28485 Individual Assignment
Corporate Business Case Template
4 pages maximum

Background

1. Name:
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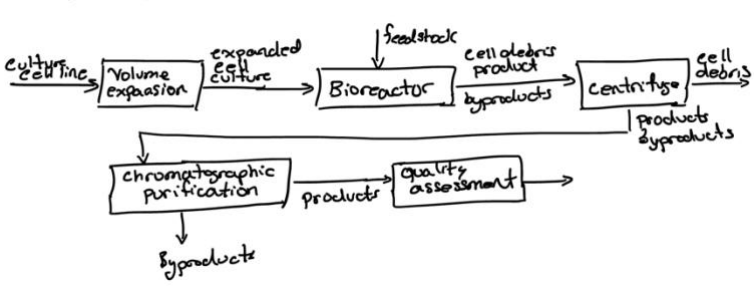
2. Title:
Implementation of a high-performance liquid chromatography (HPLC) analysis tool in the production process of biologics to reduce batch variability.

3. The problem:
Biologics are difficult to produce since minute variations in feedstock, reactor conditions, process design, and inherent variability from the cell culture can drastically change the product and impact effectiveness and safety. Unintended variation can also occur as a result of uncontrolled process variables at any step which can cause gradual or sudden shifts in product quality, also called manufacturing drift which can lead to reduced effectiveness and sometimes a recall of the drug. Currently quality assessment is done before the drug is distributed however, this can lead to an unsalvageable batch making it through the entire process before being discarded wasting time, money, and resources.

4. Business area:
The business is a large international pharmaceutical company that produces biologic drugs such as Merck or Pfizer. The market would be considered red ocean since there are many companies competing in the field of biologics. The type of molecule manufactured is large molecules. The market is currently valued at 30 billion USD as of 2021 and is expected to reach 100 billion by 2030. The value of the product varies between 25,000USD/kg to 100,000USD/kg[1] depending on the drug and the market size is between 300 t/year and 1200 t/year.



5. Base process and flowsheet:
The production of biologic drugs is a fermentation-based process that uses cell cultures to produce the desired

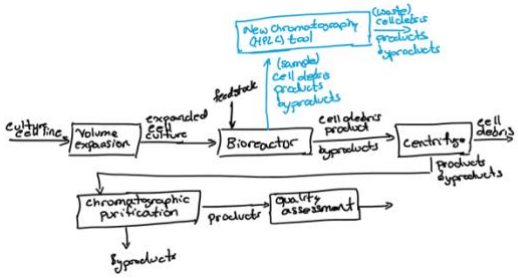
[1] https://gh.bmj.com/content/3/5/e000850

proteins[2]. The process begins in a bioreactor with a cell culture and feedstock. The cell culture will grow and produce the desired proteins however, they also produce unwanted byproducts. First the cell debris and unwanted organic matter is removed through a centrifuge or by filtration. Next the proteins are separated from the cell byproducts through chromatography columns. This concentrated product is then tested and prepared for storage. Currently one in ten batches are discarded in this step. The assumptions of the flowsheet are perfect separation of cell debris and byproducts in the centrifuge and chromatographic separator respectively.

6. The idea:
Implementing a hydrophobic chromatography tool immediately following the bioreactor allows for quality assessment screening sooner than the existing process. It would help reduce the variability in the bioreactor and reduce the number of batches discarded from one in ten to one in twelve. Implementing a chromatography analysis tool is not a direct change to the process rather it will allow for faster reaction to batch variability and prevent process drift. Hydrophobic chromatography also does not denature proteins which allows the structures of the separated proteins to be analyzed and prevent refolding steps later.

7. IP issues:
A patent would not be required in this case since the process or method of manufacturing will not change. Although this tool would be on the cutting edge of chromatography analysis, obtaining a patent for it would not eliminate any competitors. There are also other alternatives to a hydrophobic chromatography such as traditional methods like reversed phase, ion exchange chromatography, and newer methods such as hydrophilic chromatography which other companies would use to obtain similar results therefore rendering a patent useless.

8. Regulatory issues:
There are relatively few regulatory issues surrounding this idea since there is no direct change to the process, the cell culture, or the strain manufactured. Introducing a chromatography analysis tool is not modifying the organism or the process which means that less strict regulation is necessary, and it can be implemented in a much shorter time frame. The only regulation necessary is to prevent batch cross contamination by reintroducing samples from the chromatography device back into the process. Potentially regulating who is allowed to use the equipment is also necessary.



Technical

9. Process modifications:
Only minute process modifications are necessary to implement the HPLC device. A simple splitter can take a small sample from the outlet of the bioreactor which can

[2] https://www.researchgate.net/publication/320537644_The_process_defines_the_product_what_really_matters_in_biosimilar_design_and_production

then be directly fed into the device. After the samples are analyzed, they would be discarded as biologic waste.

10. Estimate the expected research and development effort:
The research and development team would require 8 FTEs for one year which at an estimated cost of 150,000USD/FTE is/ 1,200,000USD in total. The team could consist of a PHD, a research assistant, an engineer, and two assistants that would work on the HPLC. The team would also need a data scientist and statistician with an assistant to work on the data storage and processing aspect of the tool. In terms of the actual HPLC device, the cost is estimated at 100,000USD per device based on existing HPLC analysis systems. A pilot plant is unnecessary in this situation since there is no change to the overall process, units, or strain. There would also be no need to construct a new plant, rather the chromatography system can just be slotted into any plant. The running cost is estimated at 20,000USD/yr and can last up to 20 years. It would likely require a FTE to operate who would likely be an analytical chemist.

11. Risks (if any):
The largest risk in implementing this is cross batch contamination both inside the device but also by reintroducing samples to the process. It is critical that contamination is minimized to keep the visibility and accuracy of the HPLC as high as possible. A smaller risk is that the HPLC has low visibility when scaled up and implemented however if it is designed using process samples this is unlikely but possible. Another risk is that the HPLC cannot detect protein structure accurately thereby making it useless as a quality assessment tool and preventing process drift in the long term. The HPLC may also require a long time to obtain usable results from samples making it not time or resource efficient for the desired results. Since hydrophobic HPLC analysis systems are new they may be difficult and expensive to produce thus increasing development time and cost.

Enterprise

12. Financial summary:
(a) Estimated cost savings (or extra income):
Currently 10% of batches are discarded. After the implementation of the HPLC then only 8.3% of batches will be discarded which means that the remaining 1.7% of batches that would have initially been discarded can be sold, resulting in 1.7% increased profits. The exact amount of savings depends on a variety of factors such as the size of the company, the number of batches produced, and the value of each batch

(b) Estimate sustainability gains:
The main sustainability gains are reducing the number of batches thrown away after the entire process which wastes energy and resources, mostly in the form of solvents. It will help to prevent recalls and again reduce the amount of waste that needs to be dealt with. It also prevents extra refolding steps downstream which reduces the amount of enzymes required.

(c) Estimate the implementation costs:
The total cost of R&D is around 2,000,000USD which accounts for 8 FTEs for one year, multiple test devices, and data analytic tools to process data from the HPLC. The cost of implementation is around 100,000USD per device and the ongoing cost of running the HPLC is around 170,000USD/yr. This is comprised of an FTE to run the machine and process data along with the cost to run the machine which is around 20,000USD/yr, which also accounts for energy requirement and maintenance. In total this is a 2,000,000USD research and development cost, an installation cost of 100,000USD per HPLC device, and an ongoing operation cost of 170,000USD/yr.

13. Show stoppers
The three most important showstoppers are that the batch variability cannot be reliably predicted, the composition of batches cannot be accurately determined in shorter than an hour, and that the HPLC does not result in one in twelve batches being discarded. If the batch variability cannot be reliably predicted then batch variation cannot be controlled in the bioreactor. If the composition of the batch and the structure of the protein cannot be determined quickly and efficiently the HPLC will not be able to quickly and accurately analyze samples nor will it be able to help prevent process drift Finally, if the HPLC does not reduce the number of batches discarded it will not reduce waste and profit and will itself become a waste.

14. Timeline and plan as a gantt diagram

						1	2	3	4	5	6	7	8	9	10	11	12
Costing	1	2	1	2	100%												
Planning	1	3	1	3	100%												
Research	3	4	3	4	100%												
Development	4	6	4	6	100%												
Implementation	9	3	9	3	100%												

Timeline in month time scale

The major milestones that need to be met are the desired visibility must be reached by the six-month mark, the ability to detect proteins and byproducts accurately must also be achieved in six months, and the device must take less than an hour to analyze a sample must be reached by the end of development at nine months. The time for determining the visibility and ability to determine protein structure is in the research phase and the decision to continue must be made by the end of the research period at six months. The time the device takes to analyze a sample will be known somewhere around the eight-months and the same decision must be made. Towards the end of the development period and the beginning of the implementation period, around ten months, we would know if the HPLC reduces the number of batches thrown away and the final and most important decision would need to be made to continue implementing the project.