

Concerns: Solving the bottleneck in single-use bioreactor supply for vaccine production
 –Getinge | Applikon
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 Cc: 5.1.2e (MINEZK)
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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 were taken in the past months and that could be taken within the Dutch 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 steel 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.

The urgent problems caused by a failing supply of “single-use” bioreactors are rapidly becoming clear. When we approached producers of vaccines through our (sales)channels in the first half of March 2021 already various companies shared their acute needs with us. Examples were the companies Curevac (GE), Bioconnection (NL), AdaptVac (DK) and various producers of vaccines 5.1.2a Where in the first half of March 2021 a number of parties, at least to us, were still adamantly stating that they did not have any problems, they now clearly indicate that they are having problems in their bioreactor supplies. Examples of these are Wacker (NL, Otto Stapel, Purchaser), Johnson & Johnson (SUI, Nicole Hsu, Senior Sourcing Manager) or Laboratorios Hipra (ES, Raúl Soler, Supply Chain Director).

Getinge | Applikon proposed activities to supply vaccine production equipment

Two routes are proposed to alleviate the supply chain problems with “single-use” bioreactors:

- 1) Focusing on “single-use” bioreactor supply by providing Applikon “single-use” bioreactor systems and setting up a production facility for this in Delft, using mainly Applikon’s existing supply chain in The Netherlands.
- 2) Providing “multi-use” bioreactor systems, by constructing these based on the existing stainless steel product portfolio of Applikon to create production capacity independent of “single-use” components altogether.

Activity	Investment / Business risk (2021+2022)	Timeline*
REGARDING SINGLE USE BIOREACTOR SUPPLY:		
1) Single-Use Production Bioreactor development and produce first series (in partnership with Vaccine Producers)	5.1.1c	6-9 months
2) Setup Single-Use Production Bioreactor bag production (in cleanroom)		12-15 months
3) Production of Single-Use Bioreactors 5000x50L, 3000x250L, 2000x1000L (excl. first series)		6-15 months
REGARDING ALTERNATIVE MULTI USE BIOREACTOR SUPPLY:		
4) Produce Multi-Use Bioreactor systems (15 systems + CIP)		5-11 months

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

***These are sellable products for which a business risk is taken beyond the normal business risk in order to shorten the timeline for supply*

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. Since the need for the single-use bioreactors has become so pronounced we have already prioritized our development activities in this area and proceeded with higher intensity than before. However, such investment taking purely from a business perspective would be done sequentially and in the course of several years (refer to chapter on business risk comparison below for further details). 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?

Business risk comparison with and without “Euowarp”

Getinge | Applikon's normal approach to development of its SUPR product portfolio would be a stepwise approach, first introducing the smallest volume systems, using these to gather market experience and then scale up to larger volumes. Also in the first phases Applikon would not be investing immediately into setting up its own production capacity, but in stead would largely rely on external suppliers. This approach in the first 2 years would lead to an expected total cash out exposure of around 5.1.1c

5.1.1c

By implementing the Euowarp acceleration the expected total cash out exposure in the first two years would increase from 5.1.1c. This goes well beyond the normal investment risk the company is willing to take without having some sort of security on the revenues from the market:

5.1.1c

The above business risk comparison does not include the effect of the multi-use systems production, which carries an additional exposure of around 5.1.1c if done in parrallel.

Economical impact for The Netherlands

Applikon's supply chain for almost all its instrumentation components resides in The Netherlands. Only certain raw-materials, like the bag films or tubing materials will be sourced internationally, albeit from within the EU. These materials amount to less than 10% of the total product value. Given Applikon's targeted result before taxes of 15% of revenues this leaves around 75% of the extra net sales revenues having a direct contribution to the Dutch economy. Already in the first two years the Eurowarp project would bring around 5.1.1c in added value to the Dutch economy, the equivalent of around 1000 person years.

Detailed plan

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

Market Research

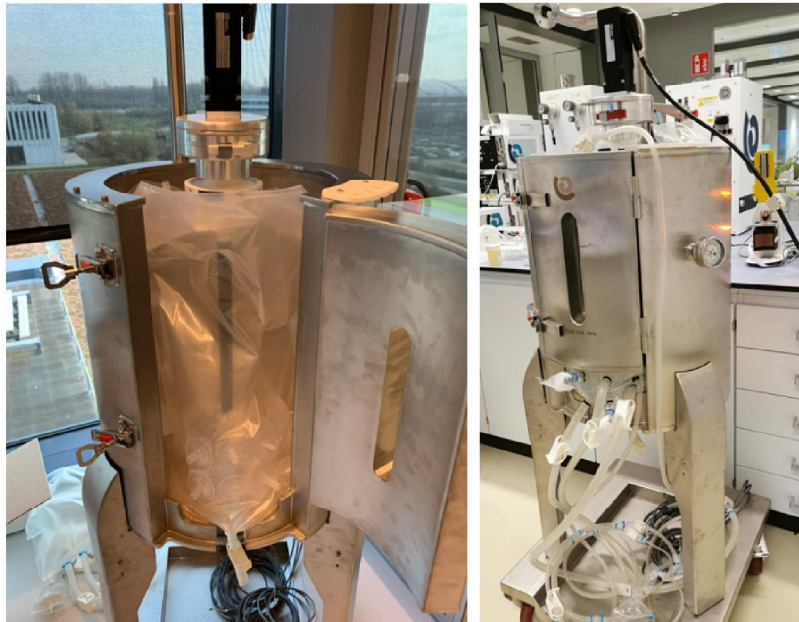
The main difficulty in the further market research is getting details on the exact configurations of the single use bioreactors and other process equipment requirements that the vaccine producers need. Since the variation in the equipment used is very high it is important to consolidate these needs and 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:



Visualization of 250L scale up design (+50L of which prototype is shown above)

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 5.1.2e

5.1.2e

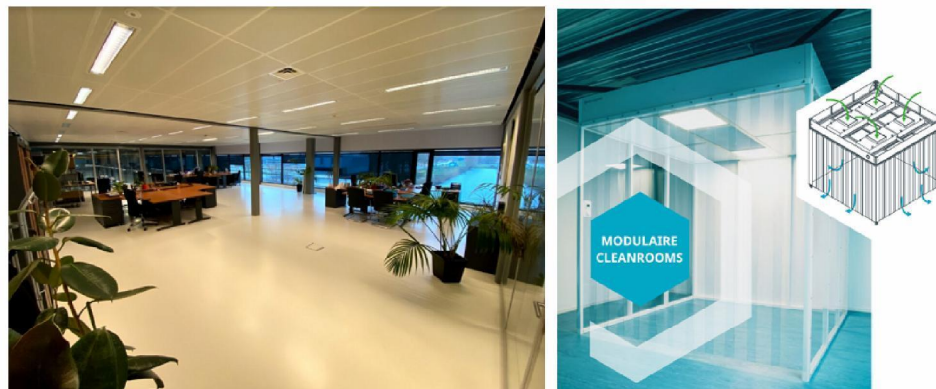
5.1.1c

2.

3. 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 m² office space, that could quickly be turned into a ca. 110 m² cleanroom by using modular cleanroom components (from the Dutch company ProCleanroom):

4.



5.

6.

The 110 m² 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

5.1.1c

SUPR Activity 2: Setup bag production	Qty, Hours, m2	5.1.1c
3D Printer	1	
Cleanroom	110	
Qualification of the Cleanroom	1	
Washing equipment (to clean material entering the clean room)		
Furniture		
Construction work to fit cleanroom in the building		
Fire protection		
Film cutting (CNC cutter?) and bag welding equipment		
Project hours	5000	
Subtotal		

7. SUPR system production

The production of the single-use bioreactor systems involves both the construction of the “holders” for the bags and the measurement & control instrumentation (together the “bundles”) as well the manufacturing of the single-use bioreactors. An overview of the business case including the acceleration according to this Eurowarp proposal is given below. The total expenses and cost of goods (potentially) sold associated with the SUPR system production over the years 2021 + 2022 cumulates to around 5.1.1c

5.1.1c

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 they 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.

5.1.1c