

**Drug Development
Clinical Science 303
Spring Quarter 2007**

Time: Wednesdays 6:00 - 9:00 pm

Location: 240 E. Huron (McGaw Bldg); Room 2-322

Course Director: Lewis J. Smith, M.D.
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Course Description:

This course introduces the rationale for, practical aspects of, and new issues in drug and device development as well as the relevant industry and government policies and regulations.

Course Objectives:

After completing the course students will be able to:

- Describe the basic concepts of drug discovery and how biotechnology and genetics are used in drug discovery and testing;
- List and describe the steps required for a new drug to be approved for human use;
- Prepare and submit investigator IND (investigational new drug) and IDE (investigational device exemption) applications;
- Define the four major clinical phases (1-4) in the drug development process and the rationale for each;
- Describe the basic concepts of clinical pharmacology including pharmacokinetics, pharmacodynamics, drug and food interactions, population pharmacokinetics, and issues related to special populations;
- Describe the pharmacoeconomic principles and tools used to evaluate new treatments;
- Describe the meaning of personalized medicine;
- Describe the role and limitations of quality of life instruments;
- Create a clinical research program for testing the safety and effectiveness of a new chemical entity in man, including protocol and budget preparation;
- Describe government rules and regulations for developing a new drug and provide the rationale for them;
- Discuss the real and perceived conflicts between the pharmaceutical industry, investigators, research subjects and other elements of society.

Grading Policies:

Class Participation 50%, Class Presentation and Project 50%

Because interaction in the classroom is an integral part of the educational experience, class attendance is mandatory. Please contact the course director promptly in the case of an expected absence. More than one missed class may be grounds for failure.

Course Materials:

Although there is no single text that is “ideal” for the course, the text by Atkinson and colleagues covers many of the topics listed below. Other materials that cannot be accessed from the NU library or via the Internet will be provided to you. Please make every effort to read the assigned materials before each session.

Text:

- Atkinson AJ Jr, Daniels CE, Dedrick RL, Grudzinskas CV, Markey SP. Principles of Clinical Pharmacology. San Diego: Academic Press, 2001.
- The Office of Human Research Protections (OHRP) (<http://www.hhs.gov/ohrp/>) and the Food and Drug Administration (FDA) websites (<http://www.fda.gov/>) have useful information.

Course Workload:

Selected readings, class attendance, participation in discussions and class exercises, final project and presentation.

Class Schedule:

Session 1: Wednesday, April 4, 2007

- **Introduction to Clinical Drug Development**
- **Regulatory Aspects of Drug and Device Development**
- **Discussion of Class Project**

Assignment:

1. Design a phase II program for testing a new therapy, device or diagnostic; or
 2. Identify a clinical trial model to complement or replace placebo-controlled trials, which offers advantages over the usual active comparator trials.
- [Outline of program due May 11, 2007; written report and presentation at last session.]

Readings:

- Atkinson text - Chapters 33 and 34: Design of Clinical Development Programs, Role of the FDA in Guiding Drug Development (pp. 419-37).
- FDA’s Critical Path Initiative - <http://www.fda.gov/oc/initiatives/criticalpath>; read the executive summary – “Innovation or Stagnation. Challenge and opportunity on the critical path to new medical products”; 2004.
- <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html#execsummary>

- Code of Federal Regulations and ICH Guidelines: 21 CFR 50, 54, 56, (General Provisions and Informed Consent, Financial Disclosure, Institutional Review Boards); 45 CFR 46 – Protection of Human Subjects; Good Clinical Practice (Federal Register May 9, 1997 and updates).

FYI

- Couzin J. Magnificent obsession. *Science* 2005; 307:1712-5.
- Rethinking Drug Discovery. Series of articles in *Science* Vol. 303, March 19, 2004. Pages 1795-1822. Read pages 1795-9.

Session 2: Wednesday, April 11, 2007

- **Drug Discovery**
- **Select Readings and Discussion in Drug Development I** - conflict of interest, pricing, phase 4 testing, university-industry partnerships, international research

Readings:

- Atkinson text - Chapter 28: Drug Discovery (pp. 365-71).
- Sams-Dodd F. Drug discovery: selecting the optimal approach. *Drug Disc Today* 2006; 11:465-72.
- Agnew B. Financial conflicts get more scrutiny in clinical trials. *Science* 2000; 289:1266-7.
- Lo B, Wolf LE, Berkeley A. Conflict of interest policies for investigators in clinical trials. *N Engl J Med* 2000; 343: 1616-20. Additional articles in same issue on pages 1621-6; 1643-5; 1646-9.
- Scherer FM. The pharmaceutical industry – prices and progress. *N Engl J Med* 2004; 351:927-32.
- Vlahakes GJ. The value of phase 4 clinical testing. *N Engl J Med* 2006; 354:413-5.
- Hall ZW, Scott C. University-industry partnership (editorial). *Science* 2001; 291:553.

FYI

- Hu W, et al. Development of a novel therapeutic suppressor of brain proinflammatory cytokine up-regulation that attenuates synaptic dysfunction and behavioral deficits. *Bioorg Med Chem Lett* 2007; 17:414-8.
- Vassilev FT, et al. *In vivo* activation of the p53 pathway by small molecule antagonists of MDM2. *Science* 2004; 303:844-8.
- Holden C. Drugs and placebos look alike in the brain. *Science* 2002; 295:947-8.
- Myers S, Baker A. Drug discovery – an operating model for a new era. *Nature Biotechnology* 2001; 19:727-30.
- Ulrich R, Friend SH. Toxicogenomics and drug discovery: will new technologies help us produce better drugs? *Nature Reviews Drug Discovery* 2002; 1:84-8.

Session 3: Wednesday, April 18, 2007

- **Clinical Pharmacology: Basic Principles**

Readings:

- Atkinson text - Chapters 1-4: Introduction to Clinical Pharmacology, Clinical Pharmacokinetics, Compartmental Analysis of Drug Distribution, Drug Absorption and Bioavailability (pp. 1-39); chapter 18: Dose Effect and Concentration-Effect Analysis (pp. 235-44).

FYI:

- White RE: High-throughput screening in drug metabolism and pharmacokinetic support of drug discovery. *Ann Rev Pharmacol Toxicol* 2000; 40:133-57.
- Holford NHG, Kimbo HC, Monteleone JPR, Peck CC: Simulation of clinical trials. *Ann Rev Pharmacol Toxicol* 2000; 40:209-34.
- Sheiner LB, Steimer J-L: Pharmacokinetic/pharmacodynamic modeling in drug development. *Ann Rev Pharmacol Toxicol* 2000; 40:67-95.

Session 4: Wednesday, April 25, 2007

- **Pre-Clinical Drug Development: Pre-Clinical Toxicology and Investigational New Drug (IND) Application**
- **Dosage Form Development and Production**

Readings:

- Atkinson text - Chapters 29 and 30: Preclinical Drug Development, Animal Scale-up (pp. 373-94).
- Code of Federal Regulations: 21 CFR 312 (Investigational New Drug Application)

FYI:

- Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs): <http://www.fda.gov/cder/forms/1571-1572-help.html>
- <http://www.fda.gov/cder/learn/CDERLearn/default.htm> [slide show]
- http://www.fda.gov/fdac/special/newdrug/ndd_toc.html [reference]

Session 5: Wednesday, May 2, 2007

- **Project Management/Team Building**

Readings:

- Atkinson text - Chapter 27 (pp. 351-64).

Session 6: Wednesday, May 9, 2007

- **Budget Preparation**
- **Challenges and Opportunities in Clinical Drug Development**

Readings:

- Pending

Session 7: Wednesday, May 16, 2007

- **Pharmacoeconomics and Quality of Life**

- **Select Readings and Discussion** – independent drug-safety boards, fast-track for drug approval, me-too products, dangers of biomedical research

Reading:

- Clancy CM, Eisenberg JM. Outcomes research: measuring the end results of health care. *Science* 1998; 282:245-6.
- Epstein RS, Sherwood LM. From outcomes research to disease management: a guide for the perplexed. *Ann Int Med* 1996; 124:832-7.
- McHorney CA, Ware JE, Rogers W, et al. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts: Results from the medical outcomes study. *Medical Care* 1992; 30 (suppl 5):M253-M265.
- Ware JE, Sherbourne CD. The MOS 36-item Short-Form health survey (SF36): I. Conceptual framework and item selection. *Medical Care* 1992; 30:473-483.

- Psaty BM, Burke SP. Institute of medicine on drug safety. *N Engl J Med* 2006; 355:1753-5.
- Ray WA, Stein CM. Reform of drug regulation – beyond an independent drug-safety board. *N Engl J Med* 2006; 354:194-201.
- A proposal for radical changes in the drug-approval process. *N Engl J Med* 2006; 355:618-23.
- Roberts TG Jr, Chabner BA. Beyond fast track for drug approvals. *N Engl J Med* 2004; 351:501-5.
- Lee TH. “Me-too” products – friend or foe? *N Engl J Med* 2004; 350:211-2.
- Caplan A. Is biomedical research too dangerous to pursue? *Science* 2004; 303:1142.

Session 8: Wednesday, May 23, 2007

- **Negotiating a Clinical Trial Agreement**

- **Filing a New Drug Application (NDA)**

Readings:

- Code of Federal Regulations: 21 CFR 314 (Applications for FDA Approval to Market a New Drug or an Antibiotic Drug)

Session 9: Wednesday, May 30, 2007

- **Biotechnology in Drug Development**

Readings:

- Atkinson text - Chapters 13 and 32: Clinical Pharmacogenetics, Pharmacokinetic and Pharmacodynamic Considerations in the Development of Biotechnology Products and Large Molecules (pp. 157-66, 401-18).
- Service RF. Going from genome to pill. *Science* 2005; 308:1858-60.
- Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. *Nature Rev Drug Disc* 2004; 3:763-9.
- Weinshilboum R, Wang L. Pharmacogenomics: Bench to bedside. *Nature Rev Drug Disc* 2004; 3:739-48.

- Pavlou AK, Reichert JM. Recombinant protein therapeutics – success rates, market trends and values to 2010. *Nature Biotech* 2004; 22:1513-9.

Session 10: Wednesday, June 6, 2007

- Presentation, Discussion and Review of Student Projects

Readings:

- None