Project Management During Pharmaceutical Preclinical R&D: Study Design, Implementation and Data Interpretation

药物临床前研发过程中的项目管理: 研究设计、试验实施及数据分析

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Agenda

- Covance China Overview
- Preclinical R&D in Current Pharmaceutical Industry
- Preclinical Project Management
- Case Studies
- Summary

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Covance China Overview

Growing Covance China Organization

COVANCE In Beijing

1998 — Opened Beijing office

2001 — Virtual CLS (collaboration with Huashan hospital)

COVANCE In Shanghai

2005 — Opened SH office

2007 — Opened CLS in SH

2008 — Opened BioA in SH

2009 — Major clinical operation expansion

2010 — Laboratory expansion

Non-clinical Safety Assessment

DMPK Services

Large molecule BioA

2011 — AAALAC Accreditation

Regulatory inspections

Continued capability development

CDARO (CDS)

OECD approval

2012 — Discovery Services (In-Vivo Pharmacology)

Clinical Development Services

Central Labs Expansion

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Covance Services in China

Regional based Staff

Additional staff to be added in 2012

Clinical Dev. Services

- Clinical operations
- CDARO (clinical data analysis and reporting)
- Medical affair
- Drug Safety
- Regulatory
- QC/QA

R&D laboratories

- Central Laboratory Services (including biomarkers, genomics)
- DTS (*in vivo* Pharmacology, PK/PD)
- DMPK Services (*In Vivo* & *In Vitro*)
- Non-clinical Safety Assessment
- Bioanalytical Services (Small and large molecules)

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Early Development Facility Highlights

Building Four

- 50,000 square feet
- 30 animal rooms
- Surgery suite
- Dose Formulation and Dose Analysis
- Clinical Pathology Ops
- Anatomic Pathology Ops

Building Three

- 40,000 square feet
- Archives
- Bioanalytical Services
- DMPK Services

Support Building

- Backup power generator
- Backup water supply

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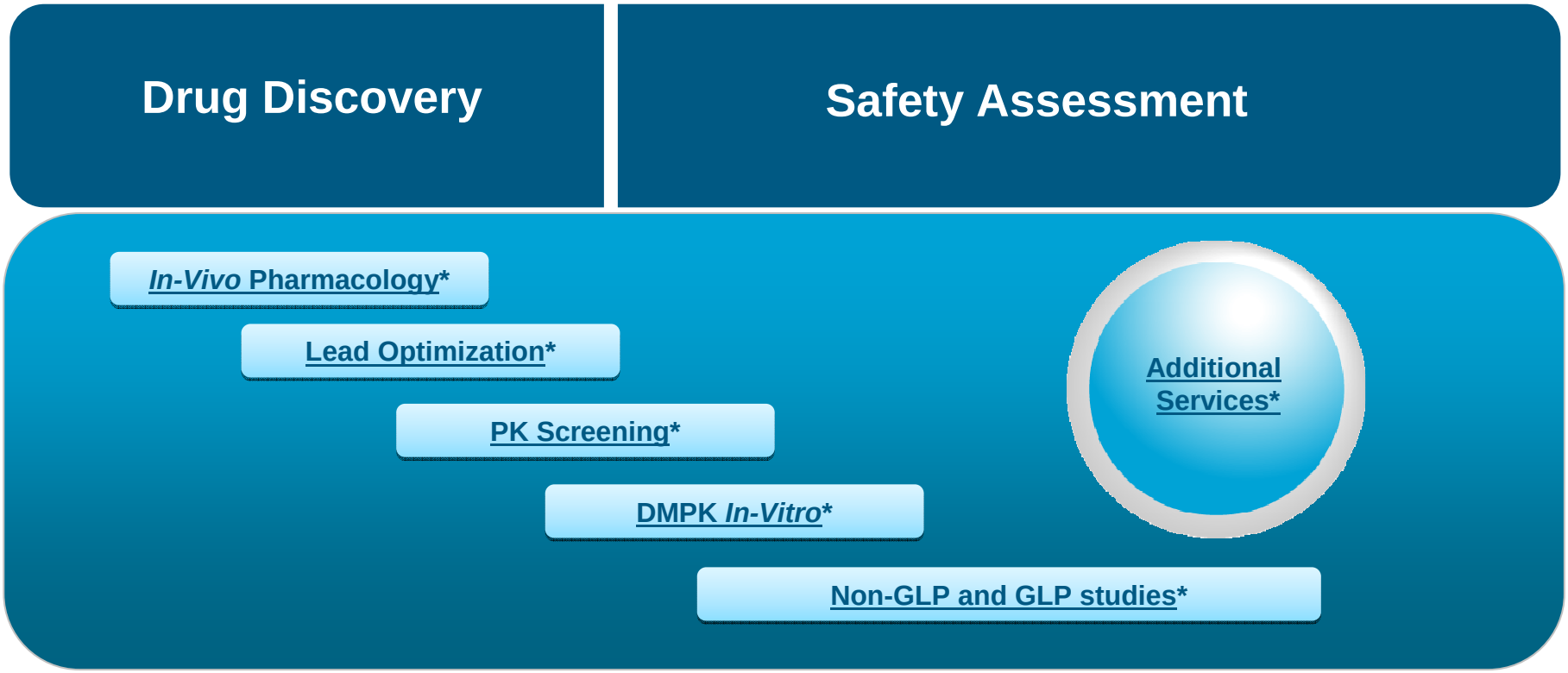
Available Capabilities In Early Development



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Preclinical R&D in Current Pharmaceutical Industry

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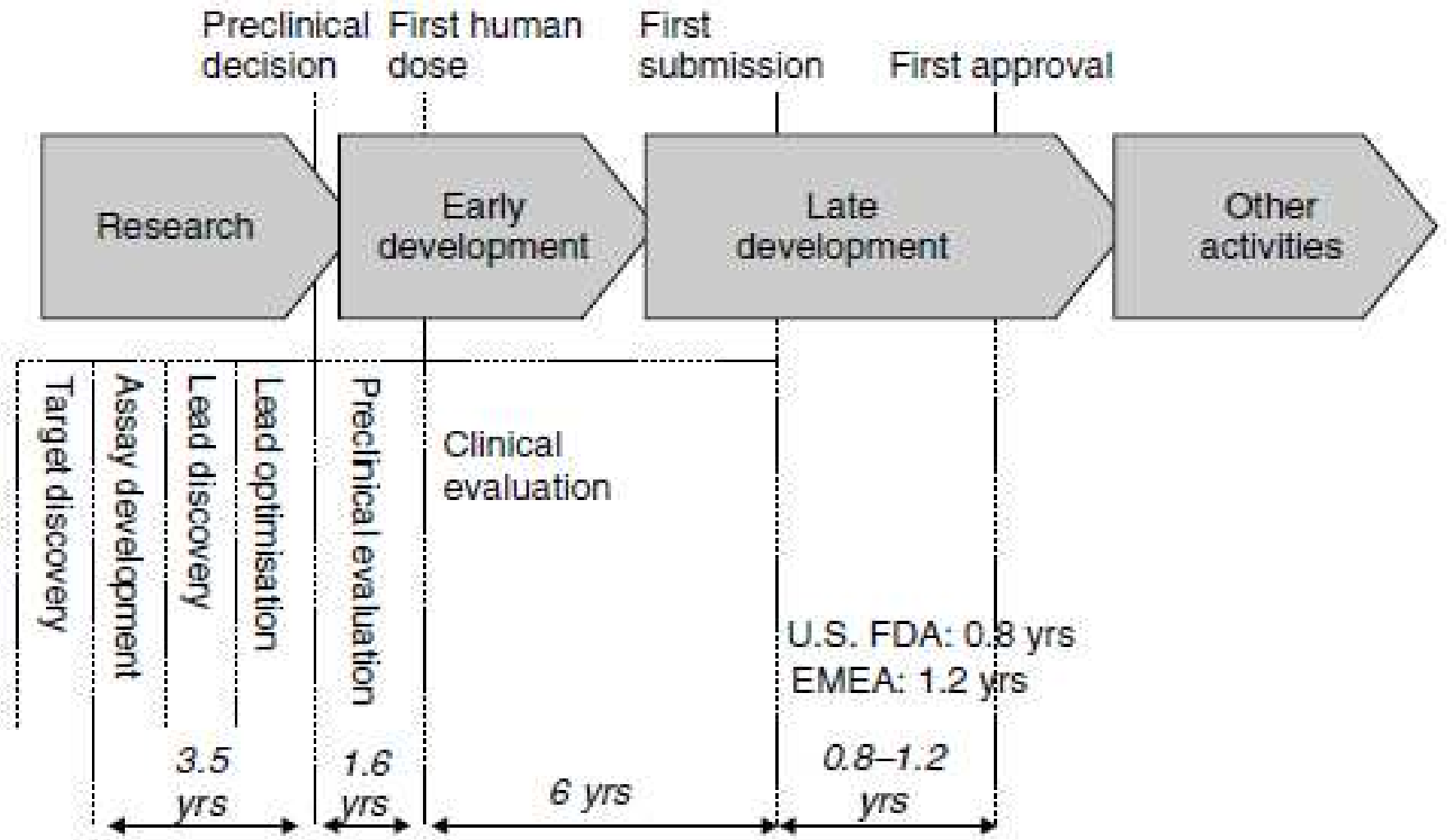
Pharmaceutical R&D Process



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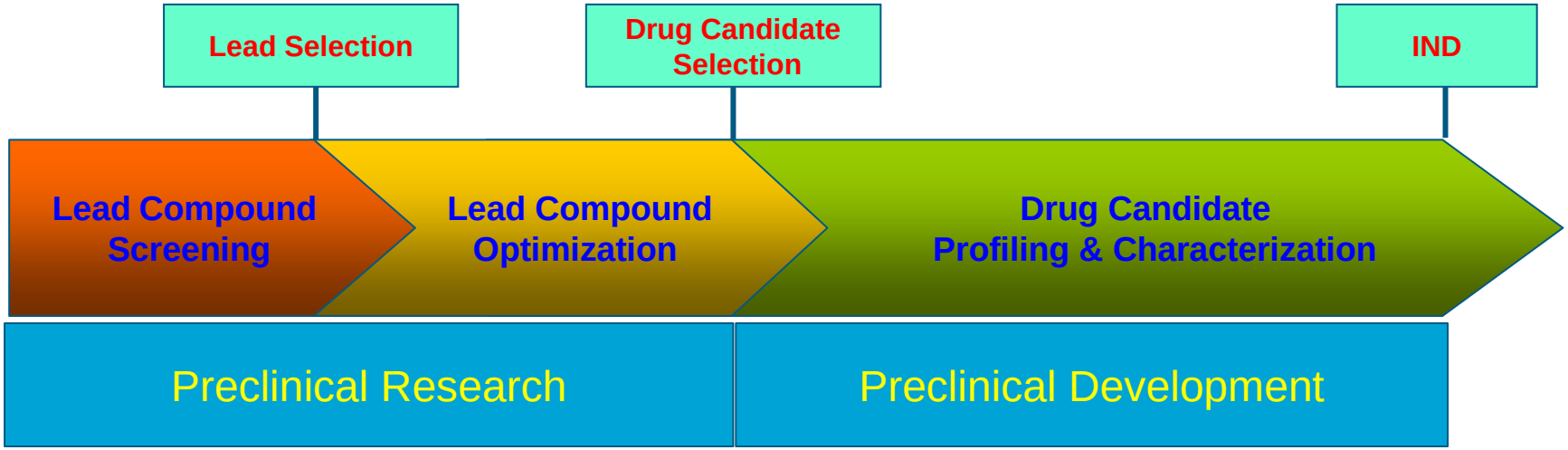
Preclinical R&D Process In Pharmaceutical R&D



- Identify the target
- Screen and identify the chemicals
- Optimize the lead chemicals to check the effectiveness against the targets
- Initiate the in vitro and in vivo PK and metabolite screening
- Check the tolerability and select the drug candidate

- Confirm the pharmacology activity in animal mode
- Characterize the ADME and PK profiles
- Perform the GLP toxicity studies and the safety assessment
- Evaluate the viability of the drug candidate
- Prepare the IND documents for regulatory filing

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Current Models of Preclinical R&D

	Biology/ Pharmacology	ADME/PK	Toxicology
Model I	In-house	In-house	Non-GLP (in-house)
Model II	In-house	In-house	Outsource
Model III	In-house	Outsource	Outsource
Model IV	Outsource	Outsource	Outsource

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Preclinical Project Management

Project Management in Drug R&D

- Pharmaceutical project management embraces the entire project procedure, from early drug discovery to the drug marketing

  - Defines the milestones and resources
  - Brings cross-functional team members together to achieve project goals and objectives
  - Determines the critical path
  - Monitors executions and implementation
  - Evaluates the results and make the recommendations for Go/Non-Go decision
  - Sets up the budget

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Project Management in Different Stages

- Preclinical Research (Discovery)
- Preclinical Development (IND enabling)
- Early Clinical Development (FIH and POC)
- Late Clinical Development (Ph III)
- Post Approval (Ph IV)

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Preclinical Research Project Management

- Goals and objectives in the preclinical research (Discovery):
  - Find the right target
  - Identify a compound series to hit the target
  - Select a suitable drug candidate from a large number of compounds screened for activity in vitro or in animal models

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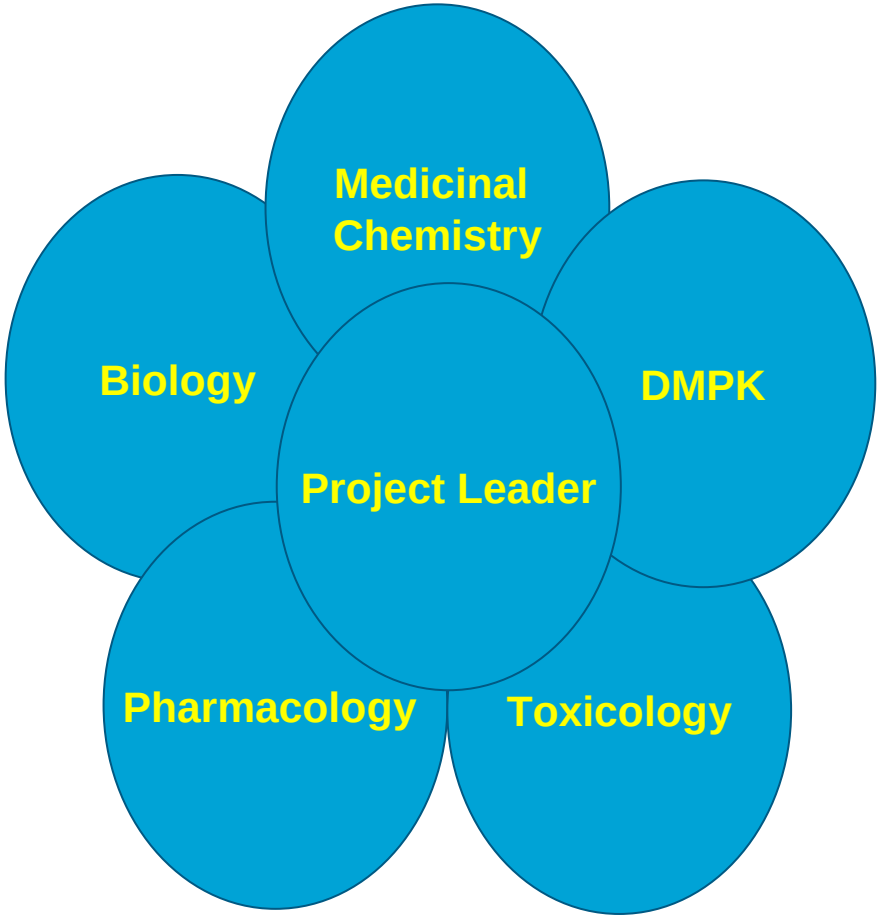
Preclinical Research Project Management



- Innovation is the key
- Scientist is the driver
- Goals and Scientist interests should be aligned
- Coordination and teamwork are critical

The key to managing innovation is to make the best use of scientists' creativity and build an innovation-fostering culture

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Preclinical Development Project Management

- Goals and objectives of preclinical development:
  - Generate adequate information to justify the safe first administration of a new drug to humans
  - Provide the safety information to ensure close monitoring of potential clinical symptoms
  - Prepare the regulatory document to obtain regulatory approval for the Phase I clinical trial

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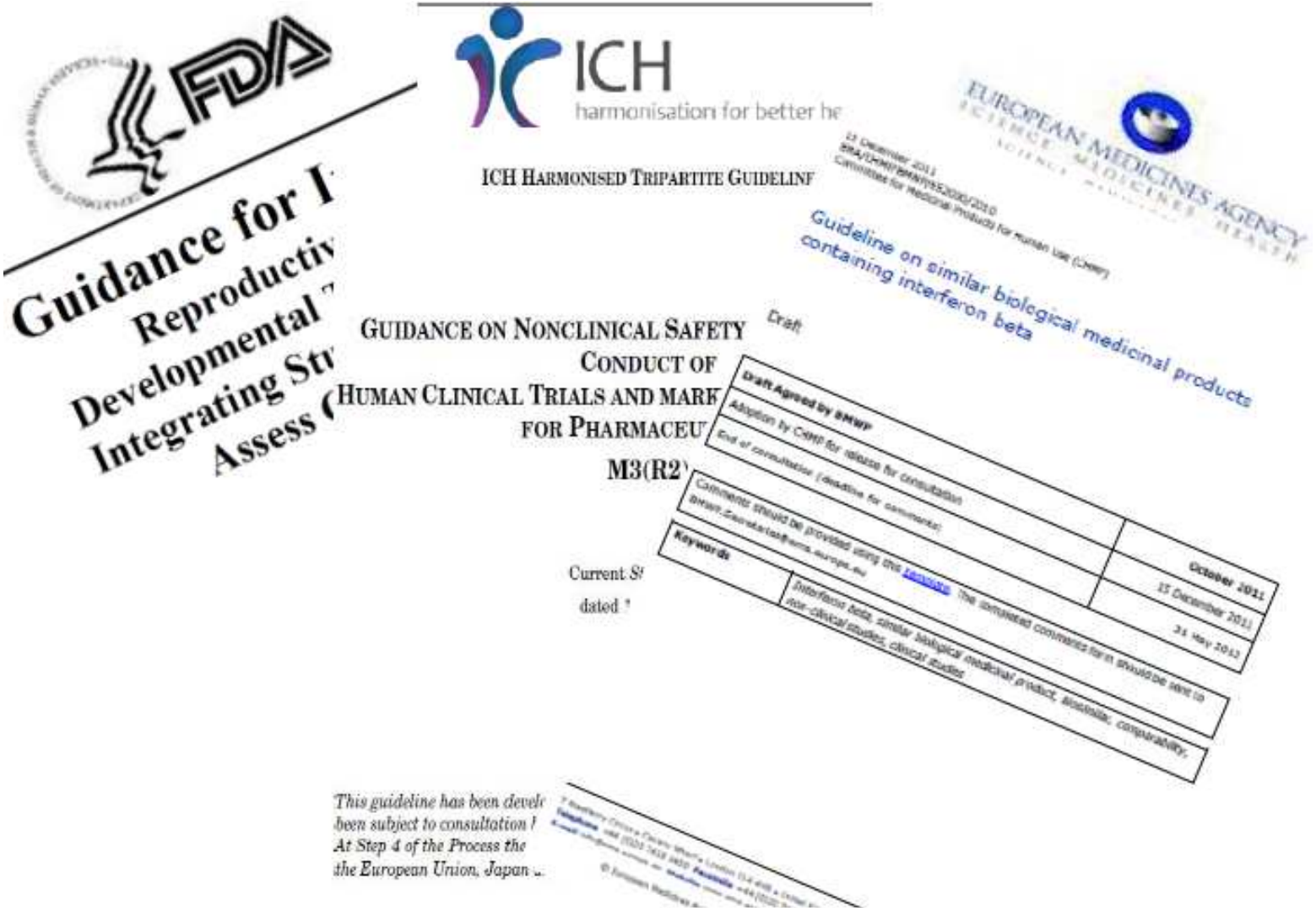
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Guideline on similar biological medicinal products
containing interferon beta
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M3(R2)
Draft
Draft Agreed by BMWP
Adoption by CHMP for release for consultation
End of consultation (deadline for comments)
October 2011
15 December 2011
31 May 2013
Keywords
Current St
dated
This guideline has been develo
been subject to consultation
At Step 4 of the Process the
the European Union, Japan

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Tasks in Preclinical Development

Toxicology	Repeat oral- or IV-dose studies in one rodent and one nonrodent species duration from 2 wks up to 3 mo Mutagenicity tests Reproduction toxicology
Safety pharmacology	Effects on cardiovascular, respiratory, gastrointestinal, renal, and CNS systems
Pharmacokinetics/metabolism	Basic kinetics and single dose ADME in 2 species; autoradiographic distribution pattern; protein binding Metabolism in vitro; toxicokinetics
Production	
API preparation and scale-up	Scale-up from laboratory to pilot scale to produce necessary amounts for phase 1 under GMP conditions; last chemical conversion step should preferably be finalized
Drug product development	Formulation with suitable stability and acceptable bioavailability for phase 1 studies

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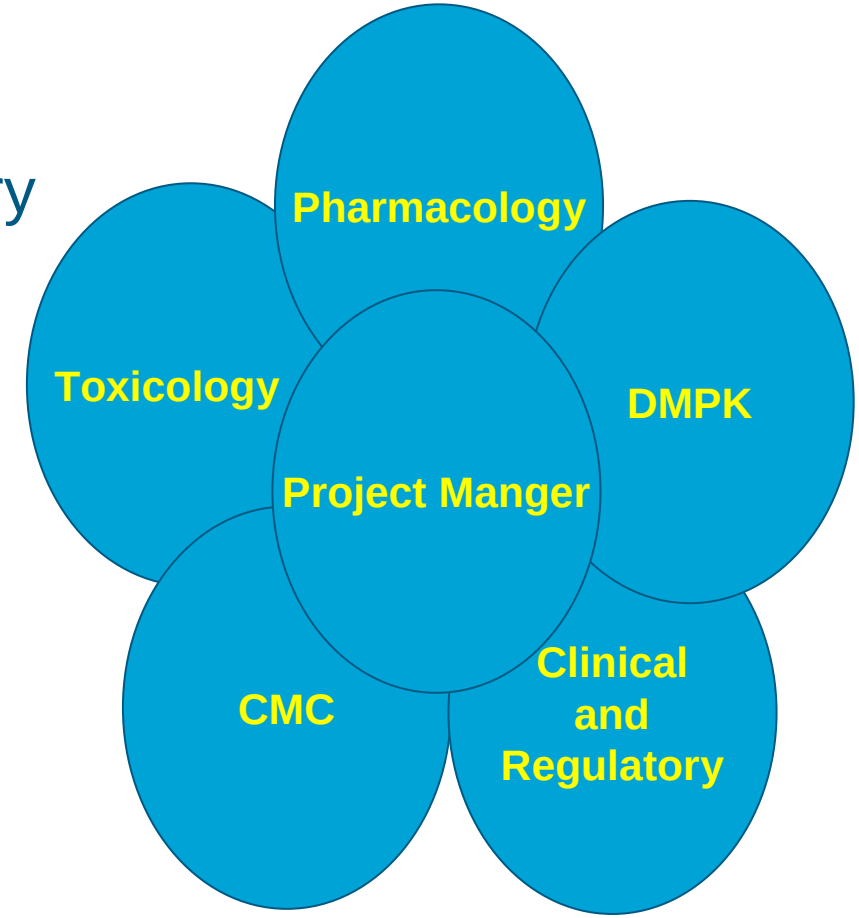
Preclinical Research Project Management

- Regulatory is the driver
  - Compliance the regulatory requirements
- Science is the base
  - Data interpretation
- Safety is the key
  - Safety margin
  - Predict human
- Timeline is the critical factor



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Case Study

Case Study 1

- Background:
  - SGX523, an orally bioavailable, potent, and selective small molecule inhibitor of c-met
  - The microsomal metabolism profile of SGX523 was similar among rats, dogs, monkeys, and humans
  - Investigational new drug-enabling studies were conducted in rats and dogs
  - Phase I clinical trial initiated, but has to be stopped due to acute renal failure at the 2nd dose level (80 mg/kg)
  - The analysis of samples from the discontinued clinical trial revealed a metabolism profile different from that of the preclinical species studied

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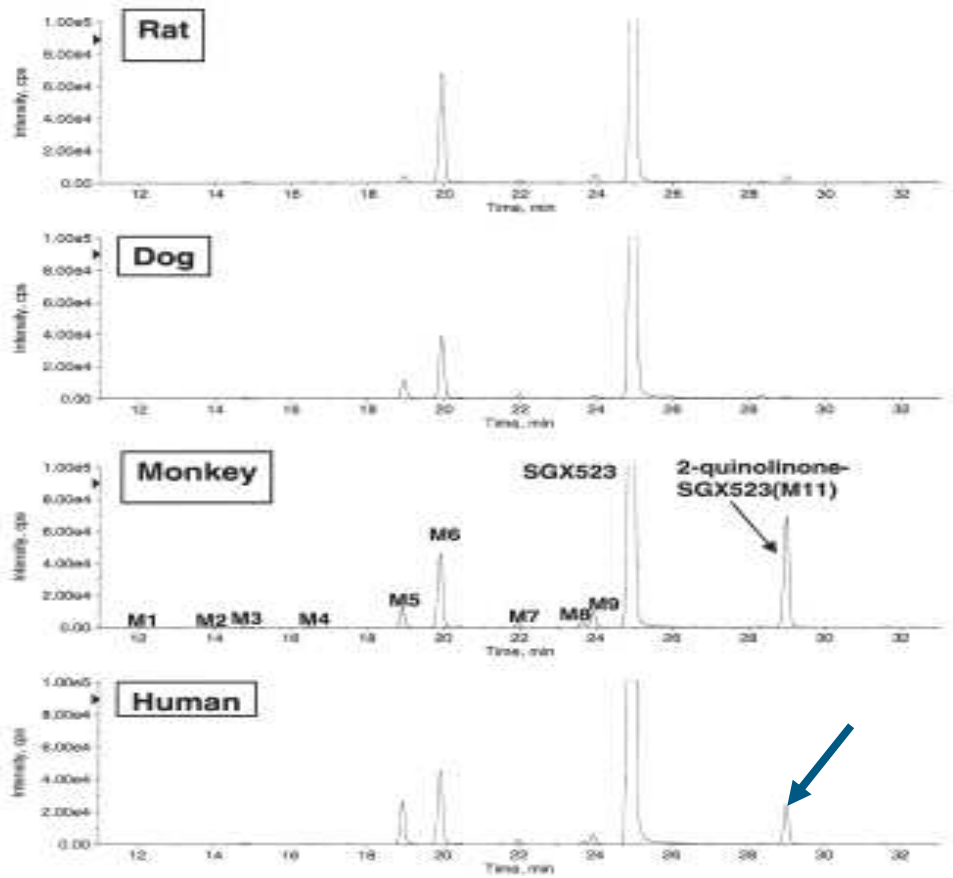
Case Study 1



- In vivo studies in monkeys showed obstructive nephropathy with intratubular crystal formation, consistent with human data
- One metabolite (M11) was not found in rats and dogs, but it presents in monkeys and humans
- M11 has very poor solubility, which is confirmed involving the drug induced renal toxicity

This study illustrates the need to conduct thorough metabolic evaluations early in drug development to select the most relevant non-clinical species for toxicological evaluation.

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Case Study 2

- Background:
  - An small molecular drug candidate for oncology
  - Very potent in pharmacology and good PK profile
  - Te NOAEL in rats and dogs are 2 mg/kg (2-fold of pharmacology dose) and 0.1 mg/kg(1.2-fold of pharmacology dose), respectively
  - All toxicology findings are reversible
  - The LD50 in dogs (0.3 mg/kg) is very close to NOAEL and only 3-fold
  - Go/Non-Go decision!

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Case Study 2

- Data interpretation:
  - Rats
  - Dogs
- Team Justification:
  - The death of the animals were mostly caused by the GI injury and stop eat. Dog GI is very sensitive compare to other species including humans. Therefore, in humans, the toxicities are expected less serious and the LD50 found in dog study may not relevant to humans.
- Recommendation:
  - Go for the IND filing and initiate the Ph I with more carefully monitoring especially GI bleeding.
- Current status of the project:
  - Ph I trial in patients has been finished. Ph II will be started soon.
  - The MTD in humans are over the therapeutic dose
  - The pharmacology responses were found some of the patients

This study illustrates the detail data interpretation is critical for Go/Non-Go decision!

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Summary

Summary

- Pharmaceutical R&D process is a long and complicate process
- Preclinical R&D is the critical stage to justify if the drug candidate can be moved into the FIH
- Project management is essential element to ensure the completion of the goals and objectives for the project
- Project manager and management team should fully understand that, in different stage of the pharmaceutical R&D, project management has different focus
- Carefully review and interpret the data and strategically thinking are critical for the recommendation to the Sr. management team for Go/Non-Go decision

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Thank You for Your Attention!

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