Development to 1st in Man

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Stages of Pharmaceutical Development

**Technical Development Stages**

- Research → Proof of Concept → Clinical → Approval/Marketing
- Early Development → Full Development → Life Cycle Management

**Technical Development Challenges**

Current status
- 1 out of 10,000 molecules synthesized becomes a drug product
- Most activities in Technical Development are conducted at risk, much before clinical outcome
How Does Technical Development Manage Risks?

- Minimize attrition: Select ‘right’ molecules through development-discovery interaction (‘developability assessment’)
- Identify optimal drug substance forms early (salts, polymorphic forms)
- Identify formulation principles and development hurdles early
- Assess potency with respect to drug product development
- Keep early clinical trial materials and formulations simple (caveat: bioequivalence)
- Keep processes simple

Selecting Right Molecule for Development

Technical Development conducts Developability Assessment

- Target & hit identification, hit validation, lead selection
- Lead optimization
- Candidate selection process
- Early clinical development

... through strong collaboration with Discovery

- Synthesis considerations
- Solubility considerations
- Assess physicochemical & biopharmaceutical properties of drug substance
- Assess synthesis hurdles
- Dosing vehicles selection
- Assess formulation feasibility
- Assess impact of dose on potential dosage forms

- Get a complete picture of bioavailability issues
- Assess impacts of drug substance properties and formulation on bioavailability

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Drug Product Design

Selection criteria for dosage forms
- Clinical needs
- Dose/Onset/Duration of action
- Product performance
- Patient acceptance
- Marketing considerations

PK in Drug Development

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Mission Statement – Translational Medicine

...... drives Innovative and Cutting Edge Science from Discovery to the Market through the selection, profiling and effective global development of successful Novartis medicines to enhance the quality of people's lives
TM’s Contribution to Development Process

Exploratory Phase
- sPoC
- ISA
- PoC

Phase 2
- DDP
- FDP
- SDP

Phase 3
- Registration

TM Deliverables/ Contributions
- Coordination of external input (PoC Summit)
- PoC Plan
- PoC conduct (incl. studies preparing PoC)
- Post-PoC and Peri-PoC plan
- Preparation of the steps toward full development

TM Contribution to IPT
- Contribution to Full Development CDP
- Support development program strategy
- Conduct Profiling Clin. Pharm. Studies
- Support steps toward commercialization

Early Project Team
- ISA=Integrated safety assessment
- PoC=Proof of concept
- DDP=Development decision point
- FDP=Full development decision point
- SDP=Submission development point

International Project Team
- Contribution to Full Development CDP
- Support development program strategy
- Conduct Profiling Clin. Pharm. Studies
- Support steps toward commercialization

Overview of TM Study Types

Exploratory Phase
- First in man (FIM) study: a single dose safety & tolerability study in healthy volunteers, or a single dose study in patients (depending on the indication). May already provide relevant PoC readout.
- Multiple dose safety & tolerability study in HVs or patients
- *PoC study
- Validation studies (e.g. supported by Clinical Innovation Fund)
- *In many cases SD and MD safety & tolerability studies results are needed for preparation of PoC study

Confirmatory Phase
- Human ADME study
- Multiple pharmacokinetic studies, e.g. relative/absolute bioavailability, dose linearity, investigation on factors food, age and gender, special populations (hepatic and renal impairment), drug-drug interaction studies
- Imaging/biomarker studies
- ECG studies (preclinical signals?)
- Phototoxicity study (preclinical signals?)
The Package Insert

ADME

Pediatric

Dosing

Special Pop*

Age

Geriatric

Renal

Overdose

Hepatic

Gender

DDI

PK

Pediatric

Dosing

Special Pop*

Age

Geriatric

Renal

Overdose

Hepatic

Gender

DDI

Types of studies – Classic Clinical Pharmacology

About 60% of the studies run by TM are simple studies with either a PK or safety focus

- FIM
- QTc
- Drug/drug interaction
- Bio-equivalent
- Bio-availability (absolute or comparative)
- Food effect
- ADME
- Special populations
  - Renal/ Hepatic/ Japanese
Types of studies (2) – Complex scientific studies

- About 40% of the studies run by TM are complex studies with a Pharmacodynamic or safety focus
  - FIM (Multiple dose)
  - POM
  - POC
  - Methodology
  - PK/PD
  - Adaptive

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Phase I (Healthy Volunteers) CROs
Specialized Hospital Clinics (Patients)
Early Phase Studies to support PoC
### Single Ascending Dose Study: Interleaved Design

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<td>1600 mg</td>
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Randomized, double blind, interleaved, ascending dose study with placebo substitution in 36 healthy volunteers (12 per cohort)

### Multiple Ascending Dose Study: Classical Design

- Design: Randomized, double-blind, placebo-controlled, parallel group, time-lagged, ascending multiple oral dose study
- Objectives: Safety, tolerability, PK and/or PD of ascending multiple oral doses in healthy volunteers
- Sample size: 24 – 36 subjects (depending on number of doses)
The Spectrum of “POC”

- Proof of Commercialization
- Proof of Efficacy
- Proof of Mechanism
- Proof of Target
- Proof of Target Modulation

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Characteristics of PoC Trials

- PoC trials typically are short and involve relatively few patients/healthy subjects
- Studies should enable intelligent Go/No-Go decisions
- Studies often lack power for statistical significance
- This places an emphasis on the quality of the read-outs (e.g. pharmacodynamic parameters, biomarkers) to yield insights into the relevant human physiology
- To ensure high-quality read-outs investigators have to be adequately trained and relevant procedures closely monitored.

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Concluding Remarks

- The journey of a new molecular entity (NME) from a chemist’s/biologist’s bench to a drug product in a patient’s bedside is a difficult, costly and high risk process.
- There is a continued pressure to shorten the journey (reduce development time) and save costs.
- Most pharmaceutical companies are developing innovative technologies and processes.
- For example, Novartis developed Gleevec® from Phase I clinical to regulatory submission in just 2.7 years, all at risk; the industry standard is 5.9 years!