**Clinical Studies and Regulation - 138009**

Mini-Semester 7 / 2021-2022

[Class location]

Thursdays ⁕ 23.12.2021 -10.2.2022 ⁕ 14:00 – 18:00

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| Teaching Staff | Lecturer 1 - Mr. Shlomi Harpaz  e-mail: [harpazshlomi@technion.ac.il](mailto:harpazshlomi@technion.ac.il)  Phone: 0548006694  Office hours: Thursday after class / by appointment |
| Lecturer 2 – Dr. Aric Orbach  e-mail: [aricorbach@gmail.com](mailto:aricorbach@gmail.com)  Phone: 0548886304  Office hours: Thursday after class / by appointment |

Credits: 2.0

Study hours per week: Lecture – 14:00- 18:00

**Course Goals and Description**

One of the premier clients for any company that designs and/or manufactures medical products – be it drugs, biologics or medical devices – is the regulator. To get the product into market requires the company to answer the requirements presented by this demanding, often troublesome, client, and the regulators' expectations and requirements continue to play a major role in shaping company work practices and activities in the post-marketing phase.

While answering the regulators' requirements is far from ensuring success in itself – the medical products graveyards are full of failed products that received clearance for marketing – failure to answer these requirements could deeply affect company profits and value, and in the case of a startup company, could easily doom it to failure.

Like other clients in the medical field, the regulators' willingness to approve a new product for use is founded, first and foremost, on the provision of valid data generated through well-controlled clinical investigations. The planning and conduct of such clinical investigations are therefore one of the major time and budget consuming activities for most companies in the medical field – and here, too, the regulators' requirements regarding the design, registration and conduct of such clinical investigations play a major role.

The goal of the present course is to introduce students to the terminology employed by regulators, to their frame-of-mind and to the basic requirements presented by them with regards to the design, approval, clinical testing and manufacturing of medical products. In addition, the present course is intended to allow students to understand how to plan a clinical study that will support future regulatory submission processes. While only serving as a basic introduction to this vast field, the knowledge to be acquired through this course is of fundamental importance to anyone aspiring to fill managerial roles in the medical products industries.

**Learning Outcomes**

At the end of the course, the student will be familiar with:

* The drug & device development process and interrelations with regulatory pathways for approval.
* How to analyze whether a given medical product is regulated as a drug, biological product, medical device, combination product – or does not constitute any of the above.
* The available routes for drug, biological product, medical device and combination product approval, including expected timetables, activities, and major challenges.
* The change in frame-of-mind when moving from R&D-focused activities to the GMP/QMS phase in a startup’s lifecycle.
* What constitutes well-documented and controlled design and manufacturing processes.
* The major categories of pre-clinical testing that apply to each type of medical product.
* How to submit a clinical investigation in Israel and what are the interactions between clinical investigation design and the regulators' requirements.
* The basic regulatory requirements that apply to medical products in the post-marketing phase.

**Course Content/Topics**

| **Lecture #** | **Date** | **Lecturer** | **Subject** | **Topics Covered** |
| --- | --- | --- | --- | --- |
| **1** | 23.12.21 | Shlomi Harpaz | General Introduction to the Regulation of Medical Products | * Brief historical review. * Introduction to division between drug, biological product and medical device. * Combination products. * Borderlines with less heavily regulated options (e.g., cosmetics, food, LDTs, wellness products). * General criteria applied by regulators in the review of medical products. * Compassionate use options. * Benefit-risk approach. * Labelling and off-label use. * Available options for preliminary discussions with regulatory agencies. |
| **2** | 30.12.21 | Aric Orbach | Drug and Biologics Approval Processes | * Overview of drug development process. * Regulatory approval in the US and EU for novel and generic drugs (small molecules & biologics). * Special conditions for accelerated approval: fast track, emergency & orphan drug approval. * Drug monographs. |
| **3** | 6.1.22 | Shlomi Harpaz | Medical Device and Combination Product Approval Processes | * Medical device classification. * PMA, de novo and 510k processes for medical devices. * Submission to Notified Bodies. * Combination product approval processes. |
| **4** | 13.1.22 | Shlomi Harpaz | GMP Requirements | * Introduction to GMP/QMS requirements with a focus on two major issues: * Design control requirements – focusing on the medical device example. * Manufacturing controls – with a focus on how to establish, validate and control a manufacturing process per GMP requirements. |
| **5** | 20.1.22 | Aric Orbach | Bench and animal testing; early phase clinical testing | * Major categories of preclinical testing for drugs, biologics and devices –efficacy, toxicity, pharmacokinetics. * Manufacturing requirements. * Requirements from animal studies. * GxP status * Early clinical phases, phase 0 (micro dosing) & Pilot testing of devices. * Clinical Phase, I and II drug testing |
| **6** | 27.1.22 | Aric Orbach | Clinical Trial Design | * Regulatory phase III requirements. * Study design in correlation with the applicable regulatory requirements – study arms, randomization, blinding, inclusion / exclusion criteria. * Advanced trail design (phase II/III, adaptive design, futility assessment, etc.) * Study sites, study monitoring, sample and data analysis. |
| **7** | 3.2.22 | Shlomi Harpaz | Clinical Trial Initiation, Conduct and Reporting | * Investigational approval submissions (IDE/IND). * Submissions to Helsinki committees. * Informed consent process. * Adverse events reporting. * Preparation of clinical investigation reports. |
| **8** | 10.2.22 | Shlomi Harpaz | Post Marketing Activities and Marketing-Related Challenges | * Adverse events reporting and recalls. * Reporting on changes. * Post marketing / phase IV clinical studies – objectives & design. * Reimbursement challenges. |

**Assignments and Grading Procedures**

* Case studies – 30% (15% each).
* Final project– 70%

3 points will be deduced for each day of an unapproved delay in submitting an assignment.

**Course Schedule (Topics, assignments, Exams)**

During the semester two home assignments will be given - each student will be asked to read and answer several questions in relation to a presented case study.

During the semester each student /student pair will be asked to choose a yet-to-be-approved drug / biological product / device / combination product (could be a product related to the student's thesis or to a company s/he is associated with, or any other medical product that is of interest to the student/s).

At the end of the semester the student / student pair will be asked to define an intended use, to determine the applicable regulatory route in the USA, and to define what is required to allow the initiation and performance of a proof-of-concept study.

**Course Requirements & Course Policies**

Lecture slides will be posted via the course's Moodle website.

Students are encouraged (but not obliged) to prepare a short presentation (up to 4 slides) of the product they have chosen and their analysis of the regulatory route to market and to present this presentation to the class during the last two lectures (up to 10 minutes of presentation). While not obligatory, the feedback received from classmates and from the lecturers could be highly beneficial.

Students are required to participate in at least 80% of lectures. Necessary absences must be discussed with the lecturer and approved in advance.

**Accommodation for Students with special needs are available.**

**Text book(s) and/or other materials**

As part of this course, students will become familiarized with the basic types of documents that govern the regulation of medical products and of clinical investigations, including both laws and regulations, the guidance documents issued by regulators, and applicable international standards.

Following are some of the documents that will be mentioned and discussed during the course:

Drug Discovery & Development Literature

* Cook, D., Brown, D., Alexander, R. et al. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. Nat Rev Drug Discov 13, 419–431 (2014).
* Morgan P, Van Der Graaf PH, Arrowsmith J, Feltner DE, Drummond KS, Wegner CD, Street SD. Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. Drug Discov Today. 2012 May;17(9-10):419-24.
* <http://csdd.tufts.edu/white-papers> Tufts CSDD produces authoritative White Papers to highlight current thinking on critical drug development issues. White Papers present findings and insights from Tufts Center analyses, as well as detailed reviews of roundtable discussions and forums hosted by CSDD.

Clinical Investigations –

* **נוהל ניסויים רפואיים בני אדם (נוהל 14 של אגף הרוקחות).**
* WMA Declaration of Helsinki – ethical principles for medical research involving human subjects.
* 21 CFR Part 50 Protection of Human Subjects; Part 54 Financial Disclosure by Clinical Investigators and Part 56 Institutional Review Boards.
* ICH E3 Structure and Content of Clinical Study Reports.
* ICH E6 (R2) Good Clinical Practice.
* ICH E8 General Considerations for Clinical Trials.
* ISO 14155:2020 Clinical investigations of medical devices – Good clinical practice.

Regulation of Drugs and Biologics -

* **פקודת הרוקחים [נוסח חדש], תשמ"א-1981.**
* **תקנות הרוקחים (תכשירים), תשמ"ו-1986.**
* 21 CFR Part 314 Applications for FDA Approval to Market a New Drug.
* 21 CFR Part 320 Bioavailability and Bioequivalence Requirements.
* 21 CFR Part 330 Over-The-Counter (OTC) Human Drugs which are Generally Recognized as Safe and Effective and not Misbranded.
* 42 USC 262: Regulation of biological products.
* Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products – FDA Guidance of May 1998.
* Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products – FDA Draft Guidance of December 2019.
* Scientific Considerations in Demonstrating Biosimilarity to a Reference Product – FDA Guidance of April 2015.
* Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment – FDA Guidance of March 2005.
* Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.
* Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.
* Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use.
* Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products.
* Guideline on Similar Medicinal Products – European Medicines Agency – 23 October 2014.
* <https://www.ich.org/page/safety-guidelines> :ICH Safety guidelines S1-S12 : special focus on preclinical safety.
* <https://www.ich.org/page/multidisciplinary-guidelines> : multidisciplinary guidelines M3(R2) guideline for Nonclinical Safety studies for the conduct of Human Clinical Trails.
* ICH E4 Dose response information to support drug registration.
* ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients.
* ICH Q8(R2) Pharmaceutical Development.
* ICH Q9 Quality Risk Management.
* ICH Q10 Pharmaceutical Quality System.
* ICH Q12 Technical and regulatory considerations for pharmaceutical product lifecycle management.

Regulation of Medical Devices –

* **חוק ציוד רפואי, התשע"ב – 2012.**
* **תקנות ציוד רפואי 2013.**
* Regulation 2017/745 of the European Parliament on Medical Devices.
* Regulation 2017/746 of the European Parliament on In Vitro Diagnostic Medical Devices.
* 21 CFR 814 Premarket Approval of Medical Devices.
* The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] – FDA Guidance of July 28, 2014.
* De Novo Classification Process (Evaluation of Automatic Class III Designation) – FDA Guidance of October 05, 2021.
* General Wellness: Policy for Low Risk Devices – FDA Guidance of September 27, 2019.
* ISO 13485:2016 Medical devices – Quality management systems – Requirements for regulatory purposes.
* ISO 14971:2019 Medical devices – Application of risk management to medical devices.

Regulation of Combination Products –

* 21 CFR Part 3 Product Jurisdiction.
* 21 CFR Part 4 Regulation of Combination Products.
* Guideline on quality documentation for medicinal products when used with a medical device – European Medicines Agency guidance of 22 July 2021.
* Requesting FDA Feedback on Combination Products – FDA Guidance of December 2020.
* Principles of Premarket Pathways for Combination Products – Draft FDA Guidance of February 2019.
* Postmarketing Safety Reporting for Combination Products – FDA Guidance of July 2019.
* Current Good Manufacturing Practice Requirements for Combination Products – FDA Guidance of January 2017.

**Academic Integrity**

Students are expected to determine the regulatory route that applies to the product of their choosing and to define the outline of the required proof-of-concept study by themselves. If working on a project that is related to a company they are employed by or to their own startup, students must not use any materials created by company employees or by external consultants. It is far better to err and to learn than to copy and remain ignorant.