PGS 380M (Unique Number: 58940)
Protein Pharmaceuticals, Biologics, and Biosimilars
Course Syllabus

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Course description:

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) amends the Public Health Service Act and other statues to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biologic products shown to be biosimilar to or interchangeable with an FDA license biological reference product (sections 7001 through 7003 of the Patent Protection and Affordable Care Act (Affordable Care Act referred to as Obama care) (Public Law 111-148) Although the 351(k) pathway applies generally to biological products.

This course will give an overview of the broad range of scientific considerations that are required to characterize biologics and therapeutic proteins with the purpose of establishing biosimilarity and therapeutic interchangeability. The course will address a broad range of issues:

- Quality attributes of therapeutic proteins and biologics
- Critical manufacturing parameters of biologics and therapeutic proteins
- Analytical methodologies and functional assays to characterize biologics and therapeutic proteins and their potency
- Stability considerations of therapeutic proteins and biologics
- Scientific considerations in demonstrating biosimilarity to a reference product
- Clinical pharmacology data to support biosimilarity

The course will integrate the knowledge of the students in protein and biologic structure, genomics, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, analytical methodologies, clinical safety and effectiveness of therapeutic proteins and biologics. In addition, it will give the student a perspective of the complexity to establish biosimilarity of therapeutic proteins and biologics.

Class Time and Location: TBA
Tentatively: PHR 3.114D

Textbooks for the course.

There are no required textbooks for this course. However, the student is responsible to read the Biologic Price Competition and Innovation Act of 2009 (BPCI).
In addition, recent scientific manuscripts, FDA guidance(s), EMA directives and ICH quality guidance(s) detailing the topics discussed in class will be assigned throughout the semester.

Required Materials:
All students are required to have access to computers. Although you may or may not use the computer during lecture, it will definitely be useful for solving and preparing assignments.

Course Prerequisites:
Graduate standing required, however, professional pharmacy students (Pharm.D.) might register for the course provided the following prerequisites are met:

PHR 342C Physical &Chemical Principles of Drugs
PHR 252C Biopharmaceutics
PHR 251C Pharmaceutical Biochemistry
PHR 356C Pharmaceutics
PHR 371S Integrated Basic & Applied Pharmacokinetics
PHR 675E Pharmacotherapeutics II

Class format
Three (3) hour lecture weekly in a block format.

Course Grading.

Attendance to class is mandatory. Every absence must be properly justified. Each absence will lower your grade by 10%.

Five assignments will be given throughout the semester. Each assignment will consist of:

1 Specific topic and/or problems related to the course assigned by the instructor. The assignments and problems are designed to expand the topics discussed in lecture, and will require the search of recent scientific literature to answer or complement the assigned topic. In addition, a brief power point presentation summarizing the assigned topic will be presented in class. Each assignment will be worth 50% of your grade.

2 A project related to a specific biologic or a therapeutic protein or some other topic will be assigned to each student. If the class is large, students will work in teams structured by the instructor. The project will consist of highlighting the chemistry, manufacturing and controls (CMC) including functional assays, UHPLC-MS.MS, clinical pharmacology, toxicity, pharmacokinetics, pharmacodynamics of branded biologics, therapeutic proteins

and approved biosimilars in Europe and in the United States. For example, some of the branded and biosimilar products may be assigned from the following list:

Xarzio (Filgrastim), Adipra (Glulisine), Lispro, Glargine, Levemir (insulin detemir [rDNA origin] injection), Prolia® (denosumab), Somatotropin, Epoetin, (interferon alfa-2a, interferon beta-1a) Avastin, Enbrel ((etanercept), Remicade ((infliximab), Rebif (interferon beta-1a), Humira (adalimumab), Rituxan (rituximab), Herceptin ((trastuzumab), Lantus, Epogen/Procrit, Neulasta, Erbitux (cetuximab), Novolog, Aranesp (darbepoetin alfa), Recombinate, Lucentis, Avonex, Nocolin, Humalog (insulin lispro), PEGasys, Cerezyme ((imiglucerase), Opdivo (Niolumab) Novoseven, Tysabri (natalizumab), Neupogen (filgrastim), Synagis, Betaseron, Humulin, Kogenate FS, Keytruda (pembrolizumab), BACE (MK-8931, AZD3293) inhibitors, vaccines and monoclonal antibodies for Alzheimer's disease.

The grade will be based on a written report (25%) and a power point presentation (25%) to the class. The rubrics at the end of this document will be used for the evaluation of the power point presentation and the written reports.

Grades will be calculated according to the following formula:

Semester average = (A1 + …….++A5)(0.5) + (P1)(0.5) where "A" is the percent of each assignment and P1 is the percent of the project.

Grade assignments will be as follows:

"A" Range:	A if semester average is:	A= 96-100 %	A- = 90-95%
"B" Range:	B+ if semester average is 87 - 89%	B= 83-86%	B- = 80-82%
"C" Range:	C+ if semester average is 77 - 79%	C= 73–76%	C- = 70-72%
"D" Range:	D+ if semester average is 67 -69%	D= 65-66%	

"F" if semester average is 6%% and below.

Students can access their exam grades via the Canvas page for this course. You will need your UTEID to login and access Canvas.

Project Presentation Dates:

TBD

Post-Assignment Remarks and Reconsideration Requests:

If there is a disagreement over the answer to a specific question in an assignment, the student should present his/her assignment plus a written explanation (with appropriate documentation) to the instructor within 72 hours. Documentation may include statements from textbooks, handouts, packets, or current scientific reprints; lecture notes are *not* authoritative documentation. The explanation must be clear, rational, and concise on your email submissions

Academic Dishonesty

The "Statement on Scholastic Dishonesty of the College of Pharmacy" reads as follows: "Pharmacy practitioners enjoy a special trust and authority based upon the profession's commitment to a code of ethical behavior in its management of client affairs. The inculcation of a sense of responsible professional behavior is a critical component of professional education, and high standards of ethical conduct are expected of pharmacy students. Students who violate University rules on scholastic dishonesty are subject to disciplinary penalties, including failure of the course involved and dismissal from the college and/or the University. Since dishonesty harms the individual, fellow students, and the integrity of the University and the College of pharmacy, policies of scholastic dishonesty will be strictly enforced in this class."

Students are expected to work independently on all assignments or in the specified team by the instructor.. Any student caught cheating will be given a "zero" on the assignment (minimum). Any student suspected of dishonesty will be reported to the Dean of the College of Pharmacy and to the Dean of Students, as per University regulations. Students are expected to have read and understood the current issue of the General Information Catalog published by the Registrar's Office for information about procedures and about what constitutes scholastic dishonesty. Students are also expected to be familiar and abide by the College Honors Code, and will be expected yo sign the Honors Statement at the end of each assignment. If students turns in an assignment or examination without signing this statement, they will not receive a grade until they meet with Dr. Stavchansky.

The Honors Statement

I have neither participated in nor witnessed any acts of academic dishonesty pertaining to the assignments and or examinations.

Printed Name_____ Signed Name_____

Students with Disabilities

The University of Texas at Austin provides upon request appropriate academic accommodations for qualified students with disabilities. All University rules concerning accommodations must be followed, including the student arranging for special accommodations prior to each assignment or examination. In the absence of such prearrangement, the student will be assumed that the student is not requesting special accommodations for that exam, and will be expected to take the exam with the rest of the class at regularly scheduled exam time. For more information, contact the Office of the Dean of Students at 512-471-6259, 512-471-4641 TTY.

THERAPEUTIC PROTEINS, BIOLOGICS, AND BIOSIMILARS

1 (1.5 HRS) INTRODUCTION: A BRIEF HISTORY OF THE PHARMACEUTICAL INDUSTRY

- 1.1 Developments in biomedicine
- 1.2 Pharmaceutical **industry enters** the 20th century
- 1.3 Chemistry driven discovery
- 1.4 Natural product chemistry
- 1.5 Target-directed drug discovery – Genomics- Bioinformatics
- 1.6 The sulfonamide story
- 1.7 Hitching and Elion and the antimetabolite concepts
- 1.8 James Black and receptor-targeted drugs
- 1.9 Accidental clinical discoveries

2 (2.0 HRS) REVIEW OF THERAPEUTIC MODALITIES

- 2.1 Advantages and Disadvantages
- 2.2 Peptide and protein mediators
- 2.3 Antibodies
- 2.4 Enzymes
- 2.5 Vaccines
- 2.6 DNA products
- 2.7 Cell Based Therapies

3 (1.5 HRS) THE DRUG DISCOVERY PROCESS

- 3.1 Case histories
  - 3.1.1 Paclitaxel
  - 3.1.2 Flecainide (Tambocor)
  - 3.1.3 Omeprazol (losec)
  - 3.1.4 Imatinib (Gleevec)
  - 3.1.5 Trastuzumab (Herceptin)

4 (1.0 HRS) REVIEW OF CONVENTIONAL STRATEGIES FOR FINDING NEW DRUG TARGETS

- 4.1 Analysis of pathophysiology
- 4.2 Analysis of mechanism of action of existing therapeutic drugs
- 4.3 The genome and all the ‘OMES’….
- 4.4 Target Validation

5 (0.5 HRS) CHOOSING THE PROJECT

- 5.1 Strategic issues
- 5.2 Unmet medical need

5.3 Market considerations
5.4 Legislation
5.5 Patent Situation

6 (2.0 HRS) HRS) REVIEW OF PROTEIN PHARMACEUTICALS

6.1 From gene to protein
6.2 Protein structure
6.3 Three dimensional structure of proteins
6.3.1 Secondary structure: Regular ways to fold the polypeptide chain
6.3.2 Tertiary structure: Globular proteins - Structure allows for different functions
6.4 Oxidation
6.5 Isomerization
6.6 Glycation
6.7 Spontaneous Deamidation and Isomerization Reactions
6.8 Disulfide bonds in proteins
6.9 Characterization of Protein Charge Heterogeneity
6.10 How to isolate proteins and other macromolecules

7 (1.5 HR) MODELING OF AGGREGATION – PRECIPITATION PHENOMENA

7.1 Formation of Primary Particles
7.2 Floccule strength
7.3 Precipitate Aging
7.4 Kinetics of precipitation
7.5 Adsorption of proteins and peptides at interfaces

8 (1.5 HR) THE EFFECT OF TEMPERATURE ON PROTEIN STRUCTURE

8.1 Protein-Water Interactions
8.2 Hydration and Thermal Stability of Proteins
8.2.1 Solid powders
8.2.2 Suspensions in Non-aqueous Solvents
8.2.3 Reversed micelles
8.2.4 Aqueous solution of polyols
8.2.5 Mechanisms of protein inactivation at low water activity

9 (2.0 HRS) CHARACTERIZATION OF PROTEINS

9.1.1 SDS-PAGE
9.1.2 Capillary Gel Electrophoresis
9.1.3 Size Exclusion Chromatography
9.2 Orthogonal methods
9.2.1 Analytical ultracentrifugation
9.2.2 Field flow fractionation

9.2.3 Light scattering

10 (1.5 HRS) REVIEW OF BIOEQUIVALENCE (GENERIC MEDICINES)

10.1.1 Bioavailability metrics

10.2 Variation and Distributional assumptions in Bioequivalence

10.3 Types of bioequivalence

10.3.1 Average bioequivalence

10.3.2 Population bioequivalence

10.3.3 Individual bioequivalence

10.4 Experimental design and statistical considerations to establish bioequivalence

10.4.1 Non-replicated designs – General Linear Model

10.4.2 Replicated crossover designs

10.5 Bioequivalence consideration for highly variable drugs and Narrow Therapeutic Drugs

10.6 Analytical aspects of bioequivalence testing

10.7 Pharmacodynamics and bioequivalence

10.8 The "ORANGE BOOK"

10.8.1 Approved Drug Products with Therapeutic Equivalence Evaluations

10.8.1.1 Classification of generic drug products

10.8.1.2 Texas Law and generic drug products

11 (3.0 HRS) FROM GENERICS TO BIOSIMILARS

11.1 Setting the scene for biosimilars

11.2 Biosimilarity: A philosophy?

11.3 Biologics Price Competition Innovation Act (BPCIA)

11.3.1 Definition of Biologics and Biosimilars

11.4 Examples of Biosimilars

11.4.1 Genetically engineered products

11.4.2 Molecular Complexity of biosimilars

11.5 Posttranslational processing of proteins

11.5.1 Concepts of Post-Translational Modifications: Glycosylation example; Erythropoietin

11.6 Critical manufacturing parameters of biosimilars - Challenges

11.6.1 Modifications linked to the process

11.6.2 Modifications linked to Conservation

11.6.3 Modification linked to formulation

11.6.4 Concept of expression cassette and vector

11.6.5 Host cell and expression system

11.6.6 Active substance production: Fermentation of cell culture conditions

11.6.7 Purification

11.6.8 Making a pharmaceutical formulations

11.7 Analytical considerations of biosimilars – Challenges

11.8 Biosimilars marketing authorization – FDA
11.9 Non Clinical and Clinical Aspects of Biosimilars
11.9.1 Preclinical approach
11.9.2 Clinical approach

12 (2.0 HRS) IMMUNOGENICITY CONSIDERATIONS OF BIOSIMILARS

12.1 Factors influencing immunogenicity
12.1.1 Structural factors
12.1.2 Primary structure
12.1.3 Glycosylation
12.1.4 Pegylation
12.1.5 Secondary and tertiary structures
12.1.6 Impurities and other production contaminants
12.1.7 Manufacturing process and formulation of the medicinal product
12.1.8 Patient and subsequent treatment factors
12.1.9 Case of monoclonal antibodies

13 (3.0 HRS) SUBSTITUTION AND INTERCHANGEABILITY OF BIOLOGICS

13.1 Substitution of generic drugs
13.2 What about substitution of biosimilar medicinal products
13.3 Interchangeability
13.4 Definition
13.5 Interchangeability practices
13.6 Medical perspective presented by a physician
13.6.1 Medical perspective G-CSF (Filgrastim, Lenograstim, rHu G-CSF, Pegfilgrastim): Onco-Hemtologist's point of view
13.6.2 Prerequisites of EMA Guideline on Similar Biological Medicinal Products Containing Recombinant G-CSF
13.7 Prerequisites of FDA Guideline on Filgrastim (Xarzio)
13.8 The "PURPLE" Book. Bbiosimilar and interchangeable biological products licensed by FDA
13.9 Biosimilars under what name? - Challenges
13.9.1 International Nonproprietary Name or brand name?

14 (3.0 HRS) ANALYTICAL CHARACTERIZATION OF A THERAPEUTIC PROTEIN

14.1.1 Amino acid analysis of a protein
14.1.2 Determination of the N-terminal residues in a protein
14.1.2.1 Sanger's reagent
14.1.2.2 Dansyl chloride
14.1.2.3 Edman reagent
14.1.3 Determination of the C-terminal residues in a protein
14.1.3.1 Hydrazinolysis

14.2 How to sequence a protein
14.2.1.1 Oxidation of disulfide bonds
14.2.1.2 Separation of products
14.2.1.3 Cleavage of beta chain with trypsin
14.2.1.4 Cleavage of beta chain with chymotrypsin
14.2.1.5 Determination of peptide sequences
14.2.1.6 Matching of peptides using overlapping sequences
14.2.2 Case study: Erythropoietin
14.3 Antibodies
14.3.1 Nomenclature of Monoclonal antibodies
14.3.2 Structure of antibodies (IgM, IgG, J chain, IgD, and IgE
14.3.3 Exons involvement
14.3.4 Somatic mutations
14.3.5 Generation of antibody diversity
14.3.6 T-cells and the cellular response
14.3.7 Immunological methods

15 (3.0 HRS) LIGAND BINDING ASSAYS AND VALIDATION

15.1 Define project goals and Ligand Binding Assay Scope
15.2 Advantages and disadvantages over other analytical methods
15.3 Antibodies (IgG, IgM, IgA, IgD, and IgE
15.4 Detecting binding
15.4.1 Enzymes (EIA or ELISA)
15.4.2 Fluorescence (FIA)
15.4.3 Radiolabels (RIA & IRMA)
15.4.4 Luminescence (MSD)
15.4.5 Immunoassays designs
15.4.6 Competitive
15.4.6.1 Disadvantages
15.4.6.2 Noncompetitive
15.4.6.2.1 Advantages and Disadvantages
15.4.7 Ligand Binding Assay Issues
15.4.7.1 Analytical Characteristics to evaluate in pre-validation and final validation
15.4.7.1.1 Dilution linearity
15.4.8 Ligand binding assays to support PK and TK of biologics
15.4.8.1 LC-MS Methodology (MS.MS, TOF, Quadrupole, Ion Trap, Electrospray)
15.4.8.2 Immunoaffinity-Capture Based LC-MS.MS
15.4.9 Applications to validate biomarkers
15.4.9.1 Common issues that complicate Biomarker Development

16 (3.0 HRS) PHARMACOKINETIC AND PHARMACODYNAMIC MODELING OF BIOLOGICS

16.1 PK/PD Modeling and Simulation
16.2 Biomarkers and Clinical End Points in PK-PD Modeling
16.3 Model-based Drug Development
16.4 Target-Mediated Drug Disposition
16.5 Disease induced PK/PD Changes
16.6 Drug Induced PK/PD Changes

RUBRIC FOR GRADING POWER POINT PRESENTATION

STUDENT'S NAME OR TEAM NUMBER: _____

CATEGORY	4	3	2	1	Points
Effectiveness and Content	Project includes all material needed to gain a comfortable understanding of the topic.	Project includes most material needed to gain a comfortable understanding of the material but is lacking one or two key elements.	Project is missing more than two key elements.	Project is lacking several key elements and has inaccuracies.	
Sequencing of Information	Information is organized in a clear, logical way. It is easy to anticipate the type of material that might be on the next slide.	Most information is organized in a clear, logical way. One slide or item of information seems out of place.	Some information is logically sequenced. An occasional slide or item of information seems out of place.	There is no clear plan for the organization of information.	
Originality	Presentation shows considerable originality and inventiveness. The content and ideas are presented in a unique and interesting way.	Presentation shows some originality and inventiveness. The content and ideas are presented in an interesting way.	Presentation shows an attempt at originality and inventiveness on 1-2 slides.	Presentation is a rehash of other people's ideas and/or graphics and shows very little attempt at original thought.	
Spelling and Grammar	Presentation has no misspellings or grammatical errors.	Presentation has 1-2 misspellings, but no grammatical errors.	Presentation has 1-2 grammatical errors but no misspellings.	Presentation has more than 2 grammatical and/or spelling errors.	
Use of Graphics	All graphics are attractive (size and colors) and support the theme/content of the presentation.	A few graphics are not attractive but all support the theme/content of the presentation.	All graphics are attractive but a few do not seem to support the theme/content of the presentation.	Several graphics are unattractive AND detract from the content of the presentation.	
Organization	PowerPoint contains a minimum of 10 slides. All parts of the task are completed fully and support the theme/content of the presentation.	PowerPoint contains a minimum of 10 slides. All parts of the task are completed partially and support the theme/content of the presentation.	PowerPoint contains fewer than 10 slides, or some slides designed do not support the theme/content of the presentation.	PowerPoint contains fewer than 10 slides and is missing several parts of the task. Slides designed do not support the theme/content of the presentation.	

Sources	All sources (information and graphics) are accurately documented in the desired format.	All sources (information and graphics) are accurately documented, but one (1) is not in the desired format.	All sources (information and graphics) are accurately documented, but two (2) or more are not in the desired format.	Some sources are not accurately documented.	

Modified form: https://www.google.com/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=rubric+for+powerpoint+presentation

If a team instead of a student is delivering the power point presentation the following will be added to the team's grade:

Team building	Team has energy and enthusiasm, each member has a clear role	Team has energy, but roles are undefined	Team has no cohesion	Points

Rubric for Grading of written reports.

The following elements will be taking into consideration:

1. Structure of the report including a one page "Executive Summary" highlighting the critical findings of the report
2. Clear understanding of the project
3. Evidence (accurate literature references) presented to support the arguments in the project
4. Logic of the structure of the report
5. Discussion of important points in the report
6. Grammar
7. Spelling
8. Formatting of the report

Based on the above elements, the rubric in the next page was developed.

1 Points

ect is lacking several
elements and has
curacies.

Rubric for Grading Project Written Report

Source: Adapted from: Whalen, S. "Rubric of Contemporary Health Issues Research Paper" http://www.cornellcollege.edu/library/faculty/focusing-on-assign ments/tools-for-assessment/research-paper-rubric.shtml

CATEGORY	4	3	2	1	Points
Integration Of Knowledge	The student/team demonstrates full understanding of the topic and has applied knowledge acquired in the course. Student/team insights are integrated in the report	The student/team for the most part understands, and has applied concepts learned in the course. Sometimes conclusions are not supported in the report	The student/team to certain extent understands the topic and has applied concepts learned in the course	The paper does not demonstrate that the student/team has fully understood and applied concepts learned in the course.	
Topic Focus	The topic is focused narrow enough for the goal of the assignment	The topic is focused but lacks direction. The student/team has not establish a position	The topic is too broad for the scope of the report	The topic is not clearly defined	
Depth of Discussion	In depth discussion in all elements of the report	In depth discussion in most elements of the report	The student/team has omitted pertinent content. Quotations from others outweigh the writer's own ideas	Cursory discussion in all sections of the report or brief discussion in only a few sections	
Cohesiveness	Ties all the information together. Report flows from one issue to the next without headings	For most part ties all information together, report has some disjointedness and understanding of the relationship among material obtained from all sources	Sometimes ties all information together. Writer's writing does not demonstrate understanding of the material obtained from all sources	Does not tie together information obtained from all sources.	
Spelling & Grammar	No spelling or grammar mistakes	Minimal (1 or 2) grammar or spelling mistakes	Noticeable spelling & grammar mistakes (3 - 4)	Unacceptable number of spelling & grammar mistakes (more than 4	
Sources	More than 7 current sources of which at least 3 are peer-reviewed journals articles or books. Web sites utilized are credible and authoritative	5 current sources of which at least 2 are peer-review journal articles or books. Web sites utilized are credible and authoritative	Fewer than 5 current sources or fewer than 2 of 5 are peer-reviewed journal articles or books. Web sites utilized are credible	Fewer than 5 current sources, or fewer than 2 of 5 are peer-reviewed journal articles or books. Not all Web sites utilized are credible, or sources are not current	

Citations	Cites all data and appropriate style is used In both text and bibliography	Cites most data from other sources and appropriate style is used in both text and bibliography	Cite some data. Citation style is inconsistent or incorrect	Does not cite sources when required	