PROCESS MODELLING AND DEBOTTLENECKING STUDY OF A VACCINE PRODUCTION

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ABSTRACT: The main objective of this research work was to model and optimise the production of a locally-developed Infectious Coryza (IC) vaccine. The simulation work was performed using a commercially available batch process simulator SuperPro Designer v5.5. Six debottlenecking schemes were analysed using throughput analysis and cost to benefit ratio (CBR) when the annual production was set to increase by 100%. Based on the economic analysis, the selected debottlenecking scheme has an annual predicted revenue of USD 240 million, with a gross margin of 9.13% and a return on investment (ROI) of 46.12%. In addition, the payback period of the selected scheme is estimated to be within three years.

ABSTRAK: Objektif utama dalam penyelidikan ini adalah untuk memodelkan dan mengoptimumkan hasil pembuatan vaksin tempatan *Coryza* berjangkit. Kerja simulasi ini dijalankan menggunakan alat simulasi *Super Pro Designer v5.5*. Sebanyak enam (6) skema khusus diujikaji menggunakan analisis pemprosesan dan kos kepada nisbah faedah (CBR) apabila pembuatan tahunan meningkat kepada 100%. Berdasarkan analisis ekonomi yang telah dilakukan, sesuatu skema khusus yang dipilih mempunyai keuntungan sebanyak USD 240 juta dengan margin kasar 9.13% dan pulangan atas pelaburan (ROI) sebanyak 46.12%. Selain itu juga, tempoh pembayaran balik bagi skema yang dipilih dianggarkan dalam tempoh tiga(3) tahun.

KEYWORDS: *process simulation; modelling; debottlenecking; optimisation*

1. INTRODUCTION

Malaysia is one of the countries with the highest chicken consumption per capita in the world at 32 kg. Some of the reasons for high chicken consumption are that chicken consumption is not against dietary prohibition or religious restrictions and chicken meat is a very low cost meat source in the country Malaysia Poultry and Products Annual 2006, 2006). Therefore, the poultry industry in Malaysia has grown from a backyard-type operation into a commercialised system in last 30 years. Due to the rapid grow of the poultry industry, the poultry diseases has poses a threat to the viability and productivity of poultry farming.

Infectious Coryza (IC) disease is identified as one of the curses in the poultry industry worldwide [1]. IC is an acute respiratory disease of chickens which is caused by the bacterium known as *Haemophilus paragallinarum* (*Hpg*) [2]. Chickens of all ages are susceptible to this type of disease. Once the chickens are infected by this disease, the chickens get swollen eyes and nose, foul smelling discharges and sneezing. Besides, the chickens' feed and water intake are reduced significantly which eventually leads to weight lost and lower production of egg [3].

In order to prevent this disease, the breeders in Malaysia normally administer vaccine which is imported from USA or Japan to the chickens [3]. However, the imported vaccines do not cure the infected chickens because the emergence of variant local strains of *Hpg* in the flocks [4]. In addition, the genetic makeup of local *Hpg* strains is different from the standard *Hpg* strains in the imported vaccines [5]. Hence, producing IC vaccine from the local *Hpg* strains is a better option to alleviate the IC disease problems in Malaysia [6]. With an effective local-made IC vaccine, the dependency of Malaysian breeders on the imported vaccines will be reduced.

Process modelling and simulation in pharmaceutical industries functions as methodologies and tools that can be used to evaluate alternatives and speed up the development effort which may immensely impact on the bottom line [7]. With the given production capacity, modeling and simulation tool such as SuperPro Designer can be used to design and predict the feasibility of different production schemes [8]. For instance, Kumaresan et al. presented an approach to model and optimise Tongkat Ali extract process via SuperPro Designer [8]. Based on the study, a base case was first generated on the overall process and then debottlenecking strategies were proposed [8]. Besides that, detail economic analysis was also conducted.

Based on the similar approach, modelling of IC vaccine production using the batch process simulation tool SuperPro Designer v5.5 is presented in this work. Due to the production capacity is limited by the current operating condition and equipment setup, debottlenecking study is performed to increase in annual production. Preliminary economic analysis is preformed to compare the debottlenecking schemes.

Figure 1 shows the process flowsheet for a typical IC vaccine production designed with SuperPro Designer v5.5. The specifications for the major equipments used in the IC vaccine production are shown in Table 1. In order to produce IC vaccine through fermentation process, the bacteria *Hpg* is first prepared and transferred from a freezer (-80°C) into a sterilized shake flask (P-1/SFR-101) contains media (nutrient and water). Note that the preparation of *Hpg* bacteria is excluded in this work. After 10 hours of pre-fermentation, the cultures were transferred to a 3 L seed fermentor (V-101), followed by a 30 L fermentor (V-103) and 300 L fermentor (V-104)., where the fermentation process is continued (see Fig. 1). It is worth mentioning that the media for the fermentation processes was pre-prepared in a media blending tank (V-102), and sterilized (in P-4 and P-6/ST-101) before it was transferred to the fermentors (V-103 and V-104) with the feed ratio of ten folds of the cultures feed.

2. INFECTIOUS CORYZA (IC) VACCINE PRODUCTION

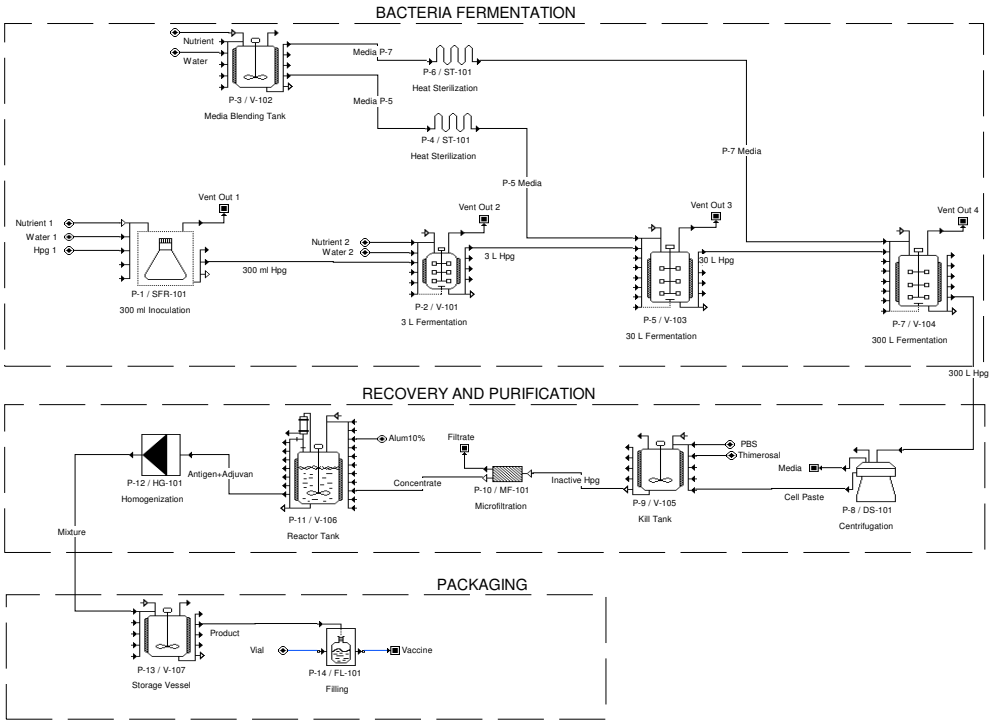

Fig. 1 Process flowsheet of IC vaccine production (base case).

Table 1: Major equipment specification for IC vaccine production.

Quantity	Procedure/ Equipment	Specification
Fermentation Section		
1	P-1/SFR-101	Volume = 500 ml
1	P-2/V-101	Volume = 5 L
1	P-3/V-102	Volume = 330 L
1	P-4/ST-101	Rated throughput of 1080 L/h (Calculated based on design mode)
1	P-5/V-103	Volume = 50 L
1	P-6/ST-101	Rated throughput of 1080 L/h (Calculated based on design mode)
1	P-7/V-104	Volume = 500 L
Recovery and Purification Section		
1	P-8/DS-101	Based on Sigma factor 39627.55 m^2 (Calculated based on design mode)
1	P-9/V-105	Volume = 107.88 L (Calculated based on design mode)
1	P-10/MF-101	0.45 µm membrane pore size
1	P-11/V-106	Volume = 77.96 L (Calculated based on design mode)
1	P-12/HG-101	Pumping efficiency of 70 %
Packaging Section		
1	P-13/V-107	Volume = 77.94 L (Calculated based on design mode)
1	P-14/FL-101	3000 entities/h (Calculated based on design mode)

After the fermentation process, the cultures were harvested using a centrifuge (DS-101) and transferred to a kill tank (V-105) where the cultures were deactivated by adding thimerosal and phosphate buffer saline (PBS) [10]. Next, the cultures were further concentrated by passing it through a microfiltration membrane (MF-101) with pore size of 0.45 μm and 99.7% removal efficiency, before it was being transferred to a reactor tank (V-106) [11]. Alum 10%, which acts as an adjuvant, was used an aid to the vaccine [12]. The adjuvant and antigen were homogenized in a homogenizer (HG-101) to ensure the same size particles. The mixture from the homogenizer was the final product and it was stored in a storage vessel (V-107) before it was sent for packing in filling machine (FL-101).Tables 2 and 3 summarise the process scheduling (SUT: setup time; PT: process time; ST: start time) for each unit operation and the details of the raw materials (amount; price) in the IC vaccine production.

3. BOTTLENECK IDENTIFICATION STRATEGIES

Based on the given information (Tables 1 – 3) and flowsheet in Fig.1, the process simulation of the based case is solved. The capital investment of the base case and the cost of production per unit are estimated as $18 million and $104.91, respectively. Based on the selling of $115 per unit, the annual revenue is computed as $123 million with 2.51 years of payback period.

Table 2: Scheduling summary for operations and procedures in the base case model.

Procedure/ Equipment	Operation	SUT (mins)	PT	ST
P-1/SFR-101	Charge Nutrient 1	-	5 mins	Beginning of batch
	Charge Water 1	-	3 mins	After Nutrient 1 charge
	Agitation	-	5 mins	After Water 1 charge
	Charge *Hpg* 1	-	3 mins	After Agitation
	Fermentation	-	10 hours	After Hpg 1 charge
	Transfer out 300 mL *Hpg* to P-2	-	3 mins	After Fermentation
P-2/V-101	Charge Nutrient 2	-	5 mins	After 12 hours of batch operation
	Charge Water 2	-	3 mins	After Nutrient 2 charge
	Agitation	-	8.4 mins	After Water 2 charge
	Transfer in 300 mL *Hpg* from P-1	-	Master-Slave with P-1 Transfer Out 300 mL Hpg	Starts with Transfer 300 ml in P-1 (to P-2)
	Fermentation	-	6 hours	After Transfer in 300 mL *Hpg* from P-1
	Transfer out 3 L *Hpg* to P-5	-	3 mins	After Fermentation
	CIP	-	15 mins	After Transfer out to P-3

Table 3 (Continued): Scheduling summary for operations and procedures in the base case model.

Procedure/ Equipment	Operation	SUT (mins)	PT	ST
P-3/V-102	Charge Nutrient	20	Calculated based on 600 L/h volumetric flowrate	After 14.3 hours of batch operation
	Charge Water	20	Calculated based on 600 L/h volumetric flowrate	After Charge Nutrient
	Agitation	-	10 mins	After Charge Water
	Transfer Out Media P-5 to P-4	20	Calculated based on 600 L/h volumetric flowrate	After Agitation
	Store	-	4.66 hours	After Transfer Out Media P-5
	Transfer Out Media P-7 to P-6	20	Calculated based on 600 L/h volumetric flowrate	After Store
	CIP	-	15 mins	After Transfer Out Media P-7
P-4/ST-101	Sterilize	-	15 mins	Starts with Transfer Out Media P-5 in P-3 (to P-4)
P-5/V-103	Transfer In Media P-5 from P-4	20	Calculated based on 600 L/h volumetric flowrate	After Sterilize in P-4
	Transfer In 3 L *Hpg* from P-2	-	Master Slave with P-2 Transfer Out 3 L *Hpg*	Starts with Transfer Out 3 L *Hpg* in P-2 (to P-5)
	Fermentation	-	5 hours	After Transfer In 3 L *Hpg*
	Transfer Out 30 L *Hpg* to P-7	20	Calculated based on 600 L/h volumetric flowrate	After Fermentation
	CIP	-	15 mins	After Transfer Out 30 L Hpg
P-6/ST-101	Sterilize	-	15 mins	Starts with Transfer Out Media P-7 in P-3 (to P-6)
P-7/V-104	Transfer In Media P-7 from P-6	20	Calculated based on 600 L/h volumetric flowrate	After Sterilize in P-6
	Transfer In 30 L *Hpg* from P-5	-	Master Slave with P-5 Transfer Out 30 L *Hpg*	Starts with Transfer Out 30 L *Hpg* in P-5 (to P-7)
	Fermentation	-	4.5 hours	After Transfer In 30 L *Hpg*
	Transfer Out Broth to P-8	-	Master Slave with P-8 Centrifuge	After Fermentation
	CIP	-	15 mins	After Transfer Out Broth

Table 4 (Continued): Scheduling summary for operations and procedures in the base case model.

Procedure/ Equipment	Operation	SUT (mins)	PT	ST
P-8/DS-101	Centrifuge	-	60 mins	Starts with Transfer Out Broth in P-7 (to P-8)
	CIP	-	15 mins	After Centrifuge
P-9/V-105	Transfer In Cell Paste from P-8	-	Master Slave with P-8 Centrifuge	Starts with Centrifuge in P-8
	Charge PBS	-	Calculated based on 600 L/h flow rate	After Transfer In Cell Paste
	Agitation	-	10 mins	After Charge PBS
	Charge Thimerosal	-	Calculated based on 600 L/h flow rate	After Agitation
	Agitation	-	15 mins	After Charge Thimerosal
	Transfer out Inactive *Hpg* to P-10	20	Calculated based on 600 L/h flow rate	After Agitation
	CIP	-	15 mins	After Transfer Out Inactive Hpg to P-10
P-10/MF-101	Filtration	-	120 mins	Starts with Transfer Out Inactive *Hpg* in P-9 (to P-10)
	CIP	-	15 mins	After Filtration
P-11/V-106	Transfer in Concentrate from P-10	20	Master Slave with P-10 Filtration	Starts with Filtration in P-10
	Charge Alum10%	-	Calculated based on 600 L/h flow rate	After Transfer In Concentrate
	Agitation	-	15 mins	After Charge Alum10%
	Transfer Out Antigen+Adjuvant to P-12	20	Calculated based on 600 L/h flow rate	After Agitation
	CIP	-	15 mins	After Transfer Out Antigen+Adjuvant
P-12/HG-101	Homogenize	-	30 mins	Starts with Transfer Out Product Antigen+Adjuvant in P-11 (to P-12)
	CIP	-	15 mins	After Homogenize
P-13/V-107	Transfer in Mixture from P-12	20	Calculated based on 600 L/h flow rate	Starts with Homogenize in P-12
	Transfer Out Product to P-13	20	Calculated based on 600 L/h flow rate	After Transfer In Mixture
	CIP	-	15 mins	After Transfer Out Product
P-14/FL-101	Filling (Fill level: 50 mL/bottle)	20	Master Slave with P-13 Transfer Out Product	Starts with Transfer Out Product in P-13 (to P-14)

(SUT: setup time; PT: process time; ST: start time)

Table 5: Raw materials used in a single batch

Raw Materials	Symbol	Approximation	Amount (kg/batch)	Price (USD/kg)
Aluminum hydroxide	Alum10%	Aluminum oxide	7.867	2.00
Chicken Serum	Chicken Serum	Protein	8.481	207.15
Glucose	Glucose	Glucose	50.886	25.14
Haemophillusparagallinarum	*Hpg*	Biomass	0.032	0.00
Disodium hydrogen phosphate	Na_2HPO_4	Sodium hydrogen phosphate	25.443	85.14
NADH	NADH	Protein	1.696	75,000.00
Phosphate buffer saline	PBS	Sodium chloride	38.701	14.29
Peptone	Peptone	Protein	50.886	128.00
Sodium chloride	Sodium Chloride	Sodium chloride	32.228	8.57
Thimerosal	Thimerosal	Ethyl benzene	0.013	10.17
Water	Water	Water	7,318.739	0.02

As the increase of the demand of IC, the management decided to increase the production capacity by 100%. Therefore, the current process is facing difficulties to meet the requirement. In order to overcome the problem, the process bottleneck is first identified. Based on the set target, throughput analysis is first performed to identify the process bottlenecks, i.e. scheduling or size bottlenecks. Generally, bottleneck could be caused by the limitation of equipment or resources such as utilities, labor and raw materials supply. Based on the identified bottleneck, different debottlenecking schemes are proposed, and economic analysis is carried out for selection of the scheme with highest CBR. Note that CBR is defined as the ratio of extra benefit to the extra cost as shown in Equation (1) [7].

$$CBR = \frac{Extra\ Benefit}{Extra\ capital\ cost} \quad (1)$$

In order to increase the annual process throughput to 100%, three strategies are considered, i.e. increase of batch size (the amount of product produced per batch of operation), increase number of batches or increase of both batch size and number of batches.

According to Petrides *et al*., the scheduling bottleneck can be identified by tracking the total time consumed by each equipment within its cycle time [7]. The equipment with the longest cycle time is identified as the scheduling bottleneck, and this bottleneck will determine the maximum number of batches [12]. On the other hand, the size bottleneck of a process can be determined by calculating the capacity utilisation, uptime and combined utilisation of the various processing steps such as fermentation, centrifugation and filtration [10]. Capacity utilisation of equipment is referred to the fraction of equipment capacity that is used during an operation. Meanwhile, uptime is defined as ratio of equipment's occupancy time over the plant cycle time. Combined utilisation is the product of the capacity used and the uptime. This parameter clearly shows the time and capacity of particular equipment that is being used over the process.

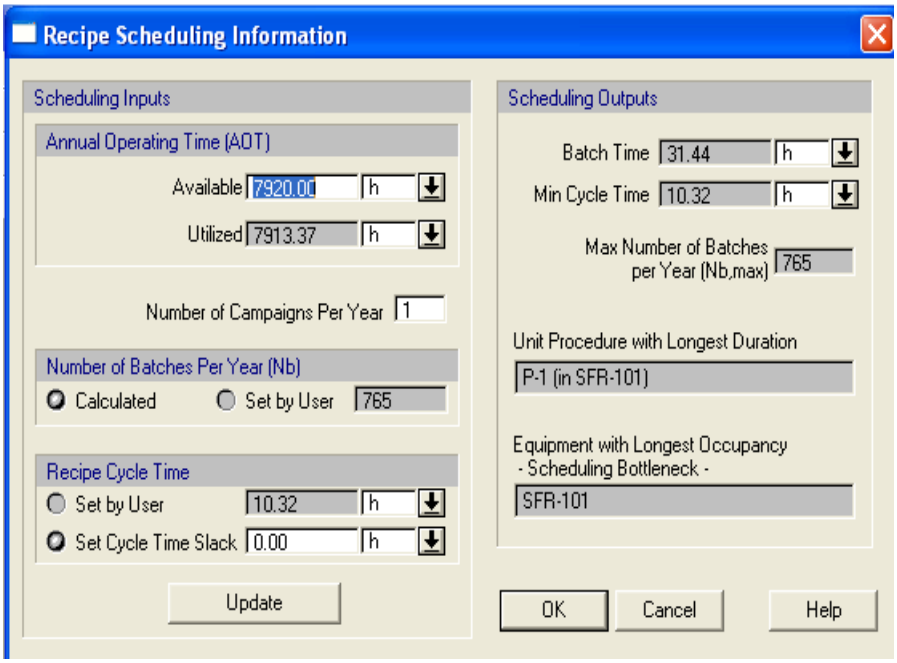

Fig. 2 The operation Gantt Chart (base case).

Figure 2 shows the operation Gantt Chart of the base case. As shown in Fig. 2, it is noted that shake flask (SFR-101) is identified as the scheduling bottleneck due to its longest occupancy (10 hours) as compare to the other equipment. The next step is to identify the debottlenecking schemes as shown in the following section.

4. DEBOTTLENECKING SCHEMES TO INCREASE PRODUCTION

After process bottleneck is identified, six debottlenecking schemes are proposed to increase the annual production of IC vaccine to 100%. As presented previously, shake flask (SFR-101) is identified as the scheduling bottleneck; hence, in order to increase the annual production, debottlenecking strategies should target to reduce the fermentation time in the shake flask.

In order to reduce the fermentation time of shake flask (SFR-101), another set of 300 mL shake flask (SFR-102) that staggered the operation is considered. By staggering the shake flask the overall cycle time of shake flask is reduced by half. In this scheme (scheme 1), the annual throughput increased 39.48% as compared to the base case (1067 batches per year), while the CBR value is calculated at 0.74. This scheme provides a good debottlenecking alternative as the cost of shake flask is very low compared with the overall capital investment. Since the annual throughput is only increased by 39.48%, the process needs to be further debottlenecked in order to achieve the targeted 100% increment.

Throughput analysis is next carried out for Scheme 2, media bleeding tank (P3/V-102) is identified as the next scheduling bottleneck. Hence, an additional media blending tank that operates in staggered mode is added. The annual throughput of this scheme is increased to 1136 batches, i.e. 48.5% increment from the base case. Meanwhile, the CBR is determined as 0.77 which is slightly higher than Scheme 1.

The throughput analysis is repeated on Scheme 2 to generate Scheme 3. In Scheme 3 an additional 5 L fermentor (V-109) is added to operate in staggered mode with the current fermentor (V-101), after Schemes 1 and 2 are considered. The annual throughput of this scheme is increased to 1141 batches, i.e. 49.2% increment from the base case. Note that, the annual number of batches does not increase much as compare with Scheme 2. Meanwhile, the CBR of this scheme is same as Scheme 2. Thus, this scheme is not as attractive as compared to Scheme 2.

In Scheme 4, throughput analysis reveals that the 500 L fermentor (V-104) emerges as the new process bottleneck due to its longest occupancy time due to its master slave relationship with centrifugation process and its long fermentation time. Hence, an extra set of 500 L fermentor is added. Based on the simulated result, the annual throughput for this scheme is increased to 1223 batches or 59.9% increment, and the CBR of this scheme is determined as 0.79.

The 50 L fementor (V-103) is next identified as the new process bottleneck for Scheme 4. In order to eliminate this process bottleneck, an additional 50 L fermentor is installed (Scheme 5). The simulated result shows that the number of batches tremendously increased to 1492 and 95.03% increment from the base case, and the CBR is calculated as 0.86. It is worth noting that the CBR for Scheme 5 is the highest CBR among all five debottleneck schemes. However, its annual production is yet to reach to 100%.

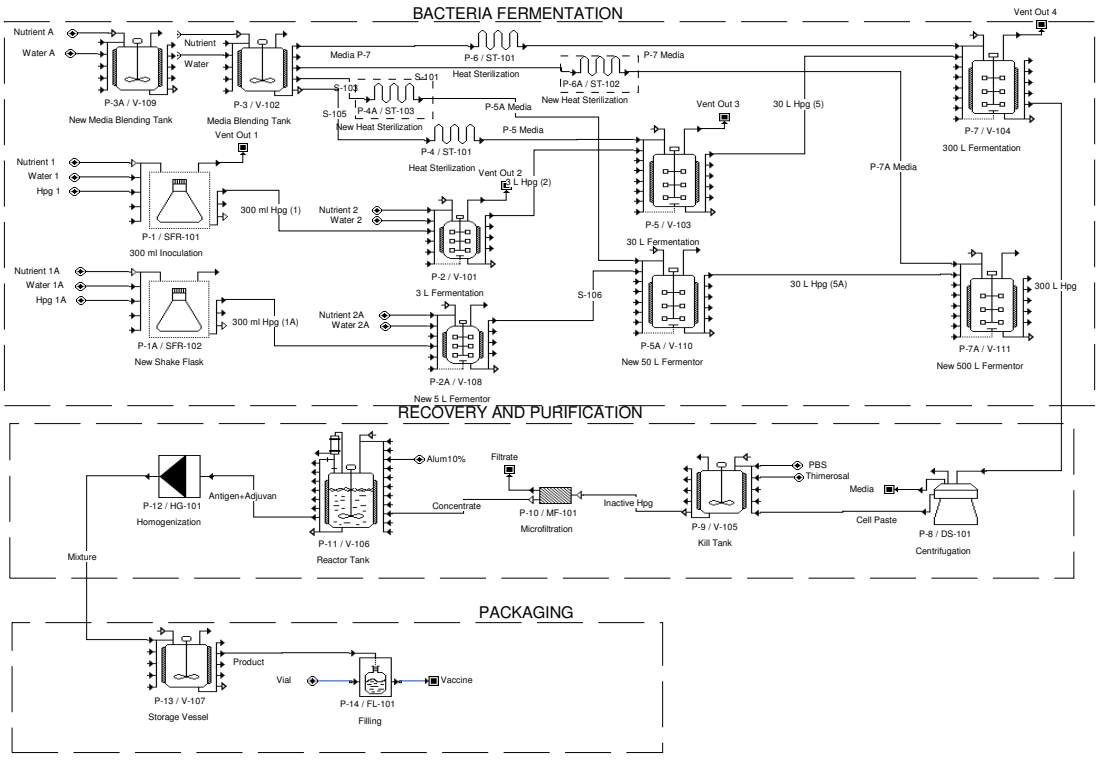

Fig. 3 Debottlenecking Scheme 6.

Scheme 6 is introduced where an additional heat steriliser is installed (see Fig. 3). This equipment is operated in staggered mode with the existing heat steriliser. The annual throughput increases to 1530 batches from 765 batches in the base case. Note that 100% increment of annual production is achieved. Even though the CBR value for Scheme 6 is computed as 0.85, which is slightly lower than that in Scheme 5, this scheme fulfils the

objective of the debottlenecking study. The debottlenecking process is a continuous process as there is always a limitation of equipment for the overall production. After completing Scheme 6, it is found that shake flask (P1/SFR-101) is once again becomes the new process bottleneck as it is now the longest process that limits the process cycle time. Although debottlenecking is a continuous process, it stops when the scheme that achieves the company's target is achieved. For instance, in this case study, debottlenecking is stopped at Scheme 6 as it met the 100% production rise as compared to the base case. Table 4 shows the summary of all debottlenecking schemes as well as the base case.

Table 6: Economic comparison of the base case study and debottlenecking strategy

Scenario	% production increase (Annual batches)	Annual Throughput (vials)	Cost of investment ($)	Annual Operating Cost ($)	Annual Revenue ($)	Unit Production Cost ($/vial)	CBR
Base case	0 % (765)	1,074,395.354	18,202,250	112,710,857	123,555,466	104.9063	-
Scheme 1	39.5% (1067)	1,498,535.742	22,184,430	156,633,492	172,331,610	104.5244	0.74
Scheme 2	48.5% (1136)	1,595,441.990	23,429,706	166,728,627	183,475,829	104.5031	0.77
Scheme 3	49.2 % (1141)	1,602,464.182	23,761,950	167,502,583	184,283,381	104.5281	0.77
Scheme 4	59.9% (1223)	1,717,628.128	26,573,045	179,740,333	197,527,235	104.6445	0.79
Scheme 5	95.0% (1492)	2,095,422.050	30,785,330	218,980,377	240,973,546	104.5042	0.86
Scheme 6	100% (1530)	2,148,790.708	32,938,306	224,803,395	247,110,931	104.6186	0.85

5. CONCLUSION

In this work, process simulation tool is used to model and simulate the IC vaccine production. Six debottleneck strategies are developed to increase the annual production to 100%. In this case study, Scheme 6 is chosen as the best scheme to debottleneck the process because it fulfills the debottlecking objective, and with reasonable high CBR values. To further increase the profit of IC vaccine production, the company may consider producing their own chicken serum (due to its high cost) instead of sourcing from external supplier.

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