The Path From Drug Discovery to Commercialization

An overview of drug development process

Ahmad-Reza Saadat

Objectives

- This is an introduction to the overall drug development process from a regulatory perspective
  - This is a general framework, but there are many exceptions
  - So, please ask questions as we go along

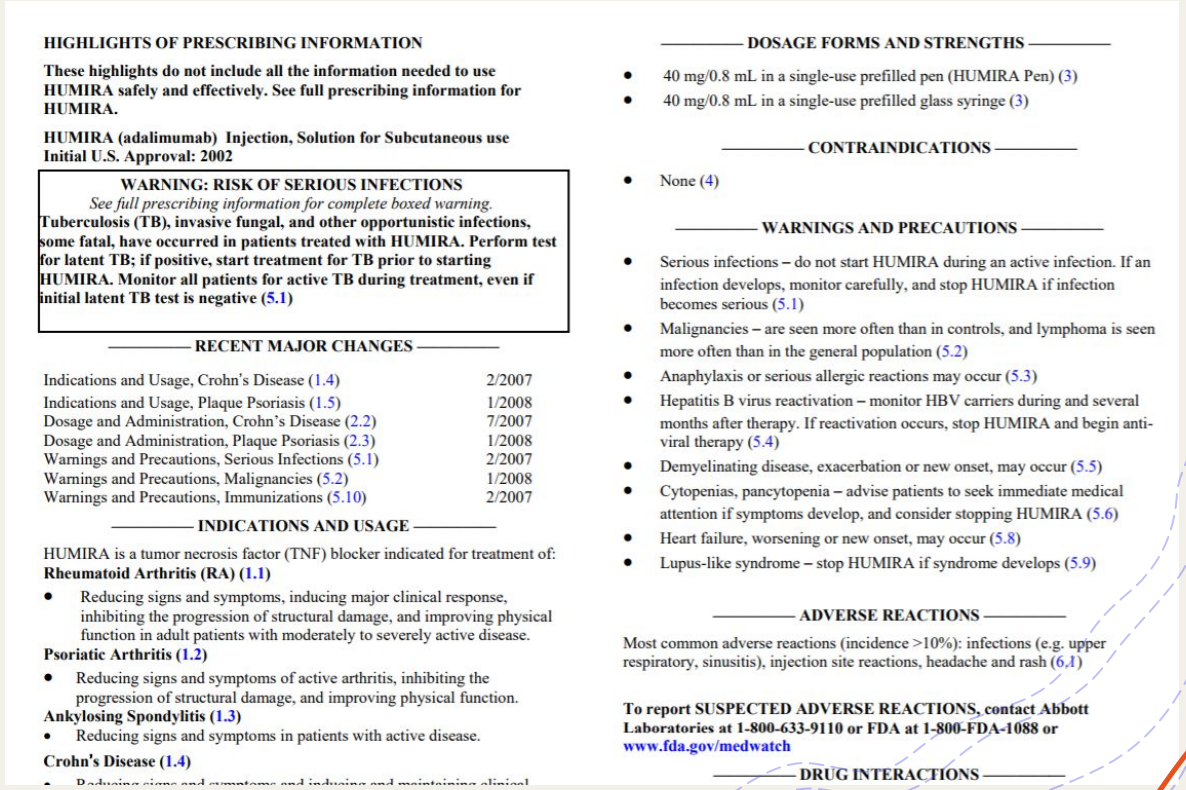
- Today is the first layer of the proverbial “Peeling of the Onion” strategy

What is the Common Goal of Every Drug Discovery and Development Program?

- Drug approval by FDA (US), EMA(EU), PMDA (Japan) or NMPA (China)
- While each may have slightly different requirements, in general, they all share the same goals
  - To approve medicines where benefits outweigh risks

The Goal: Approved Drug Label

- Drug Label is a summary of all the information the company submitted to the regulatory agency, which has been reviewed and accepted (also known as Package Insert)
- There is often, but not always, an advisory committee of external experts who vote on approvability (if rejected, the company received a Complete Response Letter (CRL)
- Click here for Humira Label
- A company can legally start selling (commercializing) a drug in US once FDA approves the drug label or package insert
- A good resource to learn more is FDA.gov, where you can find development guidelines for many diseases and modalities



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HUMIRA safely and effectively. See full prescribing information for HUMIRA.

HUMIRA (adalimumab) Injection, Solution for Subcutaneous use
Initial U.S. Approval: 2002

WARNING: RISK OF SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.
Tuberculosis (TB), invasive fungal, and other opportunistic infections, some fatal, have occurred in patients treated with HUMIRA. Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA. Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1)

RECENT MAJOR CHANGES

Indications and Usage, Crohn's Disease (1.4)	2/2007
Indications and Usage, Plaque Psoriasis (1.5)	1/2008
Dosage and Administration, Crohn's Disease (2.2)	7/2007
Dosage and Administration, Plaque Psoriasis (2.3)	1/2008
Warnings and Precautions, Serious Infections (5.1)	2/2007
Warnings and Precautions, Malignancies (5.2)	1/2008
Warnings and Precautions, Immunizations (5.10)	2/2007

INDICATIONS AND USAGE

HUMIRA is a tumor necrosis factor (TNF) blocker indicated for treatment of:
Rheumatoid Arthritis (RA) (1.1)
- Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease.

Psoriatic Arthritis (1.2)
- Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.

Ankylosing Spondylitis (1.3)
- Reducing signs and symptoms in patients with active disease.

Crohn's Disease (1.4)
- Reducing signs and symptoms and inducing and maintaining clinical

DOSAGE FORMS AND STRENGTHS
- 40 mg/0.8 mL in a single-use prefilled pen (HUMIRA Pen) (3)
- 40 mg/0.8 mL in a single-use prefilled glass syringe (3)

CONTRAINDICATIONS
- None (4)

WARNINGS AND PRECAUTIONS
- Serious infections – do not start HUMIRA during an active infection. If an infection develops, monitor carefully, and stop HUMIRA if infection becomes serious (5.1)
- Malignancies – are seen more often than in controls, and lymphoma is seen more often than in the general population (5.2)
- Anaphylaxis or serious allergic reactions may occur (5.3)
- Hepatitis B virus reactivation – monitor HBV carriers during and several months after therapy. If reactivation occurs, stop HUMIRA and begin anti-viral therapy (5.4)
- Demyelinating disease, exacerbation or new onset, may occur (5.5)
- Cytopenias, pancytopenia – advise patients to seek immediate medical attention if symptoms develop, and consider stopping HUMIRA (5.6)
- Heart failure, worsening or new onset, may occur (5.8)
- Lupus-like syndrome – stop HUMIRA if syndrome develops (5.9)

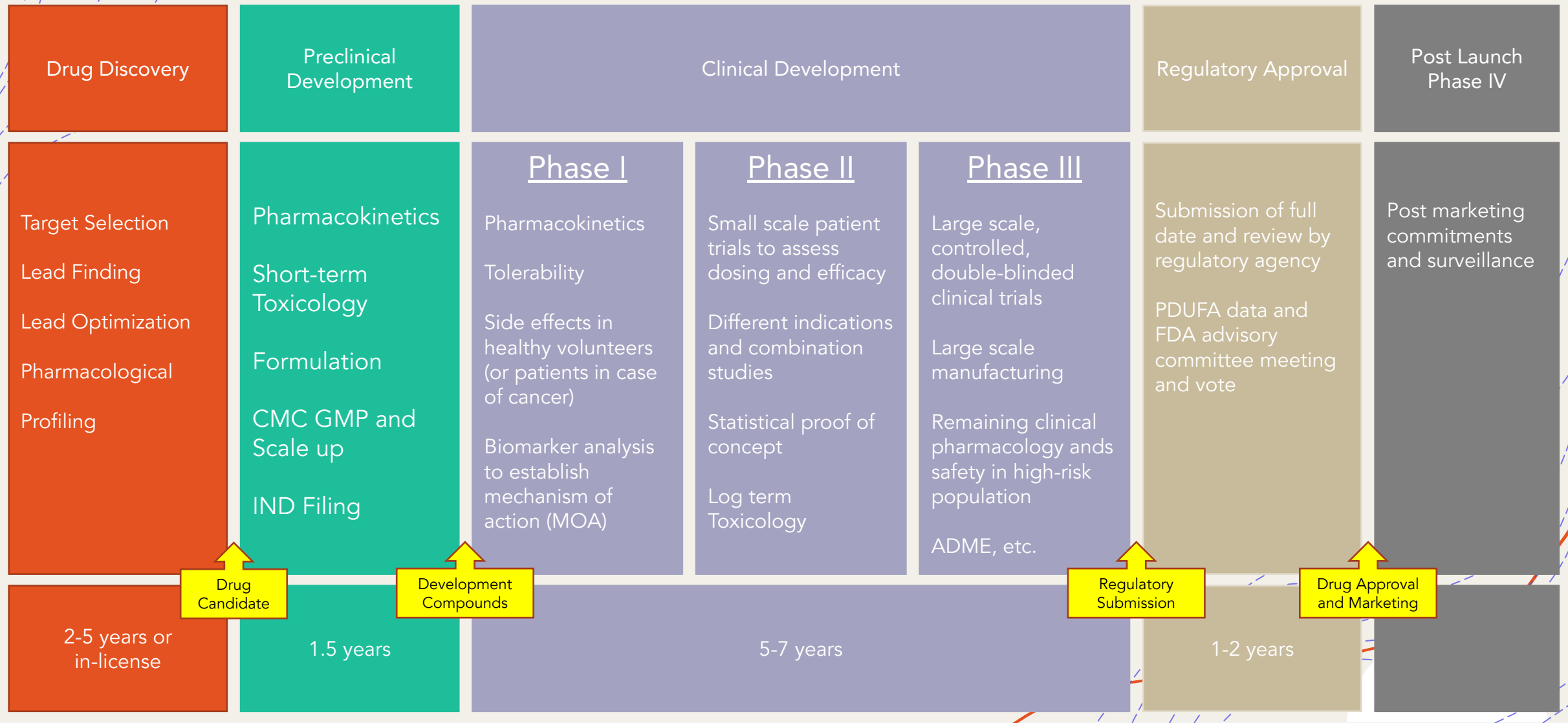
ADVERSE REACTIONS

Most common adverse reactions (incidence >10%): infections (e.g. upper respiratory, sinusitis), injection site reactions, headache and rash (6.1)

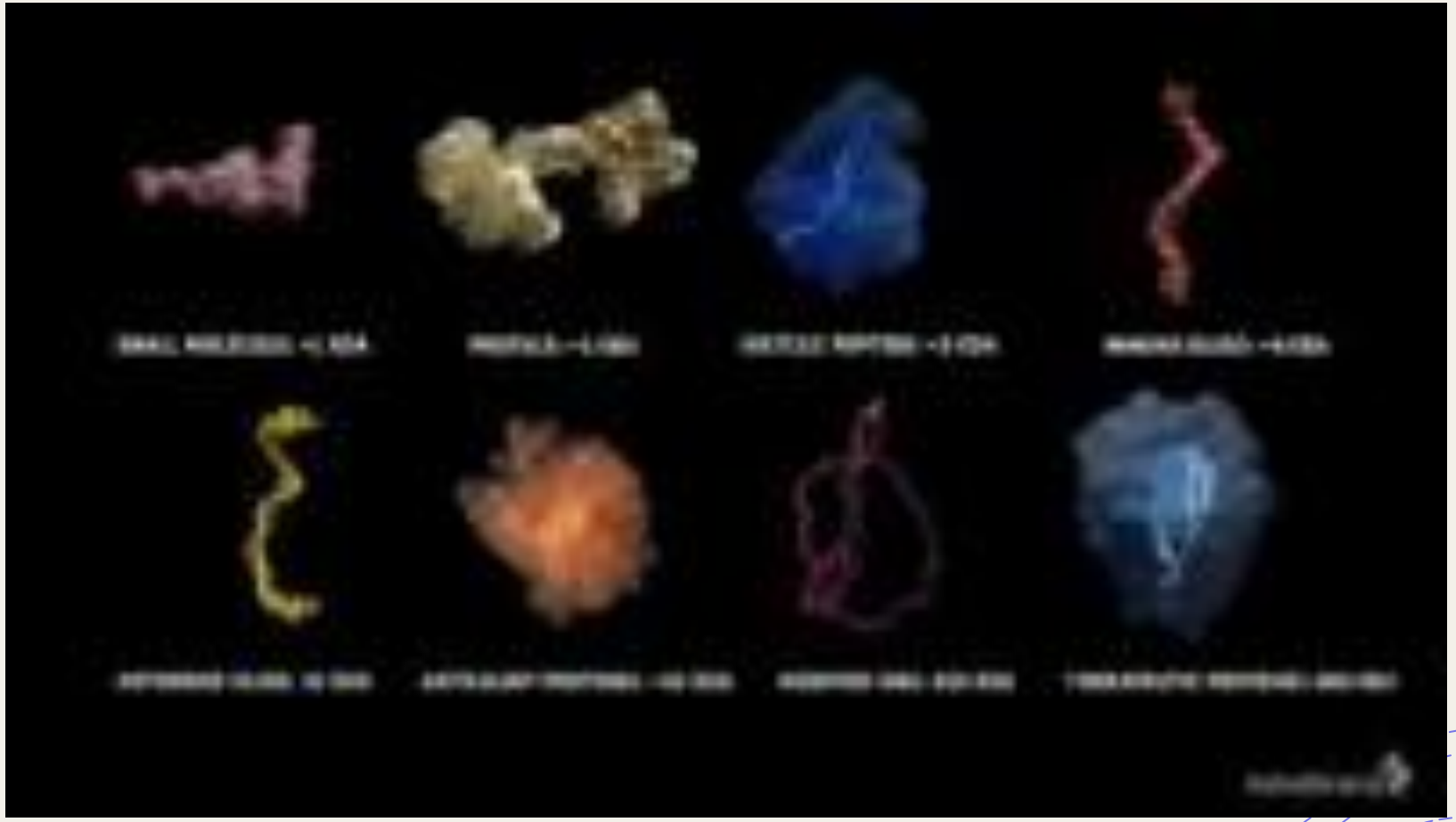
To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Drug Development Process



Drug Discovery Process Depends (somewhat) on Drug Modality



Drug Discovery and Preclinical Development

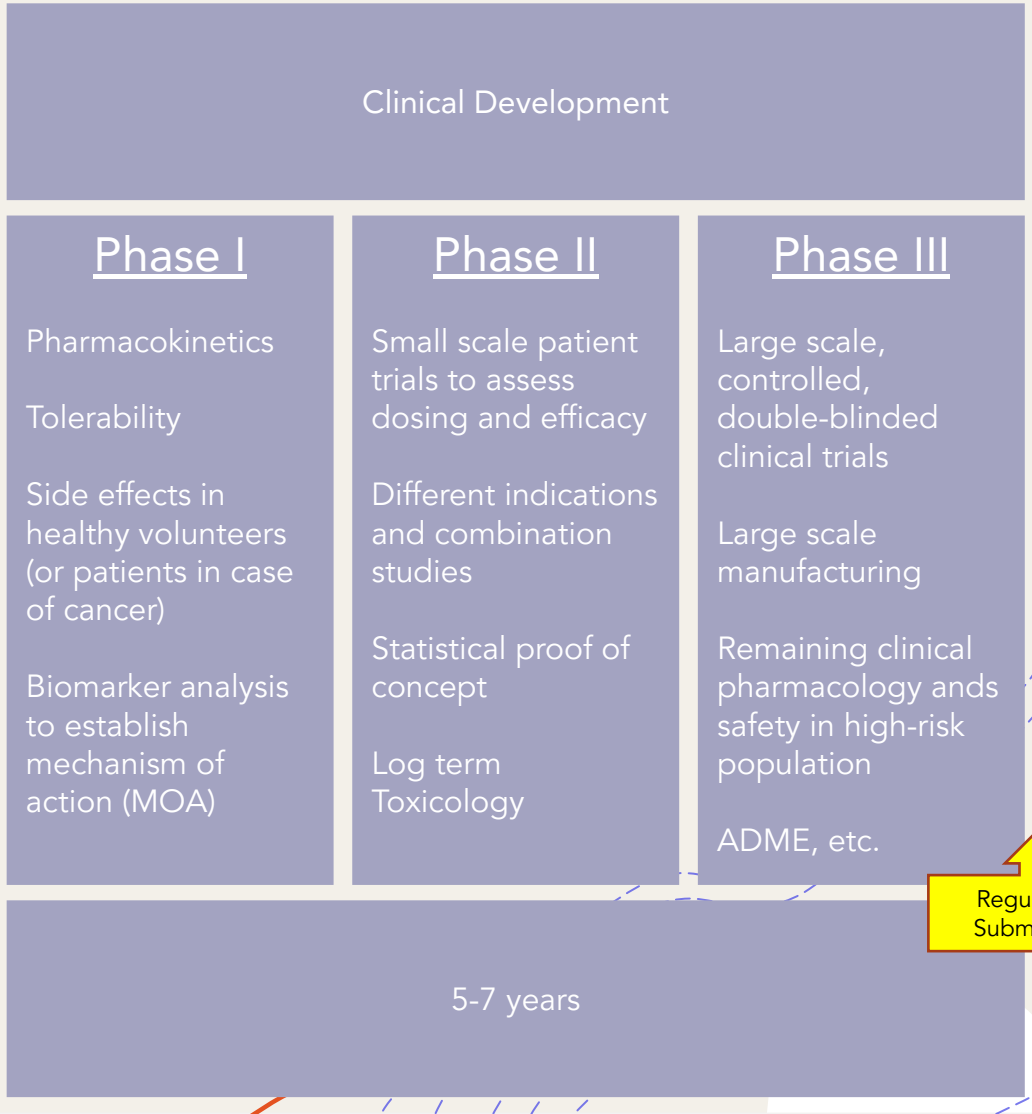
- The goal is to nominate a molecule as a lead preclinical development candidate and generate sufficient data to initiate clinical studies

	Target Discovery	Target Validation	Lead Compound Identification	Preclinical
Goal	Identify a pharmacologically active druggable target usually in vitro	In vivo experiments to confirm target	Identify potent and selective molecules with drug-like properties	• Drug testing in vivo and in vitro for activity, toxicity and side effects • Establish human study dose
Example	Example: Genetically engineered mice with lack of TNFa expression have modified immune cell profile and respond to inflammation differently	TNFa overexpression in patients suggests recruitment of destructive immune cells to joints, causing inflammation and autoimmune malfunction; and blocking it with an antibody can stop the damage in animal models	• Generate and screen library of antibodies for binding • Perform in-vivo efficacy • Initial safety assessment including selectivity	• Mouse and rate are common species • Monkeys, dogs, rabbits and pigs are sometimes considered • Product tested needs to be GLP or GMP grade (meaning well controlled process)
Skills needed	• Molecular Biologist • Pharmacology • Biochemistry • Immunologist (in this example)	• Protein engineering and production • Protein purification • Cellular biology • In vivo pharmacology • Medicinal Chemistry • X-Ray crystallography		Pharmacology (small and large animals) Toxicology CMC Regulatory Quality Assurance

File IND

Clinical Development

- CMO/Medical Director:
  - Clinical development strategy
  - Protocol synopsis/Final protocol
  - Interaction with Investigational Review Board (IRB) at Hospitals
  - Investigator meetings
- Clinical Operations
  - Interact with CROs and responsible for execution
- Pharmacovigilance and Safety Monitoring
- Biostatistician
- Medical Writing
- VP Regulatory and regulatory operations
  - Regulatory strategy and interactions with regulatory agencies



Payer Landscape

- In most countries, the government is the sole payer of medicines
- US is one of the very few companies where private insurance companies are involved in reimbursement of drugs
- There are many private insurance companies, with each having their own strategy and requirements for reimbursement
  - Interestingly, in US health insurance is an oligopoly with certain benefits/constraints determined legally by congress
- Medicare and Medicaid are two examples of US government subsidized public insurance for the elderly and for the poor respectively.
  - Together, they are a substantial part of the payer ecosystem
  - They require certain price discounts form drug manufacturers