USC Department of Regulatory and Quality Sciences

RSCI 532: Early Stage Drug Development

Units: 3

Summer term, Five full days, 9am-5pm

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Recommended Preparation

Undergraduate degree in pharmacy, biological sciences or related disciplines, medical or independent health sciences; enrollment in MS (Regulatory Science), Certificate in Preclinical Drug Development or permission of instructor

Course Description

Typically, during pharmaceutical ***drug development***, large numbers of molecules are generated with the goal of identifying the most promising candidates for further development. Promising candidates are selected using *in vitro* testing models that examine binding to receptors, effects on enzyme activities, toxic effects, or other pharmacological parameters: these tests usually require only small amounts of the drug. Candidates that are not rejected during these early tests are prepared in greater quantities for *in vivo* animal testing for efficacy and safety. Commonly, a single candidate is selected for an investigational new drug (IND) application and introduction into human subjects, initially using healthy volunteers in most cases. Less than 10 % of INDs for new molecular entities (NME) progress beyond the investigational stage to submission of a marketing application, New Drug Application (NDA). To help speed up the process of drug development, reduce the cost or number of human subjects needed for an IND, a first pass *exploratory IND study* may be first conducted. That is, *an exploratory IND study* is intended to describe a clinical trial that : 1) is conducted early in phase 1, 2) involves very limited human exposure and 3) has no therapeutic or diagnostic intent.

Overall, ***drug development*** essentially starts where drug discovery ends and comprises all the activities involved in transforming a compound from a drug candidate to a product approved for marketing by the appropriate regulatory authorities (Blass, 2015).

This course will provide a summary of the drug development process leading up to the phase I-II clinical trial phase. Specific areas of interest will center on large-scale compound formulation and dosage criteria and extensive toxicity and pharmacokinetic studies in both animals and humans in preparation for either an exploratory IND or an IND application submission. Following the conclusion of the drug development phase, this course will outline the process of ensuring product for clinical trials and scaling up for subsequent NDA submission.

Learning Objectives

For the students to acquire a strong understanding of the step-by-step process involved in pre-clinical drug development as one would expect to encounter if conducting drug development at a pharmaceutical company.

Upon successful completion of this course a student should be able to:

1. Comprehend the overall process for small molecule drug discovery
2. Access drug safety related to potential side effects (e.g. HERG activity)
3. Understand the relationship between dose and range toxicity
4. Identify potential genotoxicity, carcinogenicity and reproductive/developmental toxicology issues and how to test for them
5. Access time-related toxicity differentiating between acute and chronic toxicity exposure
6. Understand commonly used toxicity terminology (e.g., LD50, LC50, MTD, etc…)
7. Understand the development of different routes of administration
8. Understand the basic formulation challenges and solutions to new drug development
9. Comprehend different drug delivery systems

10. Differentiate the differences in drug development between a small molecule drug and a biopharmaceutical
11. Obtain a basic understanding of how human clinical trials are initiated
12. Explain the issues involved in preparing drug for clinical trials and the importance of comparability as trials progress

Course Outline:

This course focuses on the multitude of critical components that involved in drug development as viewed from the perspective of industry. Course topics will be presented in 3-4 hr blocks. Many of these blocks will be presented by experts from industry who have developed and are utilizing the science and business practices discussed in the class. In addition to these blocks, students will present and write a critical review of a published manuscripts from a journal relating to drug discovery and development such as *"Journal of Translational Medicine," "Current Opinion in Drug Discovery & Development," "Cancer Drug Discovery and Development."*

At the beginning of each term in which the course is taught, a detailed agenda will be developed that identifies the dates and times of the sessions and the names of any guest speakers for that session. In addition, students will be supplied with a binder that contains all of the information about assignments and projects, reading materials that are unique to the lectures, and biographical sketches of the instructors. All of this material is also posted and updated weekly on blackboard, which is our main tool for organizing materials.

Students will also be given information about using blackboard and our other on-line tools at that time. Each week, the instructor will identify the section of the textbook and supplementary readings in the binder that should be prepared for the session(s) that follow. Because this is an area of rapid change in policies, the readings will vary from one term to the next.

Course Requirements and Grades:

Assignment #	Title	Due Date	% of Grade
I.	Individual Assignment	TBA	30%
II.	Group Presentations – Based on Written Group Project	TBA	15%
III.	Group Written Assignment	TBA	15%
IV.	Final Examination	TBA	40%

The presentation and critical review will be assessed using the basic criteria as presented in the Objective section above and will include one or more of the topics below:

- Case study of issues faced by a start-up pharmaceutical company
- Role of CROs in new drug development
- Identification of regulatory implications
- Development products for clinical testing and comparability
- Future research opportunities
- Development of follow-on products
- Scale-up /formulation challenges
- Introduction of quality management into scale-up activities

Topics	Reading Assignments
General Review of Drug Discovery and Relation to Drug Development • Review of drug discovery • Components of drug development • Outline interface between drug discovery and development	Rang, Pg 43 – 45, 221 - 227
Pre-clinical Drug Safety / Toxicology Assessment **Session 1** • Review of good laboratory procedures (GLP) toxicology and general toxicology terminology • Overview of adverse drug effects • Introduction to safety pharmacology • Exploratory (dose range-finding) toxicology • Studies • Chronic toxicity studies **Session 2:** • Evaluation of drug for genotoxicity • Carcinogenicity and Reproductive/developmental (teratogenicity) toxicology studies • Introduction to Toxicokinetics	Rang, Pg 229 -242
Pharmaceutical Development – Formulation • Routes of drug administration • Overview of preformulation studies • Formulation criteria	Rang, Pg 243 – 253
Considerations of Drug Delivery • Different routes of delivery • Challenges of combination products • New directions in drug delivery vehicles	E.g., Patton, JS (2005) Pulmonary drug delivery comes of age. Drug Delivery Technology, 5,5:44-49 Patel M, Patel R, Patel, G, Patel J, and Patel M (2005) PEGylation: and innovative approach for protein delivery. Drug Delivery Technology 5,6:48-56 *Articles will be included in binder*
Overview of Clinical Development • Introduction to clinical trials terminology—e.g., NME, exploratory IND, INDs, NDA • Overview of clinical trials	Rang, Pg 255 - 271
Developing drugs for clinical trials • Developing placebos and active control products • Implementing quality systems	Elston, C (2005) Preparing packaging for large clinical studies. Pharmaceutical and Medical packaging. 13: 36-44 Polin, JB (2001)Sophisticated packaging for clinical trials. Pharm Med Packaging News

- Blinding challenges
- Product control and traceability

Special problems of biologics

- Development of cell banks and libraries
- Evaluation and management of allergenicity
- Managing contamination
- Generic biologics

Student presentations (2 sessions interposed in other topics)

http://www.devicelink.com/pmpn/archive/01/03/001.html
Ralston DD (2004) Can't Ignore GMPs In The Challenge of CMC Regulatory Complinace for Biopharmaceuticals Geigert J ed. Kluwer: New York, pp 57-82
Geigart J ed (2004) Are biologics really different? The Challenge CMC Regulatory Compliance for Biopharmaceuticals. Kluwer: New York, pp 17-34

Recommended Textbooks:

- Basic Principles of Drug Discovery and Development, Blass B, Academic Pross, 2015
- Clinical Development: Strategic, Clinical and Regulatory Issues, Steiner, J, Interpharm CRC, 1997

Distance Students:

Please contact Erin Chow at erinchow@usc.edu with any questions and for testing arrangements.

ALL STUDENTS:

All submissions are to be entered in to http://blackboard.usc.edu and emailed to Erin Chow at erinchow@usc.edu to ensure confirmation of receipt. Be sure to see the accompanying Getting Started sheet for directions.

Please format MS Word file titles with your last name, initial, course number and assignment number, for example: Brown_C_516_A1.doc. Be sure to include your name, the course number and title at the beginning of the text itself. If applicable, provide details of accessing course if not in a traditional classroom setting.

Statement on Academic Conduct and Support Systems

Academic Conduct:

Plagiarism – presenting someone else's ideas as your own, either verbatim or recast in your own words – is a serious academic offense with serious consequences. Please familiarize yourself with the discussion of plagiarism in SCampus in Part B, Section 11, "Behavior Violating University Standards" policy.usc.edu/scampus-part-b. Other forms of academic dishonesty are equally unacceptable. See additional information in SCampus and university policies on Research and Scholarship Misconduct.

Students and Disability Accommodations:

USC welcomes students with disabilities into all of the University's educational programs. The Office of Student Accessibility Services (OSAS) is responsible for the determination of appropriate accommodations for students who encounter disability-related barriers. Once a student has completed the OSAS process (registration, initial appointment, and submitted documentation) and accommodations are determined to be reasonable and appropriate, a Letter of Accommodation (LOA) will be available to generate for each course. The LOA must be given to each course instructor by the student and followed up with a discussion. This should be done as early in the semester as possible as accommodations are not retroactive. More information can be found at osas.usc.edu. You may contact OSAS at (213) 740-0776 or via email at osasfrontdesk@usc.edu.

Support Systems:

Counseling and Mental Health - (213) 740-9355 – 24/7 on call
studenthealth.usc.edu/counseling
Free and confidential mental health treatment for students, including short-term psychotherapy, group counseling, stress fitness workshops, and crisis intervention.

National Suicide Prevention Lifeline - 1 (800) 273-8255 – 24/7 on call
suicidepreventionlifeline.org
Free and confidential emotional support to people in suicidal crisis or emotional distress 24 hours a day, 7 days a week.

Relationship and Sexual Violence Prevention Services (RSVP) - (213) 740-9355(WELL), press "0" after hours – 24/7 on call
studenthealth.usc.edu/sexual-assault
Free and confidential therapy services, workshops, and training for situations related to gender-based harm.

Office for Equity, Equal Opportunity, and Title IX (EEO-TIX) - (213) 740-5086
eeotix.usc.edu
Information about how to get help or help someone affected by harassment or discrimination, rights of protected classes, reporting options, and additional resources for students, faculty, staff, visitors, and applicants.

Reporting Incidents of Bias or Harassment - (213) 740-5086 or (213) 821-8298
usc-advocate.symplicity.com/care_report
Avenue to report incidents of bias, hate crimes, and microaggressions to the Office for Equity, Equal Opportunity, and Title for appropriate investigation, supportive measures, and response.

The Office of Student Accessibility Services (OSAS) - (213) 740-0776
osas.usc.edu

OSAS ensures equal access for students with disabilities through providing academic accommodations and auxiliary aids in accordance with federal laws and university policy.

USC Campus Support and Intervention - (213) 821-4710

campussupport.usc.edu

Assists students and families in resolving complex personal, financial, and academic issues adversely affecting their success as a student.

Diversity, Equity and Inclusion - (213) 740-2101

diversity.usc.edu

Information on events, programs and training, the Provost's Diversity and Inclusion Council, Diversity Liaisons for each academic school, chronology, participation, and various resources for students.

USC Emergency - UPC: (213) 740-4321, HSC: (323) 442-1000 – 24/7 on call

dps.usc.edu, emergency.usc.edu

Emergency assistance and avenue to report a crime. Latest updates regarding safety, including ways in which instruction will be continued if an officially declared emergency makes travel to campus infeasible.

USC Department of Public Safety - UPC: (213) 740-6000, HSC: (323) 442-120 – 24/7 on call

dps.usc.edu

Non-emergency assistance or information.

Office of the Ombuds - (213) 821-9556 (UPC) / (323-442-0382 (HSC)

ombuds.usc.edu

A safe and confidential place to share your USC-related issues with a University Ombuds who will work with you to explore options or paths to manage your concern.

*Occupational Therapy Faculty Practice - (323) 442-33*40 or otfp@med.usc.edu

chan.usc.edu/otfp

Confidential Lifestyle Redesign services for USC students to support health promoting habits and routines that enhance quality of life and academic performance.