2016
Student Design Competition

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

Robert (Bob) Beitle PhD PE
Ralph E. Martin Department of Chemical Engineering
Associate Vice Provost for Research and Economic Development
University of Arkansas
rbeitle@uark.edu

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

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

AIChE 2016 Student Design Competition

"Cell Therapy for Spinal Cord Injuries: Commercial Manufacturing Facility"

DEADLINE FOR ELECTRONIC SUBMISSION TO AIChE IS MIDNIGHT, Friday, June 10, 2016.

November 2015

Dear Chemical Engineering Department Heads and Student Chapter Advisors,

I am pleased to send you the 2016 AIChE Student Design Competition statement. Please forward it to those faculty teaching design courses. I've included this year's challenge below:

"Cell Therapy for Spinal Cord Injuries: Commercial Manufacturing Facility"

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 10, 2016.

 An entry form is required for each participant – it's attached to this email. Please submit one form for each participant, 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 is 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.aiche.org/students/.

 Final submission of solutions to AIChE must be in electronic format (PDF and MS-Word). The main text must be 125 pages or less, and an additional 100 page or less is allowed for supplementary material only. The final submission to AIChE must consist of 2 electronic files.

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

 All submissions must be submitted in an electronic format no later than Friday, June 10, 2016. Please use the directions below and maintain a copy for your files.

- Complete this online form if it's a team submission: https://chenected.wufoo.com/forms/2016-student-design-competition-team/
- Complete this online form if it's an individual submission: https://chenected.wufoo.com/forms/2016-student-design-competition-individual/

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@aiche.org. Questions relating to the substance of the design problem should be directed to: Dr. Bob Beitle, University of Arkansas, at rbeitle@uark.edu.

Thank you for your support of this important student competition.

Sincerely,

Sarah Ewing

Sarah Ewing
AIChE Student Programs
(646) 495-1364
sarae@aiche.org

2016 AIChE Annual 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 2016 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.

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 10, 2016. 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 STUDENT MEMBERS MAY SUBMIT A SOLUTION. Non-member entries will not be considered. To become a 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 (30) 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 submitted electronically by no later than midnight on Friday, June 10, 2016.

 The finished report should be submitted to the faculty advisor within the 30-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 125 pages or less, and an additional 100 page or less is allowed for supplementary material only. The final submission to AIChE must consist of 2 electronic files.

SUBMITING 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).

 Advisors: once you have identified the entries you will submit, follow these steps:

1. Have each student fill out and sign the 2016 Entry Doc.
2. Scan the Entry Doc for each student.
3. Complete this online form if it's a team submission: https://chenected.wufoo.com/forms/2016-student-design-competition-team/
4. Complete this online form if it's an individual submission: https://chenected.wufoo.com/forms/2016-student-design-competition-individual/

DEADLINE: **Midnight on Friday, June 10, 2016.**

“Cell Therapy for Spinal Cord Injuries: Commercial Manufacturing Facility”

DEADLINE FOR ELECTRONIC SUBMISSION TO AIChE IS MIDNIGHT, Friday, June 10, 2016.

Overview:

Design a manufacturing facility for the production of a stem cell treatment for the treatment of spinal cord injuries. The manufacturing facility will also produce the material in custom designed vessels that the team will design for the culturing of the stem cells.

Introduction:

The company is currently developing a spinal cord injury regeneration therapy that will allow patients to recover from the injury and be able to move again. There is currently an unmet need in the market for the treatment of spinal cord injuries where there are significant functional improvements. Spinal cord injuries are diverse and are typically permanent leaving a patient with a lower quality of life. There are approximately 250000 people just in the US with spinal cord injuries and an additional 12000 people a year are added in the US alone (California’s Institute for Regenerative Medicine)

Design Considerations and Specifications:

You are part of a small to midsize biotechnology company that focuses on cell therapies for a number of indications and the company has one launched product but it is not in the cell therapy area.

The company is currently developing a spinal cord injury regeneration therapy that will allow patients to recover from the injury and be able to move again. There is currently an unmet need in the market for the treatment of spinal cord injuries where there are significant functional improvements. Spinal cord injuries are diverse and are typically permanent leaving a patient with a lower quality of life. There are approximately 250000 people just in the US with spinal cord injuries and an additional 12000 people a year are added in the US alone (California’s Institute for Regenerative Medicine)

The research team had been pursuing two different cell therapy systems. One therapy option uses human embryonic stem cells (hESC) and the other option uses Adult Stem Cells but the hESC program is behind the Adult Stem Cell Program. As part of the the commercialization team you will need to progress the Adult Stem Cell Therapy to market as resources are limited and time is of the essence.

The team will need to design a construct a new manufacturing facility/suite for the new therapy. Adult stem cells are very delicate cells and are typically attached cell lines so it is difficult to grow them in traditional bioreactors/fermenters which are normally designed for suspension cultures. Also note that the therapy is the “cell” itself so you need to ensure that the cells are not damaged in the production process. It is suggested that you design a new-type of low shear bioreactor system that controls pH, dissolved oxygen and temperature. There are systems on the market for growing attached cell lines as well as stem cells but your company wants a custom scale-up solution for their cell therapy division. The company would like you to review what is on the market and then create/optimize a bioreactor system to produce the spinal cord injury treatment under cGMP conditions.

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 process, the new bioreactor to grow the cells in and the production facility to make the life improving cell therapy for spinal cord injuries. 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.

Please remember to take into consideration the time needed to clean between manufacturing campaigns.

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 BD™, Life Technologies™, or Lonza™. Please design the media preparation area and select whether to use steam in place vessels, disposable vessels or both. Also ensure that there is storage for the raw materials as well as the media after it is prepared.

Vial Thaw/Expansion

You will obtain one vial of Adult stem cells that are undifferentiated 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 how the vials are prepared. For this exercise assume that the starting cell number is 100,000 adult stem cells that are not differentiated. It is not unusual for the doubling time of Adult Stem cells to be 200 hrs plus or minus. (Nowakowski) The cells will need to be thawed and expanded by passaging into larger and larger volumes and after the final scale up the culture will need to be differentiated into the spinal cord therapy (Neural cells) which will take place in the next step called differentiation in the block diagram. Please note that stem cells are typically attached cell lines so one needs to account for attachment of the cells in the process.

Differentiation:

Once the proliferation step is completed of the undifferentiated adult stem cells cells/cultures the next step is differentiation. You will need to decide, design and create the type of bioreactor you will use for the differentiation step of the process. Note that one may select to leverage the same type of bioreactor for different steps in the upstream process (expansion and differentiation). The bioreactors need to be designed so that after x number of manufacturing campaigns one is able to make the necessary amount of the stem cell therapy for the market as well as account for increases in market demand.

Downstream Purification:

Purification:

After the adult stem cells have been differentiationed into neural stem cells the product which is the cells need to be collected and sorted as not all of the cells will have differentiated and some of the cells will have differentiated incorrectly. One needs to collect the "quality" cells that will go into the therapy. Design a method process to collect/harvest the stem cells and also sort them. The group only ants cells that differentiated into the desired cell therapy.

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

Concentrating and Stabilizing Material for Shipping and Future Formulation:

After the material/cells are purified one may want to further concentrate the material please explore the options for this step using the latest technologies. Also the stem cell therapy will not be able to be formulated or given to patients onsite so design a stable formulation for the therapy before final formulation.

Testing of Raw Materials and Product:

It is critical that quality is maintained in every step of the manufacturing process and in the design one needs to account for quality control laboratories.

Storage and Shipment to an Off-Site Formulation Facility:

Please design a section of your facility to package and store the stem cell therapy until it is shipped to your formulation group within global manufacturing for final formulation and packaging for patients. Remember that the cells are the product/medication and they are very fragile.

Storage of Raw Materials and Intermediates On Site:

Please make sure to design an area where raw materials and intermediates may be stored and also discuss the amount of material that the organization would like to have on site.

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:

Spinal cord injuries are diverse and are typically permanent leaving a patient with a lower quality of life. There are approximately 250,000 people just in the US with spinal cord injuries and an additional 12,000 people a year are added in the US alone (California's Institute for Regenerative Medicine)

At the moment your manufacturing facility will be focused just on the US market with a long term goal of treating patients in Europe and beyond.

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.

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 50% for the battery limits portion of the Project.

17. Conclusions and Recommendations
18. Acknowledgements
19. Bibliography
20. Appendix

Helpful/Interesting Information:

Examples of cell therapy companies: Biotime, Cellular Dynamics, Celgene, Geron, Mesoblast, Lonza and many more.

The FDA has given suggested guidelines for the internal layout of a biopharmaceutical 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.

Blanch, Harvey W, Douglas S. Clark, *BioChemical Engineering*, Florida: CRC Press, 1997.

California Institute of Regenerative Medicine.: www.cirm.ca.gov

Chris Mason, Julian Mason, Emily J. Culme-Seymour, Gregory A. Bonfiglio, Brock C. Reeve, Cell Therapy Companies Make Strong Progress from October 2012 to March 2013 Amid Mixed Stock Market Sentiment, Cell Stem Cell, Volume 12, Issue 6, 6 June 2013, Pages 644-647, ISSN 1934-5909, http://dx.doi.org/10.1016/j.stem.2013.05.017. (http://www.sciencedirect.com/science/article/pii/S1934590913002105)

Dos Santos FF, Andrade PZ, et al. "Bioreactor Design for Clinical Grade Expansion of Stem Cells." Biotechnology Journal 8(6) June 2013 pp 644-654.

Eppendorf www.eppendorf.com – Helpful for information about lab equipment and bioreactors

GE – www.ge.com Helpful for both upstream and downstream information

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

Hambor, John E. "Manufacturing Stem Cells at Scale." Bioprocessing International, Vol 10, No 6, June 2012, pp 22-23.

King, Marita A. "Selection Criteria for WFI Production Equipment, Controlled Environments Magazine, September 2005, http://www.cemag.us/Article_Print.asp?pid=546, Obtained 28 June 2009.

Lakshmikanthan, J., *Outsourcing: Biologics Manufacturing: The CMO Advantage*, 14 BioPharm International, February 2007.

Lubiniecki, A. S., "Presentation: Global Industrial Perspective of Novel Biologicals Development," Centocor R&D/Johnson and Johnson, http://www.pmda.go.jp/english/past/pdf/7-A.LubinieckiPMDA10207.pdf, Obtained 25 September 2008.

Millipore – www.millipore.com - Helpful for both upstream and downstream information

Nowakowski, Richard S. Stem and Progenitor Cells of the Central Nervous System, Issues 2-4 Basel Karger, 2004

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

Pearson, Sue. Driving Down the Cost of Stem Cell Manufacturing. GEN http://www.genengnews.com/insight-and-intelligence/driving-down-the-cost-of-stem-cell-manufacturing/77900326/ , 3 December 2015.

Stem Cell Basics, National Institute of Health (NIH) - http://stemcells.nih.gov/info/basics/pages/basics4.aspx Obtained 17 Sept 2015

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

Shukla, Abhinav A., Mark R. Etzel, Shishir Gadam, *Process Scale Bioseparations for the Biopharmaceutical Industry.* Florida: CRC Press, 2007.

Stewart, J.M Seiberling, D., "The Secret's Out: Clean in Place" *Chemical Engineering*, 1996.

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