Drug Chemistry and Technology Basics,
Cleaner Production and Mega-Trends in Pharmaceutical Industry

Drug Design and Quality Standards

Dr. As. Prof. Anastasiya Sladkova
Dr. Sci. Prof. Natalya Loginova

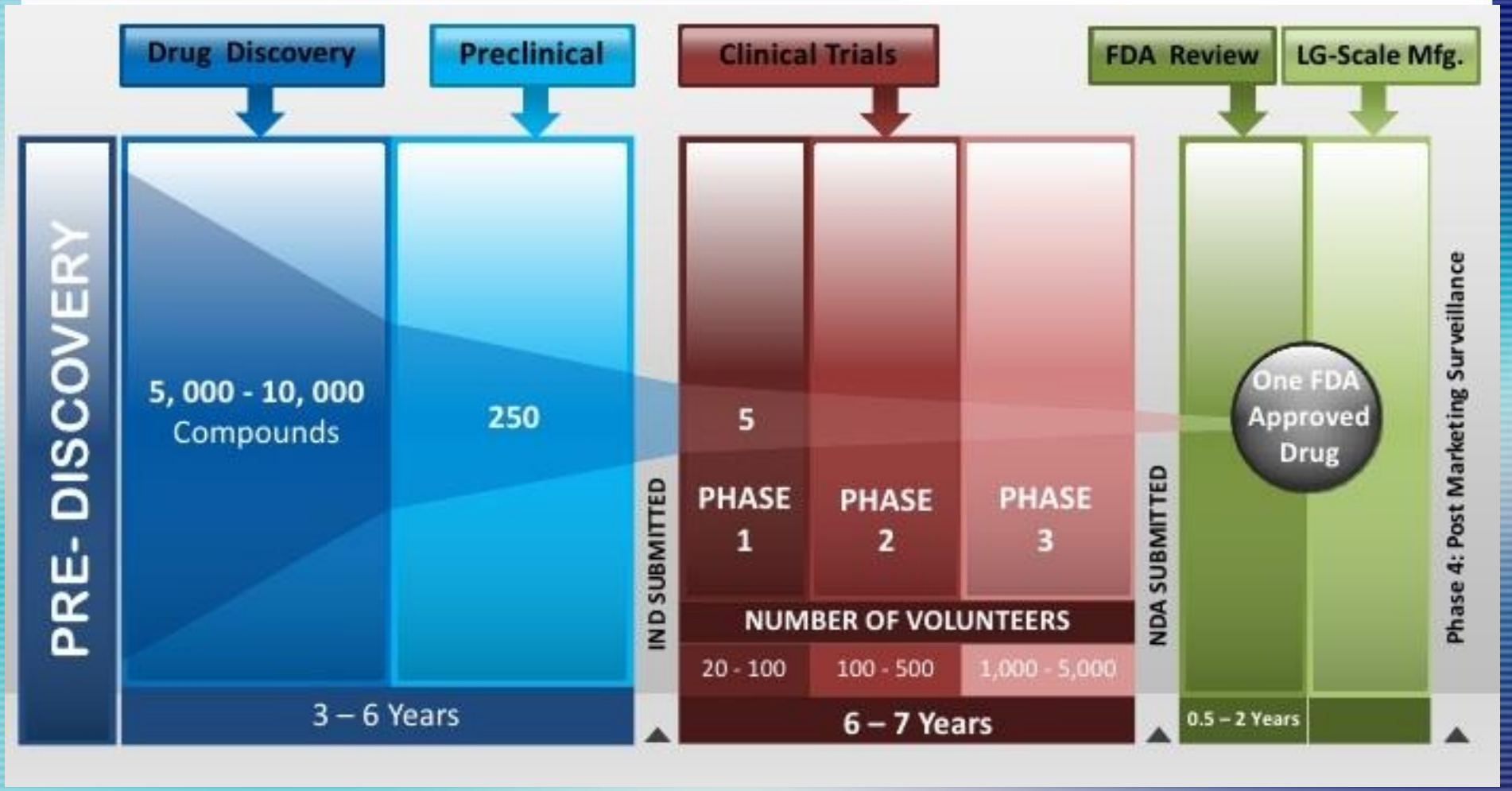
Questions

1. What dosage forms of drugs do you know?
2. What is difference between original drugs and generics?
3. Why does a 500 mg paracetamol tablet weigh more than 500 mg?
4. What is the classification of dosage forms?
5. What do “pharmaceutical equivalency” and “bioequivalency” mean? Are there any differences between bioavailability and bioequivalency?

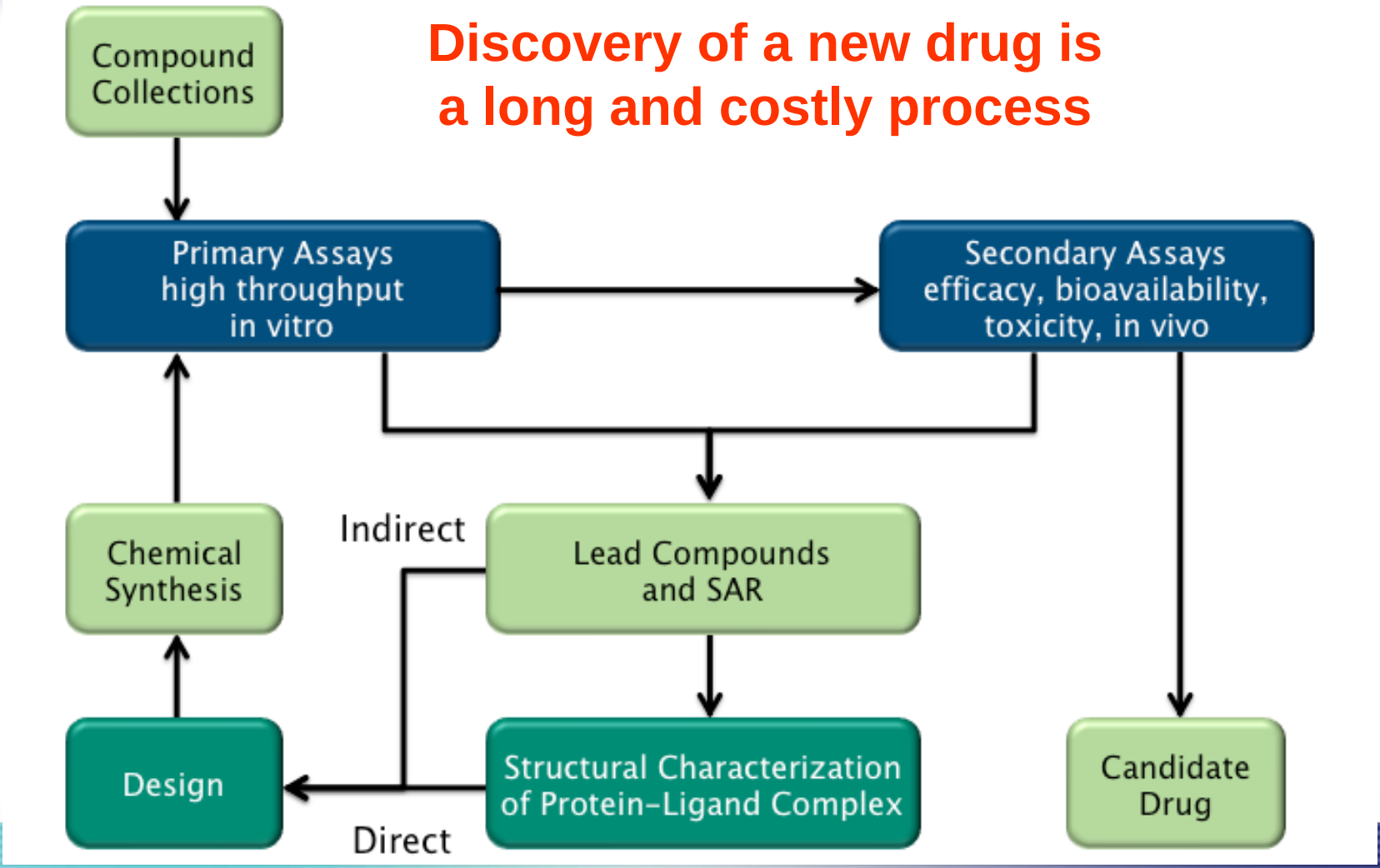
LECTURES

1. Introduction
2. Terminology of Drugs
3. → Drug Design and Quality standards
4. Falsification of Medicines
5. Quality Assurance in Medicines
6. Control by Pharmacopeias
7. Trends in Pharmaceutical Industry

Drug Discovery Process



Drug Discovery Process



QSAR

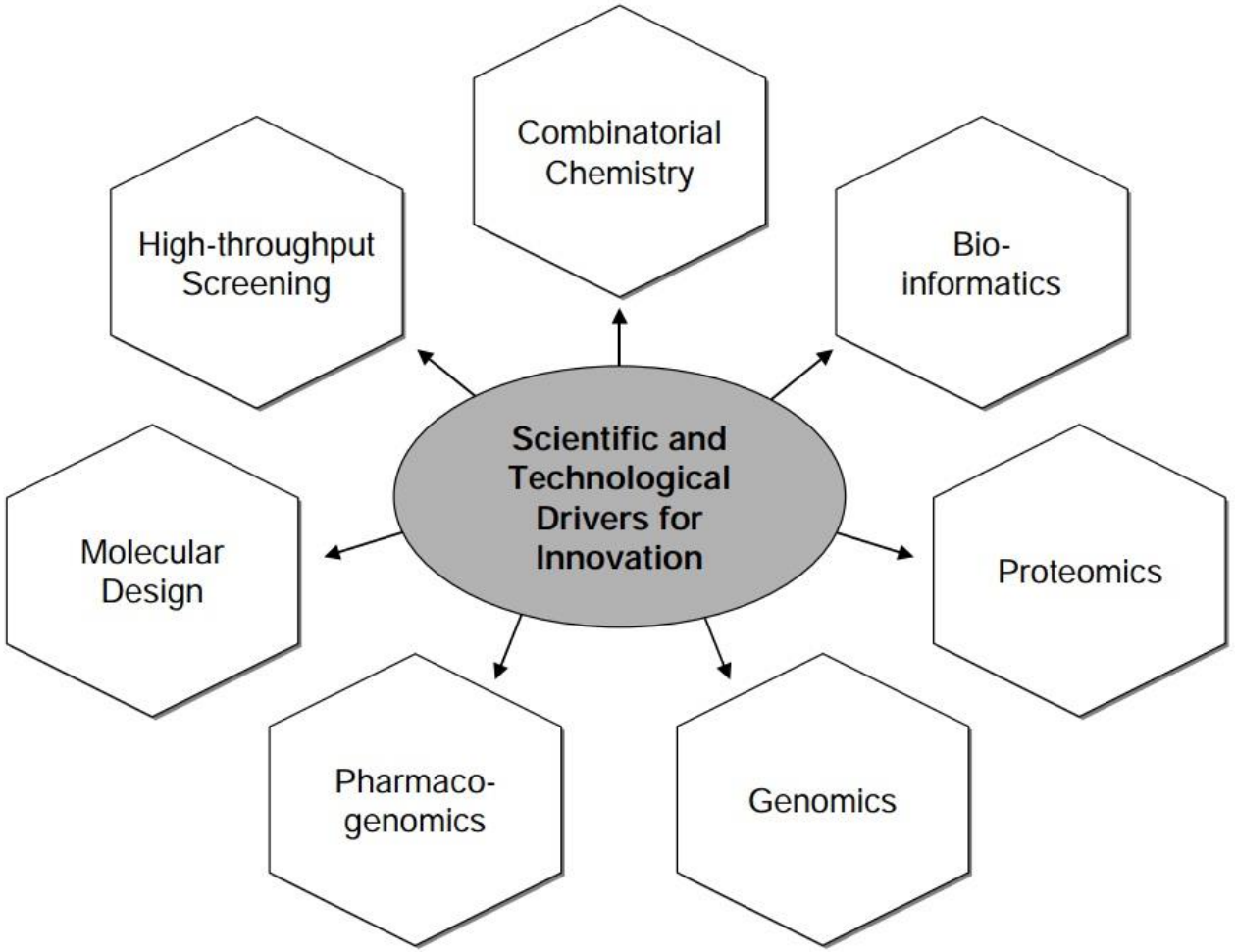
QSAR (**Q**uantitative **S**tructure–**A**ctivity **R**elationship) is a mathematical relationship between a biological activity of a molecular system and its geometric and chemical characteristics

A general formula for a quantitative structure-activity relationship (QSAR) can be given by the following:

activity = f (molecular or fragmental properties)

QSAR attempts to find consistent relationship between biological activity and molecular properties, so that these "rules" can be used to evaluate the activity of new compounds

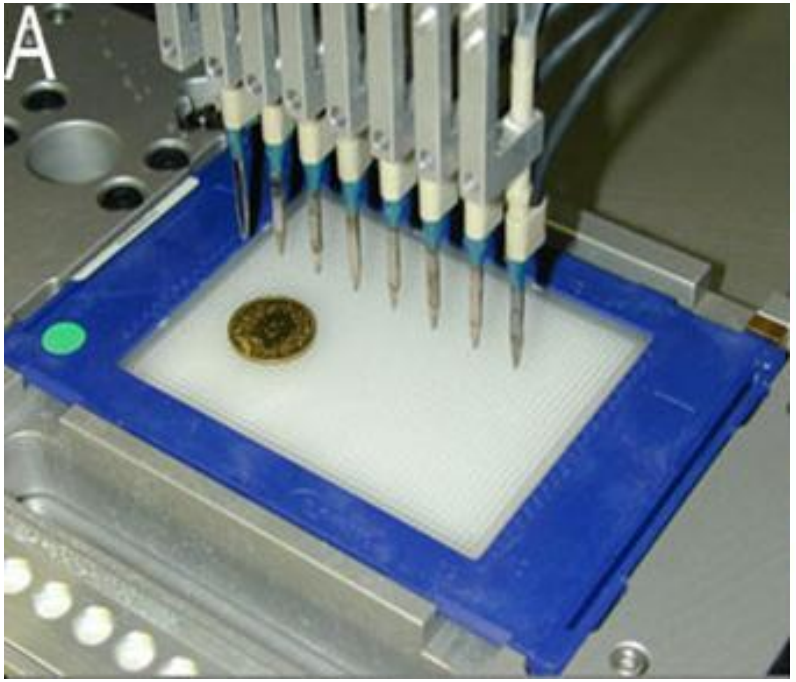
New Sciences and Technologies as Drivers for Innovation



High-Throughput Screening (HTS)

„These new plate formats have arisen as a potential answer to the problematic question being asked at most major pharmaceutical companies: How can we screen more targets and more samples cheaply?" (Houston and Banks 1997)

HTS is the biological technology that allows large numbers of chemicals to be automatically tested for their impact on biological activity, representing components of disease. It comprises of a system for data handling, an array of compounds to be tested, a robot to perform the testing and a biological test configured for automation



Combinatorial Chemistry

Combinatorial chemistry is a technology that allows large numbers of compounds to be made by the systemic and repetitive covalent connection of a set of different ‘building blocks’ of varying structures to each other

This helped pharmaceutical research be able to yield a large array of diverse molecular entities. Hence, **combinatorial chemistry is a mass-production technology that synthesizes large numbers of compounds in parallel**

Bioinformatics

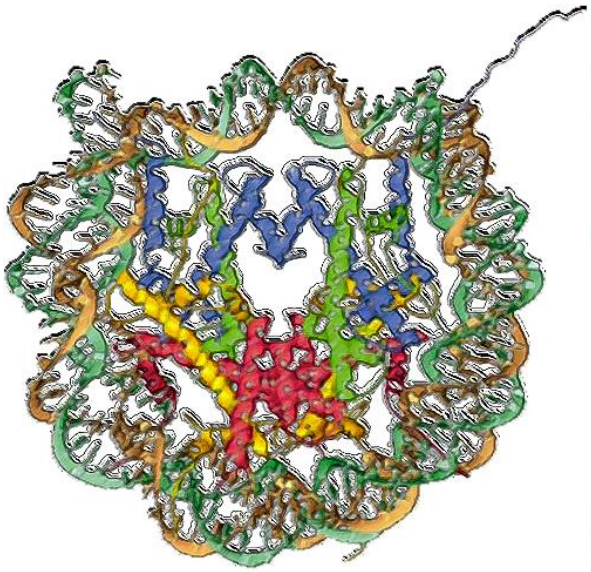
Bioinformatics is an interdisciplinary field that develops methods and software tools for understanding biological data

- ✓ To provide and manage databases for the tremendous amount of information
- ✓ To allow the generation of compound profiles for improved target identification and screening
- ✓ To manage genome and protein sequences
- ✓ To visualize 3D data
- ✓ To collect data on model organisms
- ✓ To manage the huge amount of data from the clinical tests and provide feedback to the early phases of drug discovery
- ✓ To enable accessibility and sharing of knowledge within the corporation as well as to outside collaborators

Proteomics

Most drugs work on **proteins** or **protein receptors**

Hence, a primary challenge of **proteomics** is to identify differences between the pattern of a healthy and a sick person, compare them, and identify and isolate the guilty proteins



Today, proteomics includes not only the identification and quantification of proteins, but also the determination of their localization, modifications, interactions, activities, and, ultimately, their function

Molecular Design

- After determining the **three-dimensional atomic architecture** of the **target protein** and its functionally critical regions, a variety of specialized programs on interactive graphics workstations come into play

- A design team develops and evaluates ideas for **structures of drug molecules** that complement the unique structure and electronic environment of the target protein

- The medicinal chemists then chemically **synthesize** the most promising candidate structures

Molecular Design

- Biochemists measure the ability of these newly synthesized drug candidates in order to produce the **intended effect** upon the target protein

- Crystallographers then re-determine the structure of the protein target – now **in combination with the candidate drug molecules**. They see the detailed structural interactions actually achieved by the candidate drugs with their target

- The scientists relate the performance of such compounds measured by familiar biochemical techniques to its structural interactions with the target as revealed by crystallography. The design team then incorporates the results of this analysis into its **next generation of compounds**

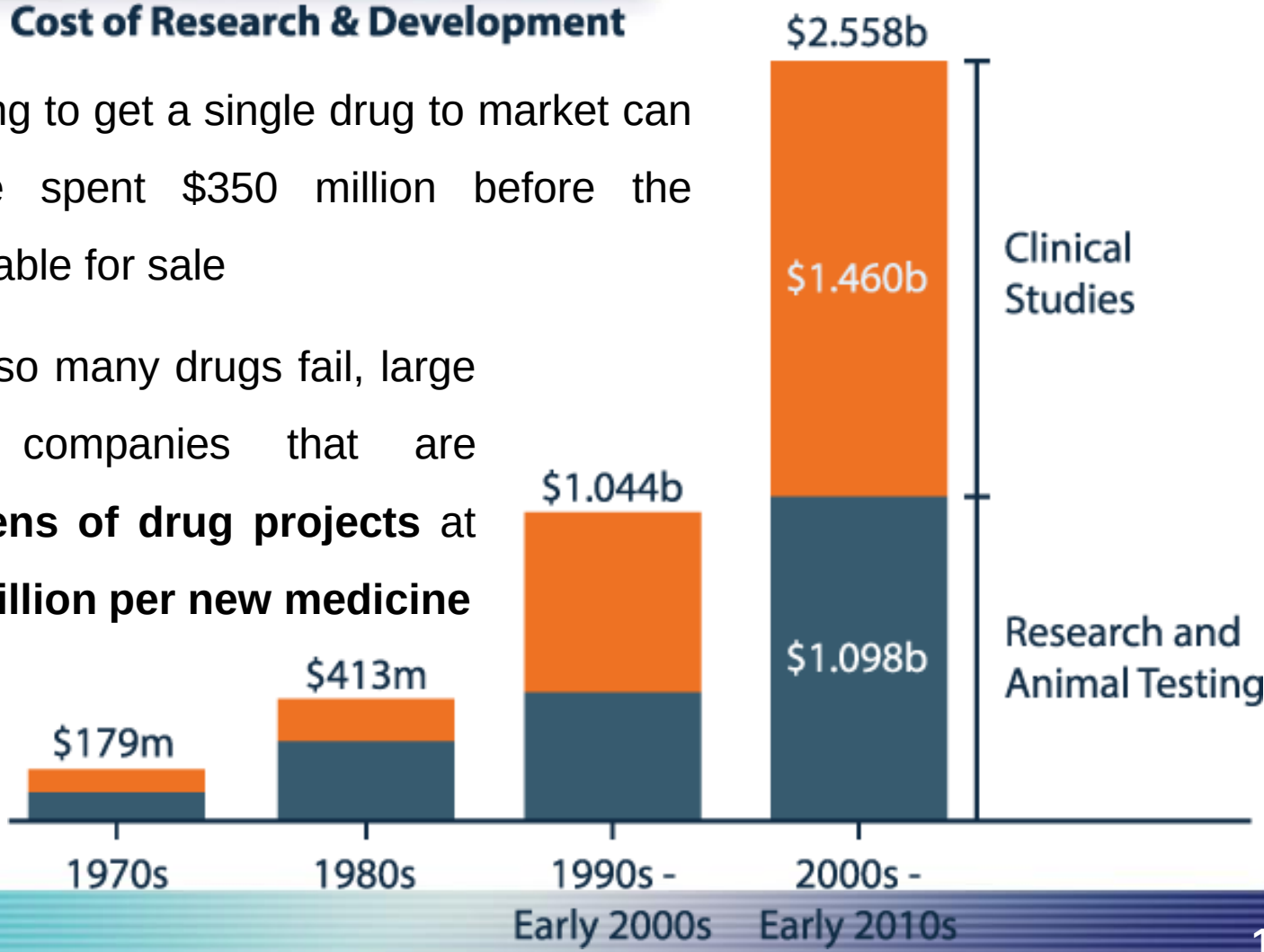
What is Molecular Medicine

Original Drugs

Cost of Research & Development

A company hoping to get a single drug to market can expect to have spent $350 million before the medicine is available for sale

In part because so many drugs fail, large pharmaceutical companies that are working on **dozens of drug projects** at once spend **$5 billion per new medicine**



High Risks in Drug Development

The risk of failure is very high

Drug development success rates

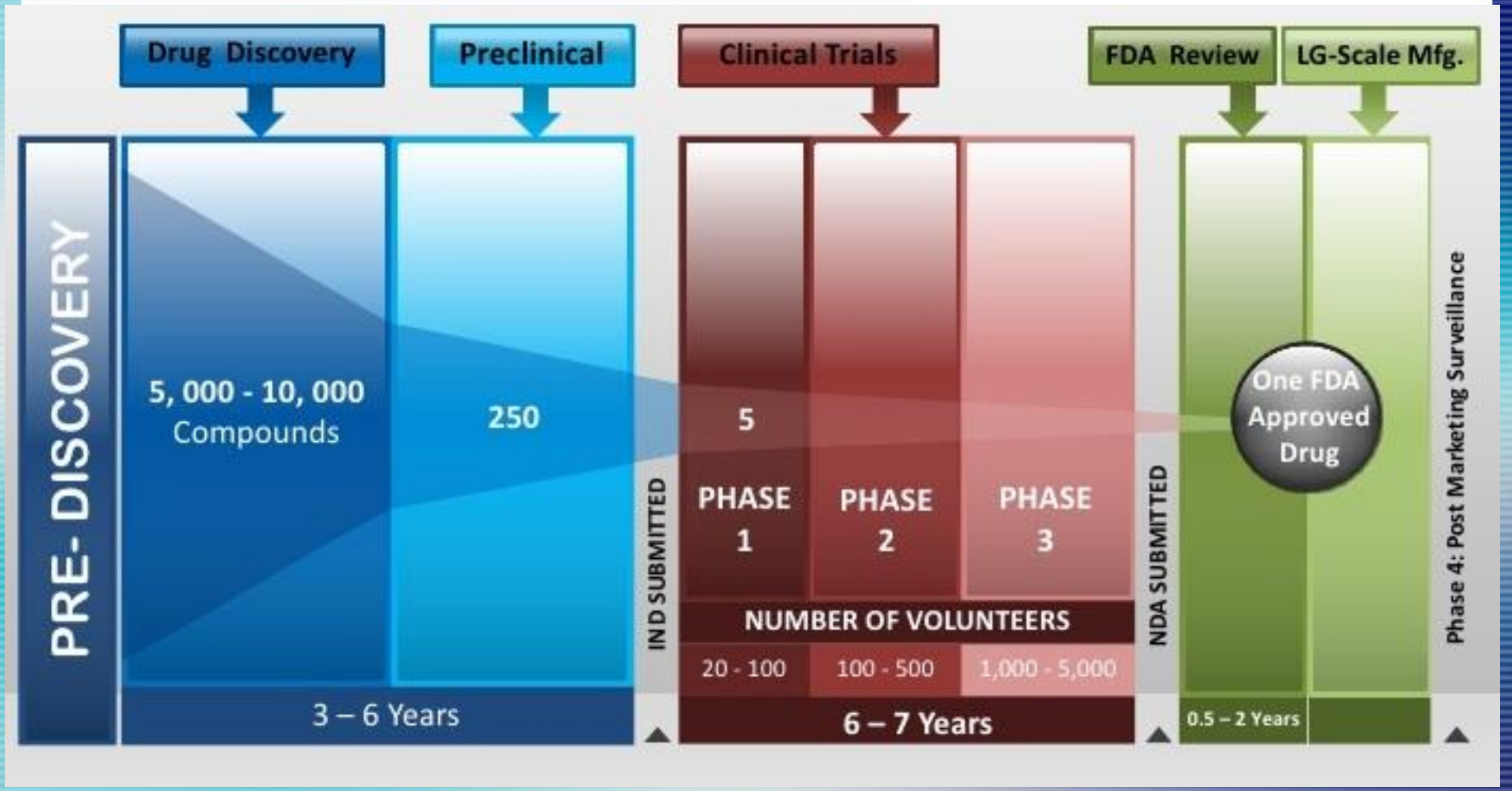
Disease Group	Rate
Central nervous system	14.5%
Cardio vascular	17.5%
Immunology	15.4%
Infections	28.1%
Oncology	15.8%

Reasons of abandonment

Reason	Rate
Efficacy	37.6%
Economics	33.8%
Safety	19.6%
Other	9.0%

Source: Bogdan, B and Villiger, R. Valuation in Life Sciences, 2007, Springer

Drug Discovery Process



7 Steps to Drug Discovery

Quality Standards

There is a drug, medicine, or pharmaceutical **regulatory agency or administration** in most countries responsible for:

- ✓ regulating the manufacture of medicines in the country, enforce good
- ✓ manufacturing practice (GMP), and ensuring that safe, effective, and quality medicines are produced approving importation, promotion, marketing, labeling, and use of drugs

Quality Standards

The European Medicines Agency (EMA) is a European Union agency for the evaluation of medicinal products

*Prior to 2004, it was known as the European Agency for the Evaluation of Medicinal Products (**EMEA**)*

The Food and Drug Administration (FDA or USFDA) is a federal agency of the United States Department of Health and Human Services.

The FDA is responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, cosmetics etc.

Quality Standards

1. GLP (Good Laboratory Practice)

2. GCP (Good Clinical Practice)

3. GMP (Good Manufacturing Practice)

4*. GSP (Good Storage Practice)

5. GDP (Good Distribution Practice)

6. GPP (Good Pharmacy Practice)

Periods of drug "life cycle"

Predicting the possibility of creating **new drugs** or **drugs with improved pharmacological properties**.
Synthesis of chemical compounds – **"candidate drug"**

Preliminary pharmacological screening of **"candidate drugs"** in order to select the most promising one.
Preclinical trials
GLP (a set of principles within which laboratory studies are planned, performed, monitored, recorded, reported and archived)

Clinical evaluation of the most promising chemical compounds
GCP (standards, which governments can transpose into regulations for clinical trials involving human subjects)

The solution of technological problems on creation of the dosage form. Manufacturing application of drug
GMP (rules of production and quality control of drugs)

The distribution of formulated drugs for the pharmacy network
GDP (good practice in wholesale trade)

Sales of formulated drugs
GPP (good pharmacy (drugstore) and good pharmacovigilance practice)

Circulation of Medicines

1. development
2. non-clinical studies
3. clinical trials
4. commercial production
5. pharmacy manufacture
6. selling
7. storage
8. transportation
9. medical use
10. return to the manufacturer or the supplier
11. destruction of medicinal products

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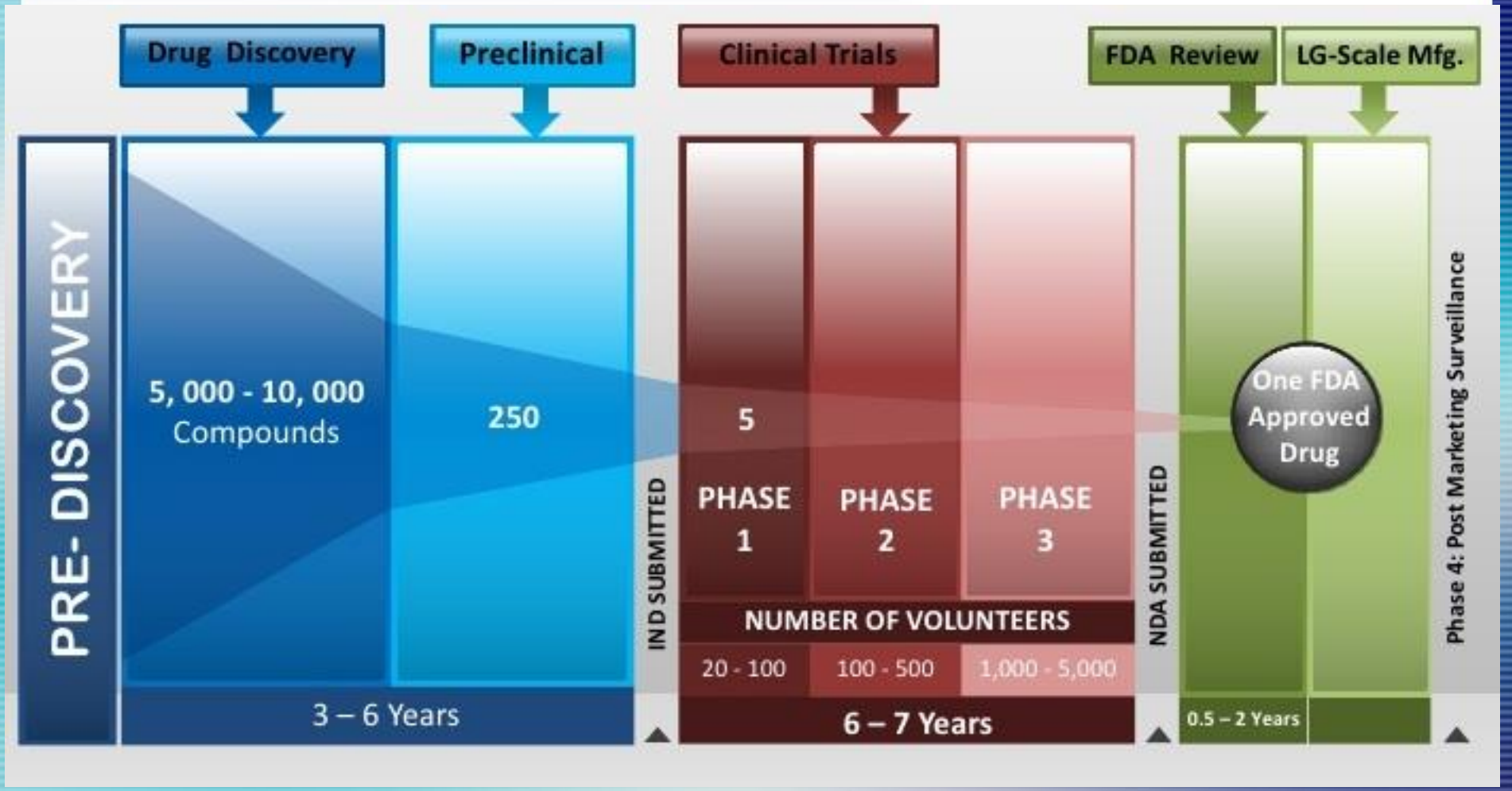


Lessons for drug safety and regulation

Quality and safety control mechanisms were introduced by national regulatory authorities in response to health disasters such as **the elixir sulfonamide** or **the thalidomide one**

The 1937 Elixir Sulfanilamide Incident

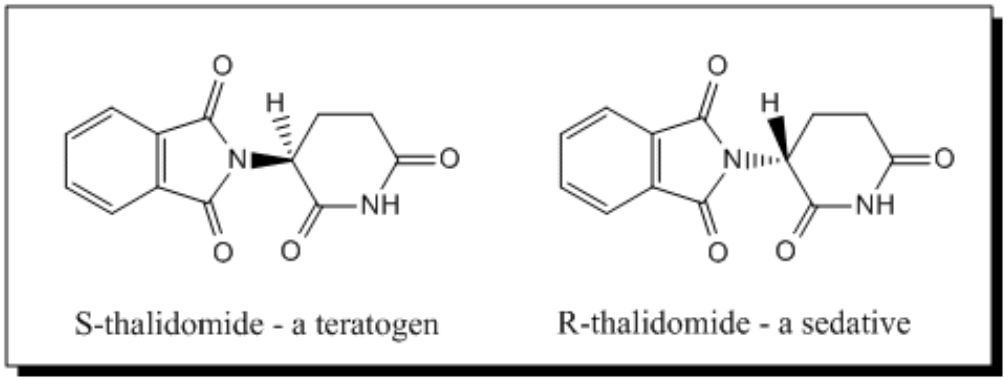
Sulfanilamide, a drug used to treat streptococcal infections, had been shown to have dramatic curative effects and had been used safely for some time in tablet and powder form. In June 1937, however, a salesman for the S.E. Massengill Co., in Bristol, Tenn., reported a demand in the southern states for the drug **in liquid form**. The company's chief chemist and pharmacist, Harold Cole Watkins, experimented and found that sulfanilamide would dissolve in **diethylene glycol**

The new formulation had not been tested for toxicity. At the time **the food and drugs law did not require that safety studies be done on new drugs**. Selling toxic drugs was, undoubtedly, bad for business and could damage a firm's reputation, but it was not illegal

The company started selling and distributing the medication in September 1937. By October 11, the American Medical Association received a report of **several deaths** caused by the medication. FDA was notified, and an extensive search was conducted to recover the distributed medicine. Frances Oldham Kelsey assisted on a research project that verified that the excipient DEG was responsible for the fatal adverse effects. At least **100 deaths** were blamed on the medication

The Thalidomide Tragedy

Thalidomide was first marketed in **1957** in West Germany under the trade-name **Contergan**. It was used against nausea and to alleviate morning sickness **in pregnant women**. Shortly after the drug was sold in West Germany, between 5,000 and 7,000 infants were born with **phocomelia (malformation of the limbs)**. Only 40% of these children survived. Throughout the world, about 10,000 cases were reported of infants with phocomelia due to thalidomide; only 50% of the 10,000 survived.



1962: FDA pharmacologist ***Frances Oldham Kelsey*** *receives the President's Award for Distinguished Federal Civilian Service from President John F. Kennedy for* ***blocking sale of thalidomide in the United States.***

The negative effects of thalidomide led to the development of more structured drug regulations and control over drug use and development

The Thalidomide Tragedy

Preclinical Research

A preclinical testing of a medicine for medical use is conducted using scientific assessment methods for the purpose of obtaining evidence of **safety, proper quality** and **efficacy** of the medicine

A preclinical testing of a medicine for medical use is conducted in compliance with **GLP**

Drugs may undergo **pharmacodynamics** (what the drug does to the body) (PD), **pharmacokinetics** (what the body does to the drug) (PK), **ADME** (absorption, distribution, metabolism, and excretion), and **toxicology testing**

Typically, both ***in vitro*** and ***in vivo*** tests will be performed

Typically, in drug development studies **animal testing** involves two species

The most commonly used models are **murine** and **canine**, although **primate** and **porcine** are also used

Clinical Research

Clinical trials of medicinal products for medical use shall be conducted for the purpose of state registration of medicinal products and for any other purposes on one or more medical institutions as required by **GCP** approved by the authorized executive body for the following purposes:

1) to establish **safety** and/or **tolerance** of medicinal products for **healthy volunteers**, except for the trials of medicinal products manufactured outside the state;

2) to select **optimal dosages** of medicinal product and course of treatment for **patients with specific disease**, optimal dosages and vaccination schemes of immunobiological medicinal products for healthy volunteers;

3) to establish **safety** and **efficacy** of a medicinal product for **patients with specific disease**, prophylactic efficacy for immunobiological medicinal products for healthy volunteers;

4) to study the possibility to widen the indication for medical use and identify **earlier unknown side effects** of registered medicinal products

Phases of Clinical Research

Phase I	Phase II	Phase III	Phase IV
20-80 participants	**100-300 participants**	**1,000-3,000 participants**	**Thousands of participants**
Up to several months	Up to (2) years	One (1) - Four (4) years	One (1) year +
Studies the safety of medication/treatment	Studies the efficacy	Studies the safety, efficacy and dosing	Studies the long-term effectiveness; cost effectiveness
70% success rate	33% success rate	25-30% success rate	70-90% success rate

Are conducted only after they have received health authority/ethics committee approval in the country where approval of the therapy is sought

Drug discovery and development process

Good Manufacturing Practice

GMP – the practices required in order to conform to the guidelines recommended by agencies that control authorization and licensing for manufacture and sale of food, drug products, and active pharmaceutical products

The principles and practices outlined in **the WHO document on "Good Practices in the Manufacture and Quality Control of Drugs"** serve as technical guidelines for the time being to governmental authorities for the development of quality control systems for medicines to be sold and distributed in the country of origin or for export

Good Manufacturing Practice

- ✓ organizational structure of the enterprise;
- ✓ responsibilities of the quality control department;
- ✓ qualified personnel;
- ✓ characteristics of buildings and premises and equipment;
- ✓ control of drug components;
- ✓ organization of the technology;
- ✓ criteria for the evaluation and use of marking materials;
- ✓ operations for packaging and labeling;
- ✓ shelf life and storage;
- ✓ laboratory control (analysis of physico-chemical parameters, determining the stability and storage of standard samples, the content of laboratory animals), recording and reporting

Questions

1. Why the discovery of a new drug is a long and costly process? Explain the different stages involved
2. What is QSAR?
3. What new sciences and technologies as drivers for drug discovery innovation do you know?
4. How chemistry connects with biology in drug design?
5. What risks exists in new drug development?

Thank You !

sladkova-an@yandex.ru