PHC 331H: Establishing the Bioequivalence of Pharmaceutical Products

I. TEACHING TEAM

INSTRUCTORS:

Dr. David Dubins Course Coordinator d.dubins@utoronto.ca Office: PB802	**Sarah Cash** Teaching Assistant sarah.cash@mail.utoronto.ca

STUDENT HOURS:
Mondays, 3 – 5p EDT (Online in January, in-person: HS 108)
Fridays, 3 – 5p EDT (Online in January, in-person: HS 108)

II. COURSE OVERVIEW

COURSE DESCRIPTION:
Welcome to PHC331! Have you ever wondered how a generic drug is reviewed and accepted in Canada, the US, and Europe, and the criteria that are involved to be deemed equivalent to the original (innovator) product?

This course will introduce you to human clinical trial design to demonstrate bioequivalence of drug products. The principles you will learn in this course are currently used by generic and innovator drug companies in the US, Canada, India, Japan, and Europe.

You will learn about the regulations, methods, techniques, pharmacokinetics, and biostatistics involved in creating bioequivalence studies, at an introductory level. You will learn how to use academic and industry resources publicly available, to characterize a drug in both pharmacokinetic and regulatory arenas. The course has a heavy mathematical bias, with a large component dedicated to mathematical modeling. After taking this course, you will understand the steps required to set up single-dose or steady-state pilot and pivotal bioequivalence trials using parallel, crossover, and replicate designs.

The goal of this course is to provide an understanding of drug development in Canada pertaining to the demonstration of bioequivalence between medicinal products. After completing this course, you will be in a position to take more advanced courses in pharmacokinetics, clinical trial design, and drug

development. This course is an elective, and will be taught assuming that you have a basic background in chemistry, biochemistry, mathematics, and pharmaceutics.

STUDENT LEARNING OUTCOMES:
By the end of PHC331, students will …

1) Understand the regulatory aspects of bioequivalence in Canada, the US, and Europe;
2) Appropriately design a clinical study for establishing bioequivalence between a given drug and the appropriate reference product based on literature data and regulatory searches;
3) Be able to analyze, interpret, and report the results of a bioequivalence trial;
4) Present themselves competitively to employers, to find and secure an entry level job in clinical science.

PREREQUISITE COURSE(S):
This course requires a basic understanding of mathematics and pharmaceutics.
The following courses are pre-requisites for PHC 331H1:
BCH210H1, CHM247H1/CHM249H1, (MAT135H1, MAT136H1)/MAT137Y1, PHC230H1, PHC330H1

READINGS:
Required Text
None.

Recommended Texts
1. Patterson S. and Jones B., Bioequivalence and Statistics in Clinical Pharmacology. Chapman & Hall/CRC, Boca Raton FL, USA; 2006

Course Resources
Presentation slides will be provided online, through Quercus. These handouts will serve as the best guide to course content and scope. It is important to mention that the field of bioequivalence is continually evolving. The lecture notes provided are the current thinking, but will lose their accuracy as the industry and regulations continue to evolve. The recommended textbook for this course is Patterson S. and Jones B., *Bioequivalence and Statistics in Clinical Pharmacology.* Chapman & Hall/CRC, Boca Raton FL, USA; 2006, and is optional (*i.e.* it will not be required to successfully complete the course, although it is an excellent reference).

For further or supportive reading, the following websites have the most updated regulatory guidelines:

Food and Drug Administration (FDA), US:
https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Therapeutic Products Directorate (TPD), Canada:
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/index-eng.php

European Medicines Agency (EMA), Europe:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000085.jsp&mid=WC0b01ac0580027549

Course notes, objectives, and information will be made available through the University of Toronto Quercus system.

III. COURSE ORGANIZATION

COURSE SCHEDULE, LOCATION, AND RELEVANT SESSIONAL DATES:

The course is organized into 9 sections. Lectures will take place in person, as permitted by the University of Toronto policies and public health guidelines. Lectures will be held in HS 108.

Section	Description	Mondays 3p-5p Fridays 3p-5p Room: HS 108
1	**Course Introduction.** History of bioequivalence, overview of drug development process, course structure, goals, and course outline. What is bioequivalence (BE)?	9-Jan-23
2.1	**Introduction to Noncompartmental Pharmacokinetics (PK) in BE Studies**: Estimation of pharmacokinetic parameters: Cmax, AUCt, lambda, half-life. Nonlinear kinetics, enterohepatic cycling. Types of drugs: immediate release, sustained release, delayed release, long half-life, etc. Demonstration: Noncompartmental PK Analysis. When is it appropriate to estimate AUCinf?	13-Jan-23
2.2†	**Statistical Principles in Bioequivalence.** Introduction to statistical principles in bioequivalence. Coefficient of variation (CV), standard deviation (SD), Standard Error (SE), normal and log-normal distributions. Regulatory guidances pertaining to Bioequivalence: The United States Food and Drug Administration (FDA), the Canadian Therapeutic Products Directorate (TPD), the European Medicines Agency (EMA).	16-Jan-23
2.3	**Sample Size:** Hypothesis testing. Variability of PK parameters. Sample size calculation in clinical trials: equivalence, bioequivalence, superiority, non-inferiority, difference between proportions. Inter- and intra-subject variability. Power, alpha error, beta error, hypothesis testing.	20-Jan-23
2.3	**Sample Size:** Calculating Sample Size. Software demonstration: Free Analysis Research Tool for Sample Size Iterative Estimation. Estimating sample sizes for crossover, parallel, replicate.	23-Jan-23
3.1	**Creating a Bioequivalence Study Design:** Types of trials (parallel, crossover, replicate, steady-state). Country-specific guidances concerning measuring metabolites.	27-Jan-23
3.1†	**Creating a Bioequivalence Study Design (cont'd):** How to conduct an effective literature search. Characterizing a drug's pharmacokinetic behaviour and variability, Calculating and selecting a sample size, planning alternates.	30-Jan-23
3.2	**Creating a Bioequivalence Study Design (cont'd):** Considerations for study structure. LLOQ, washout period. Sampling times, total blood volume, confinement period, fasting vs. fed, study population, clinical monitoring specifics.	03-Feb-23
3.2, 3.3	**Example Study Design.** (Finish up Section 3.2)	06-Feb-23
4	**Compartmental PK**: Defining noncompartmental models: IV, oral. Laplace transforms, the generalized distribution function, Heaviside Expansion Method.	09-Feb-23
4	**Compartmental PK (cont'd)**: Model fitting using R - 1 compartment oral model. Fitting a sigmoid curve. 2-compartment IV model. Occam's Razor. ****Bring a laptop to this class.**	13-Feb-23

5†	**Writing PK and statistical sections of a bioequivalence protocol**. Specification of PK parameters, bioequivalence criteria, Handling of drop-outs and withdrawals, non-compliance, vomiting subjects. Medical writing, creating protocol amendments. Regulatory process for conducting clinical trials in Canada: Institutional Review Board (IRB) approval, Clinical Trial Application (CTA) filing.	17-Feb-23
6.1	**Statistical Principles in Bioequivalence:** Statistical analysis of bioequivalence trials: handling of data (replacing subjects with alternates, decision tree for keeping subjects in analysis). Ln-transformation of data, tests of distribution. NCA Program in Excel. ANOVA Models in SAS® for statistical analysis of bioequivalence data: PROC GLM, PROC MIXED. How to find out if your study passed? Demonstration: SAS®. Nonparametric techniques: Bootstrapping and Monte Carlo simulations. Interpreting results: carry-over effects.	27-Feb-23
6.2	**Disaster Recovery - Outlier Analysis, Add-on, and Re-dosing Studies.** Normal distribution testing, bootstrapping, planning an add-on study (TPD) and a re-dosing study (FDA, EMEA)	03-Mar-23
7†	**Design and Analysis of Steady-State Studies.**	06-Mar-23
8	**Preparing a Final Clinical Report.**	10-Mar-23
	Student Oral Study Design Presentations **Final Take-home Assignment Posted on Blackboard.**	13-Mar-23
	Student Oral Study Design Presentations	17-Mar-23
	Student Oral Study Design Presentations	20-Mar-23
	Student Oral Study Design Presentations	24-Mar-23
9†	**Interview Workshop:** How to more-than-just-survive an interview.	27-Mar-23
	Student Oral Study Design Presentations	31-Mar-23
	Student Oral Study Design Presentations **Final Take-home Assignment Due.**	03-Apr-23

†Problem set handed out (due in class the following week, unless otherwise indicated).

For important academic sessional dates, visit:
https://www.artsci.utoronto.ca/current/dates-deadlines/academic-dates

LECTURES

The course is split into nine sections. Sections 1-8 trace through the scientific and regulatory principles behind clinical trial designs having the objective of demonstrating bioequivalence. Specific topics covered will be pharmacokinetics, biostatistics, the impact of the country of submission on study design, and the analysis and interpretation of bioequivalence data. Public domain programs will be provided for different types of analyses. A brief introduction to R-project and SAS® will also be provided.

Following Section 8, the course will focus on student presentations of individual study designs. Students will select a drug and perform an in-class oral presentation featuring the pharmacokinetic behaviour of the drug, their bioequivalence study design, and screening/idiosyncratic considerations which would be incorporated into a clinical study protocol. This will be followed by a brief question period.

As a strong component of the course is dedicated to discussing clinical research opportunities in industry, Section 9 discusses approaches to practicing and improving interview skills.

IV. EVALUATION/GRADING SCHEME

OVERVIEW:
The final grade will be based on one oral presentation, five problem sets, one take-home exam, and class participation. Questions on the problem sets will be drawn primarily from the lecture handouts provided in class and material discussed in the lectures. Each oral presentation will last 30 minutes, followed by a 5-minute question period. Oral presentations will take place during the second half of the course. They may be performed in groups of two depending on class size. Students will individually write a final take-home assignment.

ASSESSMENT DATES & MARK BREAKDOWN:
The schedule and weighting of the evaluative components of the course are as follows:

1) Problem Sets (5)
Weight: **35%**
Best of 5 problem sets worth 11.67%, the other 4 worth 5.83%.
Dates: To be announced.
Due: One week from receipt of problem set unless otherwise defined in class.
Material: Entire Course

2) Oral Presentation (30 + 5 minutes)
Weight: **30%**
Dates: To be determined. (Sign-up list will circulate)
Material: Student's choice from a list of provided topics

3) Final Take-Home Assignment
Weight: **25%**
Dates: Due by the last class
Material: Entire Course

4) Class Participation
Weight: **10%**
Based on: Participating in class discussions and polls. Asking questions during class. Asking questions during the question periods of oral presentations.

ORAL PRESENTATION

Students will be responsible for creating a study design for a selected drug, and presenting it during the second half of the course. Depending on the number of students, topics may be assigned in groups. If there are fewer students enrolled than the number of oral presentation lectures available, the instructor will cover the presentation topic. The key components of the study design include:

- A thorough literature search;
- Pharmacokinetic characterization of PK parameters: maximal plasma concentration (C_{max}) and its time of occurrence (T_{max}), area under the plasma concentration vs. time curve ($AUC_{0\text{-}t}$), area under the plasma concentration vs. time curve extrapolated to infinity ($AUC_{0\text{-}inf}$), terminal elimination half-life ($t_{1/2}$);
- Sample size calculation, and rationale;
- Specific regulatory requirements for the US, Canada, and Europe. How does the design change?
- Planning an appropriate sampling scheme
- Specific inclusion/exclusion criteria.

FINAL TAKE-HOME ASSIGNMENT

Students will be responsible for completing a take-home assignment. The assignment will be posted on Quercus, and will be due by electronic submission through Quercus on the final day of class. The exam is to be completed on an individual basis.

IMPORTANT: if an unexpected technical issue occurs with a university system (e.g., Quercus services, network outage) that affects availability or functionality, it may be necessary to revise the timing or weighting of the quizzes/term tests.

V. COURSE POLICIES

- Each member of this course is expected to maintain a:
  (i) professional and respectful attitude during all course activities, including classes, laboratories, and online activity.
  (ii) personal calendar/schedule/organizer to ensure that all course activities are completed, and due dates are met.
  (iii) collection of notes recorded independently based on concepts covered in course activities (students registered with Accessibility Services requiring a class note-taker will have access to this accommodation)
  (iv) familiarity with the university policy on Academic Integrity (overleaf)

Lateness Policy
Problem sets and assignments are due ***by electronic submission only, through Quercus***. Problem sets are due one week from being assigned, by the **beginning** of class. Problem sets handed in at the end of class will be considered late. For late submissions, there will be an academic penalty imposed of **10% per day**, in accordance with departmental policies. Submissions will not be accepted beyond 1 week from the original due date.

E-mail
• For course concerns or issues with non-academic problems, such as conflicts, illness and academic accommodations, please email d.dubins@utoronto.ca.
• When you e-mail an individual, the language and tone of your email professional. Email only one member of the teaching team. Most emails will receive a reply within 24 hours of being sent (except on weekends) but keep your expectations reasonable as to the degree of detail that an email reply to your enquiry can realistically provide.

Course Environment
• The University of Toronto is committed to equity, human rights and respect for diversity. All members of the learning environment in this course should strive to create an atmosphere of mutual respect where all members of our community can express themselves, engage with each other, and respect one another's differences. As a Course Instructor, I will neither condone nor tolerate behaviour that undermines the dignity or self-esteem of any individual in this course and wish to be alerted to any attempt to create an intimidating or hostile environment. It is our collective responsibility to create a space that is inclusive and welcomes discussion. Discrimination, harassment and hate speech will not be tolerated. If you have any questions, comments, or concerns, we encourage you to reach out to the staff in our Equity Offices.

Privacy Policy

• This course, including your participation, will be recorded on video and will be available to students in the course for viewing remotely and after each session.
• Course videos and materials belong to your instructor, the University, and/or other sources depending on the specific facts of each situation, and are protected by copyright. Do not download, copy, or share any course or student materials or videos without the explicit permission of the instructor.
• For questions about recording and use of videos in which you appear please contact your instructor.
• At times, you may be required to share your desktop, and/or turn on your webcam to confirm participation in course activities, and/or to troubleshoot practical activities.

Absences

Students who are absent from class for any reason (e.g., COVID, other illness or injury, family situation) and who require consideration for missed academic work should report their absence through the online absence declaration. The declaration is available on ACORN under the Profile and Settings menu. You must also advise Dr. Dubins, the course coordinator, of your illness in order to receive consideration.

VI. TECHNOLOGY REQUIREMENTS

REQUIRED EQUIPMENT

- **A laptop or desktop computer** is required for this course.
- **Microsoft Excel** (including the ability to run Macros) is required for this course.
- **R-Project** (an open-source statistical package) is required for this course.

• Specific guidance from the U of T Vice-Provost, Students regarding student technology requirements is available here: https://www.viceprovoststudents.utoronto.ca/covid-19/tech-requirements-online-learning/
• Advice for students more broadly regarding online learning is available here: https://onlinelearning.utoronto.ca/getting-ready-for-online.

• This course requires the use of computers, and technical issues are possible. When working on a piece of academic work, students are responsible for scheduling enough time to allow for reasonable delays due to technical difficulties to be overcome, so such issues will not be acceptable grounds for deadline extension. Particularly, maintaining an up-to-date independent backup copy of your work is strongly recommended to guard against hard-drive failures, corrupted files, lost computers, etc.

We appreciate that students may experience a range of circumstances that shape their ability and/or decision to participate in course activities using video. We are committed to creating equitable and inclusive learning and teaching spaces. In support of this commitment we feel it is important to give participants the choice to turn their video on/off.

For General technology concerns, please contact the Information Commons Help Desk via (416) 978-HELP (4357) OR by e-mailing help.desk@utoronto.ca. They are open evenings and weekends.
https://onesearch.library.utoronto.ca/ic-faq-categories/about-and-hours-service

Please contact the course co-ordinator with course-specific technology concerns. Please be as detailed as possible with your question by including the time/date, detailed description of the problem, web browser and device you were using (e.g. laptop/tablet etc.) and include screenshots/error message etc.

VII. INSTITUTIONAL POLICIES AND SUPPORT

ACADEMIC INTEGRITY

Academic integrity is essential to the pursuit of learning and scholarship in a university, and to ensuring that a degree from the University of Toronto is a strong signal of each student's individual academic achievement. As a result, the University treats cases of cheating and plagiarism very seriously. The University of Toronto's Code of Behaviour on Academic Matters (governingcouncil.utoronto.ca/secretariat/policies/code-behaviour-academic-matters-july-1-2019) outlines the behaviours that constitute academic dishonesty and the processes for addressing academic offences. Potential offences include, but are not limited to:

In practical work:

1. Using someone else's ideas or words without appropriate acknowledgement.
2. Submitting your own work in more than one course without the permission of the instructor.
3. Making up sources or facts.
4. Obtaining or providing unauthorized assistance on any assignment. **Please note that the use of websites (such as Chegg.com or the course discussion board) to post virtual laboratory report material/questions or to post/access answers to questions is an academic offence under the University of Toronto's Code of Behaviour on Academic Matters. Alleged instances of this nature are forwarded to the Faculty of Arts & Science Student Academic Integrity office.**

On tests:

1. Using or possessing unauthorized aids. **Please note that the use of websites (such as Chegg.com or the course discussion board) to post quiz/term test questions or to post/access answers to questions is an academic offence under the University of Toronto's Code of Behaviour on Academic Matters. Alleged instances of this nature are forwarded to the Faculty of Arts & Science Student Academic Integrity office.**
2. Looking at someone else's answers or collaborating or discussing answers during an exam or a test.
3. Misrepresenting your identity.

In general academic work:

1. Falsifying institutional documents or grades.
2. Falsifying or altering any documentation required by the University.
3. Sharing solutions to the online homework

In computer programs:

1. Not properly referencing included libraries.
2. Not properly referencing any code used to help generate your code.
3. Copying an algorithm or snippet of computer code without referencing the source and author.
4. Copying someone else's program, modifying it to make it look different, and submitting it as your own work.

All suspected cases of academic dishonesty will be investigated following procedures outlined in the Code of Behaviour on Academic Matters. If you have questions or concerns about what constitutes appropriate academic behaviour or appropriate research and citation methods, you are expected to seek out additional information on academic integrity from your instructor or from other institutional resources (see www.academicintegrity.utoronto.ca/).

PLAGIARISM DETECTION

Normally, students will be required to submit their course essays to the University's plagiarism detection tool for a review of textual similarity and detection of possible plagiarism. In doing so, students will allow their essays to be included as source documents in the tool's reference database, where they will be used solely for the purpose of detecting plagiarism. The terms that apply to the University's use of this tool are described on the Centre for Teaching Support & Innovation web site (https://uoft.me/pdt-faq).

COPYRIGHT

If a student wishes to copy or reproduce class presentations, course notes or other similar materials provided by instructors, he or she must obtain the instructor's written consent beforehand. Otherwise, all such reproduction is an infringement of copyright and is absolutely prohibited. See the ***Privacy Policy*** section in this document for more details.

ACCESSIBILITY NEEDS

Students with diverse learning styles and needs are welcome in this course. The University of Toronto is committed to accessibility: if you require accommodations for a disability, or have any other accessibility concerns about the course, please contact Accessibility Services as soon as possible.

ACCOMMODATIONS FOR RELIGIOUS OBSERVANCES

Following the University's policies, reasonable accommodations will be made for students who observe religious holy days that coincide with the due date/time of an assignment, tutorial, class or laboratory session. Students must inform the instructor **before** the session/assignment date to arrange accommodations.

ADDITIONAL SERVICES & SUPPORT

The following are some important links to help you with academic and/or technical service and support:

- General student services and resources at Student Life
- Full library service through University of Toronto Libraries
- Resources on conducting online research through University Libraries Research
- Resources on academic support from the Academic Success Centre
- Learner support at the Writing Centre
- Information for Quercus Support

ACKNOWLEDGEMENT OF TRADITIONAL LANDS

We wish to acknowledge this land on which the University of Toronto operates. For thousands of years, it has been the traditional land of the Huron-Wendat, the Seneca and, most recently, the Mississaugas of the Credit River. Today, this meeting place is still the home to many Indigenous people from across Turtle Island and we are grateful to have the opportunity to work on this land.