AC 2012-4579: REGULATORY COMPLIANCE TRAINING IN BIO/CHEMICAL ENGINEERING COURSES

Dr. Arthur Felse, Northwestern University

P. Arthur Felse is a lecturer in the master's of biotechnology program and the Department of Chemical & Biological Engineering at Northwestern University. His responsibilities include teaching, student advising, coordinating master's research training, and managing the biotechnology teaching laboratory. Before joining Northwestern University, Felse completed his postdoctoral training at the Polytechnic Institute of New York University, where he was awarded a NSF fellowship. He and his colleagues at Polytechnic Institute received the EPA's Presidential Green Chemistry Challenge Award in 2003 for their work on mild and selective polymerizations using lipases.

Regulatory Compliance Training in Bio/Chemical Engineering Courses

I WOULD LIKE THIS PAPER TO BE IN A REGULAR SESSION

Introduction:

Regulatory compliance (RC) refers to a set of federally mandated guidelines under which industrial processes and scientific experiments are planned, conducted, monitored, recorded, and reported. RC is typically achieved through a set of well-developed guidelines that are monitored by executive agencies such as Food and Drug Administration (FDA) and Environmental Protection Agency (EPA). Regulatory compliance is not just voluntary practice. It's the law enshrined in various acts of the U.S. Congress such as Toxic Substances Control Act, Emergency Planning and Community Right-to-Know act, Resource Conservation and Recovery Act, etc. Direct cost involved in assuring RC can be between 20 – 50% of operating costs, particularly in the pharma/biotech industry, and the penalty of non-compliance can be of the order of several million dollars[1]. A recent Presidential Memoranda (in Jan 2011) made it mandatory for executive agencies to publicly disclose RC information of all regulated companies including private corporations[2]. Thus, apart from direct fines and decrees, non-compliance events can lead to indirect penalties through loss of investor funding and lack of confidence in the general population.

Regulatory requirements are redefining the landscape of chemical, pharmaceutical and biotech industries to an extent not seen before in the chemical or biological engineering profession. This influence significantly impacts chemical and biological processes or products development. Contemporary technological innovations largely happen in cross-disciplinary areas and consequently many companies have created a unified framework to handle RC of new processes and products[3]. Though initially perceived as a suppressor of technological growth and profitable operation of a business enterprise, RC is now predicted to be a major driver of competitive advantage in chemical and related industries[4].

This module was in part motivated by recommendations from a group of advisors primarily from the pharma/biotech industry who serve on our Advisory Board. There is a keen interest in the pharma/biotech industry to recruit students with RC awareness in discovery, process development and manufacturing areas. The purpose of this paper is to describe strategies for inclusion of RC training modules in bio/chemical engineering courses. Training modules can be included in a theory course or in a hands-on laboratory course. Instructional approaches include case-study discussions, brainstorming sessions, role-play exercises, and guest lectures. This paper will also discuss a unified approach to connect engineering principles, regulatory guidelines and written communication. This module fits well with the recent emphasis of ABET on safety in teaching labs. Several (although not all) safety guidelines are addressed in regulatory compliance. The only prerequisite is that students have some knowledge of bio/chemical process technologies. Since RC is more of a practice than absolute science, assignments and tests developed in this module to reflect the 'practice' component will be described in this paper.

The need for regulatory compliance instruction:

Regulatory compliance is no longer a catchphrase. It has become a committed part of engineering practice. A recent survey conducted by CSC and *Chemical Week* magazine amongst leaders in the chemical industry showed that about half identified RC to have a positive effect on their business, while 75% are retooling their product development to comply with RC regulations[5]. A significant minority felt that RC has a negative effect on the industry (Figure 1).
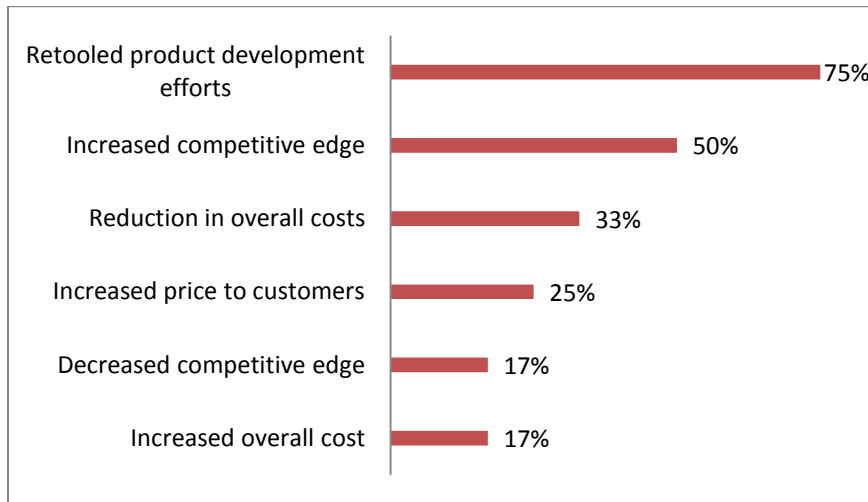

Figure 1: Impact of regulatory compliance programs on the chemical industry. Adapted from [5].

The survey also pointed to the fact that only a third of the companies were confident of being RC compliant in the year 2010 (the survey was conducted in 2009)[5]. These results suggest that a lot more needs to be done in accomplishing a fully regulatory complaint chemical industry (Figure 2). Two inferences from the results of this survey are: (i) RC is predicted to an advantage in the chemical and related industries, and (ii) there is a shortage of personnel with adequate RC exposure to handle the future needs of chemical and related industries.
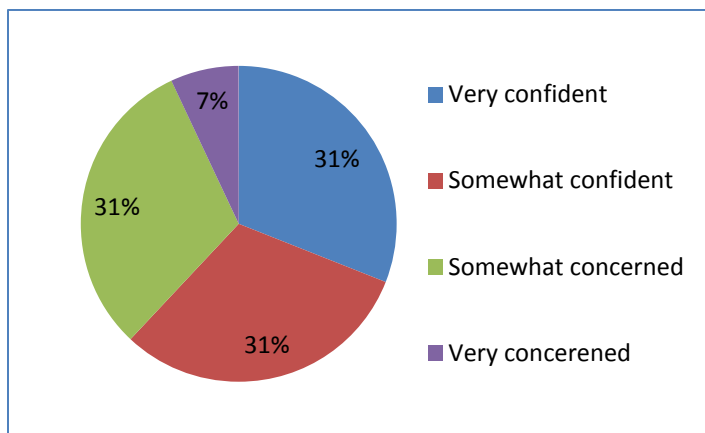

Figure 2: Confidence levels for complete compliance in 2010. Adapted from [5].

About 25% of chemical engineering graduates work in highly regulated sectors such as pharma, biotech, electronics and food industries[6]. With chemical engineers migrating to highly regulated industries, training in RC compliance is necessary and appropriate in bio/chemical engineering courses. A strong working relationship between engineers, RC personnel and regulating agencies is crucial for businesses to thrive in these areas. Consequently, a successful career for bio/chemical engineers will require an adequate functional knowledge of RC guidelines. An exposure to RC guidelines and its implementation can help chemical engineering students to become more marketable and get a head start with their careers.

It is important to prepare chemical engineering graduates who will grow to become good corporate citizens. Recent industrial disasters (such as Deepwater Horizon spill, Imperial Sugar Refinery explosion, Alumia plant accident in Hungary, etc.) have all pointed to a breach in RC and the possibility of engineering personnel's involvement in making the wrong decisions cannot be ignored. Thus it is important to cultivate chemical engineers with strong ethics and social responsibility.

Intent of this RC module:

Instructional approach in this RC module focused on both the spirit (the broad intent of regulations) as well as the letter (specific ways in which regulations are implemented, monitored and enforced). It should be noted that the purpose of this module is to educate students to obtain a working knowledge of RC and be trained at a level to liaison effectively with RC personnel. The module intends neither to retrain students to become RC professionals (though they might do this later in their careers) nor to burden students with learning or interpreting the jumble of RC guidelines. A significant focus will be on the consequence of breach of RC, both monetary and ethical. Proof of regulatory compliance is accomplished through enormous amount of paperwork and hence excellent written communication skills become essential. This module will include exercises in completing RC documentation such as standard operating procedures (SOP), batch record and FDA's inspectional observations form (also known as Form 483).

Description of topics covered:

The module described in this paper is a part of the Bioprocess Engineering Laboratory course. But it can be adapted to other courses as well. RC is typically achieved through Good X Practices (or GXP) guidelines where X can be Laboratory, Manufacturing, Clinical or Tissue. In this paper an RC module implemented through Good Laboratory Practice (GLP) is discussed. GLP guidelines are intended to promote quality, traceability and integrity of scientific data. Following topics were covered in the module: (i) Need and importance of RC with particular focus on GLP, and the consequences of breach of RC, (ii) Various GLP guidelines and its

relationship to conduct of lab experiments, (iii) setting-up a GLP compliant laboratory, (iv) conducting a lab experiment under a GLP-like environment and its comparison to a non-GLP environment, and (v) completing GLP documentation. This GLP module assumes that basic lab safety regulations such as protective wear and goggles will be followed.

Pedagogical approach:

This module used a multitude of pedagogical approaches to teach various aspects of GLP, which are outlined below:

Table 1: Pedagogical methods in teaching regulatory compliance. See foot note for definitions.

Methodology	Purpose	Topics covered	Assesment
Self-study	Overview of RC	GLP history, GLP terminology, GLP guidelines, GLP organizational structure	Quiz
Case-study discussions	Understand how RC works and RC documentation	Real compliant and noncompliant examples, citations	Student participation
Brainstorm session (full class)	Generate ideas to transition a non-compliant lab to a GLP-complaint lab	GLP guidelines related to compliant facilities	Student participation
Brainstorm session (student teams)	Generate ideas to modify an experimental protocol to satisfy GLP compliance	GLP guidelines for SOP	Marking of SOP for errors
Hands-on GLP experiment	Training to conduct an experiment under GLP constraints and generate batch record.	Experiments, GLP guidelines for completing batch records	Diligence in doing experiment, marking of batch record for errors
Role-play exercise	Understand the roles of various individuals in a GLP environment, generate Form 483	FDA inspection, Form 483, GLP organizational structure and responsibilities of various individuals in a team	Thoroughness of inspection, marking of Form 483 for errors.
Guest lectures	First hand information on real-life RC issues	Several	None

Standard operating procedures (SOPs) are documents that describe the step-wise execution of any particular operation or experiment[7].
Batch records are documents that are generated while an experiment or a process/procedure is performed[7].
Form 483 is FDA's Inspectional Observations report. FDA inspectors record violations in this form after a site inspection. Form 483 is publicly available on FDA's website[7].

Learning outcomes:

After completion of the module students should be able to:

1. Understand the purpose of regulations and its impact on product and process development
2. Understand GLP terminology and have adequate exposure to liaise effectively with RC personnel.
3. Learn the basic rules in establishing a GLP-compliant facility
4. Conduct a study under GLP conditions
5. Write and comprehend GLP documents

Grading:

A top-down approach was used for used for grading. All student teams were assigned the same maximum number of points at the beginning of the module (80 points, an additional 20 points were assigned to the quiz). Then points were deducted from this maximum based on mistakes and infractions. Teams will have to repeat the experiment if any major violations were found during the mock site inspection. The quiz on self-study material was graded by the instructor and was assigned a maximum 20 points. Students satisfactorily completed or did not satisfactorily complete this module. In the latter case they repeated parts or the entire module. Scores from this module was not a part of the final grade.

Solutions to some challenges in teaching a RC module:

Three specific challenges are addressed in this paper:

Challenge #1: Creating an environment for students to appreciate the relevance of RC to CHE

Solution: Simple regurgitation of regulatory guidelines will only lead to a bored indifference. Though RC is primarily a maze of regulations, utmost care was taken to avoid this. The module began with a brief quiz on the self-study material which gets the students acquainted with RC terminology and guidelines. The importance of RC is covered though case-study discussions on RC violations cases available publicly on the FDA website. The cases had an immediate relationship to chemical/biological processes such as a drug fill and finish facility, chemical storage facility, particle centrifugation facility, and a data collection during quality control tests. The case-study discussion demonstrated the role engineers play in successful operation of a regulated process. Students also understood how mistakes made by engineers can have serious negative consequences on the product/process through these case studies.

Challenge #2: Engaging students in the learning process

Solution: A plenty of opportunities were provided to engage students through brainstorm sessions and role-play exercises. During the first brainstorm session, the class discussed ideas to transform a non-GLP lab to a GLP-compliant facility based on published GLP guidelines (21 Code of Federal Regulations, part 58). Students generated a check list of changes that needs to made to the teaching laboratory. The check list was then implemented. Changes were made in operational areas such as storage and disposal chemicals, calibration of equipments, data storage, spacing of equipments, housekeeping etc. A certain set of internal rules-of-the-road guidelines were generated for everyone to follow. However, in an academic setting this effort was only partly complete because it is not possible to change the infrastructure.

Another opportunity for student engagement is role play exercises. This was done after the GLP lab experiment was complete. Teams exchanged documentation and performed a mock FDA site inspection. Members of the team getting inspected play the roles Associate, Study Director and Quality Control Director. All GLP documents were reviewed and mock interviews were conducted by the inspecting team. At the end of the inspection, non-compliance was discussed between teams and after-visit documentation (Form 483) was generated. Student learnt from their own and others' mistakes. This exercise provided the most student engagement and was received with highest enthusiasm.

Challenge #3: Lack of instructional materials:

Solution: To the extent we aware of, this module is the first effort of its kind. The closest precedent is the work on including safety modules in lab courses. RC training programs exist predominantly in the industry (and associated professional organizations) where it is taught in the form of workshops and seminars[8]. Hence there are almost no formal instructional materials on RC. All materials used in this course were instructor developed – study materials, lectures, case studies and GLP documents. Journal articles, trade publications and government publications were used as sources for developing instructional materials. Inputs from professionals in the industry were obtained to improve the quality of instructional materials.

Cultivating RC communication skills:

Written communication provides documented proof of RC. Three major GLP documents were addressed in the module: (i) Standard Operating Procedure (SOP), (ii) Batch Record, and (iii) Form 483. Published RC guidelines broadly mention the functions of each of these documents, but specifics on format and content is left to the judgment of the user as long as these documents satisfy their intended functions. Students generated multiple SOPs and batch records. One SOP is required for every individual part of an experiment such as making a solution or measuring pH, etc. Thus one experiment will require multiple SOPs. Examples of SOP, batch records and Form

483 were provided to students. Form 483 was developed after the mock site inspection. The importance of understanding the purpose and audience when writing RC documents was emphasized – SOPs and batch records are internal documents that are subject to federal scrutiny while Form 483 is a publicly disclosed document. SOPs and batch records serve the purpose of demonstrating regulatory compliance, while Form 483 is in many cases a citation for noncompliance. Thus writing styles and format vary largely between these documents. Students were trained to write RC documents with highest attention to purpose and audience. Services of our university's writing help desk were used to assist students with language issues (such as grammar and sentence construction). Writing also helps students to become conversant in RC terminology. Representative examples of RC documentation are given in the Appendix 1 and 2.

SOP is a document that informs of how experiments are performed and batch record is the evidence of experiment completion according to one or more SOPs. It is obvious that both SOPs and batch records are stacked with signatures which serve two purposes – an added layer of scrutiny to ensure reliability of data and to increase accountability. Students within a team take the roles of different personnel in a GLP organizational structure to review and sign these documents. Everyone signing the documents was interviewed during the mock inspection.

Discussion:

RC module has been taught for three years, but is still a work in progress. The core message that students take away from this module is: RC does not change the fundamental scientific and engineering principles underlying the experiments or the data analysis; RC only changes the way in which data is generated, recorded and stored. Thus it's the usual conduct experiment or operation of a process, but for compliance they are done in a controlled and thoroughly documented environment. When comparing compliant and noncompliant experiments students understand that a compliant experiment takes much more time and effort to complete but provides more reliable and traceable data. Students learn the importance of RC by better understanding the impact of RC violations. Through case-study discussions and mock inspections students learn that RC is not just labored bureaucracy, but in fact it is a collection of rules that ensure safety, reliability and accountability of the process. When properly managed RC can better foster scientific and engineering innovations. All RC regulations can be traced of some ethical principles which were violated at some point in the history of any particular industry. Thus, RC can be taken as ethics enforced diligently by the government. The various aspects covered by RC are given in the Figure 3.
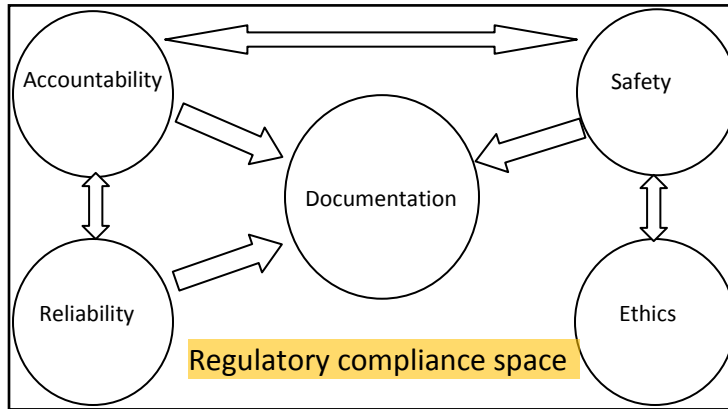
Figure 3: Various aspects covered by RC and the relation between them.

It is important to note that all students did not equally enjoy all parts of the RC module. A survey of students asked the question, "What did you like most and like least in the RC module?" The results are given in Figure 4.
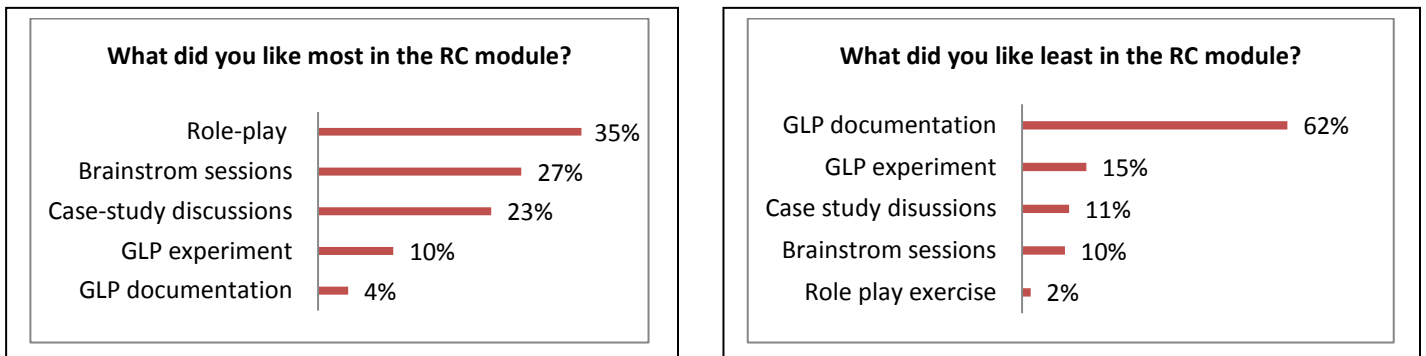
Figure 4: Student perceptions on various parts of the RC module (percentages may not sum to one hundred due or rounding off).

Students generally had a positive experience in all activities that engaged them and led to independent development of ideas (case-study discussion, brainstorm session, and role-play). On the other hand, a good majority of students felt that GLP documentation was onerous. GLP compliant documentation will be more voluminous than noncompliant documentation (such as recording data in a simple lab notebook). But this is the reality. All engineers working in a regulated environment will be required to complete RC documentation. In future, efforts will be made to make the documentation part less burdensome but still preserve the essence of RC communications.

Future plans:

Future plans will intend to refine and expand the RC module. Specific plans include:

1. Modify the GLP documentation part to make it less onerous.
2. Get feedback from industry personnel to adapt the module to meet current needs of the industry.
3. Create rubrics for objective evaluation of discussion sessions and role-play exercises and hence make the GLP module grade a part of the overall grade. Currently it is satisfactory completion of the module.
4. Develop methods for inclusion of RC training in theory courses.

References:

1. Kanarek, A. D. Good Laboratory Practices, 3rd edn., D&MD Publications, pages 1-1 to 3-7, 2007.
2. Presidential Memoranda – Regulatory compliance, http://www.whitehouse.gov/the-press-office/2011/01/18/presidential-memoranda-regulatory-compliance. Last accessed March 16, 2012.
3. Survey: How Leading Firms Manage Regulatory Change, Chemical Week Magazine, Nov. 2, 2009.
4. Regulatory Compliance Predicted to be a Major Driver of Competitive Advantage. http://www.prnewswire.com/news-releases/regulatory-compliance-predicted-to-be-a-major-driver-of-competitive-advantage-69070552.html. Last accessed March 16, 2012.
5. Regulatory compliance perspectives from global leaders. http://assets1.csc.com/chemical/downloads/Chemical_Week_CSC_Survey_Exec_Summarya.pdf. Last accessed March 16, 2012.
6. AIChE$_{100}$: A Century of Achievement-Vision for the Future: 1908-2008, Chapter 25. http://www.aiche.org/uploadedFiles/About/Centennial/Books/100/AIChE_A_Century_of_Achievements_Chap25.pdf. Last accessed March 16, 2012.

7. www.labcompliance.com. Several sections under this website. Last accessed March 16, 2012.
8. www.cfpa.com/regulatory-compliance-training. Last accessed March 16, 2012.

APPENDIX

Appendix 1: Sample batch record

Experiment Batch Record

Document #:		Order #:	

Title: Generating a standard curve

BATCH RECORD ISSUANCE

Issued By: _____
Print Name   Signature   Date

Name, address and location of the facility performing the experiment:
Date the experiment was initiated:
Date the experiment was completed:

1. SIGNATURE:

    1.1 Sign below if your initials appear in this document.

Printed Name	Signature	Initials

Experiment Batch Record

Document #:		Order #:	

Title: Generating a standard curve

2. REFERENCES:

SOP number	Title
XXXX	

3. LIST OF SUPPLIES:

Item Description	Vendor	Catalog #	Lot #	Date opened	Quantity required
15mL Polypropylene Conical tubes					

4. REAGENTS AND CHEMCIALS:

Material Description	Vendor	Catalog #	Lot #	Storage Condition	Date opended	Quantity Required	Verified By (TA signatures)
NaOH							

Experiment Batch Record

Document #:		Order #:	

Title: Generating a standard curve

5. EQUIPMENT:

Equipment Name	Make/model	Serial or ID Number	Calibration/maintnance Due Date	Calibration/ maintenance done by/Date	Calibration/maintenance verified by/Date	Person responsible for the instrument
Spectrophotometer						

6. SOFTWARE AND STATISTICAL TOOLS:

Software Name	Vendor/version	ID Number, if any	Validation due Date	Validation done by/Date	Validation verified by/Date	Person responsible for the software
Excel						

Experiment Batch Record

Document #:		Order #:	

Title: Generating a standard curve

7. PROCEDURE:

Step #	Operational Description	Data Entry		Performed by/Date	Verified by/Date
7.1	**Preparation of dilutions**				
7.1.1	Dilution #1	Dilution #1 Date			
		Dilution #1 Time			
7.1.2	Dilution #2	Dilution #2 Date			
		Dilution #2 Time			
7.1.3					
7.1.4					

Experiment Batch Record

Document #:		Order #:	

Title: Generating a standard curve

Step #	Operational Description	Data Entry	Performed by/Date	Verified by/Date
7.2	**Preparation of blank**			
7.2.1				
7.2.2				
7.2.3				
7.3	**Measurement of samples**			
7.3.1				
7.3.2				
7.3.3				

Experiment Batch Record

Document #:		Order #:	

Title: Generating a standard curve

8. COMMENTS: (INCLUDE STEP NUMBER REFERENCE)

_____
_____
_____
_____
_____

9. EXPERIMENT REVIEW BY:

Signature: _____   Date: _____
Printed Name: _____

Appendix 2: Sample standard operating procedure

	Preparation of standard curve (or other title)
	Procedure #: SOP-xxx

Study Sponsor:

Summary

1.1. Purpose (what is this procedure for? what is the use of data generated from this procedure? procedure notes such as range, scale-up, special notes, if any)

1.2. Scope (to whom and where does this procedure apply?)

1.3. Responsibility (who is responsible for the proper conduct of this experiment – title such as lab manager, study director, etc.?)

1. Materials
   1.1. Equipments needed:

Equipment	Make
Balance	
1000 μL pipetman	

   1.2. Supplies needed:

Item	Vendor	Catalog #
15 mL centrifuge tubes		
5 mL pipettes		

   1.3. Reagents and chemicals needed:

Chemicals/reagents	Vendor	Catalog #
15 mL centrifuge tubes		
5 mL pipettes		

   1.4. Reagent preparation
      1.4.1. Preparation of stock (50 mg/mL)
      1.4.2.

2. Procedure (include tables if needed, acquire all)
   1.1. Preparation of dilutions
   1.2. Preparation of blank
   1.3.
   1.4.

3. Results reporting (format for reporting data in tabular, fill-in-the-blank, or other form; include information on replicates necessary)
   1.1. OD data
   1.2. Standard curve
   1.3.

4. Errors and acceptable range (only instrument errors and their range)

5. Procedure notes

6. Records to be maintained
   1.1. SOP
      1.1.1. Store in _____ (place, identification, and location)
      1.1.2. Log information in _____ (place, identification, and location)
   1.2. Batch record
      1.2.1.
      1.2.2.
   1.3. Lab notebooks
      1.3.1.
      1.3.2.
   1.4.
   1.5.

7. References (include references if any)
   7.1.
   7.2.
   7.3.

8. Approval
   1.1. Generated by: Date: Signature:
   1.2. Accepted by: Date: Signature:
   1.3. Approved by: Date: Signature:

10. Change history (you will not do this in the lab course)
   10.1. First revision
      10.1.1. Change:
      10.1.2. Reason for the change:
      10.1.3. Generated by: Date: Signature:
      10.1.4. Accepted by: Date: Signature:
      10.1.5. Approved by: Date: Signature: