



2014

Student Design Competition

AMERICAN INSTITUTE OF CHEMICAL ENGINEERS
120 Wall Street, New York, New York 10005

If there are any questions about the design problem, Student Chapter Advisors and Design Assignments Instructors are directed to contact:

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Ralph E. Martin Department of Chemical Engineering
University of Arkansas Fayetteville, AR 72701
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Fax number: 501-575-7926
E-mail: rpenney@uark.edu

Please read the rules **before**, **during** and **after** preparing and submitting the solution to AIChE.

NOTICE: THE PAGE LIMIT FOR THE REPORT IS 125 NUMBERED PAGES!

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AIChE 2014 Student Design Competition

Manufacturing the Next Generation of Vaccines: Non-egg based platform for Influenza Vaccine

DEADLINE FOR **ELECTRONIC SUBMISSION** TO AIChE IS MIDNIGHT, June 2, 2014.

Send a WORD file and PDF file as your entry to studentchapters@aiiche.org.

*** DO NOT mail any paper copies.**

***It MUST be a WORD file in the email.**

RULES OF THE CONTEST

November 2013

Dear Chemical Engineering Department Heads and Student Chapter Advisors,

I am pleased to send you the 2014 AIChE Student Design Competition statement. Please forward it to those faculty teaching design courses. Following is this year's challenge:

“Manufacturing the Next Generation of Vaccines: Non-egg based platform for Influenza Vaccine”

As always, the names of the sponsoring organization and the authors are being withheld to ensure confidentiality. Both will be announced after the deadline- Friday, June 2, 2014.

- An entry form is required for each participant -- is available as a separate attachment, and must be submitted along with the completed solution.

We welcome participation by individuals and teams of up to three students. Please indicate the names of all team members on each entry form, and be advised that each team member is required to submit a separate entry form.

- AIChE Student Membership Required - Because the Student Design Competition is a benefit of AIChE student membership, entrants must be AIChE active student members. Any non-member submissions will not be considered. Students can join at <http://www.aiiche.org/students/>.
- All submissions must be submitted in an electronic format via email. Sent no later than Friday, June 2, 2014. Please maintain a copy for your files.

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- Submissions must be no more than two documents (1 PDF and 1 MS-Word formats only) --totaling 100 or fewer pages of main text, with an allowable 100 pages of supplementary materials – in one of the following formats: PDF and MS-Word. The requested format is a single PDF file—the Adobe Acrobat program can be used to combine pages from different sources into one document.

Student Chapter Advisors are asked to select the best solution or solutions, not to exceed two from each category (individual and team).

Please take time to review the rules, found on the following pages. It is important that all solutions strictly adhere to the Final Report Format.

If I can be of assistance, please contact me via email at studentchapters@aiiche.org. Questions relating to the substance of the design problem should be directed to: Dr. W. Roy Penney, University of Arkansas Fayetteville, office phone number 479-575-5681 and e-mail: rpenney@uark.edu.

Thank you for your support of this important student competition.

Sincerely,

Michelle Marsnick

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2014 AIChE National Student Design Competition

Contest Rules

Solutions will be graded on (a) substantial correctness of results and soundness of conclusions, (b) ingenuity and logic employed, (c) accuracy of computations, and (d) form of presentation.

Accuracy of computations is intended to mean primarily freedom from mistakes; extreme precision is not necessary.

It is to be assumed that the statement of the problem contains all the pertinent data except for those available in handbooks and literature references. The use of textbooks, handbooks, journal articles, and lecture notes is permitted.

Students may use any available commercial or library computer programs in preparing their solutions. Students are warned, however, that physical property data built into such programs may differ from data given in the problem statement. In such cases, as with data from literature sources, values given in the problem statement are most applicable. Students using commercial or library computer programs or other solution aids should so state in their reports and include proper references and documentation. Judging, however, will be based on the overall suitability of the solutions, not on skills in manipulating computer programs.

Departments, including advisors, faculty, or any other instructor, cannot provide technical aid specifically directed at the solution of the national student design competition.

The 2014 Student Design Competition is designed to be solved either by an individual chemical engineering student working entirely alone, or a group of no more than three students working together. Solutions will be judged in two categories: individual and team. There are, however, other academically sound approaches to using the problem, and it is expected that some Advisors will use the problem as classroom material. The following confidentiality rules therefore apply:

1. For individual students or teams whose solutions may be considered for the contest: The problem may not be discussed with anyone (students, faculty, or others, in or out of class) before or during the period allowed for solutions. Discussion with faculty and students at that college or university is permitted only after complete final reports have been submitted to the Chapter Advisor.
2. For students whose solutions are not intended for the contest: Discussion with faculty and with other students at that college or university who are not participating in the contest is permitted.

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3. For all students: The problem may not be discussed with students or faculty from other colleges and universities, or with individuals in the same institution who are still working on the problem for the contest, until after June 2, 2014. This is particularly important in cases where neighboring institutions may be using different schedules.

Submission of a solution for the competition implies strict adherence to the following conditions: (Failure to comply will result in solutions being returned to the appropriate Faculty Advisor for revision. Revised submissions must meet the original deadline.)

ELIGIBILITY

- ONLY AIChE NATIONAL STUDENT MEMBERS MAY SUBMIT A SOLUTION. Non-member entries will not be considered. To become a National Student member, you can join online at: <http://www.aiche.org/students/>.
- Entries must be submitted either by individuals or by teams of no more than three students. Each team member must meet all eligibility requirements.
- Each Faculty Advisor should select the best solution or solutions, not to exceed two from each category (individual and team), from his or her chapter and submit them per the instructions below.

TIMELINE FOR COMPLETING THE SOLUTION

- A period of no more than thirty-six (36) days is allowed for completion of the solution. This period may be selected at the discretion of the individual advisor, but in order to be eligible for an award, a solution must be postmarked no later than midnight June 2, 2014.
- The finished report should be submitted to the faculty advisor within the 36-day period.

REPORT FORMAT

- The body of the report must be suitable for reproduction, that is, computer-generated and in a printable format. Tables, supporting calculations and other appendix material may be handwritten.
- The solution itself must bear no reference to the students' names and institution by which it might be identified. Please expunge all such references to the degree possible.
- Final submission of solutions to AIChE must be in electronic format (PDF and MS-Word). The main text must be 100 pages or less, and an additional 100 page or less is allowable for supplementary material. The final submission to AIChE must consist of 2 electronic files.

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SENDING THE SOLUTION TO AIChE

- There should not be any variation in form or content between the solution submitted to the Faculty Advisor and that sent to AIChE. The Student Chapter Advisor, or Faculty Advisor, sponsoring the student(s), is asked to maintain the original manuscript(s).
- Email the electronic file (PDF and MS-Word), accompanied by its corresponding entry form, and email to: studentchapters@aiiche.org
- DEADLINE: Entries must be postmarked by Friday, June 2, 2014.

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Manufacturing the Next Generation of Vaccines: Non-egg based platform for Influenza Vaccine

Overview:

Design a large scale manufacturing facility for production of trivalent (i.e., three separate moieties) flu vaccine using a non-egg based expression system such as insect cells (ex SF9) or Chinese Hamster Ovary (CHO) cells. The new flu vaccine platform will eventually replace your companies egg based process for influenza vaccine. The manufacturing facility must be able to respond to an influenza pandemic.

Introduction:

Influenza is a global health concern and while there is an annual vaccine for influenza only about one-third of the population receives the vaccination. In the US alone there are 17,000 to 51,000 deaths a year due to influenza and in a global pandemic the number of deaths could reach the millions (Kang). Influenza also has a significant economic impact such as lost time due to employee illness, etc.

Influenza is a lipid RNA virus and there are two subclasses of influenza which are A and B. Influenza is seasonal so every year the World Health Organization (WHO) issues the recommendations for the influenza A and B, HA and NA variants, that are most likely to cause disease and for the Northern Hemisphere the information is released in February.

Historically the trivalent influenza vaccine has been produced in chicken eggs and this has been the process for years but it has benefits and risks. Some of the benefits are that the egg-based platform is well documented and is approved worldwide. The egg-based platform has also allowed the company to quickly develop a new vaccine every year for the market as the strains differ each year and deliver it to the patient under time constraints. There are risks with an egg-based platform and one of those is that the egg supply may become unavailable due to a bird flu outbreak for example. It is interesting to note that duck eggs are considered safer to use because ducks are less susceptible to disease compared to chickens but they also have drawbacks. Many people also have allergies to eggs and feathers so they cannot take the vaccine so this limits the number of individuals that may take the traditional influenza vaccine.

There is now regulatory precedent for a flu vaccine that is not made using eggs. Recently two companies have gained FDA approval for their non-egg based flu vaccine and they are Novartis™ (CHO expression system) and Protein Sciences™ (Insect expression system).

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Design Considerations and Specifications:

You are part of a world leading vaccine company and you are in charge of creating a new platform within your company to manufacture vaccines. You will be concentrating on influenza vaccine for this project but once you obtain proof of concept your platform will be considered for current and future products beyond influenza. Your company currently uses egg based production methods for its influenza vaccine and eventually the company wants to phase out the egg based platform.

It is suggested that you use either CHO cells or Insect cells for the new process because your sister company has considerable experience with mammalian and insect cell culture so you will be able to use them as an additional knowledge resource. Also there is regulatory precedent for using CHO and insect cells for influenza vaccine so this may increase the likelihood of vaccine approval in minimum time. The vaccine made using the alternative non-egg based process will have the same potency as the egg-based process i.e., you will need the same concentration of vaccine per patient. The vaccine you will create will also need to be trivalent and follow WHO's recommendations for the vaccine each year. You will be focused on delivering vaccine to the North American market only for this project. Also the number of doses that you will manufacture needs to be set based on historical data; for example, how many doses does Sanofi Pasteur™ or GlaxoSmithKline™ produce for the market?

Once the cell line for the new vaccine production process has been decided, you will design the GMP commercial manufacturing facility to produce the new influenza vaccine. The commercial production facility/suite will be used every year to produce the next seasons' vaccine. The commercial manufacturing facility will not be used year around because this is a "seasonal" product. Until other products are part of the portfolio this will be a single product facility. Keep in mind that you have options such as the following for a commercial manufacturing facility.

1. Traditional steam in place (SIP) and clean in place (CIP) production facility on the company site or at a contract manufacturer (CMO).
2. Traditional production facility using some disposable technologies such as disposable mixing vessels (Allegro™ by Pall) or bioreactors on the company site or at a CMO.
3. Nontraditional facility with almost all steps of the process using disposables i.e., a version of the Flex Factory on the company site or at a CMO.

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There is a movement in the industry to use disposables in manufacturing facilities, especially in contract development and contract manufacturing facilities because there are no clean-in-place (CIP) or steam-in-place (SIP) protocols. Also the vessels arrive sterilized and validated from the manufacturers; therefore, no extensive validation protocols are needed. Less initial capital is typically required for a facility that uses disposable technologies, but the facility will need a greater consumables budget, if it uses disposables.

Your manufacturing process will include everything from vial thaw to purification, but final formulation and packaging will take place offsite and should only be mentioned in your report. On completion of this project, you will have designed the production process and the production facility to make the next generation flu vaccine for your company. A diverse team of engineers, scientists, regulatory experts, as well as business leaders has been established to help you deliver on your project. Your project is on the critical path and your patients are waiting.

General Process Description:

A conceptual block flow diagram is shown in the attached figure, to accompany this process description. The block flow diagram shown here is a high level diagram and the designer is encouraged to innovate.

Note that since the vaccine is trivalent you will need to run the process three times to manufacture each of the three moieties of the vaccine, using the appropriate clone for each part of the vaccine. Please remember to take into consideration the time needed to clean between manufacturing campaigns of the individual components of the vaccine.

Upstream Processes

You will need to determine whether you will use a proprietary media formulation that is specific to your company or whether you will use an off the shelf media provided by a company such as Life Technologies™, BD™ or Lonza™. Your facility is considered to be an animal free facility so you will be using chemically defined medium in your process. The media that will be used for the process will be made onsite from powdered components. Please design the media preparation area and select whether to use steam in place vessels, disposable vessels or both.

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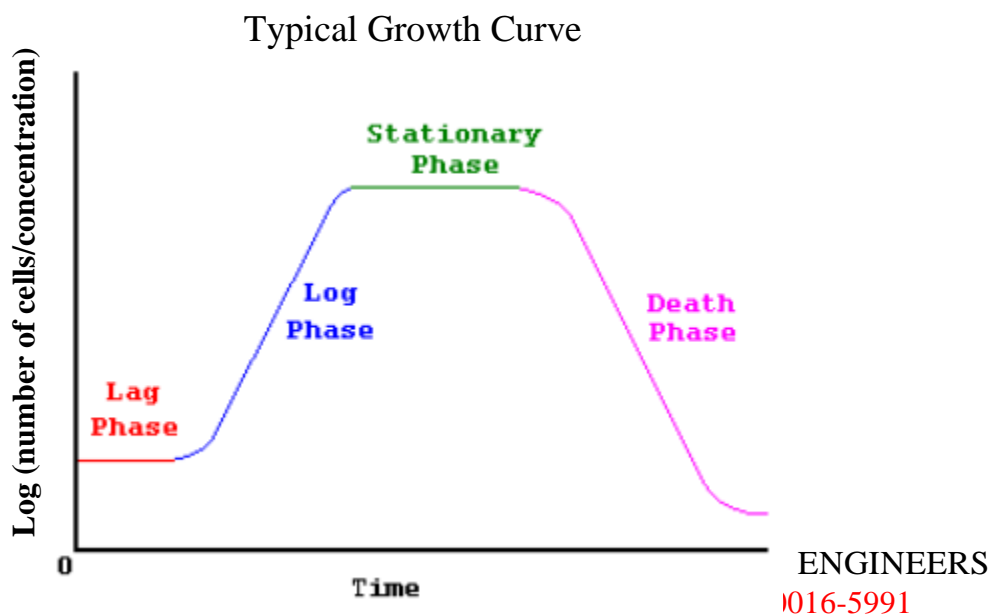
Seed Train

You will obtain one vial of CHO cells or insect cells for each batch of product that will be produced in your facility. The vial size can range from 1 ml to x mL based on the company's method of banking their master cell banks. In order to account for both old and new cell banking procedures, set the vial volume size to be 1 mL and each vial should contain 1×10^6 viable cells/ml for CHO and 1×10^7 viable cells/mL for the insect cell line. The cells will need to be expanded by passaging into larger and larger volumes and after the final scale up in the seed train, the culture will be placed in the production bioreactor(s). Note that the seed train will be a batch process.

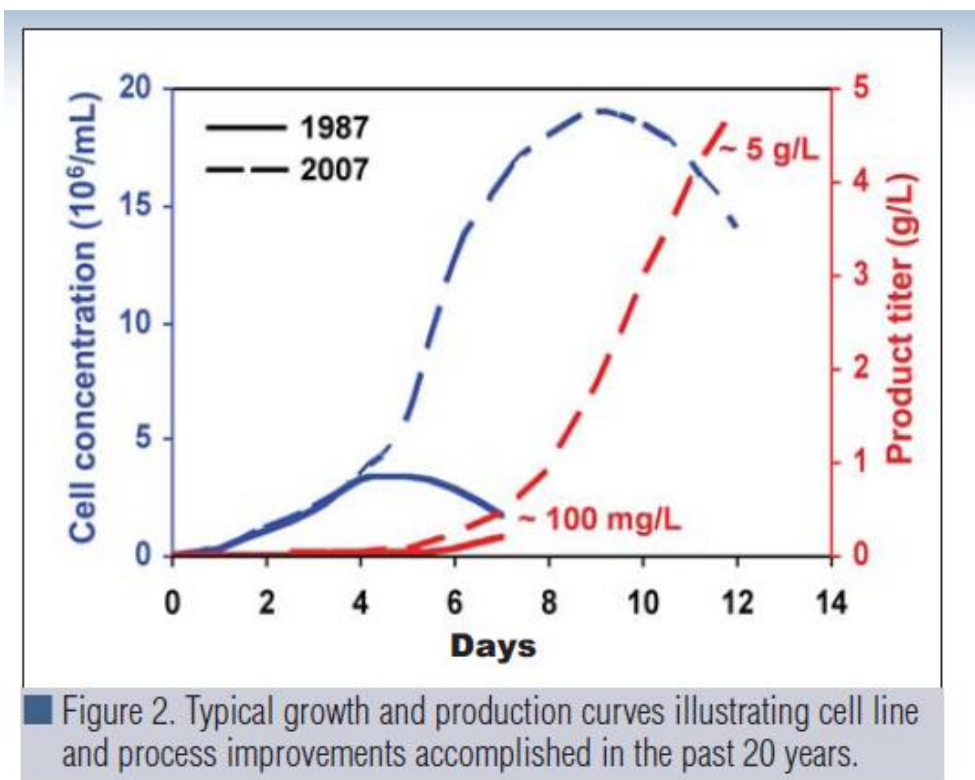
Production Bioreactors

Once your cells/cultures leave the seed train they will enter the production bioreactors. Currently there are a number of types of bioreactors used in cell culture processes. You will need to decide what type of bioreactor you will use for the process. You need to select your bioreactors to ensure that after x number of trains you are able to make the necessary amount of vaccine for the market as well as increases in market demand. You will need the capability in the production reactors to run a batch or a fed batch process based on what the process team decides is best for the production process.

The cell line that you will be using follows a typical growth curve with the following phases: Lag Phase, Log (exponential) Phase, Stationary Phase, and a Death Phase. Below is a typical growth curve.



Example Growth Curve for CHO



Jayapal, Karthik, Katie F. Wlaschin, Wei-Shou Hu, and Miranda G.S. Yap, "Recombinant Protein Therapeutics from CHO Cells – 20 Years and Counting," SBE Special Section CHO Consortium pg. 40-47. [http://pef.aibn.uq.edu.au/wordpress/wp-content/blogs.dir/1/files/Support/Mammalian/Literature/Recombinant Protein Therapeutics from CHO Cells-20 years and counting Jayapal.pdf](http://pef.aibn.uq.edu.au/wordpress/wp-content/blogs.dir/1/files/Support/Mammalian/Literature/Recombinant_Protein_Therapeutics_from_CHO_Cells-20_years_and_counting_Jayapal.pdf).

Example Growth Information for SF9 Cells:

Cell Density vs Time Data for Sf-9 Cell Growth in a Batch Culture

Time (h)	Cell density (cells/mL)	Time (h)	Cell density (cells/mL)
0.0	1.02×10^5	112.0	1.99×10^6
16.5	1.06×10^5	136.5	3.46×10^6
39.0	1.67×10^5	159.5	4.32×10^6
62.5	3.05×10^5	192.5	4.56×10^6
88.0	8.37×10^5	208.0	4.47×10^6

Amen_Haitham, "Baculovirus and Insect Cell Expression,"
http://www.academia.edu/1436672/Baculovirus_and_Insect_Cell_Expression.

Downstream Purification:

Primary Recovery: Harvest:

After the production reactor protocol is complete, the contents/product needs to be recovered/harvested. The bioreactors are harvested by removing the contents of the bioreactor and then the broth undergoes centrifugation and filtration to remove biomass, etc. You will need to design your centrifuge and filtration steps and you may need vessels to hold the contents of the bioreactor(s) while downstream processing the broth.

Density of Chinese Hamster Ovary (CHO) Cell Culture Broth: 1.06 g/cm^3 (Kubitschek, H Critical Reviews in Microbiology 1987; 14: 73-97)

Assume that Insect Cell Broth has the same density as CHO: 1.06 g/cm^3 .

Inactivation:

Virus Filtration/Inactivation is a safety step in the manufacturing process. You will need to decide where in the process this step will take place and using what method. There are a number of methods that one may utilize such as filtering, solvent/detergent treatment, low pH inactivation, heat treatment, and chromatography, to name a few. Remember you do not want to destroy the product in this step so select appropriately

Capture and Purify:

After decreasing the volume of the broth you will need to capture the product which is the vaccine parts of interest. Remember that you are making a three part vaccine and these 3 parts will be made separately and purified separately. Chromatography is used for this step traditionally and some examples of unit operations that one might want to use are ion exchange chromatography and size exclusion.

Concentrating and Stabilizing Material for Shipping and Future Formulation:

After the material is purified one may want to further concentrate the material and an example of a unit operation may be useful to further concentrate the material is TFF (Tangential Flow Filtration) but there are other ways to do this on the market so be creative.

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You will also need to freeze dry or crystallize the product so that it is stable to ship to the formulation and filling groups that are part of the wider manufacturing network and are not at the same site where you will be producing the 3 parts for the vaccine.

Storage and Shipment to an Off-Site Formulation Facility:

Please design a section of your facility to package and store the vaccine until it is shipped to your formulation group within global manufacturing for final formulation and packaging for patients. Remember that you are making a three part vaccine.

Production Waste:

The manufacturing facility will be built on an existing site. You will be able to utilize the sewer systems that are already on-site but will have to design the pretreatment, “kill tanks” that will feed into the county/city sewage facility.

Cost Data:

Electricity: \$0.05/kWhr

Sewer: \$5.00/thousand gallons

Water: \$0.543 per 1000 liters

Water for Injection: \$1000 per 1000 liters

All prices are delivered to your site and are in current year’s dollars.

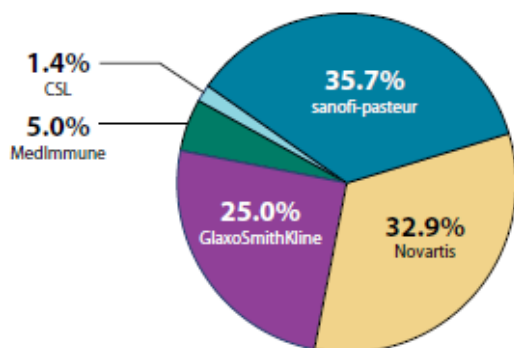
Market Information:

The CDC reported that 134.9 million doses of flu vaccine were distributed during the 2012 -2013 influenza season.

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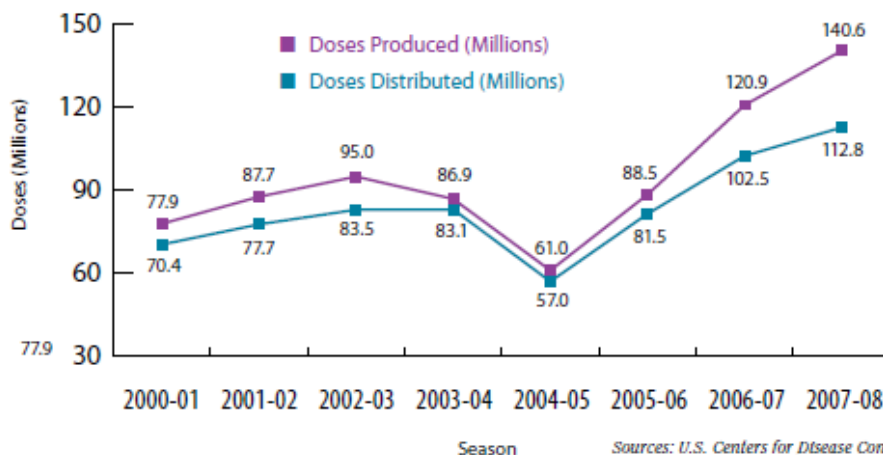
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Figure 3: Doses Produced in 2007-2008 (140 Million)



Source: Company press releases, Centers for Disease Control and Prevention

Figure 4: Influenza Vaccine Production for the U.S. Market, (2000-2001 through 2007-2008)



Sources: U.S. Centers for Disease Control and Prevention

“2007-2008 Influenza Vaccine Production and Distribution Market Brief,” Health Industry Distributors Association. http://www.preventinfluenza.org/HIDA_flubrief07-08.pdf

Report Requirements:

This report should follow the outline suggested in Seider, Seader and Lewin. Further details on what should be included in the design report can be found in that text. Write the document from the point of view of the organization’s engineer making a report and recommendation to the organizations management.

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1. Letter of Transmittal
2. Cover Page
3. Table of Contents
4. Abstract
5. Introduction
6. Process Flow Diagram and Material Balances
7. Process Description
8. Energy Balance and Utility Requirements
9. Equipment List and Unit Descriptions
10. Equipment Specification Sheets
11. Equipment Cost Summary
12. Fixed Capital Investment Summary
13. Safety, Health, and Environmental Considerations
14. Other Important Considerations
15. Manufacturing Costs (exclusive of Capital Requirements)
16. Economic Analysis
 - Product price required to achieve a minimum IRR of 25% for the battery limits portion of the Project.
 - Product price = Product price of the current egg-based versions of the flu vaccine
17. Conclusions and Recommendations
18. Acknowledgements
19. Bibliography
20. Appendix

Helpful/Interesting Information:

Examples of vaccine manufacturers: GlaxoSmithKline, Merck, Novartis, Sanofi-Pasteur and many more.

You may find that the Biopharmaceutical SUPERPRO Designer model example on Intelligen's website www.intelligen.com is helpful as you create your design project.

The FDA has given suggested guidelines for the internal layout of a biopharmaceutical facility/Vaccine Facility so you may wish to refer to their website for guidance.
www.fda.gov

Industrial trade publications: BioPharm International, BioProcess International, Pharmaceutical Manufacturing, Genetic and Engineering News (GEN), and many more.

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“2007-2008 Influenza Vaccine Production and Distribution Market Brief,” Health Industry Distributors Association. http://www.preventinfluenza.org/HIDA_flubrief07-08.pdf. Accessed 01 August 2013

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CDC influenza website for vaccine production data:
<http://www.cdc.gov/flu/professionals/vaccination/vaccinesupply.htm>
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Cox, Manon, Flublock®:Recombinant Influenza Vaccine, Protein Science Corporation. ECI Conferences International: Vaccine Technology IV May 20-25, 2012 Portugal.

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Gerson, D. F., “Paradigm Change in BioManufacturing: Technology is Transforming Manufacturing Options,” *Contract Pharma*, May 2008.

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http://tools.invitrogen.com/content/sfs/manuals/insect_man.pdf. Accessed 01 August 2013

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Jayapal, Karthik, Katie F. Wlaschin, Wei-Shou Hu, and Miranda G.S. Yap, “Recombinant Protein Therapeutics from CHO Cells – 20 Years and Counting,” SBE Special Section CHO Consortium pg. 40-47. [http://pef.aibn.uq.edu.au/wordpress/wp-content/blogs.dir/1/files/Support/Mammalian/Literature/Recombinant Protein Therapeutics from CHO Cells-20 years and counting_Jayapal.pdf](http://pef.aibn.uq.edu.au/wordpress/wp-content/blogs.dir/1/files/Support/Mammalian/Literature/Recombinant_Protein_Therapeutics_from_CHO_Cells-20_years_and_counting_Jayapal.pdf). Accessed 21 Sept 2013.

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<<http://www.bptc.com/presentation/vaccine-manufacturing-facilities-future>>.

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http://tools.lifetechnologies.com/content/sfs/manuals/insect_man.pdf Accessed: 21 Sept 2013

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<http://www.pmda.go.jp/english/past/pdf/7-A.LubinieckiPMDA10207.pdf>, Obtained 25 September 2008.

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Novais, J.L. "Economic Comparison Between Conventional and Disposables-Based Technology for the Production of Biopharmaceuticals." *BIOTECHNOLOGY AND BIOENGINEERING*. 75.2 (2001): 143-153.

Ozturk, Sadettin, and Wei-Shou Hu, *Cell Culture Technology for Pharmaceutical and Call-Based Therapies (Biotechnology and Bioprocessing Series)*, Florida: CRC Press 2005.

Pall Corporation, www.pall.com – Helpful for both upstream and downstream information

Seider, W., J.D. Seader, and D.R Lewin, *Product and Process Design Principles: Synthesis, Analysis and Evaluation*, Wiley, 2003.

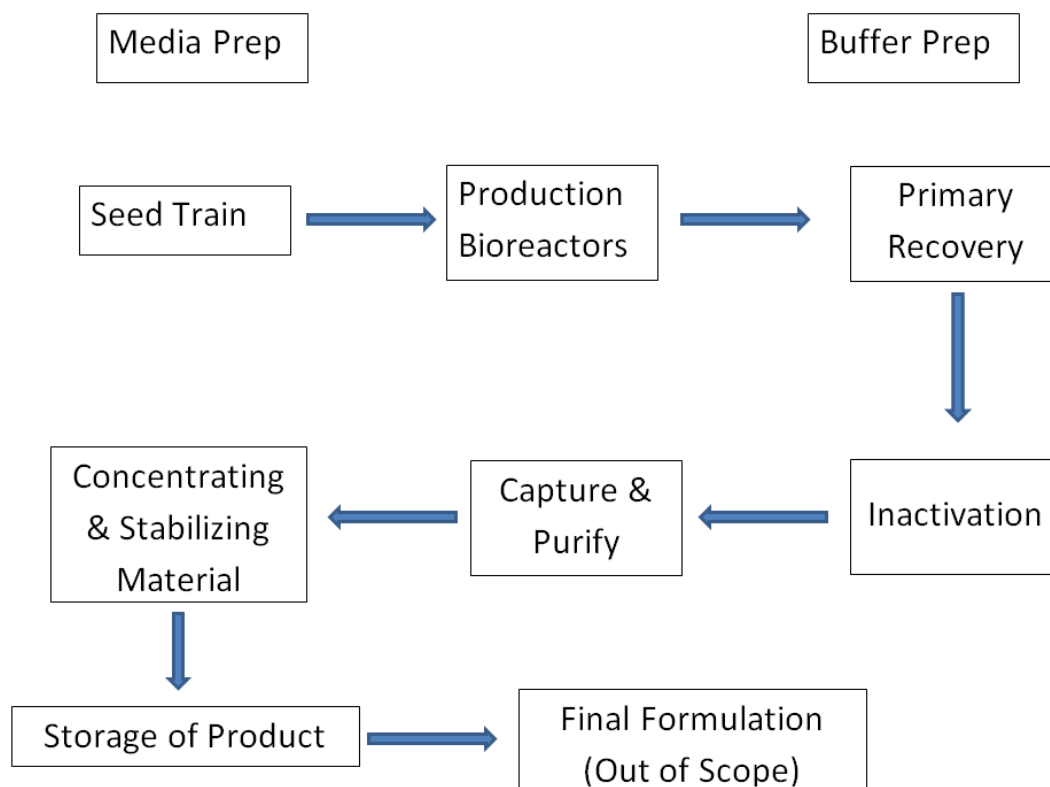
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Stewart, J.M Seiberling, D., "The Secret's Out: Clean in Place" *Chemical Engineering*, 1996.3

Note: This problem statement has some hypothetical data and thus does not necessarily represent an accurate real case.



Block Diagram of the Production Process

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* Source: CCPS, Guidelines for Hazard Evaluation Procedures, 3rd Ed., 2008, AIChE, New York Copyright © 2008, AIChE. All rights reserved. This excerpt is provided solely for the use of AIChE Undergraduate Student Members. All others must request permission by contacting ccps@aiiche.org, +1, 646-495-1371

A4

An Inherently Safer Process Checklist (Courtesy E.I. Du Pont de Nemours & Co., Inc.)

This checklist may be used to stimulate the thinking of inherent safety review and process hazard analysis teams, and any other individuals or groups working on process improvements. It is intended to promote “blue-sky” or “out-of-the-box” thinking, and to generate ideas that might be usable in an existing facility or a “plant of the future” concept.

This checklist should not be used in a rote “yes/no” manner, nor is it necessary to answer every question. The idea is to consider what might be possible, and then determine what is feasible. The checklist should be reviewed periodically throughout the life cycle of the process. As technology changes, what was once impossible becomes possible, and what was once infeasible becomes feasible.

Users of this checklist may find it helpful to rephrase questions in order to prompt maximum creativity; for example “how might it be possible to...?” This approach can lead users to consider alternative means for reducing the hazard level inherent in the process.

The topics for this checklist have been taken from CCPS, Guidelines for Engineering Design for Process Safety, AIChE, New York, 1993 and Bollinger et al., Inherently Safer Chemical Processes: A Life Cycle Approach, AIChE, New York, 1996. It was first published in this form in Johnson et al., Essential Practices for Managing Chemical Reactivity Hazards, AIChE, New York, 2003. Every effort was made to ensure that this checklist is comprehensive; therefore, there may be some redundancy or overlap in questions among the different sections. It should be noted that some of the items in this checklist employ a very broad concept of inherent safety, as presented by Bollinger et al. (1996). As such, they may address inherent aspects of passive, engineered, or even administrative controls, rather than the narrower inherent safety conception of reducing the underlying process hazards that must be contained and controlled to safely operate a facility.

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A4 • Inherently Safer Process Checklist

1 Intensification / Minimization

1.1 Do the following strategies reduce inventories of hazardous raw materials, intermediates, and/or finished products?

- Improved production scheduling
- Just-in-time deliveries
- Direct coupling of process elements
- Onsite generation and consumption

1.2 Do the following actions minimize in- process inventory?

- Eliminating or reducing the size of in- process storage vessels
- Designing processing equipment handling hazardous materials for the smallest feasible inventory
- Locating process equipment to minimize the length of hazardous material piping runs
- Reducing piping diameters

1.3 Can other types of unit operations or equipment reduce material inventories? For example:

- Wiped film stills in place of continuous still pots
- Centrifugal extractors in place of extraction columns
- Flash dryers in place of tray dryers
- Continuous reactors in place of batch
- Plug flow reactors in place of continuous-flow stirred tank reactors
- Continuous in-line mixers in place of mixing vessels

1.4 Can thermodynamic or kinetic efficiencies of reactors be improved by design upgrades (e.g., improved mixing or heat transfer) to reduce hazardous material volume?

1.5 Can equipment sets be combined (e.g., replacing reactive distillation with a separate reactor and multi-column fractionation train; installing internal reboilers or heat

exchangers) to reduce overall system volume?

1.6 Can pipeline inventories be reduced by feeding hazardous materials as a gas instead of a liquid (e.g., chlorine)?

1.7 Can process conditions be changed to avoid handling flammable liquids above their flash points?

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1.8 Can process conditions be changed to reduce production of hazardous wastes or by-products?

2 Substitution / Elimination

2.1 Is it possible to eliminate hazardous raw materials, process intermediates, or by-products by using an alternative process or chemistry?

2.2 Is it possible to eliminate in-process solvents by changing chemistry or processing conditions?

2.3 Is it possible to substitute less hazardous raw materials? For example:

- Noncombustible rather than flammable
- Less volatile
- Less reactive
- More stable
- Less toxic

2.4 Is it possible to use utilities with lower hazards (e.g., low-pressure steam instead of combustible heat transfer fluid)?

2.5 Is it possible to substitute less hazardous final product solvents?

2.6 For equipment containing materials that become unstable at elevated temperatures or freeze at low temperatures, is it possible to use heating and cooling media that limit the maximum and minimum temperature attainable?

3 Attenuation / Moderation

3.1 Is it possible to keep the supply pressure of raw materials lower than the design pressure of the vessels to which they are fed?

3.2 Is it possible to make reaction conditions (e.g., pressure or temperature) less severe by using a catalyst or by using a better catalyst?

3.3 Can the process be operated at less severe conditions using any other route? For example:

- Improved thermodynamic or kinetic efficiencies of reactors by design upgrades (e.g., improved mixing or heat transfer) to reduce operating temperatures and/or pressures
- Changes to the order in which raw materials are added
- Changes in phase of the reaction (e.g., liquid/liquid, gas/liquid, or gas/gas)

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3.4 Is it possible to dilute hazardous raw materials to reduce the hazard potential? For example, by using the following:

- Aqueous ammonia instead of anhydrous
- Aqueous HCl instead of anhydrous
- Sulfuric acid instead of oleum
- Dilute nitric acid instead of concentrated fuming nitric acid
- Wet benzoyl peroxide instead of dry

4 Limitation of Effects

4.1 Is it possible to design and construct vessels and piping to be strong enough to withstand the largest overpressure that could be generated within the process, even if the “worst credible event” occurs (eliminating the need for complex, high-pressure interlock systems and/or extensive emergency relief systems)?

4.2 Is all equipment designed to totally contain the materials that might be present inside at ambient temperature or the maximum

attainable process temperature (i.e., higher maximum allowable working temperature to accommodate loss of cooling, simplifying reliance on the proper functioning of external systems, such as refrigeration systems, to control temperature such that vapor pressure is less than equipment design pressure)?

4.3 Can passive leak-limiting technology (e.g., blowout resistant gaskets and excess flow valves) be utilized to limit potential for loss of containment?

4.4 Can process units be located to reduce or eliminate adverse effects from other adjacent hazardous installations?

4.5 Can process units be located to eliminate or minimize the following?

- Off-site impacts
- On-site impacts on employees and other plant facilities

4.6 For processes handling flammable materials, is it possible to design the facility layout to minimize the number and size of confined areas and to limit the potential for serious overpressures in the event of a loss of containment and subsequent ignition?

4.7 Can the plant be located to minimize the need for transportation of hazardous materials?

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4.8 Can materials be transported in the following ways?

- In a less hazardous form
- Via a safer transport method
- Via a safer route

5 Simplification / Error Tolerance

5.1 Is it possible to separate a single, procedurally complex, multipurpose vessel into several simpler processing steps and processing vessels, thereby reducing the potential for hazardous interactions when the complexity of the number of raw materials, utilities, and auxiliary equipment is reduced for specific vessels?

5.2 Can equipment be designed so that it is difficult to create a potentially hazardous situation due to an operating or maintenance error? For example:

- Simplifying displays
- Designing temperature-limited heat transfer equipment
- Lowering corrosion potential by use of resistant materials of construction
- Lowering operating pressure to limit release rates
- Using higher processing temperatures (to eliminate cryogenic effects such as embrittlement failures)
- Using passive vs. active controls (e.g., stronger piping and vessels)
- Using buried or shielded tanks
- Using fail-safe controls if utilities are lost
- Limiting the degree of instrumentation redundancy required
- Using refrigerated storage vs. pressurized storage
- Spreading electrical feed over independent or emergency sources
- Reducing wall area to minimize corrosion/fire exposure
- Reducing the number of connections and paths
- Minimizing the number of flanges in hazardous processes
- Valving/piping/hose designed to prevent connection error
- Using fewer bends in piping
- Increasing wall strength
- Using fewer seams and joints
- Providing extra corrosion/erosion allowance
- Reducing vibration
- Using double-walled pipes, tanks, and other containers
- Minimizing use of open-ended valves
- Eliminating open-ended, quick-opening valves in hazardous service
- Improving valve seating reliability
- Eliminating unnecessary expansion joints, hoses, and rupture disks
- Eliminating unnecessary sight glasses/glass rotameters

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5.3 Can procedures be designed so that it is difficult to create a potentially hazardous situation due to an operating or maintenance error? For example:

- Simplifying procedures
- Reducing excessive reliance on human action to control the process

5.4 Can equipment be eliminated or arranged to simplify material handling?

- Using gravity instead of pumps to transfer liquids
- Siting to minimize hazardous transport or transfer
- Reducing congestion (i.e., easier to access and maintain)
- Reducing knock-on effects from adjacent facilities
- Removing hazardous components early in the process rather than spreading them throughout the process
- Shortening flow paths

5.5 Can reactors be modified to eliminate auxiliary equipment (e.g., by creating a self-regulatory mechanism by using natural convection rather than forced convection for emergency cooling)?

5.6 Can distributed control system (DCS) modules be simplified or reconfigured such that failure of one module does not disable a large number of critical control loops?

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