Development to 1st in Man

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International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

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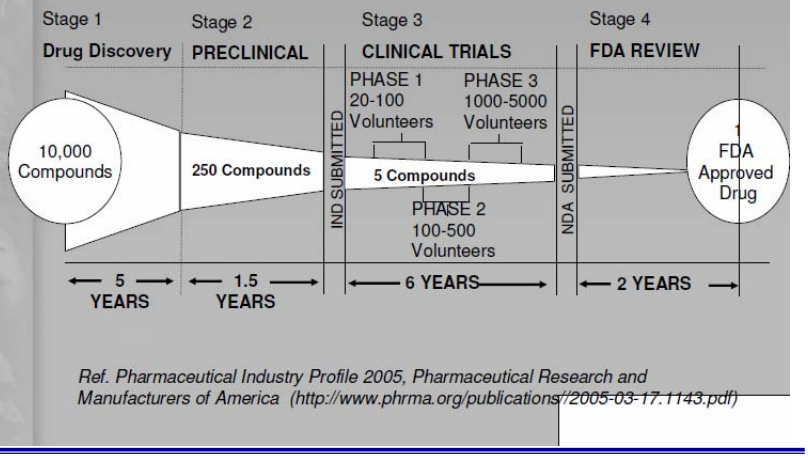
Stages of Pharmaceutical Development



Ref. Pharmaceutical Industry Profile 2005, Pharmaceutical Research and Manufacturers of America (http://www.phrma.org/publications//2005-03-17.1143.pdf)

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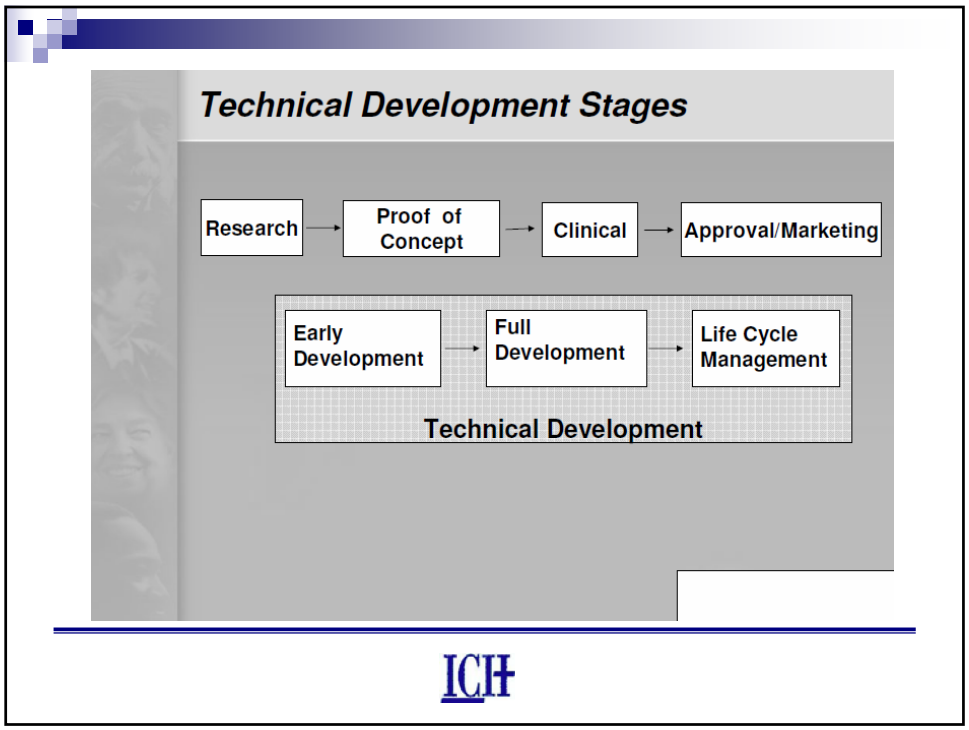
Technical Development Stages
Research
Proof of Concept
Clinical
Approval/Marketing
Early Development
Full Development
Life Cycle Management
Technical Development
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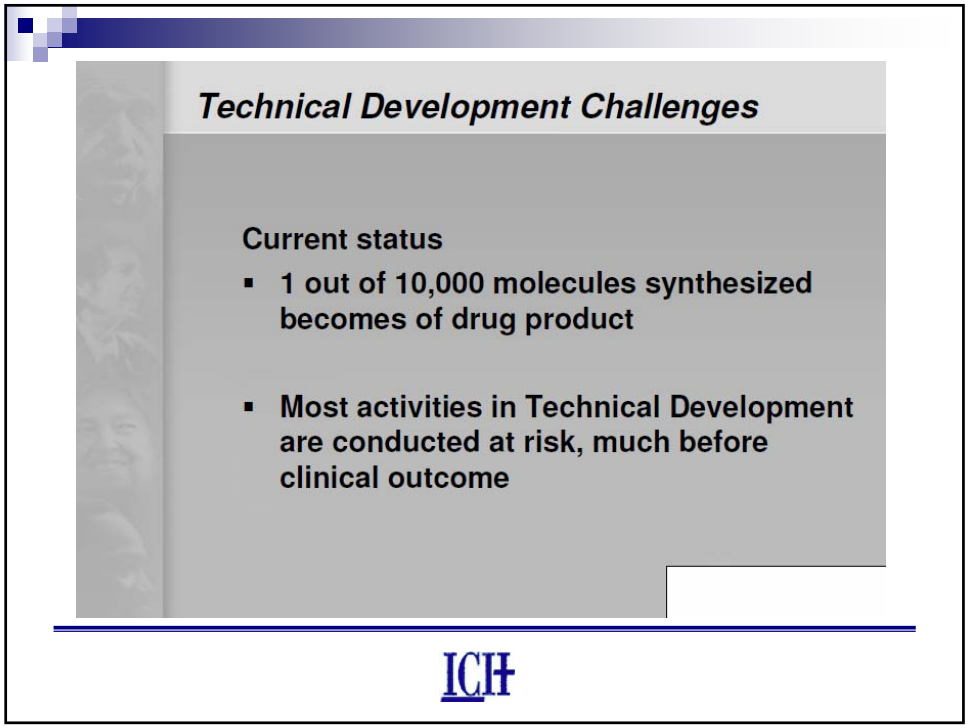
Technical Development Challenges
Current status
1 out of 10,000 molecules synthesized becomes of drug product
Most activities in Technical Development are conducted at risk, much before clinical outcome
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How Does Technical Development Manage Risks?

- 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

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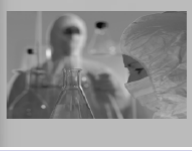
Selecting Right Molecule for Development

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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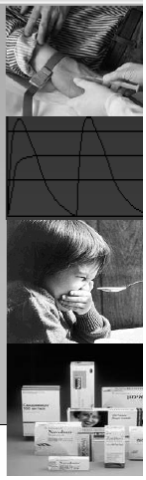
Drug Product Design

Selection criteria for dosage forms

- Clinical needs
- Dose/Onset/Duration of action
- Product performance
- Patient acceptance
- Marketing considerations



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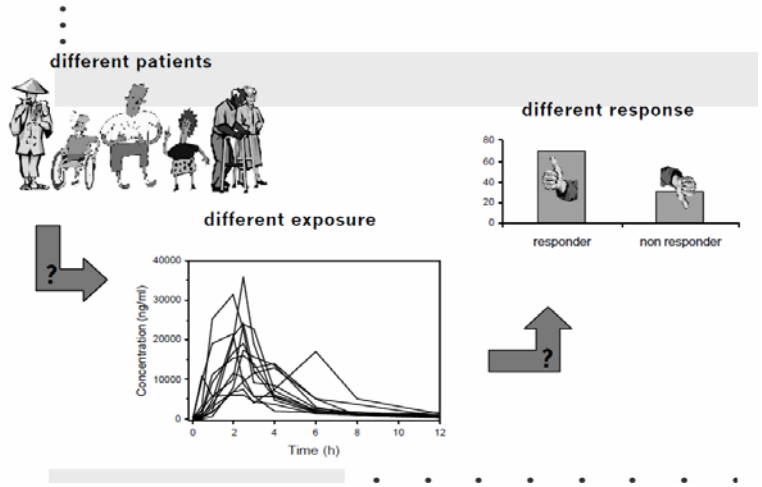
PK in Drug Development



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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

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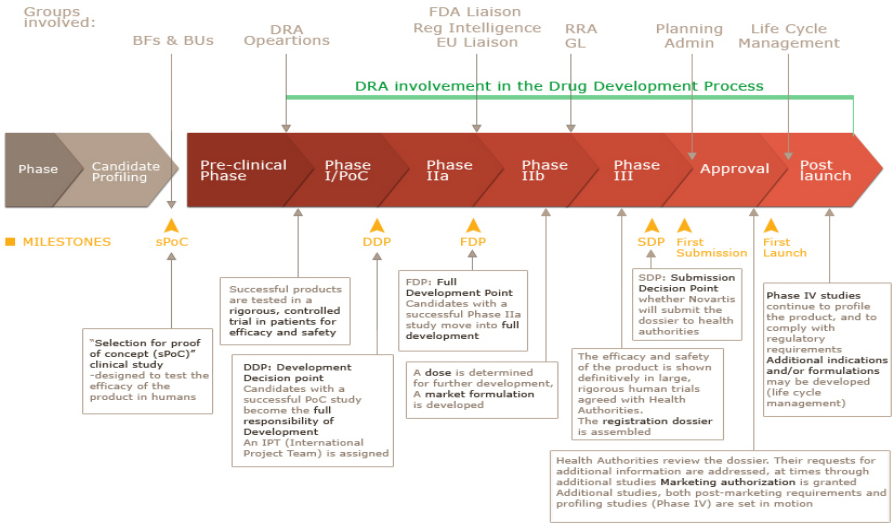
Clinical development milestone



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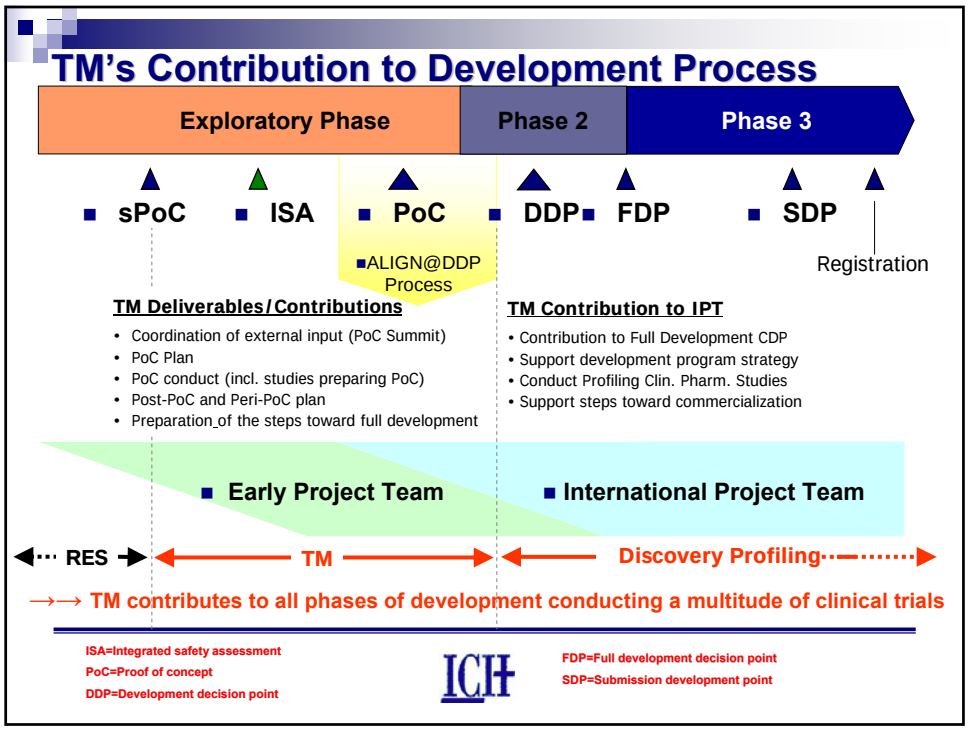
TM's Contribution to Development Process
Exploratory Phase
Phase 2
Phase 3
sPoC
ISA
PoC
DDP
FDP
SDP
ALIGN@DDP Process
Registration
TM Deliverables/Contributions
Coordination of external input (PoC Summit)
PoC Plan
PoC conduct (incl. studies preparing PoC)
Post-PoC and Peri-PoC plan
Preparation of the 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
International Project Team
RES
TM
Discovery Profiling
TM contributes to all phases of development conducting a multitude of clinical trials
ISA=Integrated safety assessment
PoC=Proof of concept
DDP=Development decision point
FDP=Full development decision point
SDP=Submission development point
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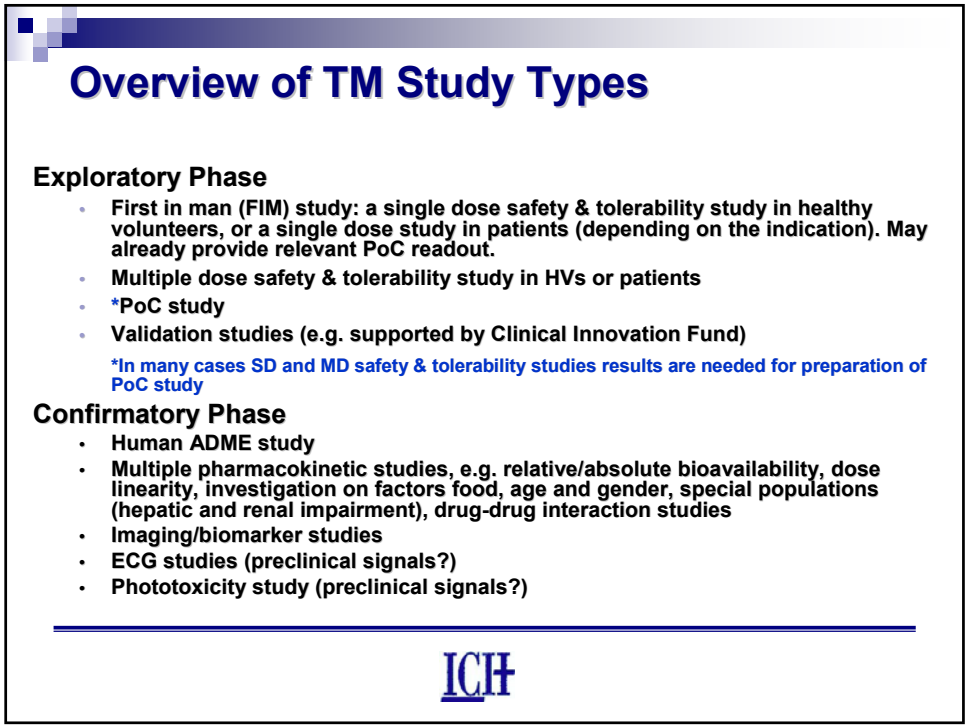
Overview of TM Study Types
Exploratory Phase
First in man (FIM) study: a single dose safety & tolerability study in healthy volunteers, or a single dose study in patients (depending on the indication). May already provide relevant PoC readout.
Multiple dose safety & tolerability study in HVs or patients
*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?)
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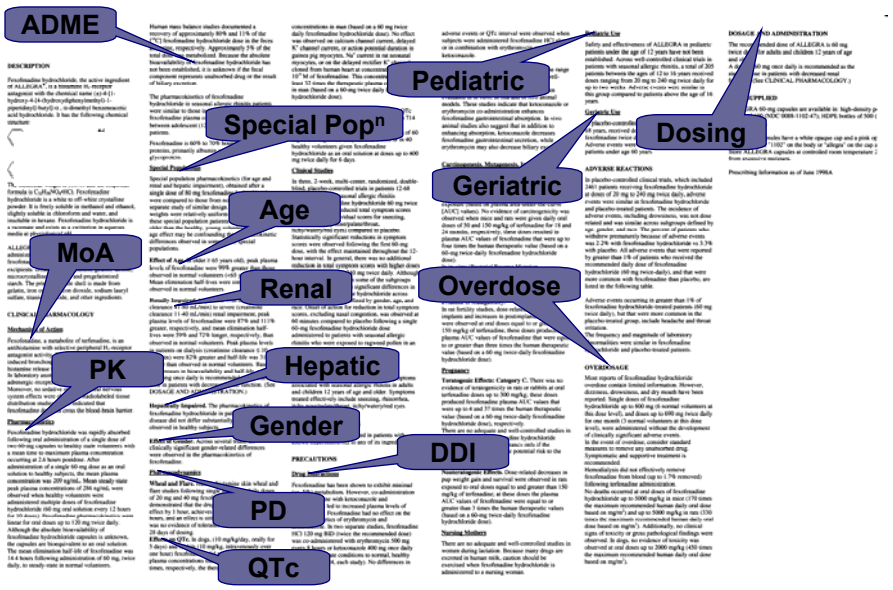
The Package Insert



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

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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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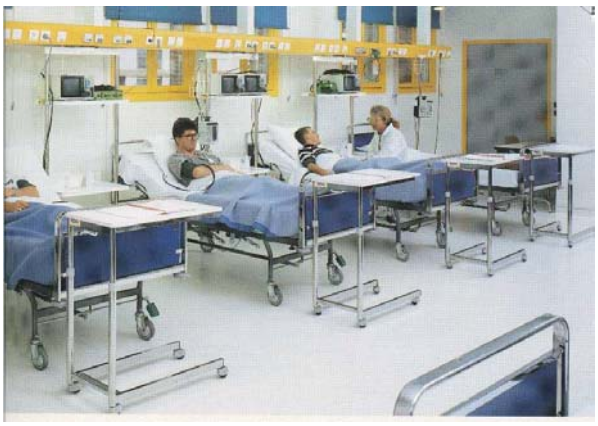
Phase I (Healthy Volunteers) CROs Specialized Hospital Clinics (Patients)



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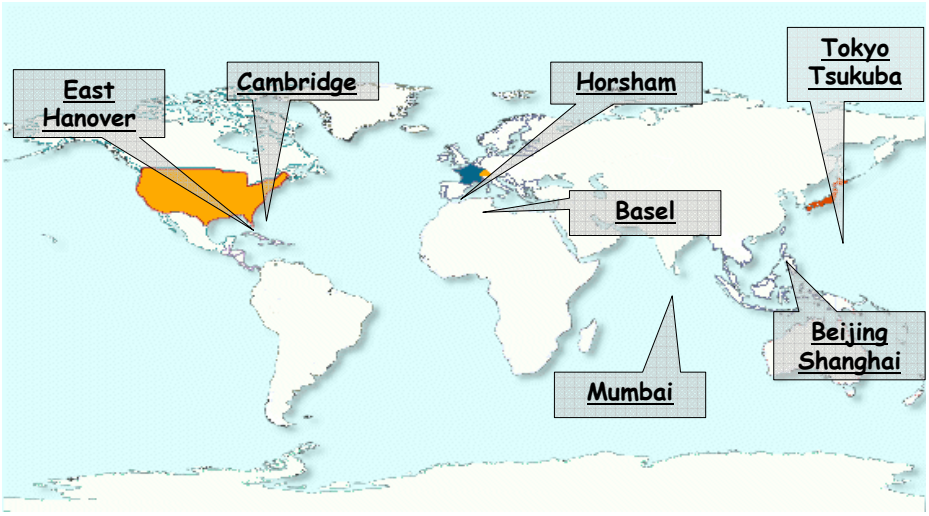
TM is Global



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Early Phase Studies to support PoC

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Single Ascending Dose Study: Interleaved Design

Weeks		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week9
Cohort 1	A	5 mg			50 mg			Plac		
	B	5 mg			Plac			400 mg		
	C	Plac			50 mg			400 mg		
Cohort 2	A		10 mg			100 mg			Plac	
	B		10 mg			Plac			800 mg	
	C		Plac			100 mg			800 mg	
Cohort 3	A			20 mg			200 mg			Plac
	B			20 mg			Plac			1600 mg
	C			Plac			200mg			1600 mg

Randomized, double blind, interleaved, ascending dose study with placebo substitution in 36 healthy volunteers (12 per cohort)

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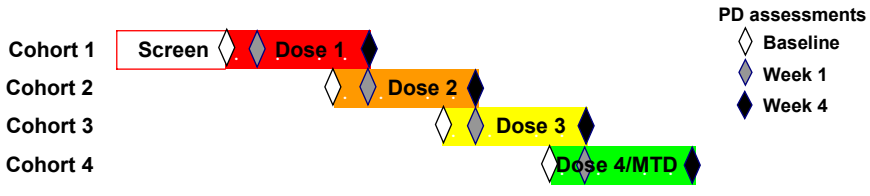
Multiple Ascending Dose Study: Classical Design

- 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)**



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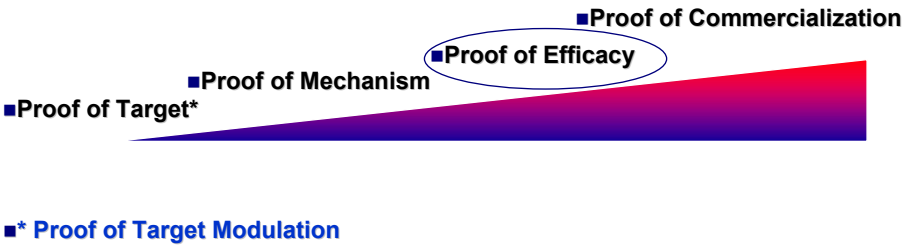
The Spectrum of "POC"



* 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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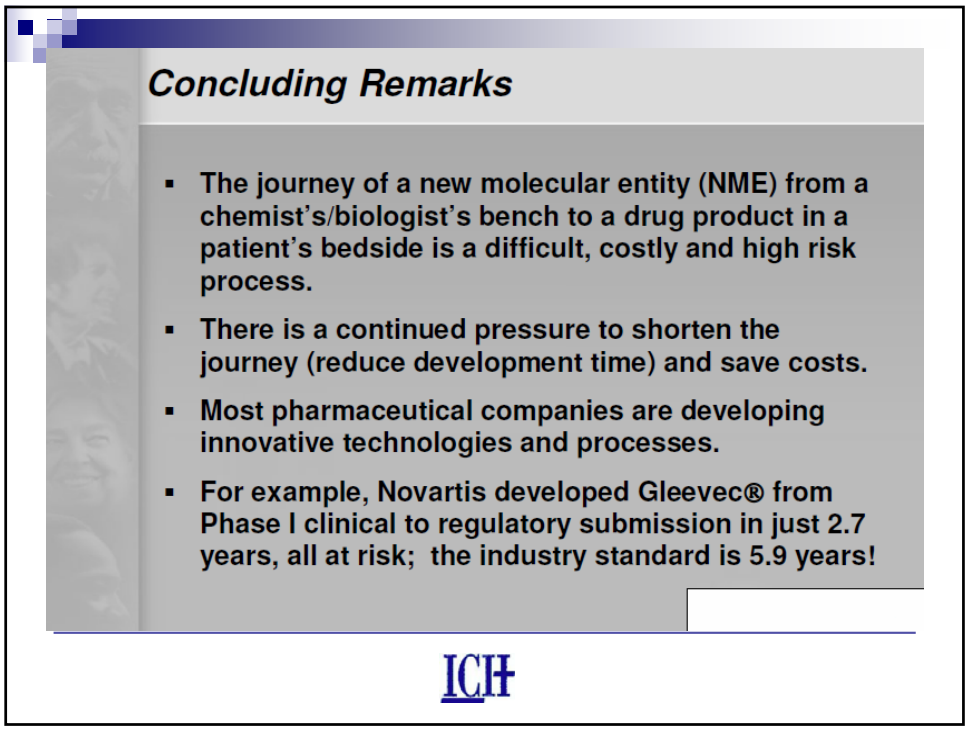
Concluding Remarks
The journey of a new molecular entity (NME) from a chemist's/biologist's bench to a drug product in a patient's bedside is a difficult, costly and high risk process.
There is a continued pressure to shorten the journey (reduce development time) and save costs.
Most pharmaceutical companies 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!
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