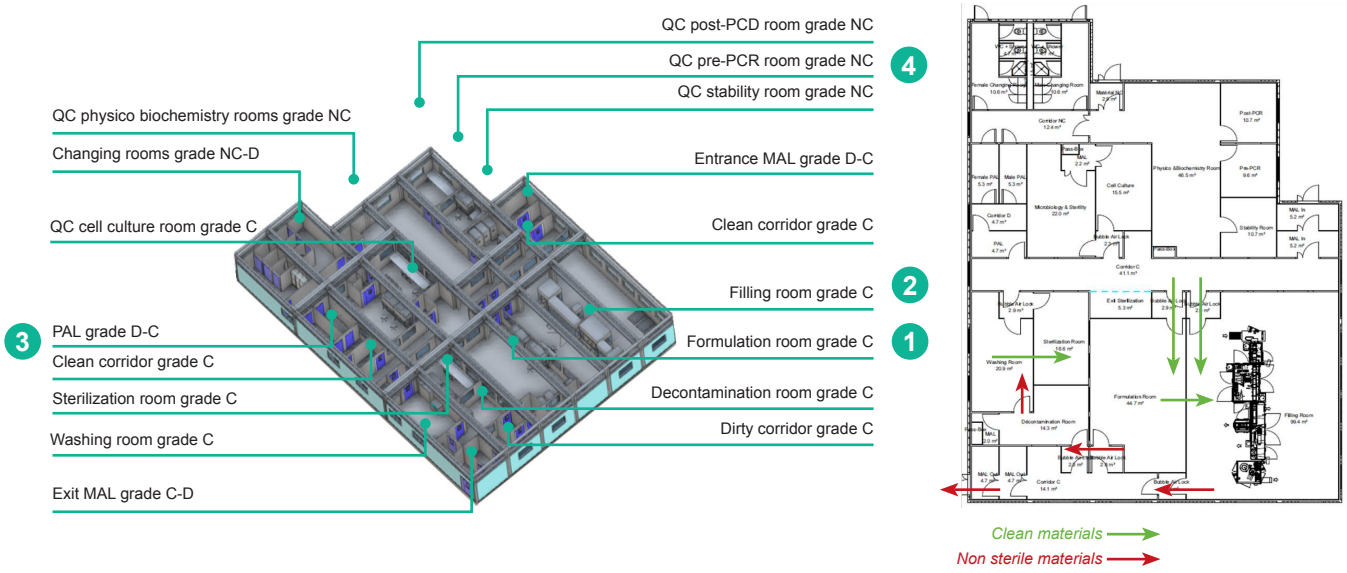
2 Investment CapEx & OpEx (excluding inflation, VAT, taxes, ...*)

- Investment CapEx, estimated: between 15,5 to 18,5 million Eur
- Investment OpEx, variable as per the services required from Unizima and the number of vaccines: project Definition & Design, products In-Licensing, Training, Tech Transfer, PM, ...

3 Estimated CoGS and profitability

- To be calculated as per client' precise business assumptions in the frame of a tailored made Feasibility study

Example of a facility layout, to be customized according to the client's needs



Scenario example 1: modular factory for vaccines Fill & Finish

1 Investments assumptions

- "Brown field" project with POD's in/out a building - POD's for Formulation, Filling, VI, Pack - QC labs, stores already in a building
- Liquid biosimilars (1 dose vial or PFS); annual volumes: **0,5 million units** (one shift), **1 million units** (two shifts)
- One Filling line **(10 units/min)** under isolator
- POD's designed in Switzerland, built in Asia
- Process equipment from reputable European suppliers

2 Investment CapEx & OpEx (excluding inflation, VAT, taxes, ...*)

- Investment CapEx, estimated: between 11,5 to 14 million Eur
- Investment OpEx, variable as per the services required from Unizima and the number of vaccines: project Definition & Design, products In-Licensing, Training, Tech Transfer, PM, ...

3 Estimated CoGS and profitability

- To be calculated as per client' precise business assumptions in the frame of a tailored made Feasibility study

13.8. Annex 08 - F/F factory, about Ready to Use (RTU) vials

RTU vials offer great advantages compared to standard vials, which are washed and sterilized in-house.

Table 26

Details about the F/F factories capacities and utilization rate

The major advantages are listed below:

- Lower CapEx (at least EUR 1 million) because there would be no need for vial washing machines or vial sterilization tunnels, and thus there would be a lower F/F factory footprint.
- Lower OpEx: fewer F/F operators, significantly lower WFI consumption (up to 600L per washing cycle on the vial washing machine), lower power consumption (up to 30 KW per tunnel), reduced monitoring of the WFI loop and related QC tests.
- Fewer QA risks on bioburden tests on WFI and on vials' siliconization.
- Shortened F/F processing time.
- Fewer F/F equipment validations/qualifications, and lower maintenance outlays.
- Lower defect rejection rates during transportation to the F/F factory and during filling operations, linked to lower 'glass-to-glass' and lower 'glass-to-metal' contacts (RTU vials are supplied in tubs with nests).

13.9. Annex 09 – F/F factory, in relation to Single Use Systems (SUS)

The pharmaceutical industry is more and more using in their manufacturing operations the Single-Use (SU) systems, instead of stainless steel, multi-use equipment and materials.

The demand for SU items is mostly dictated by the advantages they provide. A comprehensive list can be found in the following table for a fill and finish process[6]:

Table 27 - Comparison between a stainless-steel facility and a single-use system facility

Facility	Traditional stainless-steel Facility	Single-Use Facility
Clean and set-up	14 hrs	<1 hr
Cleaning Validation	Extensive	Zero
Filling Time	24 hrs	10 hrs
Average Vials/hr	3.000	10.000
Aseptic Connections	50	0
Operator Training	2 weeks	2 days
Equipment Utilization	35%	82%
Total Time	38 hrs	12 hrs

Furthermore, SU systems offer the following advantages:

- They can help to keep the process closed.
- There is no cross contamination between different products or batches on the same line. This is especially true for multi-purpose and multi-products plants.

Single-Use items may have higher procurement costs, but they support lower equipment, utilities, and maintenance costs:

- They reduce cleaning & sterilization costs (in terms of equipment and operations).
- They allow savings on water and steam costs for CIP/SIP, lines to bring the water where needed, QC to confirm the CIP, and hold additional vessels during the cleaning process.

Final filling assemblies can be designed to fit process requirements. However, Unizima recommends using 'off-the-shelf' assemblies to allow more than one supplier per item (as this decreases the risk of shortages).

[6] https://bioprocessintl.com/manufacturing/fill-finish/implementing-a-single-use-solution-for-fillfinish-manufacturing-operations-315204/

13.10. Annex 10 - F/F factory, details about the registration process

13.10.1. GMP requirements

The CMO's manufacturing and QC facilities as well as their quality system must meet WHO GMP standards. By the time the facilities are in situ the African Medicines Agency (AMA) may be operational and hence the CMO will have to comply with AMA standards. A site master file (SMF) would need to be prepared.

The manufacturing facility needs to be fully qualified. The manufacturing process would be transferred in a systematic, well-documented manner. Comparability of the product manufactured at the CMO, with that manufactured at the originally licensed sites needs to be demonstrated.

This includes not just standard product release parameters, but also critical process parameters. Statistical tools are typically required to demonstrate comparability. The consistency of manufacturing needs to be demonstrated, usually through three consecutive full scale manufacturing runs. Stability of the vaccines manufactured at the new site needs to be tested. If there are no critical changes to the product configuration (e.g. container type) and no evidence of adverse stability trends, at submission, six months' real time stability data are typically required, with the commitment to submit further data on an ongoing basis.

13.10.2. F/F factory approval process & variation' submission

In general, the role of NRAs is to oversee pharmaceutical manufacturing in their country, to ensure adequate quality of the products made there, and to authorize them for use domestically. As it is assumed that the product transferred is already licensed in the country of origin and will be used more widely, the regulatory authorities in the country of origin and the WHO will play a critical role in the process of technology transfer.

The F/F CMO factory will require a general manufacturing license, which is typically issued by the NRA. The process and timing for obtaining such a license differs between countries. In light of the regulatory harmonization currently underway in Africa, it is possible that vaccines could receive regional marketing authorizations and perhaps even continental-wide approval through the African Medicines Agency which is currently being established in Rwanda.

The addition of a manufacturing site for an approved vaccine requires the submission of a variation, which is classified as 'major'. The review of such applications typically takes 4 to 12 months, depending on the complexity and quality of the data/ dossier. Prior to approval, an inspection of the new CMO site will be carried out. In this case it might be a joint inspection by the WHO and the NRA.

The F/F CMO factory is required to fully comply with the WHO's rigorous GMP standards. This requires a high level of maturity of the organization, which can only be obtained through thorough training, and with strong training / coaching support from highly qualified experts.

An alternative scenario is that the product will receive full marketing authorization across Africa, potentially through a mutual recognition procedure. In that case, local NRAs will grant regulatory approval for the new CMO site.

13.11. Annex 11 – F/F factory, Import Duties on pharmaceutical equipment and products

For most African countries, local manufacturing of pharmaceuticals is a high priority. Investment in this sector is encouraged through incentives.

Therefore, the assumption made in this study is that tariffs on imported pharmaceutical machinery is 0% in most countries and would not impact the F/F factory investment CapEx.

Similarly, the assumption is made that tariffs on imported vaccines (be finished packed vaccines be bulks vaccines) is also 0%.

13.12. Annex 12 – F/F factory, user instructions manual for the financial model ("Five Factories Baseline")

13.12.1. How to select the F/F factories and the F/F lines

To select the F/F factories, go to tab "1.1- Pilot sheet", point "(1) General Assumptions" and click "yes" or "no" next to each F/F factory.

General Assumptions	
	Factory selection
West Factory #1	No
East Factory	Yes
North Factory	No
South Factory	No
West Factory #2	No

To select of the F/F lines for each F/F factory, on the same tab, click "yes" or "no" in front of the four vaccine F/F lines.

West Factory #1	First shift/batch	Shifts/Batches/FD	Second shift/batch
F/F Line nr1-Liquid Vaccines	Yes	2	Yes
F/F Line nr2-Liquid Vaccines	Yes	2	Yes
F/F Line nr3-Oral Vaccines and diluents	Yes	1	No
F/F Line nr4-Freezed dried Vaccines	Yes	2	Yes
F/F Biosimilars	No		No
F/F Insulins	No		No
F/F Parenterals	No		No

Click "yes" to select the F/F of biosimilars; it constitutes additional revenues up to 5 million containers corresponding to the F/F capacities unused by the vaccines. Above this limit, the vaccine volumes should be reduced to allow for larger volumes of biosimilars, in order not to exceed the maximum F/F capacities of glass vials.

Click "yes" to select the F/F of insulins. These F/F volumes must be proportional to the reduction in vaccines' F/F volumes. because of limited glass vials F/F capacities.

Click "yes" to select the F/F of parenterals, whose volumes can be defined up to 43 million BFS tubes, corresponding to the BFS F/F capacities not used by oral vaccines and diluents.

Click "yes" to select a second working shift on the two liquid vaccines F/F lines. Click "yes" to select a second batch per week on the BFS F/F line. Click "yes" to select the second freeze-dryer on the freeze-dried vaccines F/F line.

Note: When F/F factories are set on "no", the selection of F/F lines is automatically deactivated.

13.12.2. How to change the investment CapEx, investment phasing and depreciation time

To change the investment CapEx, go to tab "3.2 CAPEX", select the services, or specific equipment, or the percentages (for CQV, contingencies, transport costs and import duties) and input new costs or percentages.

Note: The changes apply to all factories simultaneously.

To change the CapEx phasing, go to tab "1.2 Pilot sheet details", select the F/F factory (from A to E), select the line "10 CAPEX" and change the start date of the specific investment phase.

To change the depreciation timeline, go to the tab "1.2 Pilot sheet details", select the F/F factory (from A to E), select the line "10 CAPEX" and insert new number(s) for the depreciation years.

CapEx

Equipment	CAPEX budget (In Eur)	Depreciation (Years)	Year
Total Engineering studies costs	830.000	10	31/12/24
Total CapEx F/F Building	6.471.364	20	31/12/24
CapEx filling department_Phase 1	18.343.080	20	31/12/25
CapEx filling department_Phase 2	18.277.000	20	31/12/25
CapEx filling department_Phase 3	14.168.000	10	31/12/25
CapEx filling department_Phase 4	7.238.000	10	31/12/26
CapEx filling department_Phase 5	6.930.000	10	31/12/29
Additionnal CapEx	-	10	31/12/29
Packing department	6.572.160	20	31/12/24
CapEx QC Lab	6.404.720	10	31/12/25
Stores room	2.234.120	10	31/12/24
Cantine	1.879.360	10	31/12/24
Technology Transfer		10	31/12/24
Consistency batches, stability studies & registrations		10	31/12/24
UNZI Project Management during all BUILD phase		10	31/12/24
TOTAL CapEx	89.347.804		

13.12.3. How to change the investment expenses and Tech Transfer costs

To change the investment expenses (Project Management and Tech Transfer support), go to tab "3.5 PM&TT support" and insert new costs.

Note: The changes apply to all factories simultaneously.

To change the Tech Transfer costs, go to tab "3.6 TT Opex" and insert new costs.

Note: The changes apply to all factories simultaneously.

13.12.4. How to change the F/F factory headcounts and salaries

To change the estimated direct/indirect headcounts, go to tab "3.4 OrgChart" to make amendments.

Note: The changes apply to all factories simultaneously.

To change the salaries, go to the same tab "3.4 OrgChart" and change them in the table as shown below. Note: the changes apply to all factories simultaneously.

13.12.5. How to change the F/F factory General & Administration (G&A) costs, and energy costs

To change the estimated G&A costs, go to tab "1.2 Pilot sheet details", select the F/F factory (from A to E), select the item "(11) G&A expenses", select the Filling line (1 to 5), and insert new costs.

To change the estimated energy costs for a specific F/F factory, go to tab "3.7 Energy costs".

G&A Expenses			
Line 1	**Budget (In Eur)**	**Type of Cost**	Yes
Energy	383.688	External services	
Diesel generator	30.000	External services	
Security/admin/ cleaning	75.000	External services	
Maintenance	390.897	Building & Facilities	
Sales/marketing	25.000	Sales & Marketing	
Insurances	25.000	Other operating expenses	
		External services	
		Other operating expenses	
		Other operating expenses	
		Building & Facilities	
		Building & Facilities	
		Building & Facilities	
		External services	
		External services	
TOTAL		**1.153.885**	

13.12.6. How to change the F/F factory raw material costs

Go to tab "3.3 RawMat", select either the glass vials raw materials or the BFS tubes raw materials, select the item(s) Formulation, Filling, Packaging or QC, select the year(s) and insert new costs.

Note: The changes apply to all factories simultaneously.

13.12.7. How to change the F/F volumes

To change the vaccines F/F volume(s), go to tab "3.1 FF volumes", select the F/F factory (from A to E), select the volumes next to the vaccine(s)/year(s) and insert new volumes.

To change the number of doses per container, go to tab "1.2 Pilot sheet details", select the F/F factory (from A to E), select the Filling line (1 to 5), select the vaccine, select "doses per vial", and change the number of doses.

Note: Reducing the number of doses impacts the F/F capacities which is highlighted in the box "Maximum capacity"; should this maximum be reached, the box will turn to red; an additional F/F line could be installed but with a CapEx impact.

13.12.8. How to change the F/F absorption costs and CMO mark-up percentage

To change the F/F absorption costs, go to tab "1.2 Pilot sheet details", select the F/F factory (from A to E), select the Filling line (1 to 5), select the item "A) F/F absorption costs and change the "absorption costs" next to the vaccine(s)/year(s).

To change the CMO mark-up percentage, follow the same steps: select the vaccine(s) and change the "mark-up".

West Factory #1				
F/F line nr1-Liquid Vaccines				
A) F/F absorption costs				
Vaccines (in Eur)	**Total absorption cost**	**Yes/NO**	**Doses per vial**	**Mark-up**
Penta-10-doses vial	1,70	Yes	10	5%
IPV-10 doses vial	1,70	Yes	10	5%
TD-10-doses vial	1,70	Yes	10	5%
PCV-4-doses vial	1,48	Yes	4	5%
Typhoid-5-doses vial	1,48	Yes	5	5%
HPV-1-dose vial	1,18	Yes	5	5%
MR-10-doses vial	1,83	Yes	1	5%
Maximum capacity	**17.472.000**			

13.12.9. How to create a new product and input F/F volumes for new products

To integrate a SKU for biosimilars/mAbs products with annual volumes of up to 5 million glass vials (corresponding to the free capacities on the glass vials F/F lines), go to tab "1.2 Pilot sheet details", select the F/F factory (from A to E), select the item "(5) F/F Line- Biosimilars & mAbs", select the item "B) Volumes (vials)" and insert new volumes in the corresponding year(s). To change the raw material and absorption costs, follow the same steps as described in preceding paragraphs.

To integrate a SKU for insulins, go to tab "1.2 Pilot sheet details", select the F/F factory (from A to E), select the item "(6) F/F Line- Insulins", select the item "B) Volumes (vials)" and insert new volumes in the corresponding year(s). Note: because of limited capacities in the glass vials filling lines, the vaccines F/F volumes would have to be reduced to accommodate insulins volumes, or an additional F/F line should be installed but this would have a CapEx impact.

To integrate a SKU for an outbreak vaccine (such as a COVID-19 or Flu pandemic), follow the same steps as for insulins and reduce the vaccines F/F volumes by the volumes corresponding to the outbreak vaccine. To change the raw materials and absorption costs, follow the same steps as other products.

To integrate a SKU for parenterals in BFS, go to tab "1.2 Pilot sheet details", select the F/F factory (from A to E), select the item "(7) F/F Line- Parenterals", select the item "B) Volumes (vials)" and insert new volumes in the corresponding year(s). To change the raw materials and absorption costs, follow the same steps as other products.

To integrate a SKU for a new injectable vaccine in BFS, follow the same steps as for parenterals. Note: the total F/F volumes of parenterals and injectable vaccines in BFS should not exceed the free F/F capacities on the BFS F/F line which has been estimated at about 43 million BFS tubes.

13.12.10. How to change the taxes, import duties and inflation parameters

To integrate the potential taxes to be paid by the F/F factory, go to tab "2.1 FinPlan", select line nr 191 "Taxes", and insert the estimated percentage.

To integrate the potential import duties on the equipment for the F/F factory investment, go to tab "3.2 CAPEX", select the line 33 "Import duties" and insert the estimated percentage.

To integrate the inflation costs into the financial model, go to tab "1.2 Pilot sheet", select the line 65 "Inflation per year" and insert the estimated percentage.

13.12.11. How to change the WACC parameters

To change the WACC parameters, go to tab "1.2 Pilot sheet details", select the F/F factory (from A to E), select the item "(12) Financing". In this section, you will find two subsections, one for the CapEx financing needs and one for the OpEx financing needs.

To adjust the total WACC, you can:

(I) increase/decrease the weight (blue percentage) of the debt in the total financing;

(II) increase/decrease the debt interest;

(III) increase/decrease the cost of equity.

You can adjust the two financing structures independently. At the end of the section, you will find a summary of the debt/equity weighting and their costs.

To change the OpEx financing percentage, follow the same steps, but select item "B Total financing needs for OPEX", and insert a new percentage.

To change the OpEx financing amount, follow the same steps, select the item "Total need (In Eur)", and insert a new amount. Then increase/decrease the debt/equity ratio according to your requirements.

13.13. Annex 13 – F/F factory, how to execute the financial simulations from the baseline financial model

- Refer to the 8 Excel files, each corresponding to one simulation; go to tab "1.2 Pilot sheet details", read the "instructions to user for the simulation" on the top right corner.

2023-04-17-GIZ-FiveFactories-Simulation1-Vaccines-18%.xlsx

2023-04-17-GIZ-FiveFactories-Simulation2-OneYearDelay.xlsx

2023-04-17-GIZ-FiveFactories-Simulation3-NoLyoVaccines.xlsx

2023-04-17-GIZ-FiveFactories-Simulation4-Salaries+20%.xlsx

2023-04-17-GIZ-FiveFactories-Simulation5-Energy%.xlsx

2023-04-17-GIZ-FiveFactories-Simulation6-FillRawMat-10%.xlsx

2023-04-17-GIZ-FiveFactories-Simulation7-Capex-15%.xlsx

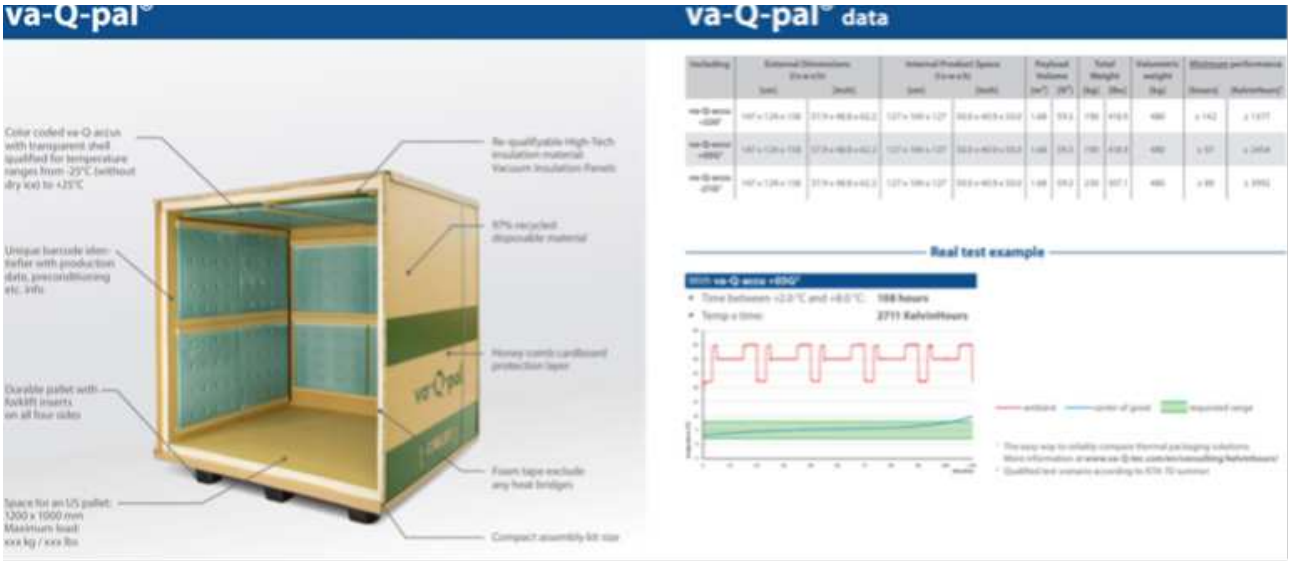
2023-04-17-GIZ-FiveFactories-Simulation8-NewBFS.xlsx

	Vaccines F/F factories - Key financial parameters	Baseline 5 factories: 332m EUR Capex, 280m containers - 1 factory: 89m EUR Capex, 80m containers	Simulation 1 Vaccines volumes down by about 18% (no HIV and MenCWY) 5 factories: 332m EUR Capex, 240m containers - 1 factory: 89m EUR Capex, 68m containers	Simulation 2 Project implementation extended by one year same as baseline	Simulation 3 No freeze-dried vaccines 5 factories: 261m EUR Capex, 250m containers - 1 factory: 75m EUR Capex, 72m containers	Simulation 4 HC and/or salaries costs increased by 20% same as baseline	Simulation 5 Energy costs increased by +50% same as baseline	Simulation 6 vials filling raw materials costs decreased by -10% same as baseline	Simulation 7 Process equipment costs down by 15% 5 factories: 296m EUR Capex, 280m containers - 1 factory: 80m EUR Capex, 80m containers	Simulation 8 Liquid injectable vaccines in multi-doses BFS tubes 5 factories: 357m EUR Capex, 240m containers - 1 factory: 97m EUR Capex, 80m containers
5 factories	NPV (6x EBITDA) - K EUR	28.028	(19.134)	1.880	31.395	(3.892)	17.828	62.367	38.702	35.905
East		449	(13.590)	(6.708)	3.736	(9.737)	(3.993)	9.849	3.689	3.078
West nr2		14.301	2.673	7.713	13.376	6.685	13.172	23.695	16.898	17.386
5 factories	Profitable from - Year	2031	2031	2031	2031	2031	2031	2030	2031	2031
East		2031	2032	2031	2031	2031	2031	2030	2031	2031
West nr2		2029	2031	2029	2029	2030	2030	2029	2029	2029
5 factories	Cumulated free cash flow in Y2040 - K EUR	204.161	64.010	148.312	174.765	132.283	177.620	278.034	214.657	219.437
East		42.249	1.028	27.272	41.237	19.238	30.864	64.045	47.976	47.518
West nr2		75.595	45.580	63.819	66.241	63.118	74.706	101.521	80.146	83.766
5 factories	TV	321.432	255.709	321.432	335.970	300.545	306.565	417.247	327.841	
East		89.075	68.814	89.075	92.352	82.233	82.453	112.914	90.357	
West nr2		106.534	86.170	106.534	109.501	100.562	104.958	132.420	107.816	
5 factories	IRR - %	14,48%	9,31%	11,67%	15,75%	11,12%	13,36%	18,26%	15,94%	15,47%
East		11,48%	6,51%	9,36%	12,85%	8,42%	10,06%	14,48%	12,58%	12,33%
West nr2		17,44%	12,95%	14,52%	18,79%	14,16%	16,91%	21,07%	18,85%	18,94%
5 factories	Pay-back period - Years	15	17	16	14	16	15	13	14	14
East		16	18	17	15	17	16	14	15	15
West nr2		13	15	14	13	14	13	12	13	13

13.14. Annex 14 – F/F factory, details about the cold-chain shipment costs of imported finished packed vaccines from India to Africa

13.14.1. Budget quotation from Biocair company for (transport 1) air shipment under +2+8°C cold chain from India to Africa.

See quotation documents in attachment.



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BACKUP Health
Dag-Hammarskjöld-Weg 1-5
65760 Eschborn / Germany
Phone + 49 6196 79- 1080
backup@giz.de
www.giz.de/backup

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