Production of the equine influenza vaccine using a baculovirus expression system in insect cell lines

Part III: Downstream & process control

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GLOBAL OBJECTIVE

Design of an industrial bioprocess plant with the simulator SuperPro Designer for the production of the equine influenza vaccine using a baculovirus expression system in insect cell lines, and subsequent analysis of its sustainability.
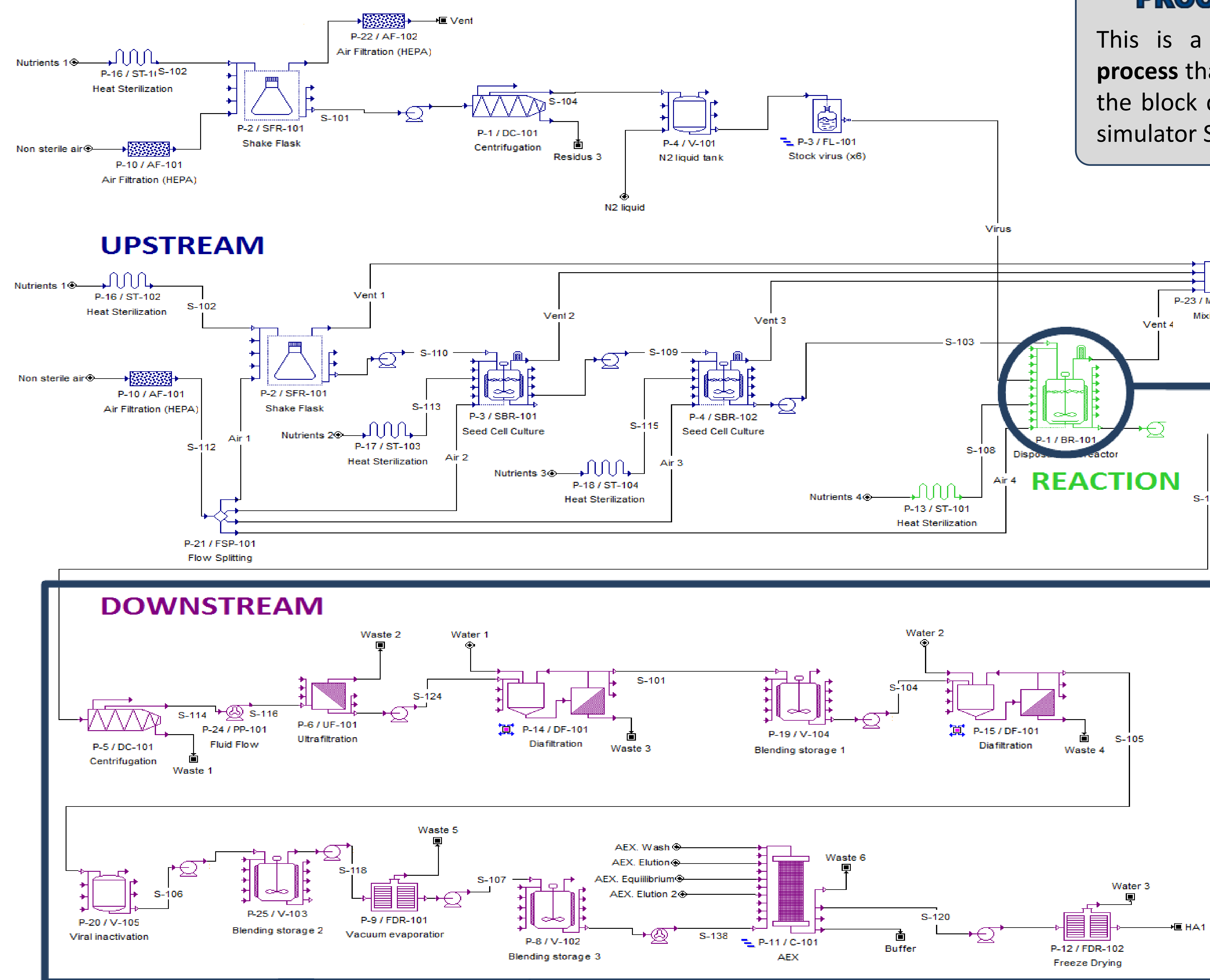
GMP PROCESS

To guarantee the **quality** of the final product, the process will be performed following the *Good Manufacturing Practices* (GMP) standards.

QbD PROGRAM

In order to attain the fulfillment of the norms GMP a program *Quality-by-Design* (QbD) that will allow to **control each point** of the process efficiently has been designed.

PROCESS FLUX DIAGRAM

PROCESS SIMULATION

This is a **simulation of the hole process** that has been obtained from the block diagram using the process simulator SuperPro Designer.

CONTROL AND INSTRUMENTATION

In order to guarantee the *Quality-by-Design* (QbD) program, instrumentation for process control has been installed. Details for the Bioreactor control and instrumentation:
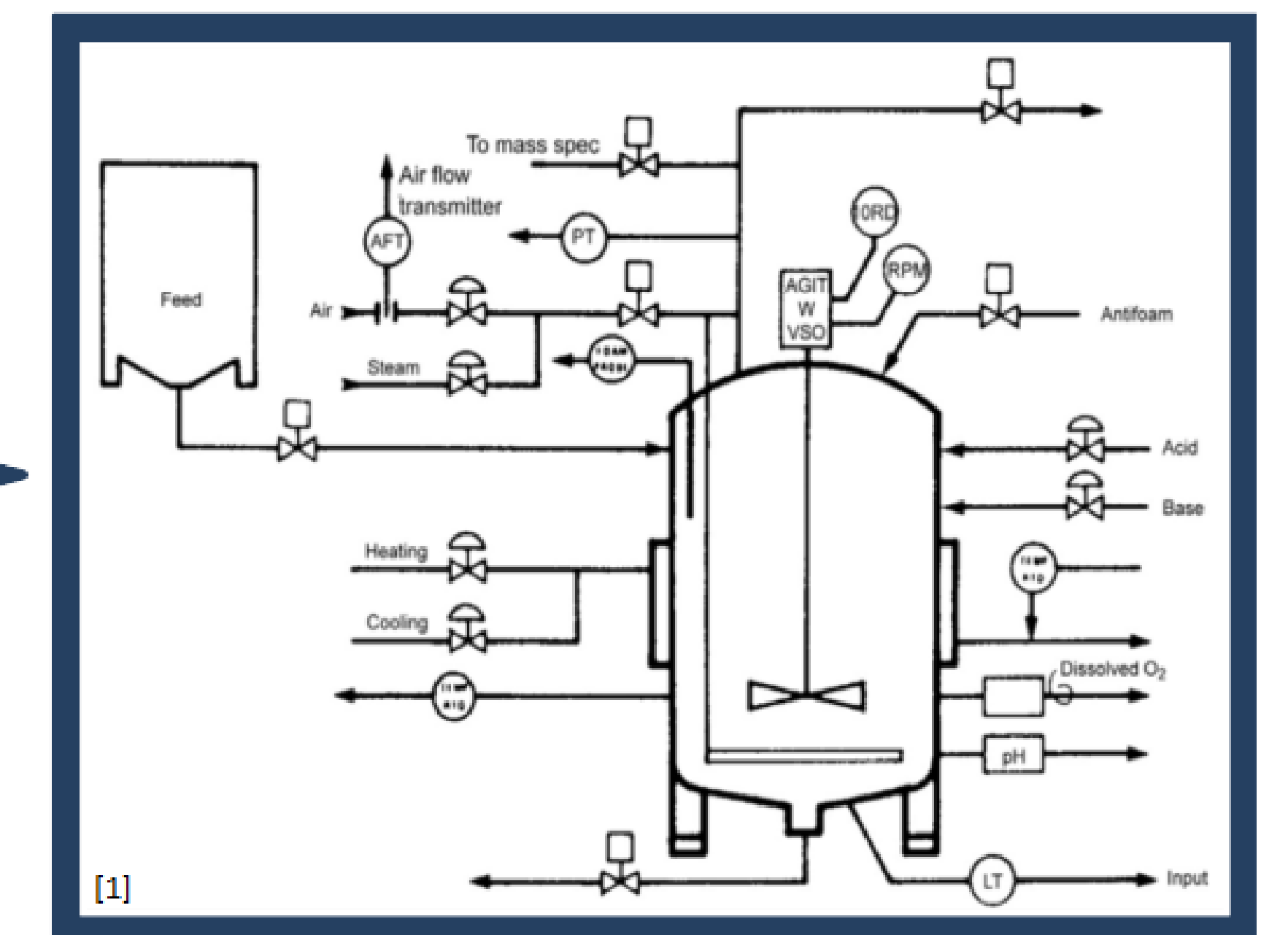
Process critical control loops:

- Air sterilization using HEPA filters
- Virus inactivation monitoring by virus quantification
- Protein production and purification

In case one of the critical variables go out of the limits established the necessary measures would be carried out to go back to the normality. A closed control loop example:

HA1 PURIFICATION

Imput	Output
29 g	21 g

YIELD 70%
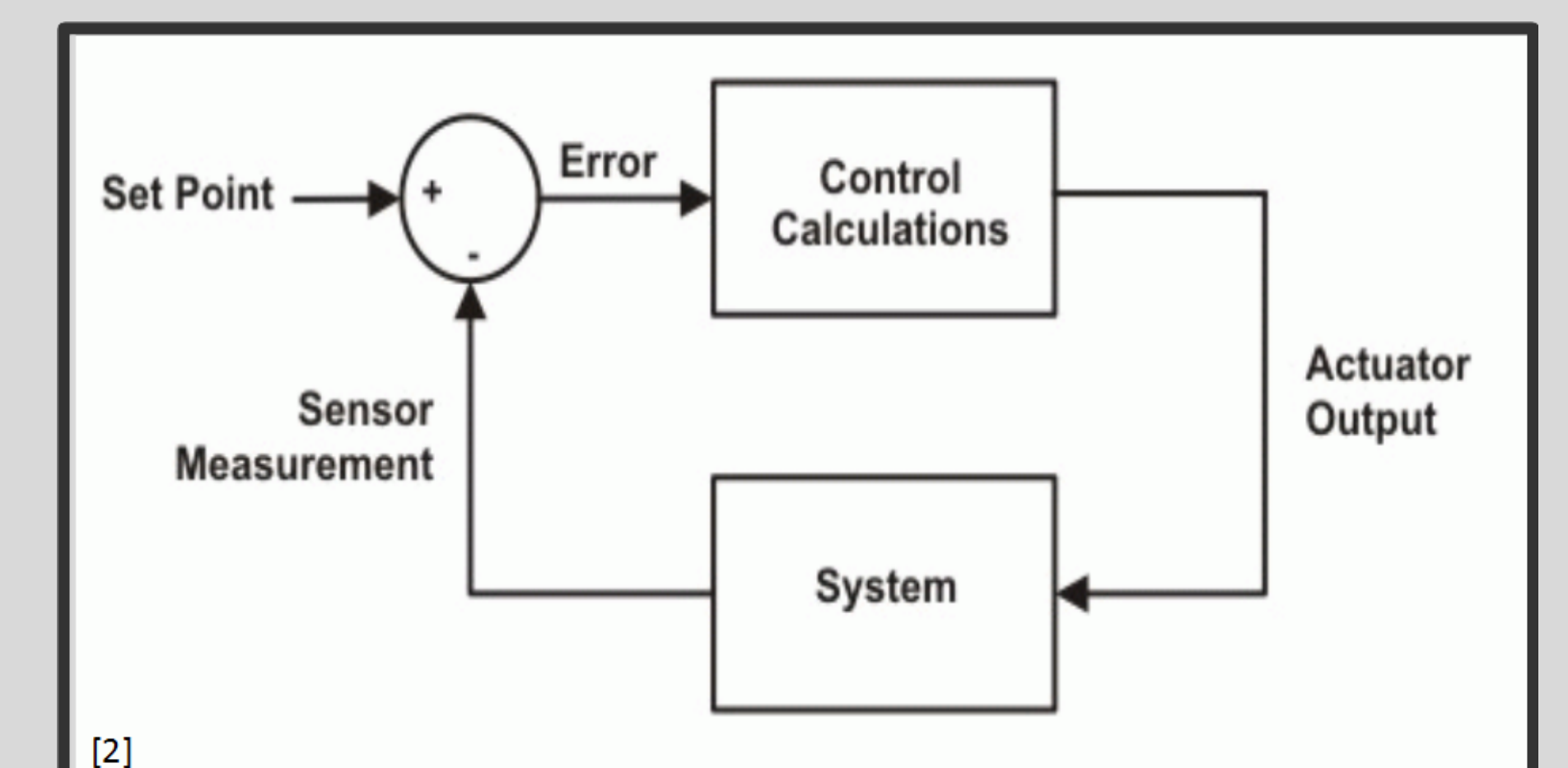
FINAL PRODUCT

21 g for each batch. HA1 is the 98.6% of the total protein at the end of the downstream. A highly purified product has been obtained.

**Process Analytical Technologies (PAT) implementation**
Control strategies by means of PAT are implemented to ensure product quality and operation efficacy in every stage of the downstream process.

Protein purification	HPLC
Ultrafiltration	Pressure control
Evaporation	Temperature and pressure control
Chromatography	Pressure control and samples analysis with spectroscopy
Viral activity	Virus quantification

VIRAL CLEARENCE
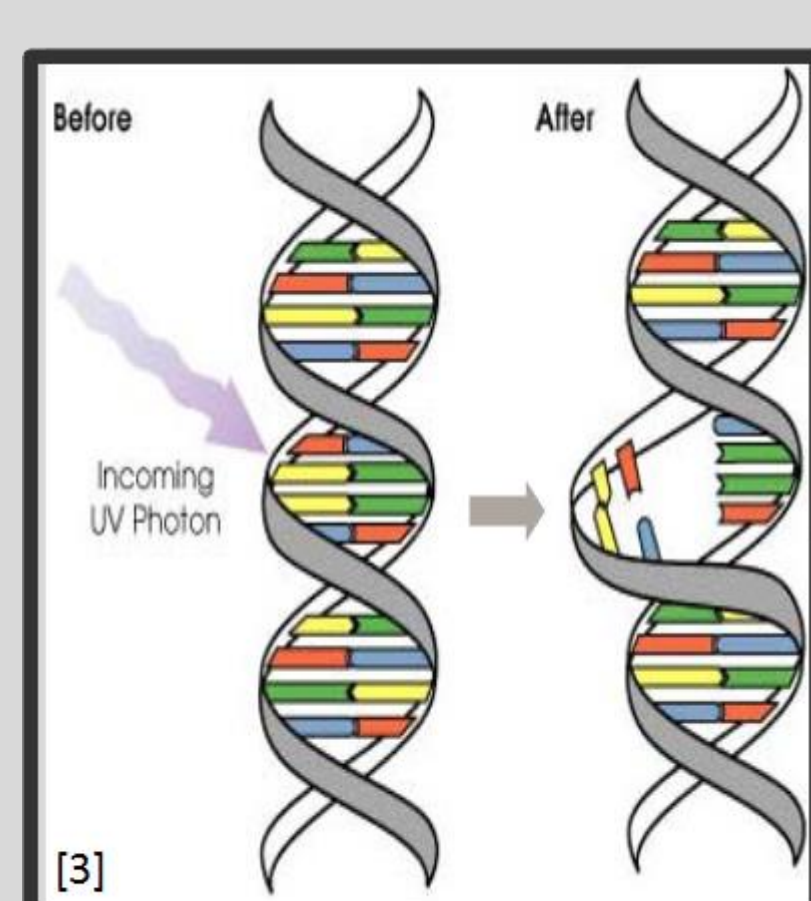
UV light damages the DNA irreversibly eliminating the viral infectivity. Thymine dimers are an example of the damages that appears in the genetic material during this treatment.
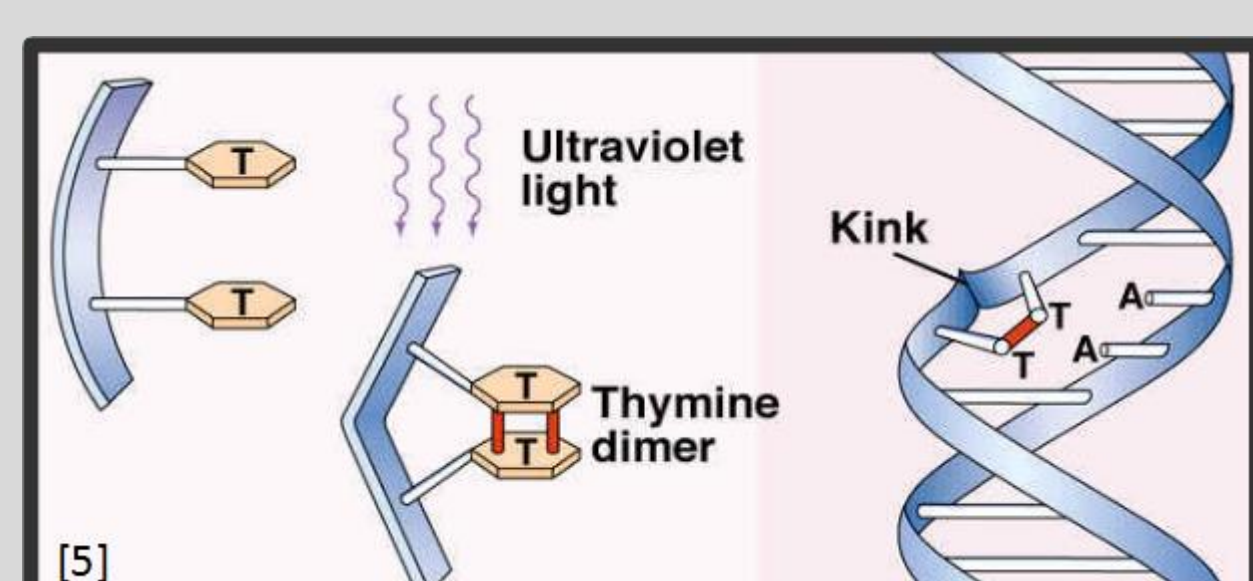
Thermal or chemical methods discarded for put in danger the stability of the protein.
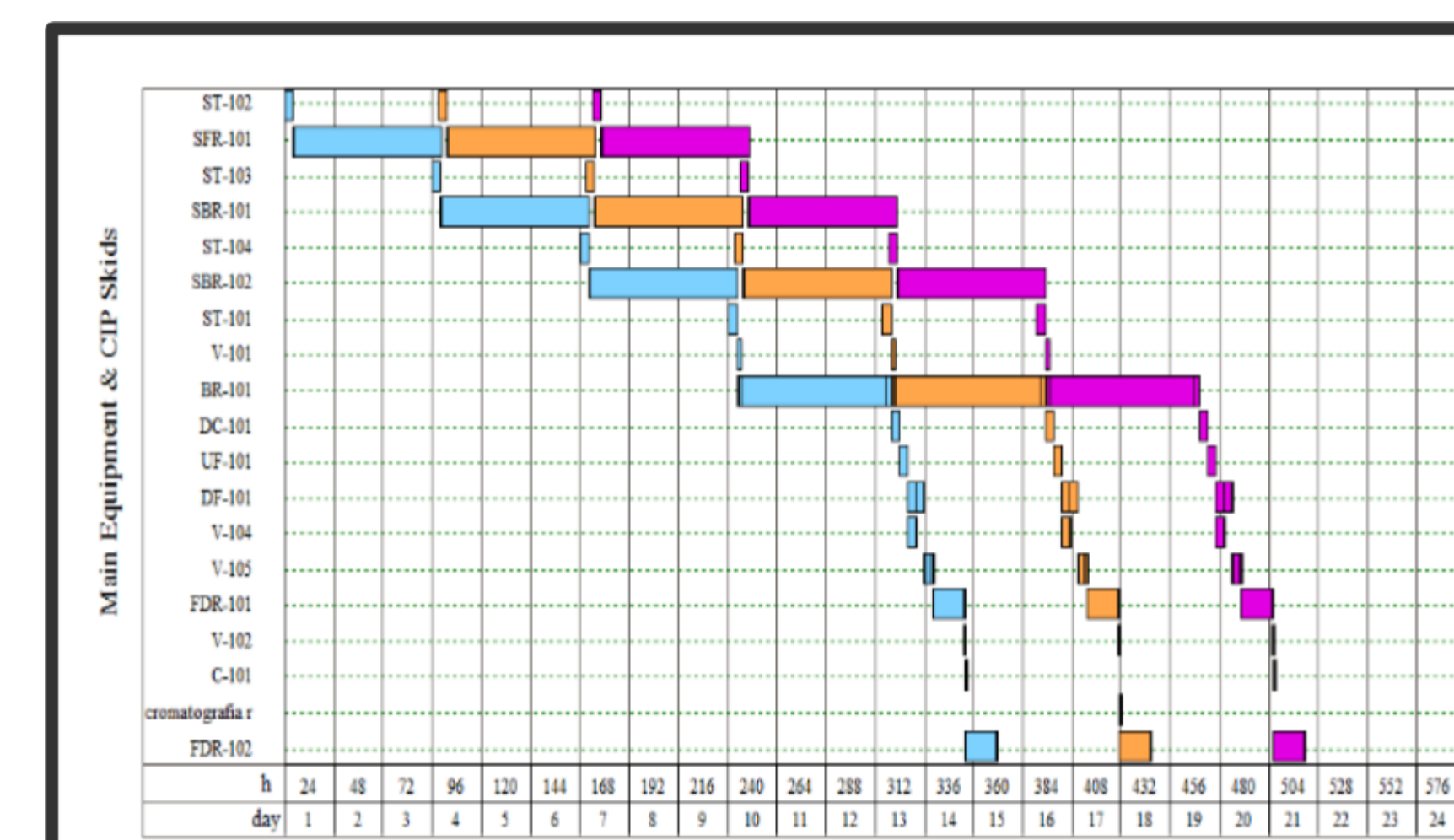

AEX chromatography binds virus and genetic material due to his negative charge. HA1 do not bind cause the working pH induces the protein to have a positive charge in his surface.

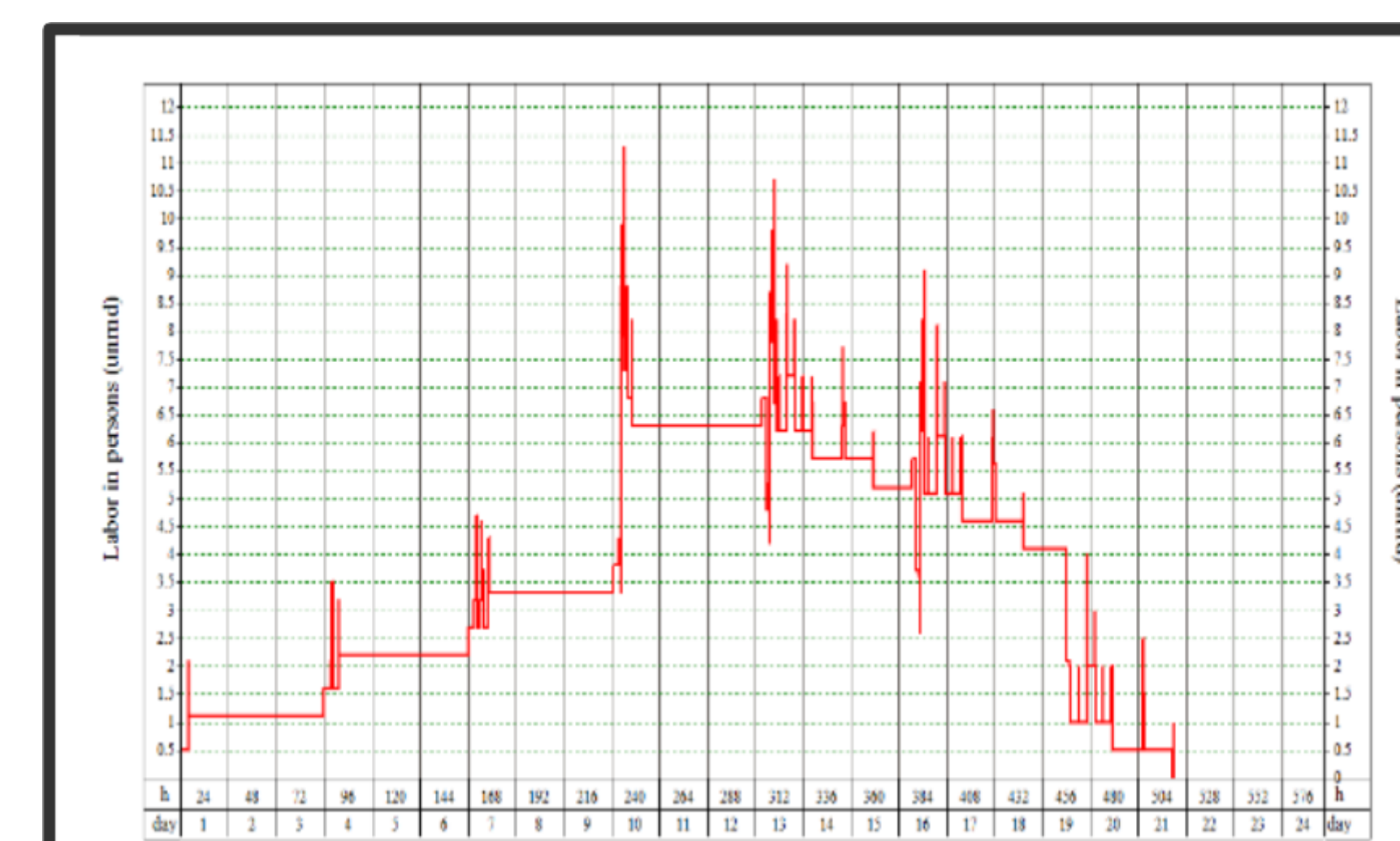As industrially stated, two different stages of viral clearence are performed.

PROCESS ORGANIZATION

GANTT CHART

Time organization in three consecutives batches with a total duration of **21 days**. The critical step, and consequently the bottle neck is the bioreaction.

LABOR CHART

Employers requirement during three consecutives batches. The employers demand is higher in the critical step with a peak of **12 workers**.

REFERENCES

[1] → P.K.John. *Instrumentation and Control Systems. Chapter 20.* p. 411. Accessed 18th April 2015
[2] → http://learn.parallax.com/pid-control. Accessed 27th May 2015
[3] → http://commons.wikimedia.org/wiki/File:DNA_UV_mutation.png. Accessed 11th April 2015
[4] → http://www.sartorius.es/fileadmin/DID/pdf/DID_Lit_Collection/Data_UVivatec_GMP_Lab-System_SPK2096-e.pdf . Accessed 14th May 2015
[5] → http://faculty.southwest.tn.edu/rburkett/gb-Final%20Exam.htm. Accessed 21th April 2015
[6] → http://www.verdotips2.com/our-products/easypack-chromatography-column/. Accessed 16th February 2015
[7] → http://en.wikipedia.org/wiki/Ion_exchange. Accessed 16th May 2015