Phase I: Overview

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March, Bangkok

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The information within this presentation is based on the presenter’s expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
Stages of Pharmaceutical Development

Stage 1: Drug Discovery
- 10,000 Compounds
- 5 YEARS

Stage 2: Preclinical
- 250 Compounds
- 1.5 YEARS

Stage 3: Clinical Trials
- Phase 1
  - 20-100 Volunteers
- Phase 2
  - 100-500 Volunteers
- Phase 3
  - 1000-5000 Volunteers
- IND Submitted
- 6 YEARS

Stage 4: FDA Review
- NDA Submitted
- 2 YEARS

Drug Product Development Challenges for New Chemical Entities

Formulation Issues

- Poor aqueous solubility
- Poor physical and chemical stability
- Low permeability
- First-pass metabolism
- Poor bioavailability
- Short half life and duration of action
- Inappropriate dose
Drug Product Development Challenges for New Chemical Entities

Formulation Issues

- Invasive dosage forms (injections)
- Non-injectable formulations are usually poorly bioavailable and ineffectacious
- Stable only under frozen conditions (liquid forms) or low temperature (lyophiles at 2-8°C)
- Short duration of action for most proteins (non-mAbs)
- Need for prolonged release formulations
## Drug Product Design Options: Conventional Dosage Forms

<table>
<thead>
<tr>
<th>Routes</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL</strong></td>
<td>Tablets, capsules, solutions</td>
</tr>
<tr>
<td><strong>PARENTERAL</strong></td>
<td>Sterile s.c., i.m., i.v. injectables</td>
</tr>
<tr>
<td><strong>INHALATION</strong></td>
<td>Pressurized multidose inhalers</td>
</tr>
<tr>
<td><strong>TOPICAL</strong></td>
<td>Creams, ointments, gels</td>
</tr>
<tr>
<td><strong>TRANSDERMAL</strong></td>
<td>Patches (passive diffusion)</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
</tr>
<tr>
<td>• BUCCAL/SUBLINGUAL</td>
<td></td>
</tr>
<tr>
<td>• RECTAL</td>
<td></td>
</tr>
<tr>
<td>• OPHTHALMIC</td>
<td></td>
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<tr>
<td>• NASAL</td>
<td></td>
</tr>
</tbody>
</table>
## Dose Limitations in Drug Delivery Systems

<table>
<thead>
<tr>
<th>Delivery Opportunities</th>
<th>Max. Dose (approx.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depot system (monthly)</td>
<td>1-2 mcg (per day)</td>
</tr>
<tr>
<td>Inhalation</td>
<td>1 mg</td>
</tr>
<tr>
<td>Transdermal (passive)</td>
<td>5-10 mg (per day)</td>
</tr>
<tr>
<td>Sublingual</td>
<td>10 mg</td>
</tr>
<tr>
<td>Injection (s.c./i.m.)</td>
<td>50 mg</td>
</tr>
<tr>
<td>Fast melt tablet</td>
<td>250 mg</td>
</tr>
<tr>
<td>Conventional capsule</td>
<td>300 mg</td>
</tr>
<tr>
<td>Intravenous (bolus)</td>
<td>750 mg</td>
</tr>
<tr>
<td>Controlled release tablet</td>
<td>500-750 mg</td>
</tr>
<tr>
<td>Conventional tablet</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td>Intravenous infusion</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>
Drug Product Design Options: Special Drug Delivery Systems

What does a Drug Delivery System Do?

- Enhance absorption
- Control release
- Reduce variability
- Target systemic delivery
- Introduce mechanical devices, when necessary
- Increase patient convenience
- Better therapy
<table>
<thead>
<tr>
<th>Routes</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORAL</td>
<td>Multi-particulate controlled release systems, matrix systems, solid dispersions, nanosuspensions, microemulsions</td>
</tr>
<tr>
<td>PARENTERAL</td>
<td>Liposomes, microspheres, needleless injections, implants, depot forms (for proteins)</td>
</tr>
<tr>
<td>INHALATION</td>
<td>Dry powder inhalers (DPI)</td>
</tr>
<tr>
<td>TRANSDERMAL</td>
<td>Permeation enhancers, iontophoretic delivery</td>
</tr>
<tr>
<td>NASAL</td>
<td>Protein &amp; peptide delivery</td>
</tr>
</tbody>
</table>
Technical Development Stages

1. 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 of 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
Drug Product Design

Selection criteria for dosage forms

- Clinical needs
- Dose/Onset/Duration of action
- Product performance
- Patient acceptance
- Marketing considerations
... And it's a Collaborative Effort

- Project Management
- Marketing
- Research
- Drug Regulatory Affairs
- Clinical Research
- Drug Product Design & Development
- Early Clinical Dev. / PK
- Drug Safety
- Technical Operations
Understanding Causal Chain of Drug Action

Dose → Exposure → Biomarker → Response

Dose → Exposure → Response

PK ← → PD
Where does PK play a role in Drug Development?

- Pharmacokinetics is either directly or indirectly associated with just about every part of pharmaceutical business
  - Research and the selection of a promising molecule
  - Dosage formulation development
  - Dose regimen
  - Toxicology and safety assessment
  - Dosing recommendations for age groups & sub-populations (renal/hepatic/race/DDI)
  - Effect of meals and dosing
  - Marketing claims and promotion
  - Generic substitution
  - Manufacturing changes
PK in Drug Development

- Different patients
- Different exposure
- Different response

Graph showing concentration over time for responders and non-responders.
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

**TM Deliverables/Contributions**
- Coordination of external input (PoC Summit)
- PoC Plan as approved by TRTD
- 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
- Conduct mechanistic studies

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**Exploratory Phase**
- sPoC
- ISA

**Phase 2**
- PoC
- ALIGN@DDP Process

**Phase 3**
- DD P
- FDP
- SDP

**Registration**

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**tm’s contribution to all phases of development conducting a multitude of clinical trials**
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, “mechanistic” studies
  - ECG studies (preclinical signals?)
  - Phototoxicity study (preclinical signals?)
  - Abuse liability study (study in drug experienced subjects)
About 60% of the studies run by TM are simple studies with either a PK or safety focus

- FIM (Single dose S&T)
- 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 S&T)
  - POM
  - POC
  - Mechanistic
  - Methodology
  - PK/PD
  - Adaptive
Study Sites

Phase I (Healthy Volunteers) CROs
Specialized Hospital Clinics (Patients)
TM is Global
Early Phase Studies to support PoC
Single Ascending Dose Study: Classical Design

Randomized, double-blind, placebo-controlled, time lagged, parallel-group, ascending single dose study in HVs to explore safety, tolerability, pharmacokinetics and pharmacodynamics

<table>
<thead>
<tr>
<th>Cohort</th>
<th>week 1</th>
<th>week 2</th>
<th>week 3</th>
<th>week 4</th>
<th>week 5</th>
<th>week 6</th>
<th>week 7</th>
<th>week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>0.3 mg 1) (seq. dosing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cohort 2</td>
<td></td>
<td>1 mg</td>
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<td></td>
</tr>
<tr>
<td>Cohort 3</td>
<td></td>
<td></td>
<td>3 mg</td>
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</tr>
<tr>
<td>Cohort 4</td>
<td></td>
<td></td>
<td></td>
<td>10 mg</td>
<td></td>
<td>10 mg fed</td>
<td></td>
<td></td>
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<tr>
<td>Cohort 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30 mg</td>
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<tr>
<td>Cohort 6</td>
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<td></td>
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<td></td>
<td></td>
<td>100 mg</td>
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</tr>
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</table>

1) start dosing in sequence e.g. 48 hours apart
# Single Ascending Dose Study: Interleaved Design

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
<th>Week 9</th>
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<tbody>
<tr>
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<td>A</td>
<td>5 mg</td>
<td></td>
<td>50 mg</td>
<td></td>
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<td></td>
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<td>Plac</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>5 mg</td>
<td></td>
<td>Plac</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Plac</td>
<td></td>
<td>50 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mg</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>A</td>
<td>10 mg</td>
<td></td>
<td>100 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plac</td>
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<tr>
<td></td>
<td>B</td>
<td>10 mg</td>
<td></td>
<td>Plac</td>
<td></td>
<td></td>
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<td></td>
<td>800 mg</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Plac</td>
<td></td>
<td>100 mg</td>
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<td>800 mg</td>
</tr>
<tr>
<td>Cohort 3</td>
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<td></td>
<td>20 mg</td>
<td></td>
<td>200 mg</td>
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<td></td>
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<td>Plac</td>
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<tr>
<td></td>
<td>B</td>
<td>20 mg</td>
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<td>600 mg</td>
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<td>C</td>
<td>Plac</td>
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<td>200 mg</td>
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<td></td>
<td></td>
<td></td>
<td>600 mg</td>
</tr>
</tbody>
</table>

- 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)
Combination of SD/MD: Interwoven Design

Timing assumes no safety issues

Doses for SD cohorts
SD 6 +7 optional
1st Doses for MD cohorts
MD 5 + 6 optional

Week 1

$\frac{1}{2}$ of SD 3mg
SD 10 mg
SD 25 mg
SD 50 mg Fast
SD 100 mg

Expanded safety review

SD 300 mg

Week 2

$\frac{1}{2}$ of SD 3mg

Week 3

Week 4

Week 5

Week 6

Week 7

Week 8

Week 9

MD 10 mg
MD 25 mg
MD 50 mg
MD 100 mg
MD 200 mg
MD 300 mg
The Spectrum of “POC”

- Proof of Target*
- Proof of Mechanism
- Proof of Efficacy
- Proof of Commercialization

* Proof of Target Modulation
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.
Confirmatory Phase Study Examples
PK: 2 period cross-over
PK: 4 period cross-over

<table>
<thead>
<tr>
<th>Period 1</th>
<th>Washout</th>
<th>Period 2</th>
<th>Washout</th>
<th>Period 3</th>
<th>Washout</th>
<th>Period 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug 1</td>
<td></td>
<td>Drug 1</td>
<td></td>
<td>Drug 1</td>
<td></td>
<td>Drug 1</td>
</tr>
<tr>
<td>Drug 2</td>
<td></td>
<td>Drug 2</td>
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<td>Drug 2</td>
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<td>Drug 4</td>
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<td>Drug 4</td>
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<td>Drug 4</td>
</tr>
</tbody>
</table>

Wks-2 0 1 2 3 4 5 6 7
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!