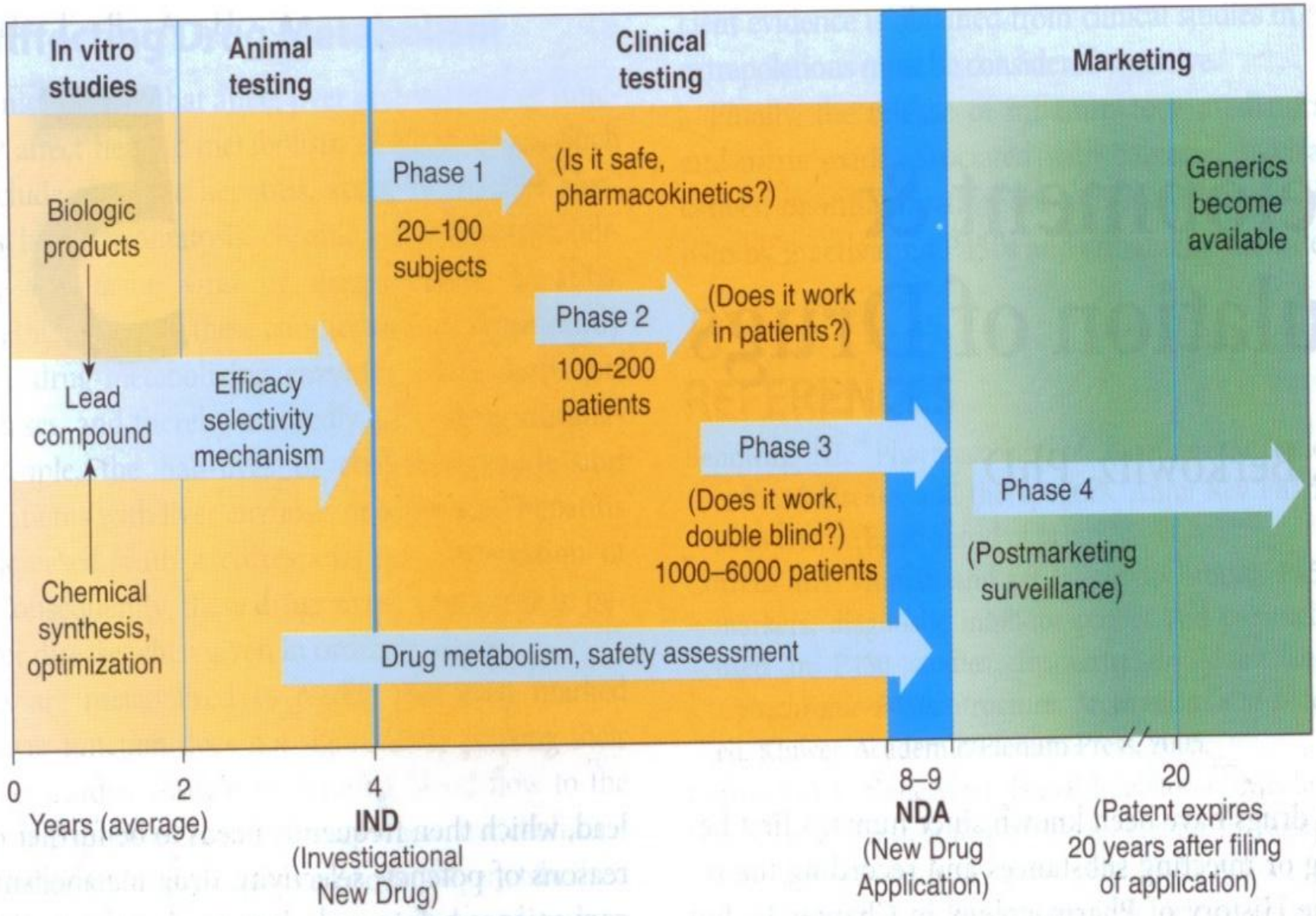
DRUG DEVELOPMENT

Ilona Benkő M.D., Ph.D.
associate professor
Inst. of Pharmacology and Pharmacotherapy
University of Debrecen



Rang and Dale's Pharmacology textbook

DRUG DEVELOPMENT

GMP=good manufacturing practice,
GLP=good laboratory practice, GCP=good clinical practice

Double controll

1. **By Authorities: OGYI (**Hungary) **FDA = Food and Drug Administration (USA)**

and

2. By Societies (Ethical comittees)

Research plan bases on economical, clinical requirements and scientific data

PRECLINICAL PHASE

I. **DRUG SCREENING – obtaining drug candidate for investigation**

leader compound
with some hopeful effect in pharmacological screening

to determine active ingredients, chemical structure
physicochemical properties
chemical synthesis

methods for quality control
planning drug formule
experimental manufacturing

II. Pharmacological experiments

To define pharmacological profile

in vitro screening
at molecular
cellular
System levels
Isolated Organ

in vivo animal experiments

To define mechanism of action
and therapeutic dose range

Preclinical safety, toxicity testing

Acute
Subacute toxicity
chronic

Effect on
- Reproductive performance
- Teratogenicity
- Mutagenicity
- Carcinogenic potential

Therapeutic window, therapeutic index, selectivity

Pharmacokinetics

absorpion, distribution
metabolism, metabolits
excretion, cumulation
plasma concentrations and influencing factors
effect of chronic diseases of kidney and liver
Drug interactions

Type of Test	Approach and Goals
Acute toxicity	Usually two species, two routes. Determine the no-effect dose and the maximum tolerated dose. In some cases, determine the acute dose that is lethal in approximately 50% of animals.
Subacute or subchronic toxicity	Three doses, two species. 2 weeks to 3 months of testing may be necessary before clinical trial. The longer the duration of expected clinical use, the longer the subacute test. Determine biochemical, physiologic effects.
Chronic toxicity	Rodent and nonrodent species for ≥ 6 months. Required when drug is intended to be used in humans for prolonged periods. Usually run concurrently with clinical trials. Determine same end points as subacute toxicity tests.
Effect on reproductive performance	Two species, usually one rodent and rabbits. Test effects on animal mating behavior, reproduction, parturition, progeny, birth defects, postnatal development.
Carcinogenic potential	Two years, two species. Required when drug is intended to be used in humans for prolonged periods. Determine gross and histologic pathology.
Mutagenic potential	Test effects on genetic stability and mutations in bacteria (Ames test) or mammalian cells in culture; dominant lethal test and clastogenicity in mice.
Investigative toxicology	Determine sequence and mechanisms of toxic action. Discover the genes, proteins, pathways involved. Develop new methods for assessing toxicity; use computer-assisted modeling.

Katzung et al Basic and Clinical Pharmacology textbook

CLINICAL PHARMACOLOGY

Clinical testing of drug candidates in HUMANS

Clinical Pharmacology	Clinical trials
Human phase I. safety, maximal tolerated dose pharmacokinetics	20-100 volunteers
Human phase II. therapeutical effect	100-200 patients
Human phase III. multicentrical studies	1000-6000 patients

Approval to market

POSTMARKETING SURVEILLANCE

Human phase IV.

TABLE 5–2 Major legislation pertaining to drugs in the United States.

Law	Purpose and Effect
Pure Food and Drug Act of 1906	Prohibited mislabeling and adulteration of drugs.
Opium Exclusion Act of 1909	Prohibited importation of opium.
Amendment (1912) to the Pure Food and Drug Act	Prohibited false or fraudulent advertising claims.
Harrison Narcotic Act of 1914	Established regulations for use of opium, opiates, and cocaine (marijuana added in 1937).
Food, Drug, and Cosmetic Act of 1938	Required that new drugs be safe as well as pure (but did not require proof of efficacy). Enforcement by FDA.
Durham-Humphrey Act of 1952	Vested in the FDA the power to determine which products could be sold without prescription.
Kefauver-Harris Amendments (1962) to the Food, Drug, and Cosmetic Act	Required proof of efficacy as well as safety for new drugs and for drugs released since 1938; established guidelines for reporting of information about adverse reactions, clinical testing, and advertising of new drugs.
Comprehensive Drug Abuse Prevention and Control Act (1970)	Outlined strict controls in the manufacture, distribution, and prescribing of habit-forming drugs; established drug schedules and programs to prevent and treat drug addiction.
Orphan Drug Amendments of 1983	Provided incentives for development of drugs that treat diseases with less than 200,000 patients in USA.
Drug Price Competition and Patent Restoration Act of 1984	Abbreviated new drug applications for generic drugs. Required bioequivalence data. Patent life extended by amount of time drug delayed by FDA review process. Cannot exceed 5 extra years or extend to more than 14 years post-NDA approval.
Prescription Drug User Fee Act (1992, reauthorized 2007)	Manufacturers pay user fees for certain new drug applications.
Dietary Supplement Health and Education Act (1994)	Established standards with respect to dietary supplements but prohibited full FDA review of supplements and botanicals as drugs. Required the establishment of specific ingredient and nutrition information labeling that defines dietary supplements and classifies them as part of the food supply but allows unregulated advertising.
Bioterrorism Act of 2002	Enhanced controls on dangerous biologic agents and toxins. Seeks to protect safety of food, water, and drug supply.
Food and Drug Administration Amendments Act of 2007	Grants FDA greater authority over drug marketing, labeling, and direct-to-consumer advertising; requires post-approval studies, establishes active surveillance systems, makes clinical trial operations and results more visible to the public.