N. Tomoney
New Jersey Institute of Technology
September 7, 2016

VALIDATION AND REGULATORY ISSUES IN THE PHARMACEUTICAL INDUSTRY

PHEN 604-101

(WEDNESDAY NJIT CAMPUS SECTION)

Syllabus

Term	2016 Fall Semester
Course Title	Validation and Regulatory Issues in the Pharmaceutical Industry
NJIT Course Number	PHEN 604, Section 101
Classroom	104 Kupfrian Hall, NJIT
Course Instructor	Nancy Tomoney, Adjunct / Industry Professional New Jersey Institute of Technology Otto H. York Department of Chemical, Biological and Pharmaceutical Engineering University Heights Newark, NJ 07102-9895 Telephone: (732) 542-1191 ext 7991; Cell (732) 887-3829 Nancy.E.Tomoney@njit.edu

INSTRUCTOR'S OFFICE HOURS:

Ms. Tomoney is an industry professional and does not have an NJIT office. Office hours will be by appointment. Students are strongly encouraged to contact Ms.Tomoney via e-mail to arrange for a meeting. *Please note that Ms.Tomoney will **not** be available for consultation when she is on business travel.*

Course Day and Time: Wednesday, 6:00 - 9:05 p.m.

COURSE NOTES, TEXTBOOKS, AND OTHER REFERENCE MATERIAL:

- **Notes**: Tomoney, N., 2016, *Validation and Regulatory Issues in the Pharmaceutical Industry: Course Notes*. The *Notes* are duplications of the overheads used in class. The *Notes* are available on the internet and can be accessed using the procedure described below.
- **Textbooks**: The following textbooks are required:
  - *The Jungle*, Upton Sinclair
  - Current - *Federal Food, Drug, and Cosmetic Act (FD&C Act)*, available on the FDA website at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/default.htm
- **Textbooks**: The following textbooks are suggested:
  - *New Drugs: An Insider's Guide to the FDA's New Drug Approval Process for Scientists, Investors and Patients*, Lawrence T. Friedhoff
  - *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*, Philip J. Hilts
  - Original - *Federal Food, Drug, and Cosmetic Act (FD&C Act)*, to be provided first class by PDF
- **Additional reference books in NJIT Library** (suggested but not required):
  - *Design And Validation Of Computer Protocols*, Holzmann, Gerard J., NJIT Library Code: TK5105.5 .H645 1991
  - *Independent Verification And Validation: A Life Cycle Engineering Process For Quality Software*, Robert O. Lewis., NJIT Library Code: QA76.76.V47 L48 1992

- *Software Validation, Verification, Testing, And Documentation*, edited by Stephen J. Andriole, NJIT Library Code: QA76.76.V47 S66 1986
- *Pharmaceutical Process Validation*, edited by Robert A. Nash, Alfred H. Wachter, NJIT Library Code: RS189 .P46 2003
- *Pharmaceutical Water: System Design, Operation, And Validation*, Collentro, William V., NJIT Library Code: RS199.W37 C64
- *Validation Of Pharmaceutical Processes*, edited by James Agalloco, Frederick J. Carleton, NJIT Library Code: RS199.S73 V345 2008
- *Pharmaceutical Master Validation Plan: The Ultimate Guide To FDA, GMP, And GLP Compliance*, Haider, Syed Imtiaz, 2002
- *FDA And Worldwide Quality System Requirements Guide Book For Medical Devices*, Kimberly A. Trautman, NJIT Library Code: KF3827.M4 T73
- *PAT Applied In Biopharmaceutical Process Development And Manufacturing : An Enabling Tool For Quality-By-Design*, edited by Cenk Undey... [et al.], NJIT Library Code: RS380 .P37 2012.

- Other additional reference books/articles (see end)

Additional References

- *The United States Pharmacopoeia & The National Formulary. The Official Compendia of Standards, USP 38–NF 33*, Pharmacopeial Convention Inc., 2015 (official as of May 1, 2015).
- *ISPE Baseline Pharmaceutical Engineering Guides* (the following volumes are available from ISPE; www.ispe.org):
  - Water and Steam Systems
  - Commissioning and Qualification
  - Packaging and Warehousing
  - Bulk Pharmaceutical Chemicals
  - Oral Solid Dosage Forms
  - Sterile Manufacturing Facilities
  - Biotechnology
  - R&D Facilities
  - Oral Liquids and Aerosols
- Michael Levin (ed.), *Pharmaceutical Process Scale-Up*, 3rd Ed., Informa Health Care, New York, 2011.
- Allen, L. V., Popovich, N. G., and Ansel, H. C., *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*, 9th Edition, Lippincott Williams & Wilkins Publishers, 2010. [Remark: this is the textbook used in PhEn 601].
- Hickey, A. J. and Ganderton, D., *Pharmaceutical Process Engineering*, Marcel Dekker, New York, 2001.
- Banker, G. S. and Rhodes, C. T., *Modern Pharmaceutics*, 3rd Edition, Marcel Dekker, New York, 1995.
- Lieberman, H. A., Rieger, M. M., and Banker, G. S. (eds.), *Pharmaceutical Dosage Forms: Dispersed Systems*, Vol. 1 (1996); Vol. 2 (1996), Vol. 3, (1998), Marcel Dekker, New York.
- Lieberman, H. A., Lachman, L. and Schwartz, J. B. (eds.), *Pharmaceutical Dosage Forms: Tablets*, Vol. 1 (1989); Vol. 2 (1990), Vol. 3 (1990), Marcel Dekker, New York.
- Avis. K. E. Lieberman, Lieberman, H. A., and Lachman, L. (eds.), *Pharmaceutical Dosage Forms: Parenteral Medications*, Vol. 1 (1991); Vol. 2 (1992), Vol. 3 (1993), Marcel Dekker, New York.
- Cole, G., *Pharmaceutical Production Facilities: Design and Applications*, 2nd Edition, Taylor & Francis, 1998.
- Avis, K. E. and Wu, V. L. (eds.), *Biotechnology and Biopharmaceutical Manufacturing, Processing, and Preservation* (Vol. 2), Interpharm Press, 1996..

AVAILABILITY OF COURSE NOTES, HOMEWORK ASSIGNMENTS, TEXTBOOK, AND REFERENCES:

- *"Validation and Regulatory Issues in the Pharmaceutical Industry: Course Notes"* will posted on the internet as PDF files (i.e., you will need Adobe Acrobat to read and print them). The *Course Notes* can be downloaded from the NJIT website using Moodle. Students can **either** access Moodle directly (http://moodle.njit.edu/) and follow the instructions there, **or** go through Highlander Pipeline as follows:
  1. Go to http://my.njit.edu and login using your UCID

2. Click on the “My Courses” tab
3. Click on the link towards the bottom of the screen for “NJIT Moodle Rooms: Click here to access your course in Moodle”
4. You will automatically be logged into NJIT’s new Moodle server
5. Locate your course and click on the link with the course title
6. If at any time you are experiencing problems and are unable to log in please let the helpdesk know at 973-596-2900.

- The homework is also posted weekly through Moodle
- The projects will be posted through Moodle.
- Additional material (reading material, etc.) will be distributed in class or placed on Library Reserve. For additional information, please contact Ms. Tomoney
- Most additional references (not required as textbooks) as well as the textbooks are available in most university libraries, including the NJIT library.

COURSE PREREQUISITES:

- Graduate Standing
- NJIT UCID & MOODLE Account (Required)
- PhEn601 (preferred, but not required)
- Technical Writing & Formal Argument skills (strongly recommended)

COURSE OBJECTIVE:

The course is one of the common courses for the Pharmaceutical Engineering (PhEn) and Pharmaceutical Bioprocessing (PhB) MS Degree Programs.

- This course is focused on the development of a working knowledge of the United States Code of Federal Regulations and its impact on the pharmaceutical and allied industries.
    - The history of the Federal Government's regulation of the pharmaceutical industry is studied.
    - Also covered is the industry's response and the methodologies it uses to comply with these regulations.
- This class was designed to provide the students with as much of the background, fact, and interpretation of the pharmaceutical industry’s underlying governmental regulations. The emphasis is primarily on the application of those regulations to quality compliance including validation of processes and systems used to manufacture pharmaceutical, biologic and medical device products.

COURSE DESCRIPTION:

This course is focused on the development of a working knowledge of Title 21 of the CFR and its interpretations and applications within the pharmaceutical and allied industries. In this pursuit, we shall study the history and role of the FDA, and the reasons underlying the regulations that now shape the way pharmaceutical companies do business. Of primary focus shall be the roles of “cGXPs” as we know (and are required to use) them today.

The concept of “Validation”, primarily known to the pharmaceutical industry will be covered. As Validation is a primary activity for ensuring safety and efficacy of a FDA Regulated products, as well as the quality and integrity of the data supporting these assurances, we shall study this concept in such a manner that the student should be able to anticipate the requirements and apply sound principles for validation of any new process, system, equipment, or laboratory method.

That is a lot of material; the Code of Federal Regulations (CFR) is vast. There are reasons for the regulations and we will cover the critical portions during this course as they relate to the pharmaceutical, biologic and medical device industry. You will acquire a working familiarity with the law and regulations; it is not a goal that you become able to quote regulations "by the book". It is much more important that you gain an appreciation for WHY we have and HOW we use the various regulations, guidelines, and standards that we follow in the pharmaceutical industry. You will gain this understanding by viewing the entire industry, from drug discovery through post-marketing. We will highlight most of the major regulatory concepts, and their reasons for existence.

COURSE OUTLINE BY TOPIC AREAS:

Pure Food, Drug & Cosmetic Act, Code of Federal Regulations - Title 21, Validation, Commissioning, GxPs, other similar International Regulations.

COURSE REQUIREMENTS:

- **Quizzes**: Assigned by the instructor during some classes
- **Examinations**: Two exams, i.e., a midterm exam and a final exam
- **Homework**: Assigned by the instructor at the end of some classes
- **Mid-term Paper**: Assigned due by October 26, 2016
- **Projects**: One, or possibly two, short projects will be assigned during the term

GRADING POLICY*:

- Quizzes* 10%
- In-Term Paper 10%
- Midterm exam* 25%
- Final exam* 25%
- Homework 10%
- Projects 20%

  Total 100%

(*) Students performing very poorly on the exams will **fail** the course *irrespective* of their performance in the homework and projects, as specified below.

COURSE FINAL GRADE:

A tentative guideline for the assignment of final grades is the following:

Cumulative Points	Overall Grade
90 to 100%	A
80 to 89%	B/B+
70 to 79%	C/C+
>69%	"F"

The grade of "D" is not assigned to students taking graduate courses. Students averaging a cumulative point score corresponding to a "D" in the above table could receive either a C or an F, depending on their overall performance.

Please remember that this is only a guideline designed to help the students understand how they are performing in the course. Ms. Tomoney will feel free to change the grading scale (both ways) when assigning the final grades.

IMPORTANT REMARK:

Each exam (midterm and final) will be graded on a point scale from 0 to 100 (100 points in an each exam=each exam is 25% of the final grade; see above). In other words, students who perform extremely poorly in the exams will not be able to use the homework and the projects to pass the course. If this minimum requirement is satisfied, the final grade will be assigned based on the grading policy outlined above.

EXAMS:

- a calendar of exams is included in the Course Outline given below;
- all exams are typically 3 hours long unless otherwise stated;
- all exams are typically closed book/note. However, changes could be made and will be announced by the instructor prior to the exams;
- the final exam will be on all material covered throughout the course (although the main emphasis of the exam will be on the material covered after the midterm exam);
- make-up exams will only be given to students who cannot attend the regular exam time, *and only under documented and extraordinary circumstances*. In any case, no student will be allowed to take a make-up exam unless he/she has the prior consent of the instructor. *If a student will simply not come to an exam, the exam grade will automatically be zero.*

HOMEWORK:

it will be assigned at the end of selected class periods, collected the following week at the beginning of the class period, and returned the week after that. No late homework will be accepted. The homework problems will be posted on the internet and can be retrieved by the students as described previously for the *Class Notes*. If appropriate (typically for quantitative problems) homework solutions will be posted on the internet (as described for the *Class Notes*) after the homework has been collected.

IMPORTANT:

Previous experience has clearly shown that those students who do not due the assigned readings or homework typically perform *very poorly* on the exams.

HOMEWORK GRADING:

The homework will be graded using a simplified grading scale, i.e., 0 (no or minimal effort); 5 (intermediate effort); 10 (significant effort). Any questions regarding the homework grade should be discussed with the instructor.

PROJECTS:

Every student will complete one, or possibly two, small projects, which will be assigned.

CLASS ATTENDANCE:

As with all graduate courses at NJIT, attendance is not mandatory, but strongly recommended. Experience shows that students who do not regularly attend class typically perform poorly in the course. In addition, examples are worked out during the lectures. These examples are not in the *Class Notes*. Students are responsible for all material covered in class.

NJIT HONOR CODE:

The NJIT honor code is being upheld on all issues related to the course. Students are expected to be familiar with the code and conduct themselves accordingly.

Important dates are available on the web at the following site: http://www.njit.edu/registrar/calendars/index.php.

COURSE OUTLINE:

Class Date	Class	Topic	Basic Points Covered	Major Assignment / Exam
07 September 2016	**1**	Introduction & Regulatory History	Introduction International Regulatory Framework US Law and Agencies	"*The Jungle*" – Chapters 1-5 (Pp. 1-53) Read 1906 Pure Food & Drug Act. (Available in Moodle) Download and Read *Code of Federal Regulations Title 21--Food And Drugs Chapter I--food And Drug Administration Department Of Health And Human Services Subchapter A--General Part 7 Enforcement Policy*
14 September 2016	**2**	FDA Operations	FDA Structure & Organization FDA Regulations ,Inspections and Tools for Compliance FDA Regulated Products	*Protecting America's Health*, Hilts Prologue, and Chapters 1-11 (Pp. 3-177) CPGMs: 7346.832, Pre-Approval Inspections/Investigations 7346.843, Post-Approval Audit Inspections 7356.002, Drug Manufacturing Inspections 7356.002A, Sterile Drug Process Inspections 7356.002B,Drug Repackers and Relabelers 7356.008, Drug Quality Sampling and Testing - Human Drugs On the FDA website find the CPG website identify the Recall document. Download the Regulatory Procedure Manual from the FDA website Continue reading "The Jungle"

Class Date	Class	Topic	Basic Points Covered	Major Assignment / Exam
21 September 2016	**3**	Compliance & Validation in Early Stages in the Developing of New Molecular Entity, New Devices, or Biosimilars	R&D, GLPs, & Investigational Applications	**Required Reading**: "The Jungle" – Chapters 6-12 (Pp. 53-104) **Reference Reading**: Title 21 Subchapter D -Drugs For Human Use Parts: §300 General §312 Investigational new drug application Title 21 Subchapter E -Animal Drugs, Feeds, And Related Products: §510 New animal drugs §511 New animal drugs for investigational use §514 New animal drug applications Title 21 Subchapter F –Biologics: §600 Biological products: general §601 Licensing Title 21 Subchapter H –Medical Devices: §812 Investigational device exemptions §814 Premarket approval of medical devices
28 September 2016	**4**	Clinical Trials and Product Applications / Licenses	GCPs & Clinical Trials Informed Consent & IRBs Applications – ANDA/NDA, BLA, PMS & 510 K	**Required Reading** *Protecting America's Health*, Hilts Chapters 18-21 & Epilogue (Pp. 278 - 343) "The Jungle" – Chapters 13-19 (Pp. 104-159) Title 21 Subchapter D—Drugs For Human Use Parts: §310 New drugs §314 Applications for FDA approval to market a new drug §315 Diagnostic radiopharmaceuticals §316 Orphan drugs §320 Bioavailability and bioequivalence requirements
05 October 2016	**5**	CMC Chemistry & Manufacturing Controls for Production and the Good Manufacturing Practices (GMPs)	Ethics Adulteration & Misbranding The role played by FDA and Compendia (USP-NF) SUPAC, Non application changes and Annual Reporting GMPs	**Required Reading** "The Jungle" – Chapters 20-25 (Pp. 159-203) *"New Drugs: An Insider's Guide to the FDA's New Drug Approval Process for Scientists, Investors and Patients"*, Lawrence T. Friedhoff All Preface, Chapters 1-21, Glossary, Appendices 1-4 (Pp. xi - 243) 21 CFR 210 & 211

Class Date	Class	Topic	Basic Points Covered	Major Assignment / Exam
12 October 2016	**6**	The Validation Program & Documentation	VMPs & PVPs Protocols and Reports Discrepancies & Deviations GDPs	**Required Reading** "The Jungle" – Chapters 26-31 (Pp. 203-290) ISPE GAMP 5
19 October 2016	**7**	Good Engineering Practices (GEP) & Equipment Qualification	RS, FS, DS, and the Traceability Matrix GEP: DQ, Commissioning, FAT, & SAT Equipment Qualification: IQ, OQ, PQ Handover & Post-Handover Programs	**Required Reading** ISPE Good Engineering Practice
26 October 2016	**8**	**MID-TERM EXAM** **MID-TERM PAPER & PROJECTS DUE**		
02 November 2016	**9**	Primary & Secondary Manufacturing Process Validation Facilities and Utilities	Process Validation ICH Q8A Overview Facility Design & Validation (Overview) HVAC & ISO 14644 Acceptance Criteria Utilities Design & Validation (Overview) USP PW, WFI & Compressed Air Acceptance Criteria	**Required Reading** ISPE GPG HVAC
09 November 2016	**10**	Process Validation	Process Validation ICH Q8A Overview	**Required Reading** TBD
16 November 2016	**11**	Introduction to Cleaning Validation	Cleaning Validation and Continuous Cleaning Verification CIP, SIP Automated versus Manual Cleaning	**Required Reading** TBD Handout
23 November 2016	**12**	Laboratory Operations Computer System Validation (CSV) & 21 CFR Part 11	Continuous Sampling: AQLs & ANSI Z1.4 Analytical Testing "Figures of Merit" System Suitability Analytical & Bio-analytical Method Validation Microbiology & Sterility Testing Stability Testing CSV and 21 CFR 11 Good Automated Manufacturing Practices	**Required Reading** TBD

Class Date	Class	Topic	Basic Points Covered	Major Assignment / Exam
30 November 2016	**13**	The Quality Challenge, Quality Systems, Regulatory Inspections, and Audits	Quality Risk Management FDA Inspections and Outcomes Other Inspections and Audits	**Required Reading** TBD
07 December 2016	**14**	Process Analytical Technology (PAT) & Ethical Issues	PAT PDMA Other Topics (as time allows)	**Required Reading** TBD ``
14 December 2016	**15**			
21 December 2016	**16**	**Final Exam**		

Important: It is conceivable that some changes in the above outline will take place, depending on the overall performance of the class and the time actually required to cover the most important subjects of the course.