PURDUE
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DEPARTMENT OF AGRICULTURAL & BIOLOGICAL ENGINEERING

TO: The Faculty of the College of Engineering

FROM: Bernard A. Engel, Department Head Agricultural & Biological Engineering

DATE: November 21, 2018

RE: New Graduate Course, ABE 51500 – EFD 69-19

The faculty of the School of Agricultural & Biological Engineering has approved the following new course. This submission is recommended to the Engineering Faculty for approval.

ABE 51500 Molecular Basis of Manufacturing
Lecture, Cr. 3

Course Description

This course addresses important Chemistry Manufacturing and Control (CMC) issues related to manufacturing and quality by design. The course provides important information on strategies for quality by design, manufacturing strategies for early development, the best approaches to analyzing data, and strategies for reporting the information to the FDA. This course will also focus on product design and processing. Using product and process design helps achieve quality by design (QbD), strong development reports, excellent regulatory submissions and allows continuous improvement. The course includes laboratory exercises, laboratory tours, and/or workshops outlining how to interpret the data.

Justification

Modern biotechnology companies must conduct drug discovery, development, manufacturing and marketing in a highly regulated environment with increasing competition and pricing pressures. Systems for quality manufacturing, quality by design of manufacturing processes, process analytical technology, and on-line measurement are critical elements for success in this complex and evolving environment. The cost of poor quality and the penalties for non-compliance are unacceptable in today's drug development business. Knowledge of effective quality manufacturing principles and practices is critical to getting things *right the first time*. This course will provide information on best-in-class methods for quality manufacturing, quality by design and formulation.

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This course is a core course for both the Biotechnology Quality and Regulatory Compliance graduate certificate and the Area of Specialization in Biotechnology Innovation and Regulatory Science.

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TLI 52500: Molecular Basis of Manufacturing

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Course Rationale:

Modern biotechnology companies must conduct drug discovery, development, manufacturing and marketing in a highly regulated environment with increasing competition and pricing pressures. Systems for quality manufacturing, quality by design of manufacturing processes, process analytical technology, and on-line measurement are critical elements for success in this complex and evolving environment. The cost of poor quality and the penalties for non-compliance are unacceptable in today's drug development business. Knowledge of effective quality manufacturing principles and practices is critical to getting things *right the first time*. This course will provide information on best-in-class methods for quality manufacturing, quality by design and formulation.

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LEARNING OUTCOMES

The overall learning outcomes for the program include:

Comprehension: The student shall comprehend strategies used for biotechnology innovation: regulatory and quality documents and materials in the areas of drug development and discovery.

Integrative competence: The student shall be able to meld theory and practice

Critical thinking and decision making abilities: The student shall examine issues rationally, logically, and coherently; and shall acquire, evaluate, and synthesize information and knowledge relevant to an identified problem; and shall make sound decisions in both familiar and unfamiliar contexts.

Communication abilities: The student shall read, write, speak, listen, and use data, media and computers to send and respond effectively to communications for varied audiences and purposes.

Responsible use of values and ethical principles: The student shall demonstrate sensitivity to and facility with personal values and ethical principles in professional and social contexts.

COURSE LEARNING OUTCOMES

Framework---Students will learn the principles, strategies, and molecular concepts involved in manufacturing drug products under Good Manufacturing Practices.

Learning Outcome 1: Students will learn manufacturing following GMP in a laboratory course. Students will learn GMP manufacturing procedures and how drug products (especially tablets) are manufactured.

- Students will learn about the various steps in manufacturing including blending, granulation, drying, compression, coating, etc.
- Students will learn about the specifications in manufacturing

Learning Outcome 2: Students will learn the regulations governing the manufacture of drugs, including the methods used to prove quality, validation of those methods, and validation of manufacture.

- Students will learn about compliance to GMP and warning letters

Learning Outcome 3: Students will learn how drug products are characterized and some of the steps used to characterize a drug product including:

- Dissolution
- Weight variation
- Content uniformity
- Instrumental methods including X-ray diffraction

Learning Outcome 4: Students will learn how the Quality Overall Summary and the critical quality attributes diagram is constructed

- Students will understand general approaches to determining critical attributes and factors that influence quality of the final product

Learning Outcome 5. Students will learn about Quality by Design and the new FDA quality initiative.

Learning Outcome 6: Students will learn how technology and innovation impact the manufacturing process

- Students will learn about the emerging areas including Process Analytical Technology and on line monitoring of the process.

- Students will learn about innovation in manufacturing especially as related to quality by design

Learning Outcome 7: Students will learn how the global environment impacts the manufacturing process

Learning Outcome 8: Students will learn about accelerating drug development and manufacturing drugs for the treatment of rare diseases.

Reference and reading materials:

- Textbook: *Theory and Practice of Industrial Pharmacy* by Leon Lachman, Herbert A. Lieberman, and Joseph L. Kanig, Stipes Publishing, LLC)
- Laboratory book: *Introduction to Pharmaceutical Unit Operations* by David A. Engers and Peter L.D. Wildfong, Stipes Publishing, LLC)

Both of these textbooks will be used to provide a foundational background.

Online lectures, quizzes, case studies, and other assignments as well as other current reading material and resources will be provided through the Purdue course management system, Blackboard Learn (BBL) http://www.itap.purdue.edu/learning/tools/blackboard/

Additional Resources:

- *The Theory and practice of industrial pharmacy*. 3rd ed. ed.; Philadelphia: Lea & Febiger: Philadelphia, 1986.
- *Guidance for industry ANDAs, pharmaceutical solid polymorphism, chemistry, manufacturing and controls information*. Rockville, MD: U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research: Rockville, MD, 2007.
- *Good manufacturing practices for pharmaceuticals*. 6th ed. / edited by Joseph D. Nally.. ed.; New York: Informa Healthcare: New York, 2007.
- *Pharmaceutical manufacturing handbook: production and processes*. Hoboken, N.J.: Wiley-Interscience: Hoboken, N.J., 2008.
- *Risk management applications in pharmaceutical and biopharmaceutical products manufacturing*. Hoboken, New Jersey: John Wiley & Sons, Inc.: 2013.
- *Continuous processing in pharmaceutical manufacturing*. :Weinheim: Wiley-VCH: 2015.

- Behme, S., *Manufacturing of pharmaceutical proteins: from technology to economy*. Second, revised and expanded edition. ed.; Weinheim, Germany: Wiley-VCH: 2015.
- Cipich, M. N. C. Real time steady-state data reconciliation and gross error detection in continuous pharmaceutical manufacturing. Thesis (M.S.Ch.E.)--Purdue University, 2009., 2009.
- Ciurczak, E. W., *Pharmaceutical and Medical Applications of Near-Infrared Spectroscopy, Second Edition*. 2nd ed.; Hoboken: Taylor and Francis: Hoboken, 2014.
- Eyjolfsson, R., *Design and Manufacture of Pharmaceutical Tablets*. Burlington: Elsevier Science: Burlington, 2014.
- Jolliffe, H. G.; Gerogiorgis, D. I., *Systematic Solvent Evaluation for Artemisinin Recovery in Continuous Pharmaceutical Manufacturing*. 2016; Vol. 38, p 1027-1032.
- Publishing, W. A., *Pharmaceutical Manufacturing Encyclopedia*. 3rd ed.; Burlington: Elsevier Science: Burlington, 2006.
- Subramanian, G., *Continuous Processing in Pharmaceutical Manufacturing*. 2015; p 1-504.

Pedagogy

A blended pedagogical approach for course delivery will be used. Class time will focus on interactive and engaging sessions, to learn and practice the application of course material. Guest lectures will be provided from professional experts from industry, focused on current topic lectures and discussions. Additional resources and fundamental core content is provided online using the Blackboard Learn course management system.

Student evaluation is based upon case studies, quizzes, reflections and a final project with application to drug development. Students also work in groups and practice professional communication through presentations and discussions surrounding the course topics, case studies and final project.

Assessment:

Assigned Readings.

Readings will be assigned to provide more information and background on the course concepts. There will be oral discussions in class over the readings, quizzes and case studies.

Quizzes.

Quizzes will be given to evaluate your course progress. They will cover lecture material and course readings. Quiz items may be short answer, true-false, multiple choices, a short problem, or a combination of these.

Case Studies:

Case studies will be assigned to give you practice using the concepts learned in class that will provide a foundation for your final project. Therefore, it is particularly important that you personally do the work. Working with other individuals is fine as long as you actively participate; learning is virtually eliminated when simply copying another person's work. Due dates for case studies will be posted on Blackboard Learn.

Grading:

The final grades for the course will be determined by a total accumulation of points from all activities and assignments. Individual progress toward course learning outcomes and final grades will be computed based on the following weights:

Assignments	**Percentage**
Content Quizzes	10
Case Studies	60
Attendance and Class Participation	30
Total	100

Grading Scale:

Grade	**GPA Value**	**% Range**
A	4.0	93-100
A-	3.7	90.0-92.9
B+	3.3	87.0-89.9
B	3.0	83.0-86.9
B-	2.7	80.0-82.9
C+	2.3	77.0-79.9
C	2.0	73.0-76.9
C-	1.7	70.0-72.9

D+	1.3	67.0-69.9
D	1.0	63.0-66.9
D-	0.7	60.0-62.9
F	0.0	<60.0

Academic Dishonesty

Purdue prohibits "dishonesty in connection with any University activity. Cheating, plagiarism, or knowingly furnishing false information to the University are examples of dishonesty." [Part 5, Section III-B-2-a, Student Regulations] Furthermore, the University Senate has stipulated that "the commitment of acts of cheating, lying, and deceit in any of their diverse forms (such as the use of substitutes for taking examinations, the use of illegal cribs, plagiarism, and copying during examinations) is dishonest and must not be tolerated. Moreover, knowingly to aid and abet, directly or indirectly, other parties in committing dishonest acts is in itself dishonest." [University Senate Document 72-18, December 15, 1972]

Please refer to Purdue's student guide for academic integrity for additional information: https://www.purdue.edu/odos/academic-integrity/

Use of Copyrighted Materials

Students are expected, within the context of the Regulations Governing Student Conduct and other applicable University policies, to act responsibly and ethically by applying the appropriate exception under the Copyright Act to the use of copyrighted works in their activities and studies. The University does not assume legal responsibility for violations of copyright law by students who are not employees of the University.

A Copyrightable Work created by any person subject to this policy primarily to express and preserve scholarship as evidence of academic advancement or academic accomplishment. Such works may include, but are not limited to, scholarly publications, journal articles, research bulletins, monographs, books, plays, poems, musical compositions and other works of artistic imagination, and works of students created in the course of their education, such as exams, projects, theses or dissertations, papers and articles.

Please refer to the University Regulations on policies: http://www.purdue.edu/policies/academic-research-affairs/ia3.html

Attendance

Purdue University policy states that all students are expected to be present for every meeting of the classes in which they are enrolled. Only the instructor can excuse a student from a course requirement or responsibility. When conflicts or absences can be anticipated, such as for many University sponsored activities and religious observations, the student should inform the instructor of the situation as far in advance as possible…For unanticipated or emergency absences when advance notification to an instructor is not possible, the student should contact the instructor as soon as possible by email, or by contacting the main office that offers the course. When the student is unable to make direct contact with the instructor and is unable to leave word with the instructor's department because of circumstances beyond the student's control, and in cases of bereavement, the student or the student's representative should contact the Office of the Dean of Students.

The link to the complete policy and implications can be found at:
http://www.purdue.edu/studentregulations/regulations_procedures/classes.html

Missed or Late Work
Assignments must be turned in at the beginning of class or submitted via Blackboard Learn. Assignments will not be accepted via email unless special arrangements have been made in advance.

Late assignments will not be accepted unless special arrangements have been made with the instructor, preferably in advance. If prior arrangements have not been made, missed or late assignments will not receive credit. See policy above regarding arriving late/leaving early. Assignments can be accepted early.

Grief Absence Policy for Students
Purdue University recognizes that a time of bereavement is very difficult for a student. The University therefore provides the following rights to students facing the loss of a family member through the Grief Absence Policy for Students (GAPS). GAPS Policy: Students will be excused for funeral leave and given the opportunity to earn equivalent credit and to demonstrate evidence of meeting the learning outcomes for misses assignments or assessments in the event of the death of a member of the student's family.

See the University's website for additional information:
http://www.purdue.edu/studentregulations/regulations_procedures/classes.html

Violent Behavior Policy
Purdue University is committed to providing a safe and secure campus environment for members of the university community. Purdue strives to create an educational environment for students and a work environment for employees that promote educational and career goals. Violent Behavior impedes such goals. Therefore, Violent Behavior is prohibited in or on any University Facility or while participating in any university activity.

See the University's website for additional information:

http://www.purdue.edu/policies/facilities-safety/iva3.html

Emergencies
In the event of a major campus emergency, course requirements, deadlines and grading percentages are subject to changes that may be necessitated by a revised semester calendar or other circumstances beyond the instructor's control. Relevant changes to this course will be posted onto the course website or can be obtained by contacting the instructors or TAs via email or phone. You are expected to read your @purdue.edu email on a frequent basis.

See the University's website for additional information:
https://www.purdue.edu/ehps/emergency_preparedness/

Accessibility and Accommodations
Purdue University strives to make learning experiences as accessible as possible. If you anticipate or experience physical or academic barriers based on disability, you are welcome to let me know so that we can discuss options. You are also encouraged to contact the Disability Resource Center at: drc@purdue.edu or by phone: 765-494-1247.

Nondiscrimination
Purdue University is committed to maintaining a community which recognizes and values the inherent worth and dignity of every person; fosters tolerance, sensitivity, understanding, and mutual respect among its members; and encourages each individual to strive to reach his or her own potential. In pursuit of its goal of academic excellence, the University seeks to develop and nurture diversity. The University believes that diversity among its many members strengthens the institution, stimulates creativity, promotes the exchange of ideas, and enriches campus life.

Purdue University prohibits discrimination against any member of the University community on the basis of race, religion, color, sex, age, national origin or ancestry, genetic information, marital status, parental status, sexual orientation, gender identity and expression, disability, or status as a veteran. The University will conduct its programs, services and activities consistent with applicable federal, state and local laws, regulations and orders and in conformance with the procedures and limitations as set forth in Executive Memorandum No. D-1, which provides specific contractual rights and remedies. Any student who believes they have been discriminated against may visit www.purdue.edu/report-hate to submit a complaint to the Office of Institutional Equity. Information may be reported anonymously.

Please refer students to Purdue's nondiscrimination statement:
http://www.purdue.edu/purdue/ea_eou_statement.html

Lecture Topics and Laboratory Learning Activities

Students will complete approximately 16 contact hours of laboratory work. They will carry out a complete manufacturing process in the College of Pharmacy's pilot-scale manufacturing lab. The process will include various unit operations, blending, wet granulation, drying, tableting and coating. Participants use on-line NIR to monitor some of these unit operations and will use Chemometrics to analyze some of the on-line data. In addition, various off-line techniques will be used or demonstrated. The goal is to provide enough information to allow the student to apply their acquired skills in the place of work.

Pre-Lab: Lecture Outline

Big questions for Developing a Candidate through Proof of Concept
Overview of Pharmaceutical Unit Operations-Drug Product
Mixing
Flow and Blending
Particle Size Reduction
Introduction to Drying Basics
Granulation
Tablet Compression
Tablet analysis
Coating

Laboratory Experiments Outline

Safety First and laboratory Format
Total Quality and Manufacturing Documentation I. Introduction II. Standard Operating Procedures III. Master Formula IV. Batch Records
Production Project Overview

I. Introduction II. Granulation III. Tablet Compression IV. Film Coating V. Dissolution VI. Characterization VII. Considerations For Presentation Of Batch Data
Alternative manufacturing technologies
Training Batch Records
Production Batch Records

Post-Lab: Lecture Outline

QbD Concepts: Science of Design and the Socratic Review
ICH and International Thinking on Quality by Design & Development
Development Report
ICH Q9 Quality Risk Management
Quality Systems
Introduction to API Management
API Crystallization
API Synthesis, Isolation, & Drying
Impurities
Residual Solvents in API Manufacturing
Powders & Mechanical Properties
Hard Shell Gelatin Capsules
Powder Formulations
Process Validation

Cleaning Verification in Pharmaceutical Manufacturing
Method Validation SOP
Solubility and Dissolution Testing
Dissolution Methods Validation ANDA Section XV Dissolution
API Certificate of Analysis
Certificate of Analysis Drug Product
Validation of PAT Methods