Chapter 1
Overview of Drug Development and Regulatory Approval

Host Introduction

Learning Objectives

1) Describe the roles and contributions of pharmaceutical companies in advancing new therapies
2) Demonstrate an understanding of the general pathway from drug discovery to the marketplace
3) Identify the key stakeholders, including healthcare professionals, in drug development. Describe both the roles they play individually and how they interact
4) Define bioethics and discuss its importance in drug development

Table of Contents

I. Drug Development Process
   – Overview of drug development life-cycle
   – Introduction to the FDA
   – Interactive exercise: Develop a timeline for a potential drug, based on provided background information, to illustrate how long it takes to develop a drug from molecule to patient
   – Resources for the Industry
   – Knowledge Check Quiz

II. Phases of Drug Development
   – Drug discovery: Identifying drug candidates
   – Non-clinical studies:
     o Test safety, perform testing with cells, biologic materials, and non-human models
     o Develop IND (Investigational New Drug application)
   – Phase 1: Test safety, clinical activity, and pharmacology of the investigational drug in humans
   – Phase 2: Evaluate the safety and efficacy of the drug in a well-defined population of patients with a specific disease or condition
   – Phase 3: Compare the safety and efficacy of a new drug with that of the current standard of care
   – Discussion of rare diseases and orphan drugs
   – NDA (New Drug Application) submission
   – FDA Approval: The sponsor files a complete package to support a standard review by the FDA.
   – Approval Letter
   – Complete Response Letter
   – Phase 4: Conducted to further characterize a drug and its effects on patients
Interactive exercise: Develop a timeline for a potential drug, based on provided background information, to illustrate how long it takes to develop a drug from molecule to patient

− Define key players in drug development process
− Collaborations with healthcare professionals
− Knowledge Check Quiz

III. Working With Regulatory and Advising Authorities
− Trade Associations - PhRMA, BIO, Global Organizations
− The Role of the FDA
− Laws and Regulations
− Approving New Drugs
− Branded versus Generics
− Medical Devices
− FDA Video - Dr. Brenda Vaughan

IV. Bioethics
− Evolution
− The Four Principles
− Bioethics Video - Dr. Michael Turik
− NIH Requirements
− Informed Consent and Institutional Review Boards
− Bioethics Safeguards
− HIPPA Requirements
− Registering Clinical Trials in the Public Domain

Summary
Chapter 1 Test
# Chapter 1: Learning Competencies

1. ACGME IV.A.5.b/AAMC-PCRS-COMP-c0200: Medical Knowledge-Demonstrate knowledge of established and evolving biomedical, clinical, epidemiological and social-behavior sciences, as well as the application of this knowledge to patient care.

2. AACOM II: Medical knowledge-Articulate basic biomedical science and epidemiological and clinical science principles related to patient presentation.

3. ACGME IV.A.5.c/AAMC-PCRS-COMP-c0300: Practice-based Learning and Improvement – Demonstrate the ability to investigate and evaluate their care of patient care based on constant self-evaluation and life-long learning.

4. IV.A.5.c).(7)/AAMC-PCRS-COMP-c0307: Use information technology to optimize learning.

5. AACOM VI: Practice-Based Learning and Improvement-Describe and apply evidence-based medical principles and practices. Interpret features and meanings of different types of data, quantitative and qualitative, and different types of variables, including nominal, dichotomous, ordinal, continuous, ratio, and proportion.

6. VI.3.d: Utilize information technology to manage and access online medical information.
Chapter 2
Which Comes First: The Indication or the Drug?

Host Introduction
Learning Objectives
1) Learn why and how drugs are identified for development
2) Define unmet medical needs that may be filled by new drug candidates
3) Describe common methods for screening drug candidates
4) Examine the high-risk nature of the drug development enterprise
5) Explain why drugs cost so much to develop

Table of Contents
I. Introduction to Drug Discovery
   – Drug Development-Challenge
   – NIH Video-Dr. John Gallin
   – Drug Development-Role of Healthcare Professionals
II. Pathways to Drug Discovery
   – Lead identification and optimization
   – 2 Main Pathways to Drug Discovery
   – Indication
   – Drug
   – Knowledge Check
   – Case studies: Pathways to drug discovery
     1. Imatinib mesylate for chronic myelogenous leukemia
     2. Naltrexone/bupropion for weight loss
     3. Terazosin for benign prostatic hyperplasia
     4. Mitoxantrone for multiple sclerosis
III. Drug Development Challenges
   – Development Risks

Summary
Chapter 2 Test
Chapter 2: Learning Competencies

1. ACGME IV.A.5.b/AAMC-PCRS-COMP-c0200: Medical Knowledge-Demonstrate knowledge of established and evolving biomedical, clinical, epidemiological and social-behavior sciences, as well as the application of this knowledge to patient care.

2. AACOM II: Medical knowledge-Articulate basic biomedical science and epidemiological and clinical science principles related to patient presentation.

3. ACGME IV.A.5.c/AAMC-PCRS-COMP-c0300: Practice-based Learning and Improvement – Demonstrate the ability to investigate and evaluate their care of patient care based on constant self-evaluation and life-long learning.

4. IV.A.5.c).(7)/AAMC-PCRS-COMP-c0307: Use information technology to optimize learning.

5. AACOM VI: Practice-Based Learning and Improvement-Describe and apply evidence-based medical principles and practices. Interpret features and meanings of different types of data, quantitative and qualitative, and different types of variables, including nominal, dichotomous, ordinal, continuous, ratio, and proportion.

6. VI.3.d: Utilize information technology to manage and access online medical information.
Chapter 3
A Rational Approach to Drug Development

Host Introduction
Learning Objectives
1) Describe the key factors that drive the overall drug development strategy
2) Identify key decision points for drug development and the factors that affect those decisions
3) Examine the concept of “benefit-risk” in the drug development and approval process

Table of Contents
I. Drug Development Strategy
   – Fulfilling an Unmet Need
   – NIH Video-Dr. John Gallin
   – Benefit-Risk Profile
II. Decision Points
   – Identification
   – Who Decides
   – Clinical Development
   – Early Discontinuation
   – Late-phase Discontinuation
   – Modification & Expansion
   – Patient Population
   – Clinical Development Interactive Exercise: Decide if a multi-targeted kinase inhibitor should be investigated as a treatment for chronic myeloid leukemia (CML)
   – Knowledge Check
III. Submitting a Drug Candidate for FDA Approval
   – FDA Review Pathways
   – Regulatory Submission
   – Standard vs. Accelerated Approval
   – Breakthrough Therapy
   – FDA Rejection
IV. Market Considerations
   – Market Potential
   – Cost Effectiveness
   – The Right Fit
   – Go/No Go Influences
   – Actual Usage

Summary
Chapter 3 Test
Chapter 3: Learning Competencies

1. ACGME IV.A.5.b/AAMC-PCRS-COMP-c0200: Medical Knowledge-Demonstrate knowledge of established and evolving biomedical, clinical, epidemiological and social-behavior sciences, as well as the application of this knowledge to patient care.

2. AACOM II: Medical knowledge-Articulate basic biomedical science and epidemiological and clinical science principles related to patient presentation.

3. ACGME IV.A.5.c/AAMC-PCRS-COMP-c0300: Practice-based Learning and Improvement – Demonstrate the ability to investigate and evaluate their care of patient care based on constant self-evaluation and life-long learning.

4. AACOM VI: Practice-Based Learning and Improvement-Describe and apply evidence-based medical principles and practices. Interpret features and meanings of different types of data, quantitative and qualitative, and different types of variables, including nominal, dichotomous, ordinal, continuous, ratio, and proportion.

5. VI.3.d: Utilize information technology to manage and access online medical information.

6. ACGME IV.A.5.F/AAMC-PCRS-COMP-c0600: Systems-based Practice-Residents must demonstrate an awareness of and responsiveness to the larger context and system of healthcare, as well as the ability to call effectively on other resources in the system to provide optimal health care.

7. IV.A.5.c)(7)/AAMC-PCRS-COMP-c0307: Use information technology to optimize learning.

8. AACOM VII: Systems-Based Practice-The candidate must demonstrate understanding of variant health delivery systems and their effect on the practice of a physician and the health care of patients.
Chapter 4
From Molecule to Medicine: Nonclinical/Early Clinical Testing

Host Introduction
Learning Objectives
1) Describe the objectives and regulatory requirements for non-clinical testing
2) Identify the components of an Investigational New Drug Application (IND)
3) Explain chemistry, manufacturing, and controls (CMC) for a new drug
4) Describe the requirements for pharmacologic testing
5) Examine what factors determine whether a drug moves into human (clinical) trials

Table of Contents
I. Drug Discovery
   – Sources
   – Pathways
   – New Molecular Entity
   – Why Molecules are not Developed

II. Non-clinical Studies
   – Goals
   – Conducting the Research
   – Animal Research
   – Toxicology
   – Non-Clinical Studies Interactive Exercise: Timeline that allows the user to move back and forth in time to review key decision making points
   – Pharmacology
   – Knowledge Check

III. Production, Quality Control, and Chemistry, Manufacturing, and Controls (CMC)
   – Defining CMC
   – Formulation
   – Administration Route

IV. Investigational New Drug Application (IND)
   – Deciding to File
   – FDA Approval
   – Submission Content

V. Phase I Clinical Study
   Objectives
   – Clinical Pharmacology Studies
   – Clinical Activity
   – Example – What a typical phase 1 study might look like.

Summary
Chapter 4 Test
Chapter 4: Learning Competencies

1. ACGME IV.A.5.b/AAMC-PCRS-COMP-c0200: Medical Knowledge-Demonstrate knowledge of established and evolving biomedical, clinical, epidemiological and social-behavior sciences, as well as the application of this knowledge to patient care.

2. AACOM II: Medical knowledge-Articulate basic biomedical science and epidemiological and clinical science principles related to patient presentation.

3. ACGME IV.A.5.c/AAMC-PCRS-COMP-c0300: Practice-based Learning and Improvement – Demonstrate the ability to investigate and evaluate their care of patient care based on constant self-evaluation and life-long learning.

4. IV.A.5.c).(7)/AAMC-PCRS-COMP-c0307: Use information technology to optimize learning.

5. AACOM VI: Practice-Based Learning and Improvement-Describe and apply evidence-based medical principles and practices. Interpret features and meanings of different types of data, quantitative and qualitative, and different types of variables, including nominal, dichotomous, ordinal, continuous, ratio, and proportion.

6. VI.3.d: Utilize information technology to manage and access online medical information.
Chapter 5
Late Stage Development: Human Phase 2 and 3 Trials

Host Introduction

Learning Objectives
1) Outline the differences between phase 2 and 3 clinical trials
2) Identify the key players responsible for designing and conducting a phase 2 or 3 clinical trial
3) Examine the factors that must be considered when designing phase 2 or 3 clinical trials
4) Learn the important operational aspects involved in conducting phase 2 or 3 clinical trials

Table of Contents
I. Clinical Trial Objectives
   - Setting Objectives
   - Design
   - Life Threatening vs Non-Life Threatening Diseases
II. Designing a Clinical Trial
   - Phase 2 Design
   - Phase 3 Design
   - Clinical Trial Components
   - Interactive Exercise: Develop a clinical trial and apply your knowledge about the design
   - Interactive Exercise: Designing a Phase 3 trial
   - Clinical Trial Design Randomized vs. Single-Arm
   - Interactive Exercise: Choosing a randomized study scheme
   - Interactive Exercise: Phase 3 comparator
   - Patient Populations
   - Interactive Exercise: Choosing the correct patient populations for Phase 3 trials
   - Designing a Feasible Study
   - Interactive Exercise: Study Feasibility
   - Endpoints
   - Interactive Exercise: Primary Endpoint
   - Open Label vs. Blinded
   - Interactive Exercise: Blinded Study
   - Statistical Considerations
   - Clinical Trial Protocol
   - Knowledge Check
III. Clinical Trial Scenarios
   - Considering Unique Features
   - Rare Disease vs. Common Disease
   - Rare Disease – Dr. John Gallin
   - Real World Applications
   - Acute vs. Chronic
Course Outline

- Established Indication vs. New Indication
- Disease Modification vs. Symptom Treatment
- The Approval Pathway
  - Accelerated
  - Standard Approval
- Clinical Trial Video - Dr. Michael Koren

IV. Conducting a Clinical Trial
- FDA Submission
- Patient Recruitment
- Ethics and Transparency

V. Key Players in Clinical Trials
- Development Team
- Data Safety Monitoring Board
- Institutional Review Board
- Physicians
- Research Nurses
- Pharmacists
- Scientists
- Contract Research Organization

VI. Wrapping up Clinical Trials
- Clinical Trial Close-Out Activities
- Publishing the Data

Summary
Chapter 5 Test
## Chapter 5: Learning Competencies

1. **ACGME IV.A.5.b/AAMC-PCRS-COMP-c0200**: Medical Knowledge-Demonstrate knowledge of established and evolving biomedical, clinical, epidemiological and social-behavior sciences, as well as the application of this knowledge to patient care.

2. **AACOM II**: Medical knowledge-Articulate basic biomedical science and epidemiological and clinical science principles related to patient presentation.

3. **ACGME IV.A.5.c/AAMC-PCRS-COMP-c0300**: Practice-based Learning and Improvement—Demonstrate the ability to investigate and evaluate their care of patient care based on constant self-evaluation and life-long learning.

4. **IV.A.5.c).(7)/AAMC-PCRS-COMP-c0307**: Use information technology to optimize learning.

5. **AACOM VI**: Practice-Based Learning and Improvement—Describe and apply evidence-based medical principles and practices. Interpret features and meanings of different types of data, quantitative and qualitative, and different types of variables, including nominal, dichotomous, ordinal, continuous, ratio, and proportion.

6. **VI.3.d**: Utilize information technology to manage and access online medical information.

7. **IV.A.5.e)**: Professionalism—Residents must demonstrate a commitment to carrying out professional responsibilities and an adherence to ethical principles.

8. **AACOM V**: Professionalism—Knowledge-Demonstrate knowledge of the behavioral and social sciences that provide the foundation for the professionalism competency, including medical ethics, social accountability and responsibility, and commitment to professional virtues and responsibilities.

9. **IV.A.5.f)**: Systems based Practice—Residents must demonstrate an awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on the other resources in the system to provide optimal health care.

10. **AACOM VII**: Systems-Based Practice-The candidate must demonstrate understanding of variant health delivery systems and their effect on the practice of a physician and the health care of patients.
Chapter 6
Drug Approval Process: Benefit and Risk Assessment

Host Introduction
Learning Objectives

1) Demonstrate an understanding of the activities undertaken by a pharmaceutical company or institution in preparing to submit a New Drug Application (NDA) to the US Food and Drug Administration (FDA)
2) Identify the major components of an NDA
3) Demonstrate an understanding of the FDA review and approval process
4) Describe the major principles of risk management and post-approval activities

Table of Contents
I. Preparing for Submission
   – Introduction
   – Creating a Product Label
   – Evaluating Benefit-Risk Profile
   – Compiling the Data
II. Regulatory Submission
    – CTD Components
III. US Food and Drug Administration (FDA) Review and Negotiations
    – Congressional Legislation
    – The Review Team
    – Review Timeframe
    – FDA Reviewer Video-Dr. Brenda Vaughan
    – Expedited Review
    – Accelerated Approval
    – Advisory Committees
    – Knowledge Check
IV. Product Labeling
    – Definition
    – Negotiations
    – Organization and Content
    – Additional Information
    – Interactive Exercise: Learning the sections of the Label
V. Patient Safety Strategies
    – Managing Risks
    – Evolution of the Drug Safety Monitoring
    – Risk Management Plan
    – Medication Guide
    – Pharmacovigilance
    – Risk Evaluation and Mitigation Strategies (REMS)
    – Interactive Case Study: Patient Safety Strategies
VI. FDA Approval
Course Outline

- Making the Decision
- Prescription Drug User Fee Act (PDUFA) date
- Priority Review
- Standard Review
- Approval Packages

Summary
Chapter 6 Test
Chapter 6: Learning Competencies

1. ACGME IV.A.5.b/AAMC-PCRS-COMP-c0200: Medical Knowledge-Demonstrate knowledge of established and evolving biomedical, clinical, epidemiological and social-behavior sciences, as well as the application of this knowledge to patient care.

2. AACOM II: Medical knowledge-Articulate basic biomedical science and epidemiological and clinical science principles related to patient presentation.

3. ACGME IV.A.5.c/AAMC-PCRS-COMP-c0300: Practice-based Learning and Improvement – Demonstrate the ability to investigate and evaluate their care of patient care based on constant self-evaluation and life-long learning.

4. IV.A.5.c).(7)/AAMC-PCRS-COMP-c0307: Use information technology to optimize learning.

5. AACOM VI: Practice-Based Learning and Improvement-Describe and apply evidence-based medical principles and practices. Interpret features and meanings of different types of data, quantitative and qualitative, and different types of variables, including nominal, dichotomous, ordinal, continuous, ratio, and proportion.

6. VI.3.d: Utilize information technology to manage and access online medical information.

7. IV.A.5.f): Systems based Practice – Residents must demonstrate an awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on the other resources in the system to provide optimal health care.

8. IV.A.5.f).(3)/AAMC-PCRS-COMP-c0603: incorporate considerations of cost awareness and risk-benefit analysis in patient and/or population-based care as appropriate.

9. AACOM VII: Systems-Based Practice-The candidate must demonstrate understanding of variant health delivery systems and their effect on the practice of a physician and the health care of patients.
Chapter 7
Continuous Development: Ongoing Responsibilities, Accountabilities, and Activities

Host Introduction
Learning Objectives
1) Examine the role of payers in evaluating patient access to necessary drugs
2) Describe pharmacovigilance and ongoing safety monitoring
3) Examine the role of phase 4 studies in life-cycle management
4) Identify the legal and regulatory controls over marketing and promotion of approved drugs

Table of Contents
I. Patient Access
   - Stakeholders
   - Payers
   - Assistance Programs
   - Expanded Access

II. Outcomes Research
   - Health Economics and Outcomes Research (HEOR)
   - Clinical Outcomes
   - Patient-Reported Outcomes (PRO)

III. Pharmacovigilance
   - Adverse Events
   - Patient Registries
   - Risk Evaluation and Mitigation Strategies (REMS)

IV. Lifecycle Management
   - Accelerated Approval
   - Pediatric
   - Pharmacoepidemiology
   - Supplemental Indications

V. Promotional Material
   - Guidelines
   - Fair Balance
   - Review Boards
   - FDA Oversight
   - Ongoing Drug Monitoring After Drug Approval

VI. Healthcare Professional – Industry Relations
   - Industry Interactions

Summary
Chapter 7 Test
Chapter 7: Learning Competencies

1. ACGME IV.A.5.b/AAMC-PCRS-COMP-c0200: Medical Knowledge-Demonstrate knowledge of established and evolving biomedical, clinical, epidemiological and social-behavior sciences, as well as the application of this knowledge to patient care.

2. AACOM II: Medical knowledge-Articulate basic biomedical science and epidemiological and clinical science principles related to patient presentation.

3. ACGME IV.A.5.c/AAMC-PCRS-COMP-c0300: Practice-based Learning and Improvement – Demonstrate the ability to investigate and evaluate their care of patient care based on constant self-evaluation and life-long learning.

4. IV.A.5.c).(7)/AAMC-PCRS-COMP-c0307: Use information technology to optimize learning.

5. AACOM VI: Practice-Based Learning and Improvement-Describe and apply evidence-based medical principles and practices. Interpret features and meanings of different types of data, quantitative and qualitative, and different types of variables, including nominal, dichotomous, ordinal, continuous, ratio, and proportion.

6. VI.3.d: Utilize information technology to manage and access online medical information.

7. IV.A.5.f): Systems based Practice – Residents must demonstrate an awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on the other resources in the system to provide optimal health care.

8. IV.A.5.f).(3)/AAMC-PCRS-COMP-c0603: incorporate considerations of cost awareness and risk-benefit analysis in patient and/or population-based care as appropriate.

9. AACOM VII: Systems-Based Practice-The candidate must demonstrate understanding of variant health delivery systems and their effect on the practice of a physician and the health care of patients.