

Innovative Approaches to Nonclinical Development and Risk Management of Novel Pharmaceutical Agents

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Pharmaceutical Business Climate

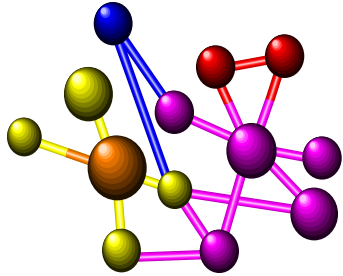
- Patent expirations
- Poor R&D productivity
- Escalating costs of development
- Greater technical challenges
- Increased regulatory hurdles
- Hostile media/political environment
- Pricing constraints
- Liability exposure

Challenges in Drug Development

- Greatest patient benefits are in areas of unmet medical need and unprecedented technology where risks and costs are highest
- High failure rate in preclinical development (50%)
- >50% failure rate in late stage clinical trials
- <10% of compounds entering human clinical trials will eventually be approved as drugs

Phases of Drug Development

Discovery

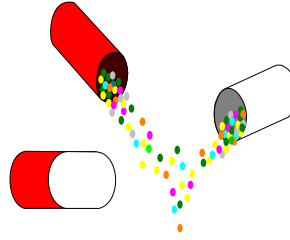


Candidates

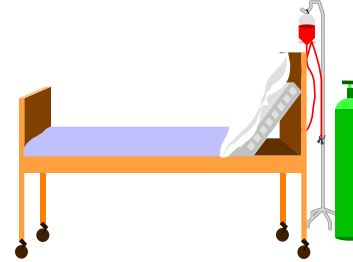


Lead

IND/FIH



Phase II/III



Marketing



Candidate selection

Using screening data to select a leading compound

Candidate survival

Using safety and efficacy data (disease models) to take attrition early

Product differentiation

Using safety and efficacy data to distinguish the test compound from marketed drugs

Labeling

Using safety and efficacy data to develop accurate labeling

Increasing confidence in safety and rationale

Typical Discovery Phase Studies (Candidate Selection)

Cardiovascular Risk

- ^3H -dofetilide binding assay
- HERG functional assay

In Vivo Toleration

- Clinical tolerance
- Organ systems

Screening Safety Pharm

- CNS, CV, Pulmonary

Screening Genetox

- Bacterial mutagenicity
- In vitro clastogenicity

Biomarker development

In vitro screens (low bulk requiring assays)

Investigative support

- Toxicology
- Pathology

Computational Tox (DEREK, etc.)

Typical Investigational New Drug (IND) Studies (Candidate Survival)

Acute and repeated-dose toxicity

- mortality, clinical signs, body weight, food and water consumption
- clinical laboratory parameters
- gross pathology, organ weights, histopathology
- toxicokinetics

CNS Safety Pharmacology

- behavior, reflex/activity, neurofunctional parameters

Cardiovascular Safety Pharmacology

- heart rate, blood pressure, rhythm, QT

Pulmonary Safety Pharmacology

- rate, resistance, compliance, volume

Genotoxicity

- bacterial mutagenicity (Ames test)
- clastogenicity (in vitro chromosomal aberration, in vivo bone marrow micronucleus assays)

Typical Labeling Studies (Product Differentiation)

Reproductive Toxicity Studies

- Fertility and early embryonic development (male and female rats)
- Embryo-fetal development (rat, rabbit)
- Peri- and postnatal development (rat)

Carcinogenicity Studies

- 2-Year study in rats
and
- 2-Year study in mice
or
- 6-month study in p53 (or other) knock-out mice

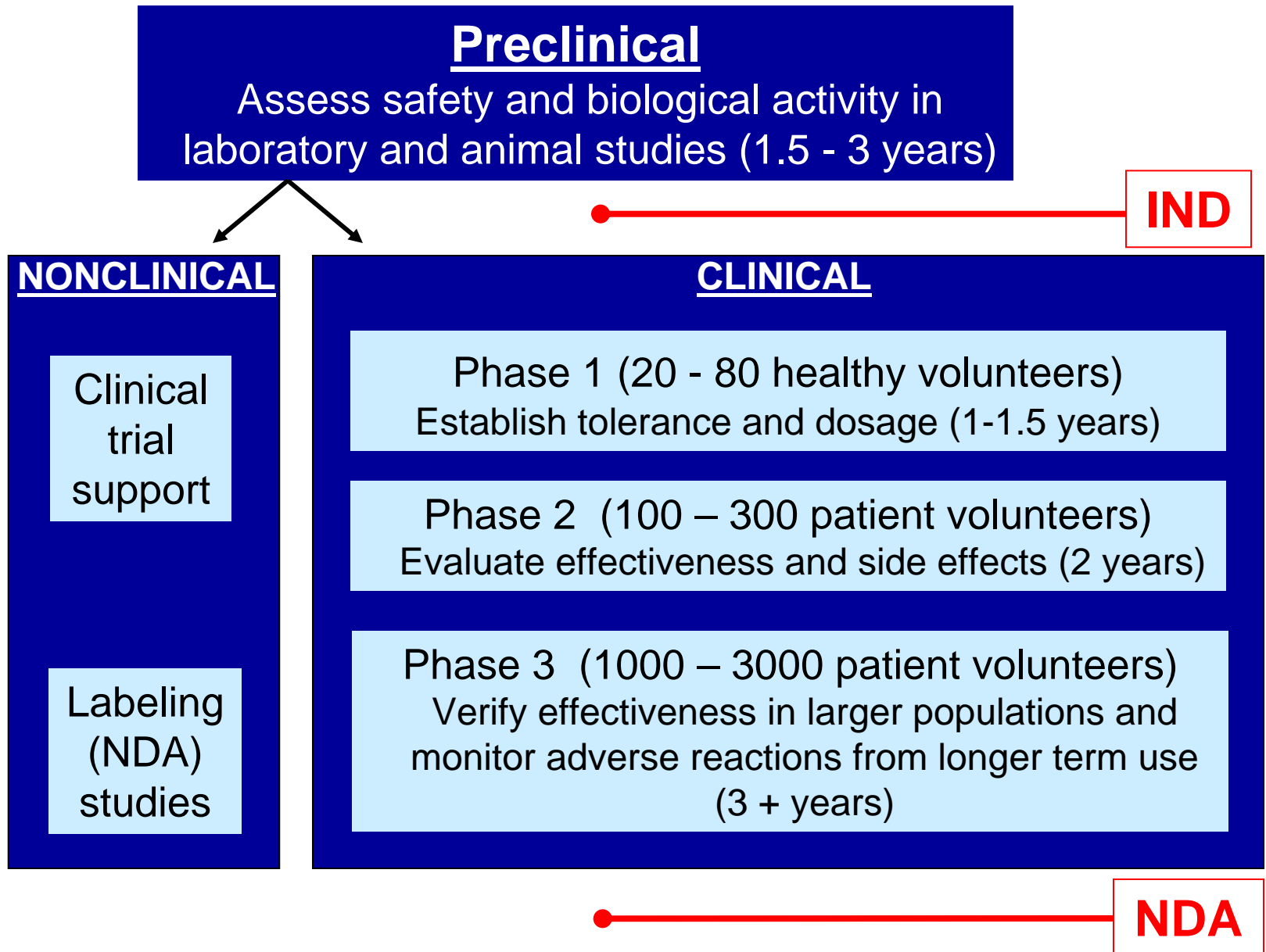
Duration of Repeated-Dose Studies (ICH)

Duration of Clinical Trials

Minimum Duration of Toxicity Studies

	Rodents	Non-Rodents
Up to 2 Weeks	1 Month	1 Month
Up to 1 Month	3 Months	3 Months
Up to 3 Months	6 Months	6 Months
> 3 Months	6 Months	9 or 12 Months

Nonclinical and Clinical Phases of Drug Development



NON-CLINICAL DRUG SAFETY EVALUATION.... JUST WHAT ARE WE TRYING TO ACCOMPLISH?

- The purpose of non-clinical safety studies is to characterize toxic potential, and help understand and minimize risk to humans.
- Predict the consequences and probability of similar injury occurring in humans/patients. Drug candidates are not inherently safe, but clinical experimentation ought to be so.
- Allow clinical to select the FIH starting dose and dose escalation regimen.
- Assure that risks entailed in clinical evaluation and use of the drug are reasonable – Risk/benefit analysis
- Provide for INFORMED CONSENT in clinical trials

Comparison of FIH Strategies

	IND	Microdosing	MOA Related to Efficacy	Pharmacologic Endpoint
Clinical Outcome	Tolerance, PK, PD	PK	Target modulation	PK, Target modulation
Clinical Dosing	Multiple dose Full dose profile to MTD	Single dose Subpharmacologic (dependent upon ultrasensitive analytics)	≤ 7 days Pharmacologically active	≤ 7 days Pharmacologically active
Nonclinical Studies	2 species, 2 weeks by clinical route Genetic toxicity Safety Phm	1 species, single dose by clinical route with extended observation period	2 species, modified pharmacologic and safety studies with mechanistic endpoints	1 species (rat), 2 weeks by clinical route Validation study in nonrodent Genetic toxicity Safety Phm
API (nonclinical)	1 – 3 Kg	1 – 50 g	100 – 1000 g	10 – 300 g
Preclinical (Lead cmpd to IND)	9 – 18 months	3 – 6 months	6 – 10 months	3 – 6 months

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