Roadmap of

Drug development

laboratory phase

TRL 1

TRL 2

basic research — acquire knowledge

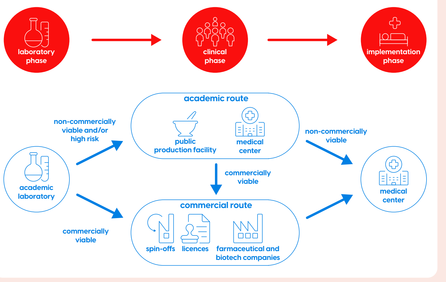
activities
- understanding mechanisms
- understanding pathways
- contact technology transfer office (TTO) and possibly apply for patent

endpoint / starting point
- lead identification

credentialing — discovery of target

activities
- screening of candidates
- directed search for intervention
- contact technology transfer office (TTO) and possibly apply for patent

Academic and commerial routes for drug development



TRL 3/4

endpoint / starting point
- hypothesis

creation of modality — select one or more CD's for each target for pre-clinical safety evaluation

activities
- testing and identification of potential candidate drugs
- optimisation of drug-like properties (i.e. chemical modification)
- sensitivity and specificity analysis
- technical development of candidate drugs
- prototyping
- demonstrate activity in in-vitro models and in-vivo animal model
- retrospective study
- fit with practice
- preliminary safety and formulation tests
- confirm pharmacological mode of action (potency and selectivity)
- preliminary pharmacokinetics (PK)

TRL 5

endpoint / starting point
- target identified

pre-clinical research — confirm safety of use in cell and animal models

activities
- toxicology
- safety
- pharmacokinetics (PK)
- drug plasma concentrations
- investigational new drug application (IND)
- good manufacturing practice (GMP)
- regulatory approval
- feasibility studies
- risk analysis
- candidate drug must meet the definition of investigational medicinal product (IMP)
- early Health Technology Assessment (HTA)
- orphan drug designation via European Medicines Agency (EMA)
- contact College ter Beoordeling van Geneesmiddelen (CBG) for scientific and regulatory advice

endpoint / starting point
- identified target safety reports good manufacturing practice (GMP)
- pre-clinical data good laboratory practice (GLP)

clinical phase

TRL 6

phase I clinical study — determine safety profile of drug and clinical benefit

activities
- single or multiple ascending dose pharmacokinetics (PK)
- food effect
- pharmacokinetics (PK) and pharmacodynamics (PD)
- effectivity
- side effects
- proof of mechanism
- good clinical practice (GCP): clinical research
- good clinical practice (GCP) and good pharmacovigilance practice (GPVP): pharmacovigilance
- good manufacturing practice (GMP): investigational medicinal product (IMP) manufacturing
- safety
- tolerance
- starting dose determination for phase II

endpoint / starting point
- clinical study reports (CSR)
- data to support the creation of the Common Technical Document (CTD) for submission for marketing application
- trial master file (TMP)

TRL 7

phase II clinical study — determine efficacy of drug

activities
- proof of concept at tolerated doses
- drug-drug interactions
- pharmacokinetics (PK) in subpopulations
- preparing marketing authorisation application (MAA) / new drug application (NDA) dossier
- verification of effectiveness
- drug dose selection
- further monitoring of safety data
- dose-response, type of patiënt, frequency of dosing
- contact Dutch Oncology Research Platform (DORP)

endpoint / starting point
- clinical study reports (CSR)
- trial master file (TMP)
- data to support the dosssier (chemistry manufacturing control, CMC)
- identified target safety reports

TRL 8/9

phase III clinical study — registration study (efficacy and safety of drug) to obtain approval by EMA/FDA

activities
- efficacy in large number of patients
- safety
- prospective study
- randomised clinical trial (RCT)
- side effects reports
- important data for authorisation
- Health Technology Assessment (HTA) analysis

endpoint / starting point
- common technical document
- prepare marketing authorisation application (MAA) / new drug application (NDA) dossier
- licenced / compliant manufacturing facility
- finalise company core safety information
- prepare regions prescribing information
- propose clinical phase IIIb and IV plans
- develop life cycle management plans
- benefit-risk confirmed
- patient risk management plan implemented

implementation

implementation phase — implementation in daily practice

activities
- training users
- inclusion in guidelines
- inclusion in insurance package
- Zorginstituut Nederland ZIN review (reimbursement)
- post-marketing monitoring (pharmacovigilance , PV)
- yearly pharmacovigilance (PV) reports
- European Medicines Agency (EMA) / Food and Drug Administration (FDA) registration
- positive opinion Committee for Medicinal Products for Human Use (CHMP)
- phase 4 studies (post-marketing authorisation study, interaction, long-term administration of the drug product)

endpoint
- product licence
- label and regulatory approval finalised
- sustain and maximise sales by introducing life cycle management (LCM) line extensions
- strategy for post-launch surveillance defined

KWF

Please note: this roadmap serves as a tool to give you an overview of the most important steps during the drug development process. We do not have the illusion this overview is exhaustive and we therefore strongly recommend you to consult the experts on each step, starting with your technology transfer officer.