Concerns: Solving the bottleneck in single-use bioreactor supply for vaccine production –Getinge | Applikon
Date: 14-3-2021
Status: Final 1.0
To: 5.1.2e (special envoy vaccines Dutch Ministry Health)
Cc: 5.1.2e (MINEZK)
By: Getinge | Applikon "EUROWARP" team
Contact: 5.1.2e

Introduction

On March 5th, 2021 the Applikon (NL) site of Getinge (SE) was approached with a "request for help" from the Dutch special envoy vaccines regarding bottlenecks that are being observed in the production of Vaccines, both in The Netherlands as well as in other European countries. In an exploratory meeting on March 6th it quickly became clear that one of the bottlenecks concerned the lack of Single Use Bioreactor bags (SUBs), which are commonly used in the upstream cultivation processes of vaccine manufacturers to produce raw active ingredients for the vaccines. Getinge | Applikon expressed their strong commitment to investigate what actions could be taken by them and their supply chain to try and alleviate this particular bottleneck. This proposal is the outline of actions that could be taken based on the first week of addressing this topic by a task force assembled within the Getinge | Applikon organization.

Explorative research

Relevant background from report "Towards Vaccinating The World" dated March 9th, 2021:

"Bioreactor assemblies are used for cell culture and fermentation, to produce biologicals in vaccine production. Bioreactors are available in single-use (bags, disposed after use) format and in multi-use (stainless steel) format. Single-use assemblies consist of plastic components that are used in diverse bioprocessing steps (e.g. tubing). Depending on the pandemic outbreak vaccines can be produced using micro-organisms or mammalian cells. These two production methods require different design of the cultivation systems. Single-Use systems are more flexible when switching between production platforms since they allow fast and easy changes of mixing and aeration systems.

These single-use components however show signals of potential supply challenges during pandemic outbreaks. Supply chains are challenged to manage the sudden increase in demand of single use components which are subject to export controls of local governments. This in combination with the increase of safety stock by vaccine producers to guarantee availability of production means, and the lack of interchangeability of single use components between different suppliers, can be limiting production capacity in times of pandemics.

In general, bioreactor bags can be substituted by stainless steel; this, however, takes 6-12 months taking into consideration order lead times and validation. Stainless teel systems have the advantage that no single-use bags are needed for production, so this specific single-use supply challenge is eliminated."

We conducted a market survey in European countries interviewing potential (covid) vaccine producers identified through via the "covid tracker" and based on our local contacts and market know-how in these countries.

During our market survey we found that currently lead times for single-use bioreactors have increased from approx. 12 weeks to 9 – 12 months. It seems like local (national US) vaccine producers claim priority delivery under the "defense priority allocation" act in the USA, leaving non-USA targeted producers with hampered production capacity. Also other biologicals and vaccines will be on short supply in the near and further future due to the lack of production means since everything is being claimed for Covid vaccine development. European producers seem to have sufficient skilled personnel and qualified facilities, but basic materials are lacking (bags, media etc.). There is also no known local "European only" supply chain for these single-use systems.

Information received from potential producers is limited since they do not want to spread information about their (potential) bottlenecks in production, unless the bottleneck is already causing serious problems.

For details see Annex 1 with the summarized outcome of the contacts made.

Getinge | Applikon proposed activities to supply vaccine production equipment

Activity	Investment	Timeline*
REGARDING SINGLE USE BIOREACTOR SUPPLY:		
Finalize Single-Use Production Bioreactor development and produce first series (in partnership with Saint-Gobain and Vaccine Producers)	4.6 M€	6-9 months
Setup Single-Use Production Bioreactor bag production (in cleanroom)	2.1 M€	12-15 months
Production of Single-Use Bioreactors 5000x50L, 3000x250L, 2000x1000L	73.0 M€	6-15 months
REGARDING ALTERNATIVE MULTI USE BIOREACTOR SUPPLY:		
Produce Multi-Use Bioreactor systems (15 systems + CIP)	5.4 M€	5-11 months

**Timelines mentioned are the range between first validated end-products leaving the factory and end of ramp up period*

What Getinge | Applikon needs to successfully complete these activities

Getinge | Applikon is and will be investing into the above-mentioned developments since it is part of our core business, providing bioreactor systems capacity worldwide. However, such investment taking purely from a business perspective would be done sequentially and in the course of several years. Getinge | Applikon is certainly willing to carry part of the investments on its own account. The current need however, asks for a parallel and much more intensified approach, where inherently much more risks are taken. We therefore ask for support on the following:

1) Priority in supply (both in material as in manpower, customs support/transport)

- A statement of urgency from governmental level would provide strong support

2) Security and support for the investments made

- Can some sort of "purchase security" be given for the products manufactured?

Detailed plan

The plan as presented on the previous pages will now be further detailed.

Market Research

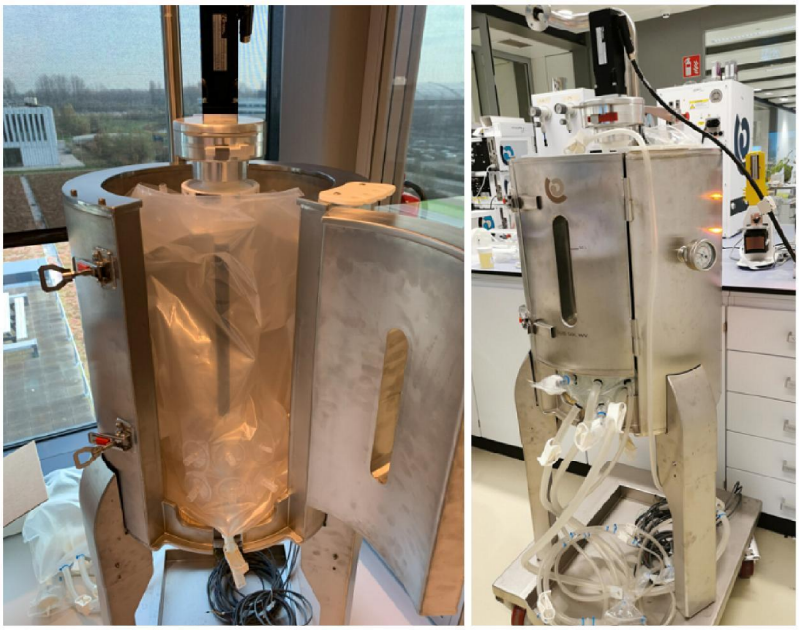
The main difficulty in the further market research is getting details on the exact configurations of the single use bioreactors and other process equipment requirements that the vaccine producers need. Since the variation in the equipment used is very high it is important to consolidate these needs and focus the development activities and supply chain scale up on these exact configurations as much as possible. However, vaccine producers are very hesitant to provide such detailed information on their processes. It would help if a generic structure is put in place on a European level that provides protection to the vaccine producers that do provide such information.

Working intimately together with several vaccine producers in the development of the SUBs is crucial for achieving the timelines mentioned above.

Single-Use Production Bioreactor Systems development and production

Since 2018, Applikon has been working on the development of a design and a supply chain for single-use bioreactor systems for drug and vaccine production. This 'SUPR' project (abbreviation of Single-Use Production Reactors), has been intensified when Applikon was acquired by Getinge (on the first of January, 2020). Getinge has decades of experience in manufacturing single-use sterile transfer bags that are used in fill finish lines for vaccine production. These sterile transfer bags are manufactured in clean rooms, with similar techniques as used for manufacturing the bags for SUPR systems.

At the end of 2020, through a partnership with Saint-Gobain, Getinge | Applikon completed the proof of concept of the SUPR system:

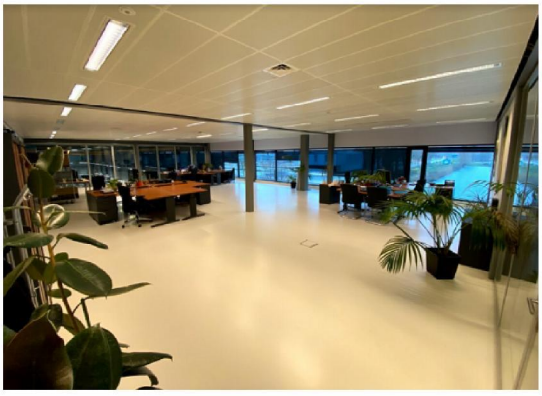


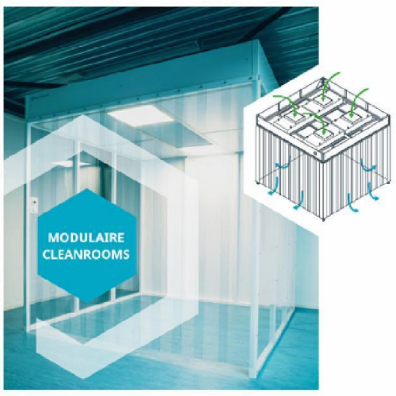
To help alleviate bottlenecks in the European vaccine production, Getinge | Applikon has created a plan to speed-up the SUPR project through the following activities:

1. Finalize SUPR design and produce first series.
   To complete this activity as quickly as possible, Getinge | Applikon will partner directly with vaccine producers to focus the development towards the most needed configuration. We will leverage our existing partnership with Saint-Gobain, a French company with bioreactor bag production facilities in the USA and China. We already have verbal confirmation that they are willing to produce the first series of the SUPR bags as quickly as possible, and we are working on written agreements with them. Validation and qualification of the first series of SUPR bags will be done in close cooperation with Saint-Gobain and the vaccine producers, such that the first series systems will be operational as quickly as possible.
   We expect this activity to be completed in 6-9 months, and to require a total investment of 4.6 M€.

SUPR Activity 1: Finalize design and produce first series	**Qty, Hours, m2**	**Rate**	**Costs**
Engineering			
Finalize 50L design drawings (holder and bag)	150	€ 150	€ 22,500
Make 250L design drawings (holder and bag)	300	€ 150	€ 45,000
Make 1000L design drawings (holder and bag)	300	€ 150	€ 45,000
Subtotal	**750**		**€ 112,500**
Prototypes			
50L holder	5	€ 80,000	€ 400,000
Controller for with 50L proto's	5	€ 105,000	€ 525,000
50L prototype bags	25	€ 6,000	€ 150,000
250L holder	5	€ 110,000	€ 550,000
Controller for with 250L proto's	5	€ 110,000	€ 550,000
250L prototype bags	25	€ 7,000	€ 175,000
1000L holder	5	€ 150,000	€ 750,000
Controller for with 1000L proto's	5	€ 115,000	€ 575,000
1000L prototype bags	25	€ 11,000	€ 275,000
Production Support (to achieve faster realization)	200	€ 150	€ 30,000
Subtotal			**€ 3,980,000**
Validation			
Consumables for testing (gas, media, etc..)			€ 15,000
Test 50L	150	€ 150	€ 22,500
Test 250L	100	€ 150	€ 15,000
Test 1000L	100	€ 150	€ 15,000
Qualification studies	3	€ 150,000	€ 450,000
Subtotal			**€ 517,500**
Total			**€ 4,610,000**

2. Setup SUPR bag production
   To guarantee supply of SUPR bags to the European market, Getinge | Applikon is developing cleanroom production capabilities. In our building in Delft, The Netherlands, we have ca. 150 m^2 office space, that could quickly be turned into a ca. 110 m^2 cleanroom by using modular cleanroom components (from the Dutch company ProCleanroom):





The 110 m^2 cleanroom will be sufficient to produce 5000-10000 SUPR bags per year, of different sizes and configurations.
We expect activity 2 to be completed in 12-15 months, and to require a total investment of 2.1 M€.

SUPR Activity 2: Setup bag production	**Qty, Hours, m2**	**Rate**	**Costs**
3D Printer	1	€ 450,000	€ 450,000
Cleanroom	110	€ 2,000	€ 220,000
Qualification of the Cleanroom	1	€ 50,000	€ 50,000
Washing equipment (to clean material entering the clean room)			€ 200,000
Furniture			€ 30,000
Construction work to fit cleanroom in the building			€ 50,000
Fire protection			€ 50,000
Film cutting (CNC cutter?) and bag welding equipment			€ 300,000
Project hours	5000	€ 150	€ 750,000
Subtotal			**€ 2,100,000**

Production and installation of multi-use stainless steel bioreactor systems

Getinge | Applikon has over 20 years of experience and knowledge in the design and supply of multi-use bioreactor systems for upstream bioprocessing. A broad range of cell types and organisms can be cultivated in these bioreactors and fermentors and the come in various sizes for cultures of a few milliliters to thousands of liters.

Production systems are generally built to customer specifications and these turnkey systems include the custom designed bioreactors, automated control and supervisory control software.

Getinge | Applikon also designs associated automated clean-in-place systems (CIP). Liquid flows, pressure, temperatures, and cleaning agents are designed for optimal cleaning of the systems involved.

By installing multi-use stainless steel bioreactor systems, the vaccine production capacity will increase on short-term. Even more important, vaccine producers are no longer dependent on the few specific bioreactor bag manufacturers and bottlenecks in their supply chain. Production is secured.

Getinge | Applikon can supply “Standard” stainless steel production systems. These predesigned systems will be engineered and manufactured at our facility in Delft and with help of our know and validated partners all located in the Netherlands.

Engineering Phase	**Qty, Hours**	**Rate**	**Investment**
Define config.	120	€ 150	€ 18,000
Finalize 70L with Procontrol	200	€ 150	€ 30,000
Finalize 270L with Procontrol	200	€ 150	€ 30,000
Standardize 1000L with Procontrol	1000	€ 150	€ 150,000
Mobile CIP unit development	640	€ 150	€ 96,000
Automation Engineering	900	€ 150	€ 135,000
Project Management	600	€ 150	€ 90,000
Subtotal			**€ 549,000**
Production / Verification Phase			
70L Systems with Procontrol (2 Pcs)	600	€ 100	€ 60,000
140L System with Procontrol (3 Pcs)	1200	€ 100	€ 120,000
270L Systems with Procontrol (5 Pcs)	2250	€ 100	€ 225,000
1000L Systems with Procontrol (5 Pcs)	4000	€ 100	€ 400,000
Mobile CIP (5 Pcs)	375	€ 100	€ 37,500
Production organization (3,5 fte)	5600	€ 100	€ 560,000

Subtotal			**€ 1,402,500**
Material cost			
70L Systems with Procontrol	2	€ 153,501	€ 307,003
140L Systems with Procontrol	3	€ 171,429	€ 514,286
270L Systems with Procontrol	5	€ 198,711	€ 993,554
1000L Systems with Procontrol	5	€ 315,645	€ 1,578,223
Mobile CIP	5	€ 22,940	€ 114,699
Subtotal			**€ 3,507,766**
Total Investment			**€ 5,459,266**

Planning: Engineering-Production Multi-Use Stainless steel systems.