Drug Discovery & Development:

Preclinical & Clinical Study

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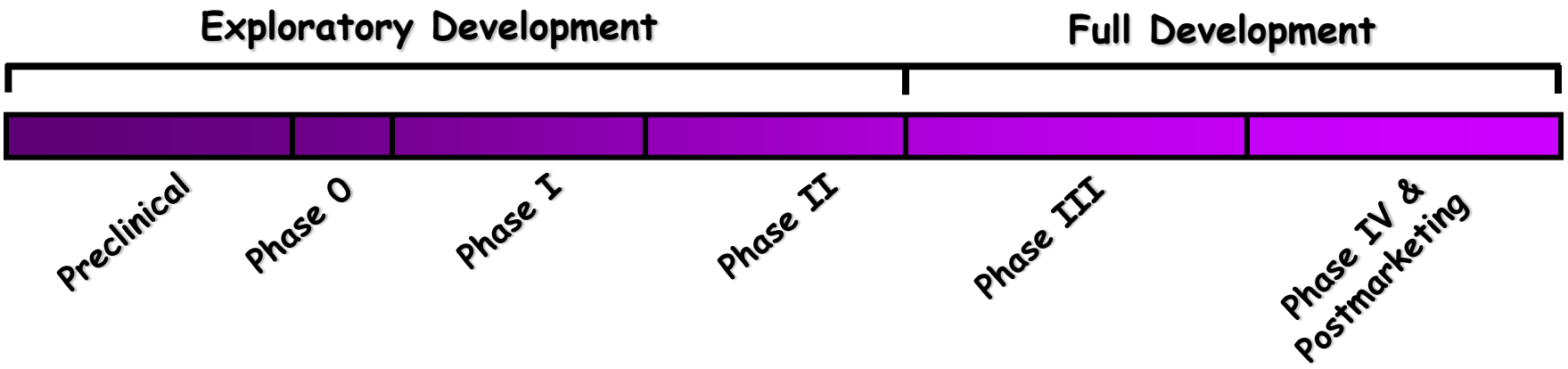
Timeline of Drug Development

From test tubes to patients



Preclinical Study: Proof of Principle for Efficacy, Safety & Feasibility

Objectives of preclinical study:

- ***Support for human pharmacology***
- ***Support for human toxicology***
- ***Prediction of human pharmacokinetics***
- ***Dose & formulation assessment***
- ***Feasibility for large scale production***

(1)What does the drug do to the body (pharmacodynamics/PD)?
(2)What does the body do to the drug (pharmacokinetics/PK)?
(3) Feasibility for clinic trails?

Objectives & Approaches of Preclinical Study

Preclinical Pharmacology & Toxicology → Safety & Efficacy

Specific objectives:

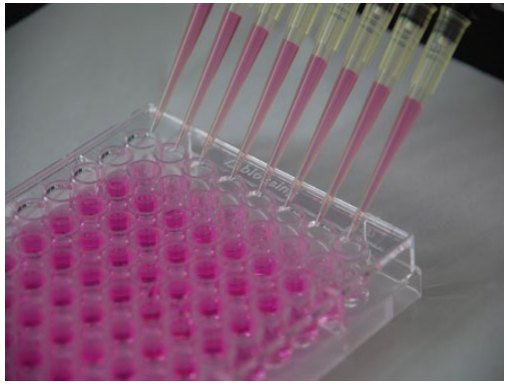
- ***Molecular targets, action mechanisms & Pharmacodynamic***
- ***Short-term & long-term toxicity***
- ***Pharmacokinetic properties: ADME***

Approaches:

- ***Extensive in vitro, in vivo, in situ & ex vivo experiments***

Components of Preclinical Pharmacology & Toxicology: *In vitro* Experiments

- ***In vitro studies: macromolecules, cell cultures & isolated tissues/organs***
  - ***Molecular targets & action mechanisms***
  - ***Molecular pharmacology***
  - ***Intracellular pharmacodynamics***
  - ***Toxicology***
  - ***In vitro drug metabolism***
  - ***Efficacy, dose response & drug resistance***



In vitro Approaches for Preclinical Pharmacology & Toxicology

- Ames bacterial mutation & mouse lymphoma assay → genotoxicity

  In vitro human peripheral lymphocytes for chromosome aberration

- hERG-K+ conductance assay using CHO cells → cardiovascular toxicity

  Drugs intended for prolonged or life-time use in human

- Human Caco-2 cell permeability assay → intestinal drug absorption

  Madin-Darby canine kidney cell or parallel artificial membrane permeability assays

- Cytochrome P450 superfamily enzymes → drug metabolism

  In vitro human liver microsomes, heptatocytes, liver slices

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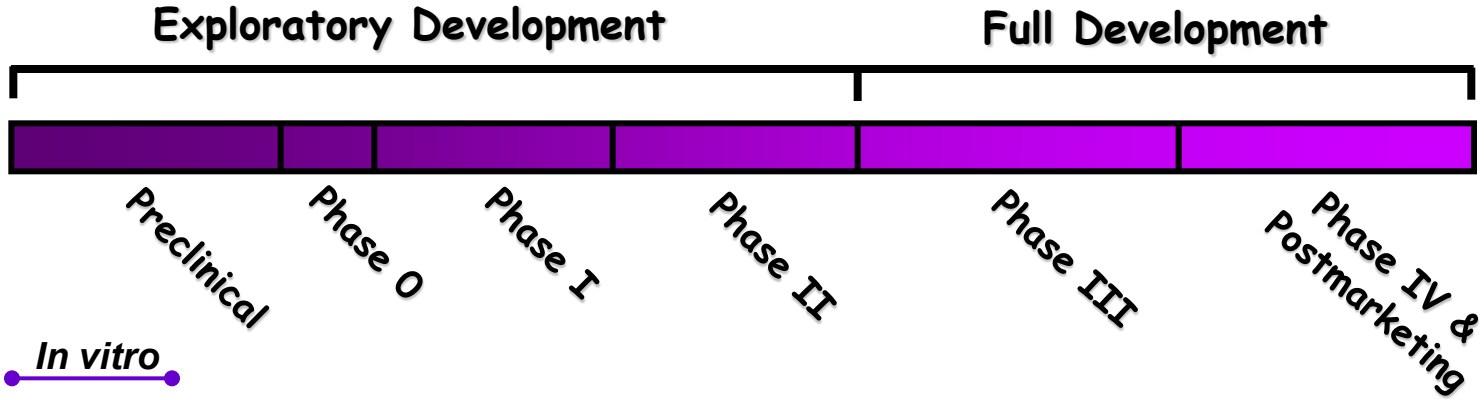


Pharmacology ☺

Toxicology ☺

ADME ☺

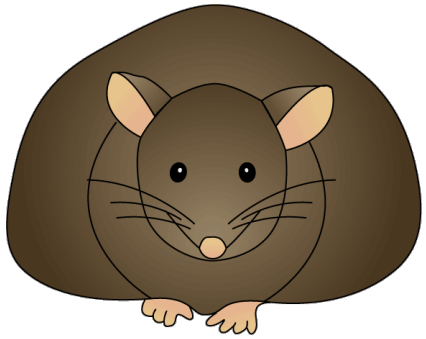
Dose & Formulation ☺

Production ☺

Components of Preclinical Pharmacology & Toxicology: *In vivo* Studies

- ***In vivo studies: animal models and xenograft***
  - ***Proof of therapeutic principle & pharmacodynamics***
  - ***Animal toxicity***
  - ***Animal pharmacokinetics: ADME***
  - ***Starting dose and safety schedule***

    Usually 1/10 LD10 used as starting point and empirical choices for schedule such as Bolus, 24 H infusion, weekly, 5 d infusion, daily x 5.



Approaches of Preclinical Toxicology: Animal Models

- *Two mammalian species: rodent & nonrodent (primate?)*
- *Single-dose escalation and short-duration multiple-dose studies*
- *Equal or exceed the duration of the human clinical trials proposed*
  - ► *5-day dosing or longer than proposed treatment*
  - ► *6 mon in rodents and > 9 mon in nonrodents for chronic treatments*
- *Physiological functions (life, cardiovascular, respiratory, and central nervous system).*
- *Special consideration such as reproductive age, unmet medical need or little alternative therapy.*

Safety Margin: maximal safety dose or exposure > 10 expected pharmacological exposure in rodents (> 6 in nonrodents).

Objectives of Preclinical Toxicology

- ***Determine LD10 for 2 species (mouse, dog)***

  Single dose of a compound that causes 10% mortality. If discrepancy, then third species.

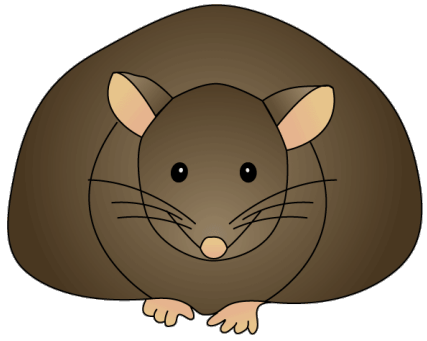
- ***Examine LD10 for specific organ toxicity***

  28 day observation of mice, 60 day observation for dogs.

  - ***Subchronic vs chronic dosing toxicity***

    Repeated daily dose for rodent & non-rodent species, for instance 3 mon vs 2 yr for rat.

  - ***Histopathology of all animals***



From Preclinical Study to Clinical Trail

Limitations of Preclinical Study:

- ***Toxicity testing is time-consuming & expensive***
- ***Large numbers of animals must be used***
- ***Rare adverse effects are unlikely to be detected***
- ***Extrapolation of ADME & toxicity data from animals to humans?***

Investigational New Drug (IND):

- ***Composition & source of drug, manufacturing information***
- ***All preclinical data.***
- ***Protocols for clinical studies***
- ***Names & qualifications of physicians***

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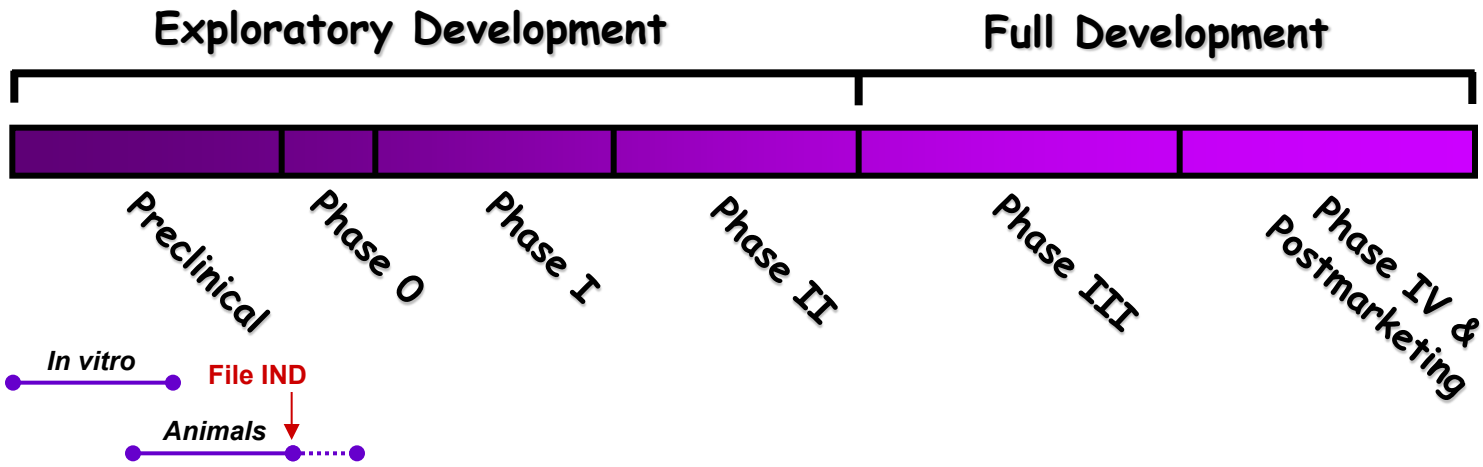

Pharmacology	☺	☺
Toxicology	☺	☺
ADME	☺	☺
Dose & Formulation	☺	☺
Production	☺	

Clinical Trail: Phase 0

- ***Microdosing studies in a very early stage to establish whether a drug behaves in human subjects as was expected from preclinical studies.***
  - ***Single subtherapeutic doses***
  - ***A small number of subjects (10-15)***
  - ***Data of pharmacokinetictics and pharmacodynamics***
  - ***No data on safety or efficacy***
- ***Questions: useful, ethically acceptable, feasible, speed up the process or save money, whether there is room for improvement?***

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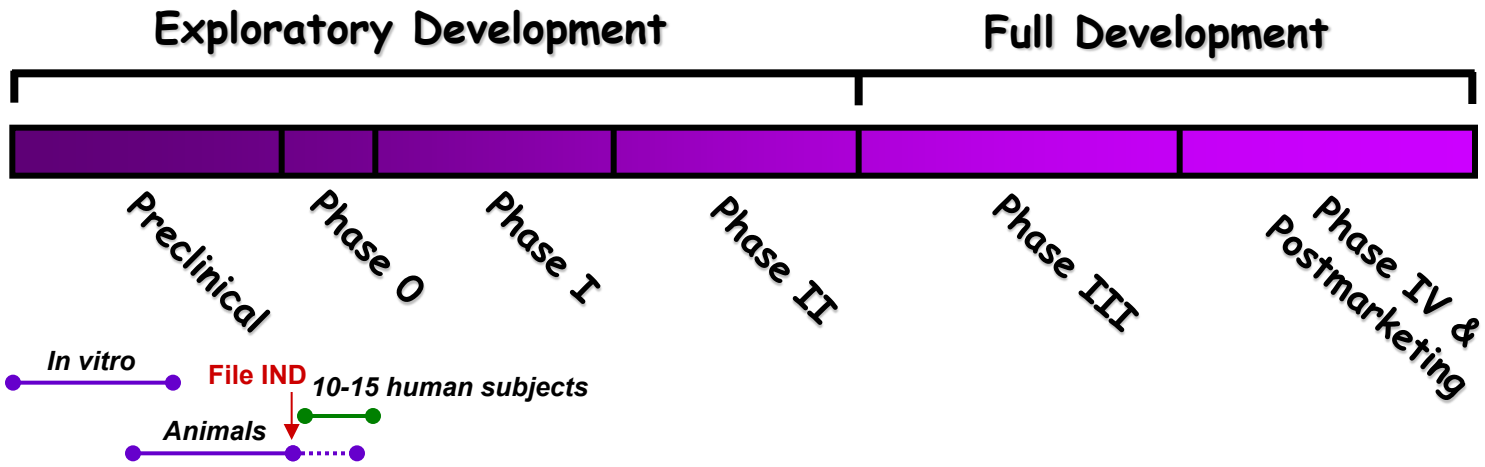

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ADME	☺	☺	☺
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Production	☺		

Clinical Trail: Phase I for Safety

- ***Assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of a drug in human subjects.***
  - ***Open design***
  - ***A small number of subjects(20-50)***
  - ***Healthy volunteers (real patients who have terminal diseases)***
  - ***Dose-ranging or dose escalation***
  - ***A surrogate endpoint***

Phase I Clinical Trail: Dose Escalation Schemes

- ***Challenge: too slow vs too fast***
  - **Many patients**
  - **Many patients receive ineffective doses**
  - **Too much time elapses**
  - **Poor estimation of actual MTD**

vs

  - **Too much risk of toxic dosing**

- ***Approach:***
  - **Modified Fibonacci, 100% → 67% → 50% → 40% → 33% → 33% → →**
  - **Pharmacokinetically Guided (LD10, Cmax or AUC → MTD)**
  - **Pharmacodynamic Guidance**
  - **Statistical Simulations (Accelerated Schemes or Bayesian Schemes)**

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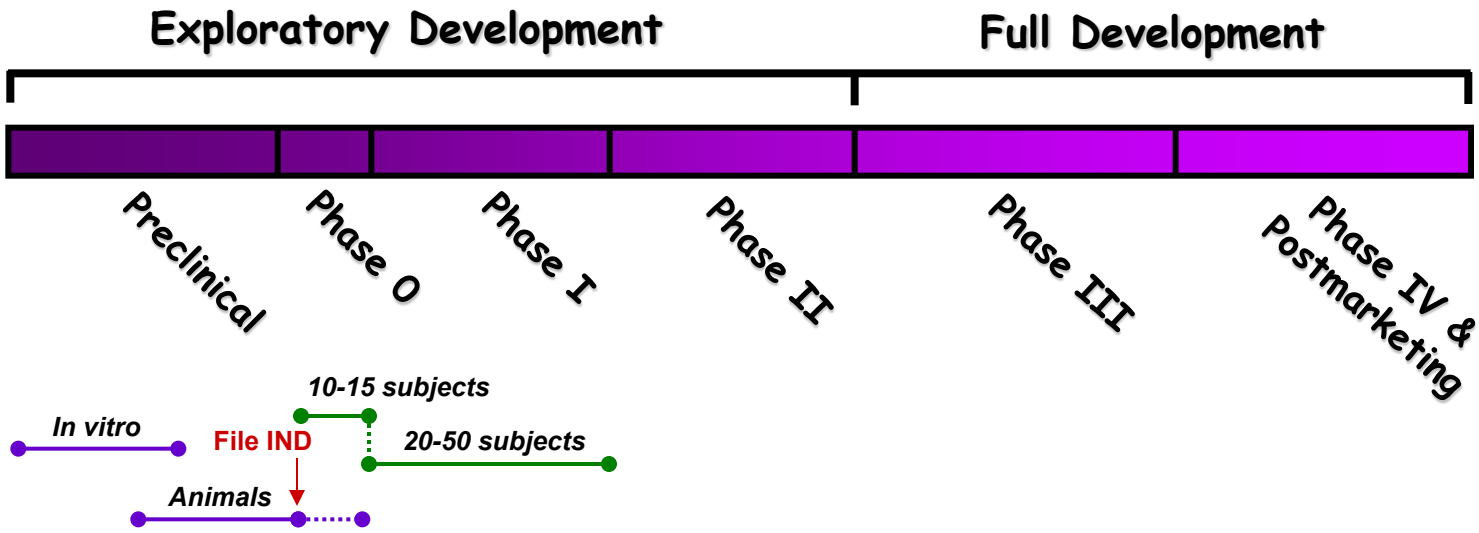
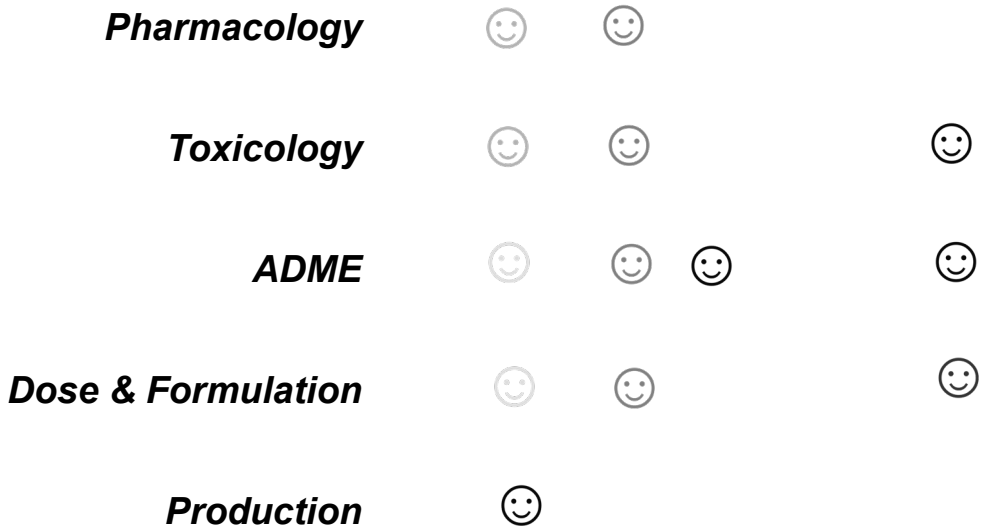


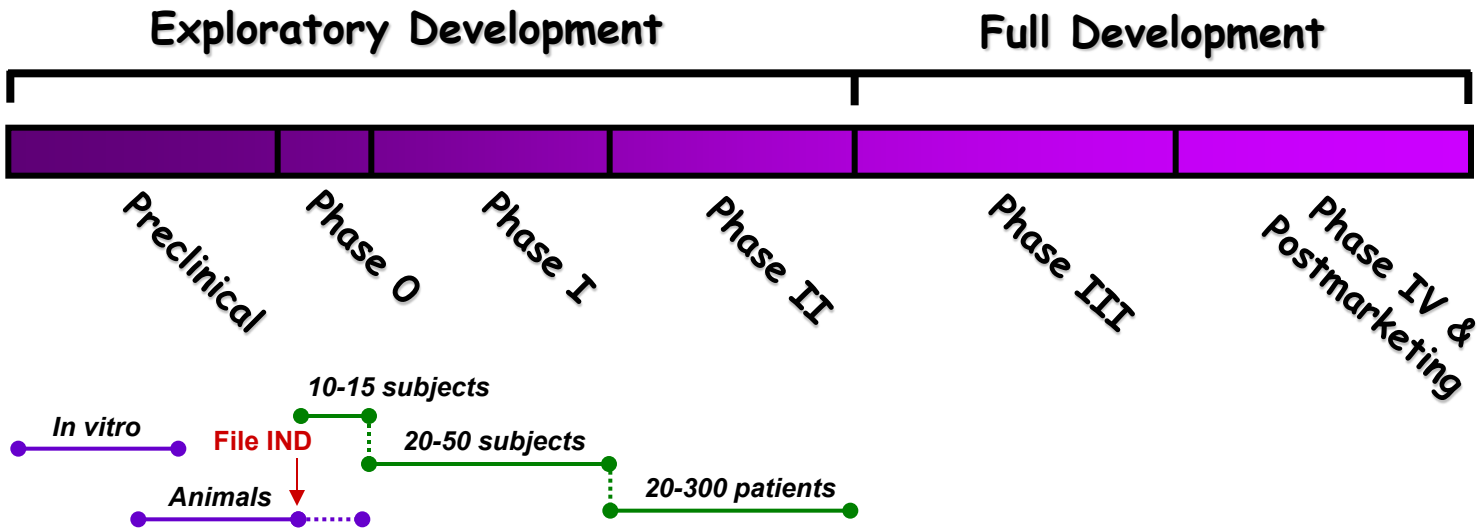


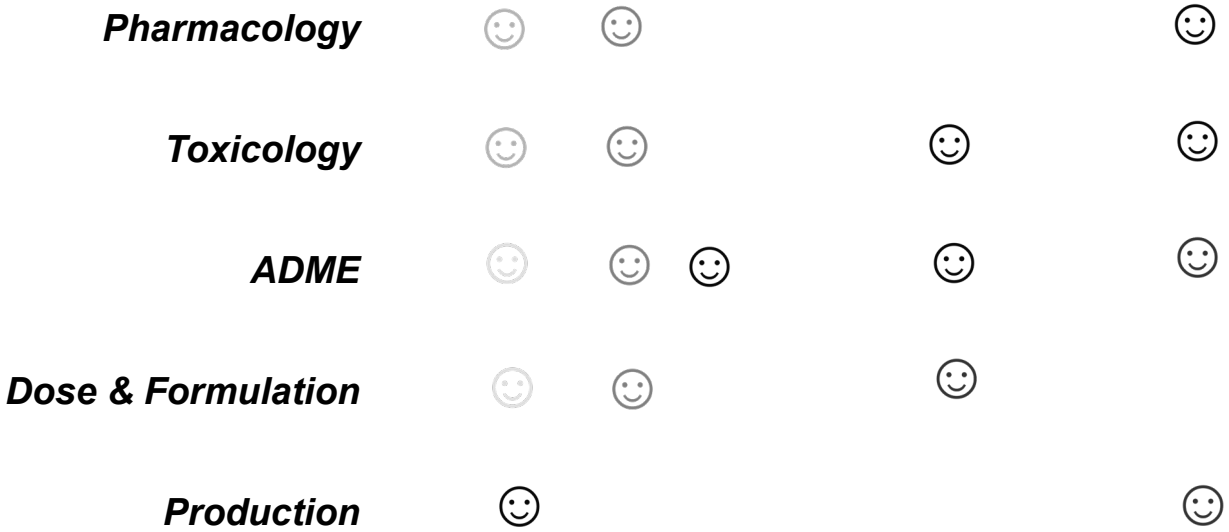
Clinical Trail: Phase II for Efficacy

- ***Assess efficacy and safety in patients.***
  - ***A number of patients (20-300)***
  - ***Randomized design, double blind and placebo-controlled***
  - ***Dose or dose range for Phase III clinical trail***
  - ***Pharmacokinetics, metabolism & safety***

Expected outcome: the minimal dose that is maximally or sufficiently effective and free of significant toxicity.

Timeline of Drug Development



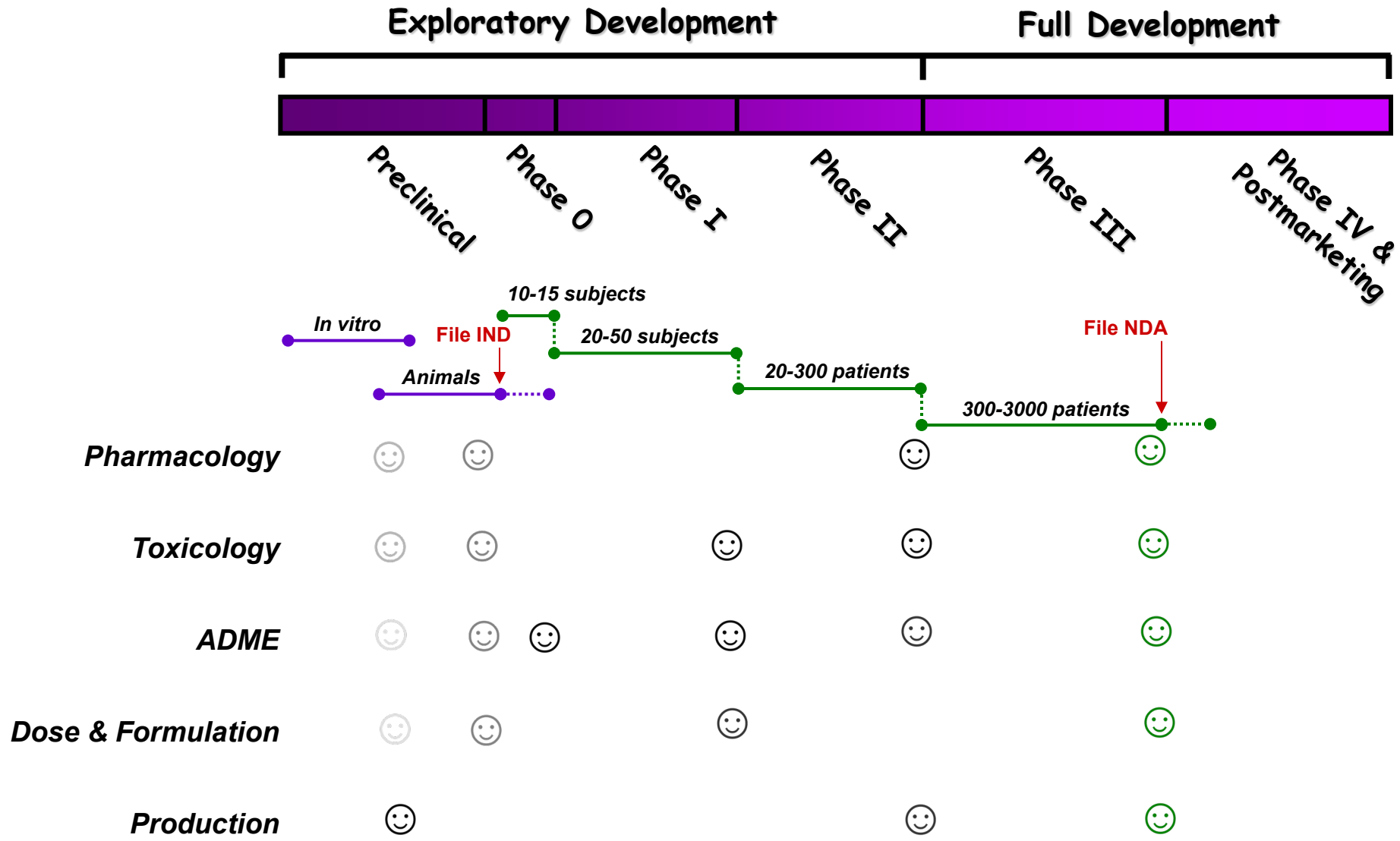


Clinical Trail: Phase III

- ***Definitively assess efficacy and safety in patients.***
  - ***A large number of patients (300-3000)***
  - ***Randomized & cross design and double blind***
  - ***Placebo-controlled or compared with "gold standard" treatment***
  - ***Pharmacokinetics, metabolism & safety***
  - ***"Label expansion" (drug works for additional types of patients)***

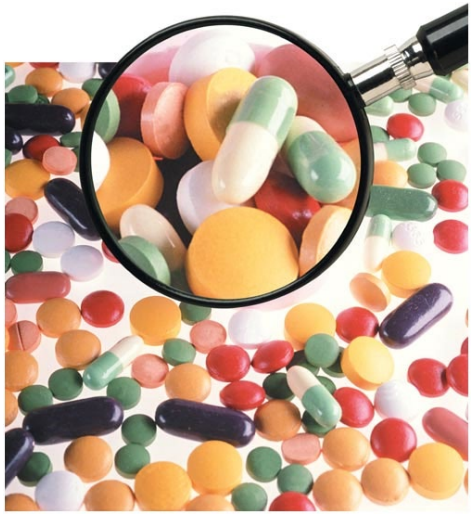
Provide basis for a New Drug Application (NDA)

Timeline of Drug Development



Phase IV or Post Marketing Surveillance Trail

- ***Safety surveillance and ongoing technical support***
  - ***Relative efficacy compared to alternative drugs***
  - ***Cost-effectiveness of the drug***
  - ***Assessment of the improvement in the patient's quality of life***
  - ***Safety assessment in an unselected patient population***
  - ***Opportunities for additional indications***
  - ***Detecting any rare or long-term adverse effects***



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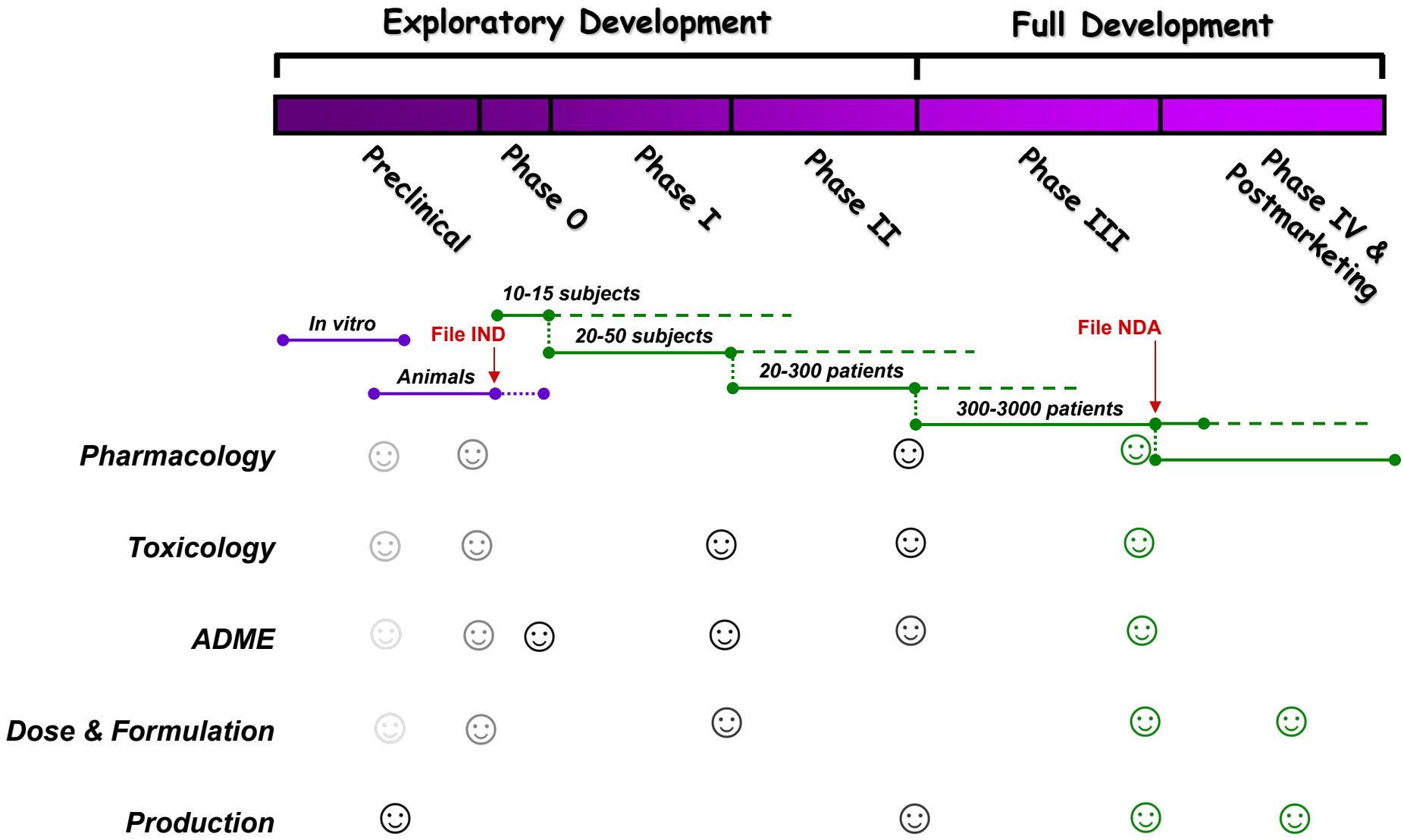

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From test tubes to Market