

STRATEGIC DRUG DEVELOPMENT: The 33,000-Foot Overview

Out of Research and into Development: From IND to NDA

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Development Program

- NCE/Biotechnology Compound
- Orphan Drug
- Approved Compound
 - New Formulation
 - New Indication
 - New Dosing Regimen



Traditional Drug Development Timelines (Old Paradigm)

- Phase 1: 12 to 18 months
- Phase 2a: 15 months
- Phase 2b: 18 months
- Phase 3: 35 months
- Registration: 12 to 18 months

- Total Cost (averaged over industry): \$467 M

Source: IBM Life Sciences Solutions



Basic Definitions

- Phase 1: Safety
- Phase 2: Efficacy (Small Groups)
- Phase 3: Safety and Efficacy (Large Groups)
- Registration: FDA Review and Approval
- Phase 4: Market Surveillance or Market Optimization



Sponsor's Role

- Full Drug Development
- Out-License Product
- Partnership with Pharma Company



Drug Registration Statistics (2007)

(Source: Center for Drug Evaluation and Research Update, US Department of Health and Human Services, Food and Drug Administration, 2007)

- Approvals
 - 76 Drugs
 - 2 Biologics
- 18 Truly New Medicines
 - 16 Drug NMEs
 - 2 Biologic NMEs
- 13 Tentative NDA Approvals
- 8 Orphan Drug Approvals
- Median Review & Approval Time: 12 months



Chemistry, Manufacturing and Controls (CM &C)

- Drug Substance
 - Synthesis
- Drug Product
 - Nonclinical and Clinical Programs
 - Stability Program
 - Packaging
- GMP Regulations



Nonclinical Pharmacology

- GLP
- Relevant Animal Species
- Exposure-Response Data



Bioanalytical Assay

- Validation
- Concentration Ranges



Toxicology

- Two (2) Species
- Minimum: Single Dose
- Program Dependent on Clinical Program



Safety Pharmacology

- Cardiac Safety Testing
 - *In vitro*
 - *In vivo*
- Hepatic Safety Testing



Safety Pharmacology

■ Biotechnology Compounds vs. Small Molecules

- Between 2003 and 2006, biologicals represented 24% and 22% of all new chemical entities approved by the US and EU regulatory authorities, respectively.
- Sales of biotechnology products in the United States showed an annual growth rate of 20% between 2001 and 2006 compared with 6% to 8% in the pharmaceutical market.



Safety Pharmacology

- Biotechnology Compounds vs. Small Molecules
- Early thinking: Monoclonal Antibodies do not need any cardiovascular safety pharmacology.....But.....



Safety Pharmacology: Published Data

From Expert Review of Anticancer Therapy

Cardiotoxicity Associated With the Use of Trastuzumab in Breast Cancer Patients

Patrick J. Perik, MD, PhD; Maarten Alexander de Korte; Dirk J. van Veldhuisen, MD, PhD; Jourik A. Gietema, MD, PhD; Dirk T. Sleijfer, MD, PhD; Elisabeth G.E. de Vries, MD, PhD

Authors and Disclosures

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Safety Pharmacology: Published Data

- The risk of cardiotoxicity with trastuzumab has been reported to be 4% with monotherapy and 27% when administered in combination with an anthracycline and cyclophosphamide.
- Signs and symptoms are similar to those observed in patients who develop anthracycline-induced cardiomyopathy and include tachycardia, palpitations, and exertional dyspnea, which may progress to congestive heart failure.
- The pathogenesis and histologic changes responsible for trastuzumab-associated cardiotoxicity currently are under investigation.

(Keefe DL. Trastuzumab-associated cardiotoxicity. *Cancer*. 2002 Oct 1;95(7):1592-600.)



Safety Pharmacology: Published Data

■ Biotechnology Compounds vs. Small Molecules First-in-Man-Studies



The NEW ENGLAND
JOURNAL of MEDICINE
Volume 355:1018-1028 September 7, 2006 Number 10

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P., Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A., Michael D. Brunner, F.R.C.A., and Nicki Panoskaltzis, M.D., Ph.D.

- The predictability of preclinical data to humans is limited for biologicals due to the species-specific action and immunogenic properties in animals.
- Occurrence of serious adverse events in healthy volunteers participating in a Phase 1 clinical study of TeGenero's TGN1412, a CD28 agonist monoclonal antibody.
- Cytokine storm following infusion had not been observed in the preclinical studies of TGN1412.

PK/ADME/Metabolism

- *In Vitro*
- *In Vivo*
- CYP450 Isozymes



IND Submission

- Pre-IND Meeting (US) vs. Ex-US IND
- IND Package for Ex-US Authorities
- 1st-Time-In-Man Study
 - NCE/Biotechnology Compound
 - Approved Compound
 - New Formulation
 - New Indication
 - New Dosing Regimen



1st-Time-in-Man Study

- SAD and MAD Studies (Cardiac Safety???)
- Metabolism ¹⁴-C
- Patients vs. Normal Volunteers
- Safety
- PK and/or PD/Efficacy Data



For US FDA Submission with Ex-US Clinical Data

- Pre-IND meeting
- File US IND
- Prepare Phase 1b or 2a Program



Phase 2 Clinical Program

- Efficacy in Labeled Patient Population
- PK/PD in Patients
- PK/Safety Data in Patients
- Proof of Concept (POC or POP Studies)



End-of-Phase 2 Meeting

- Prepare for Phase 3 Program
- Get FDA Buy-In on Efficacy Parameters and Statistical Analyses
- Get FDA Buy-In on Supportive Phase 1/2 Clinical Trials



Additional Critical Development Functions

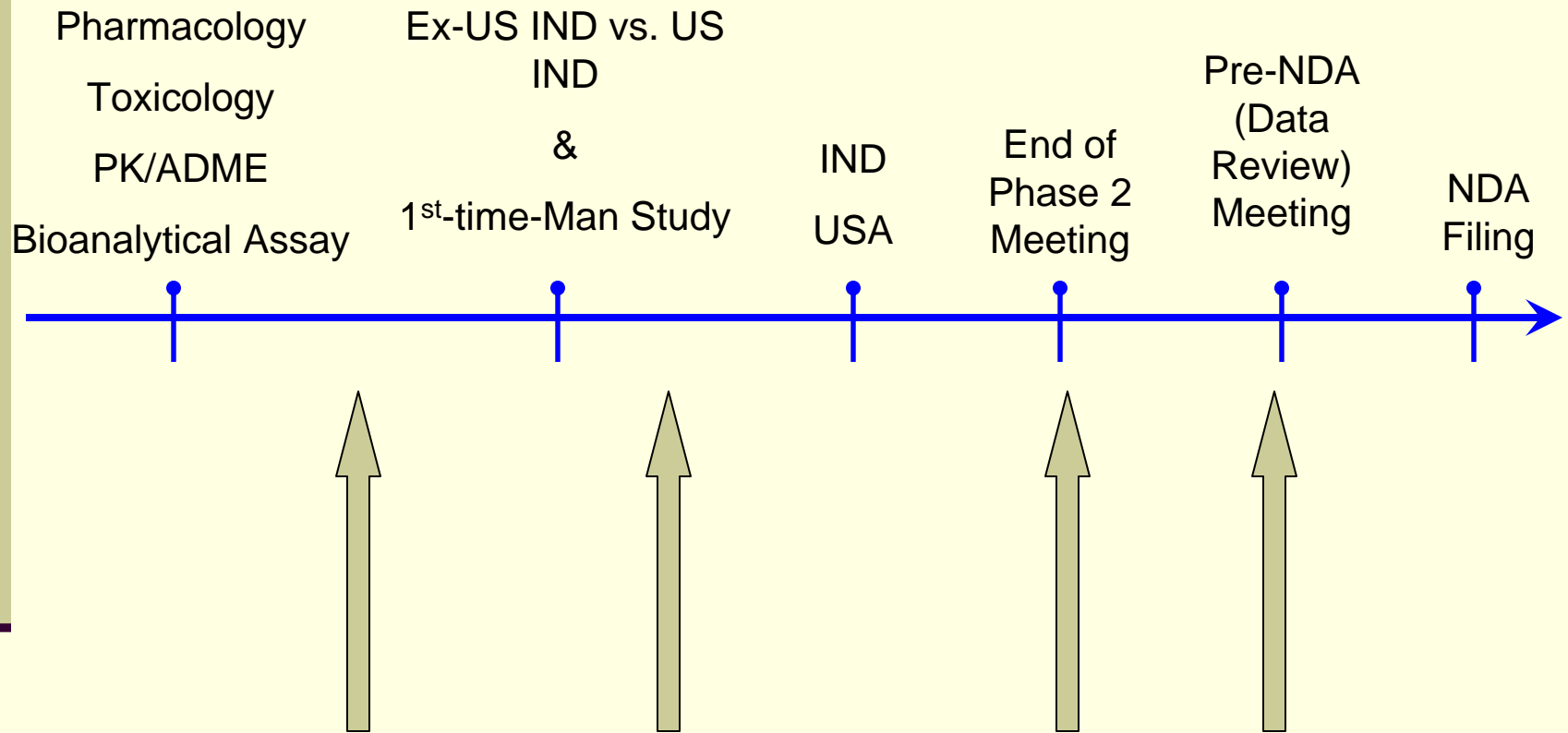
- Project Management
- Regulatory Affairs
- Pharmacovigilance
- Medical/Scientific Writing
- QA/QC
- Pharmacokinetics
- Statistics
- Upscale Manufacturing
- Marketing Strategy

NDA

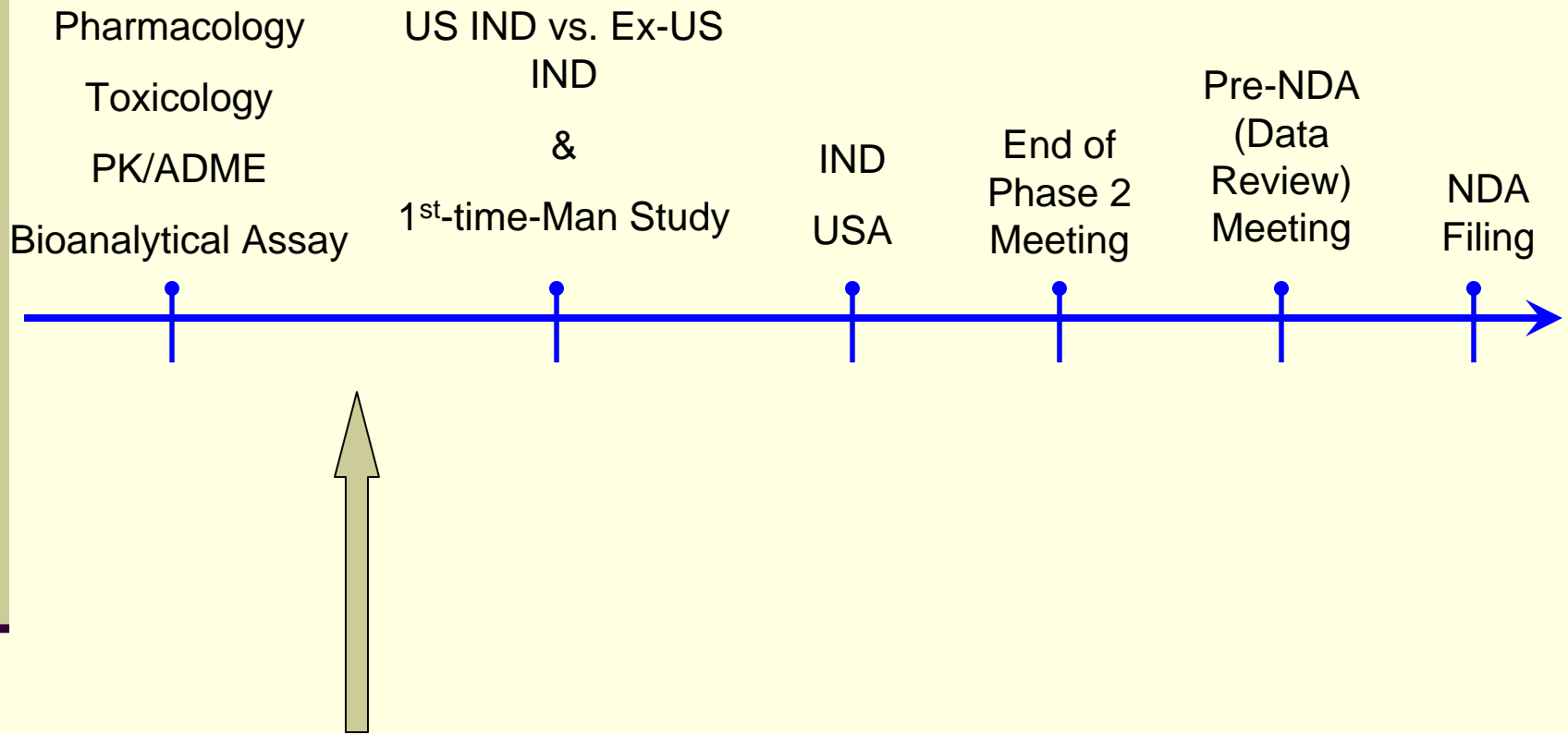
- Final Efficacy/Safety
- Supportive Clinical Pharmacology Package
- Adequate Toxicology and Nonclinical Package
- CMC Package
- Package Insert



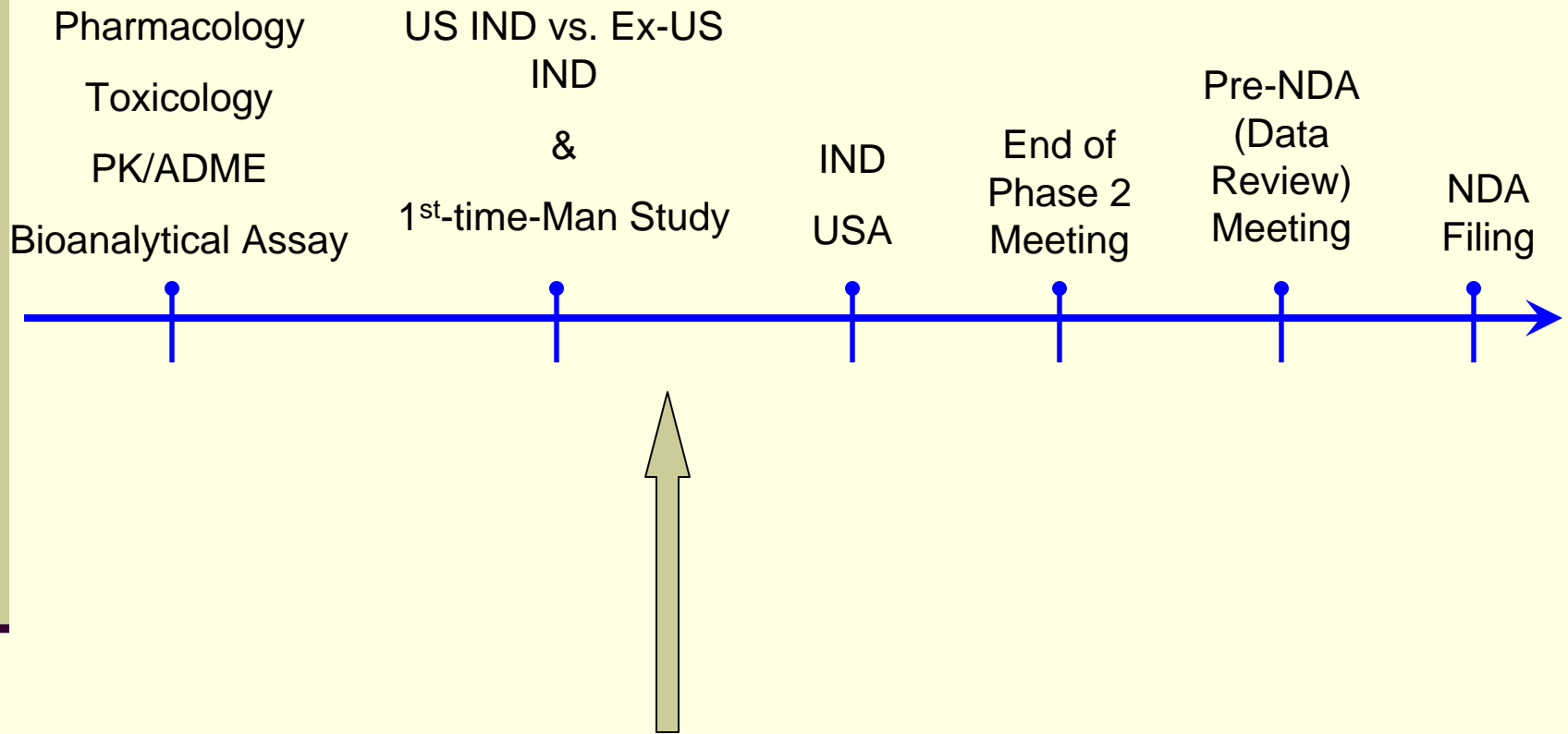
When to Meet with FDA



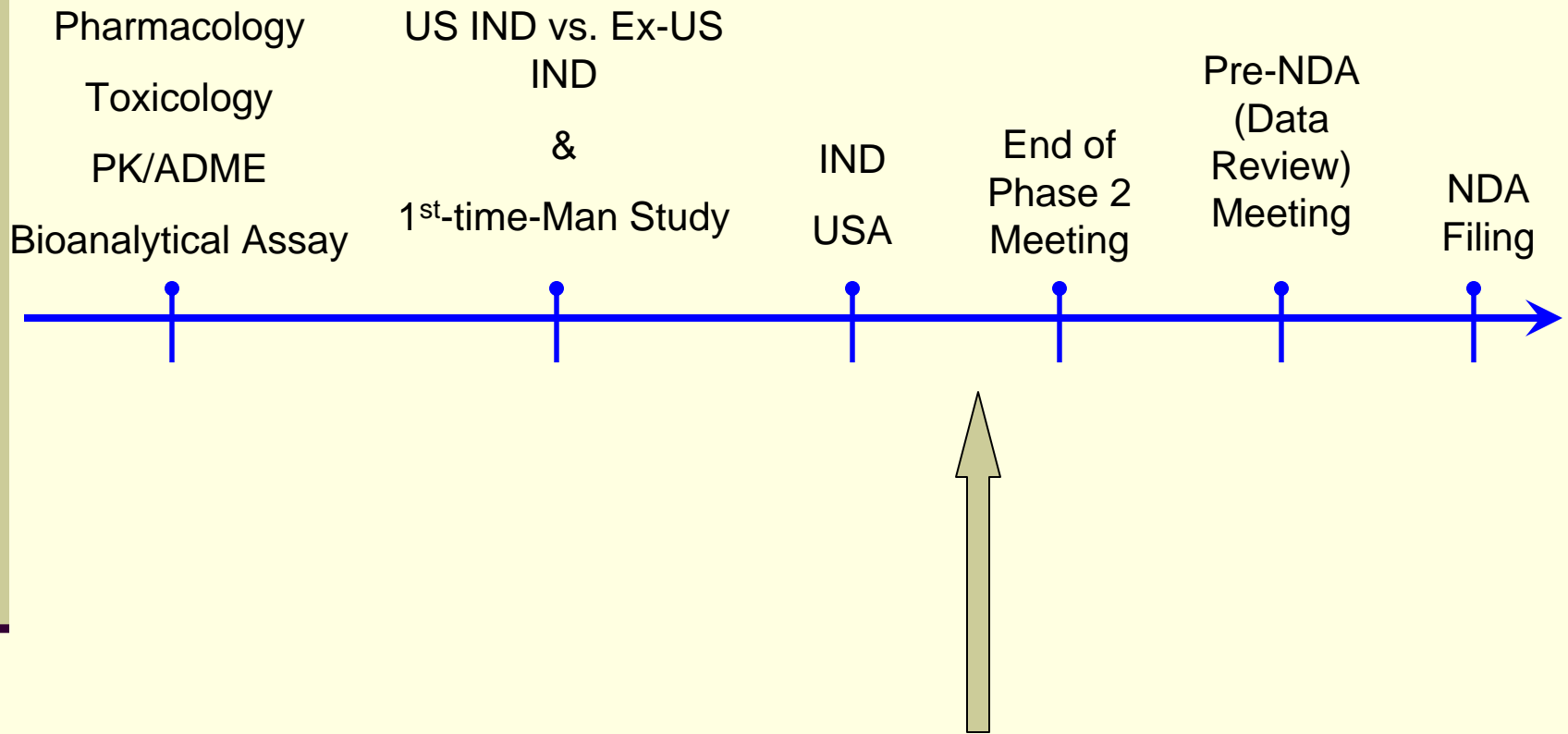
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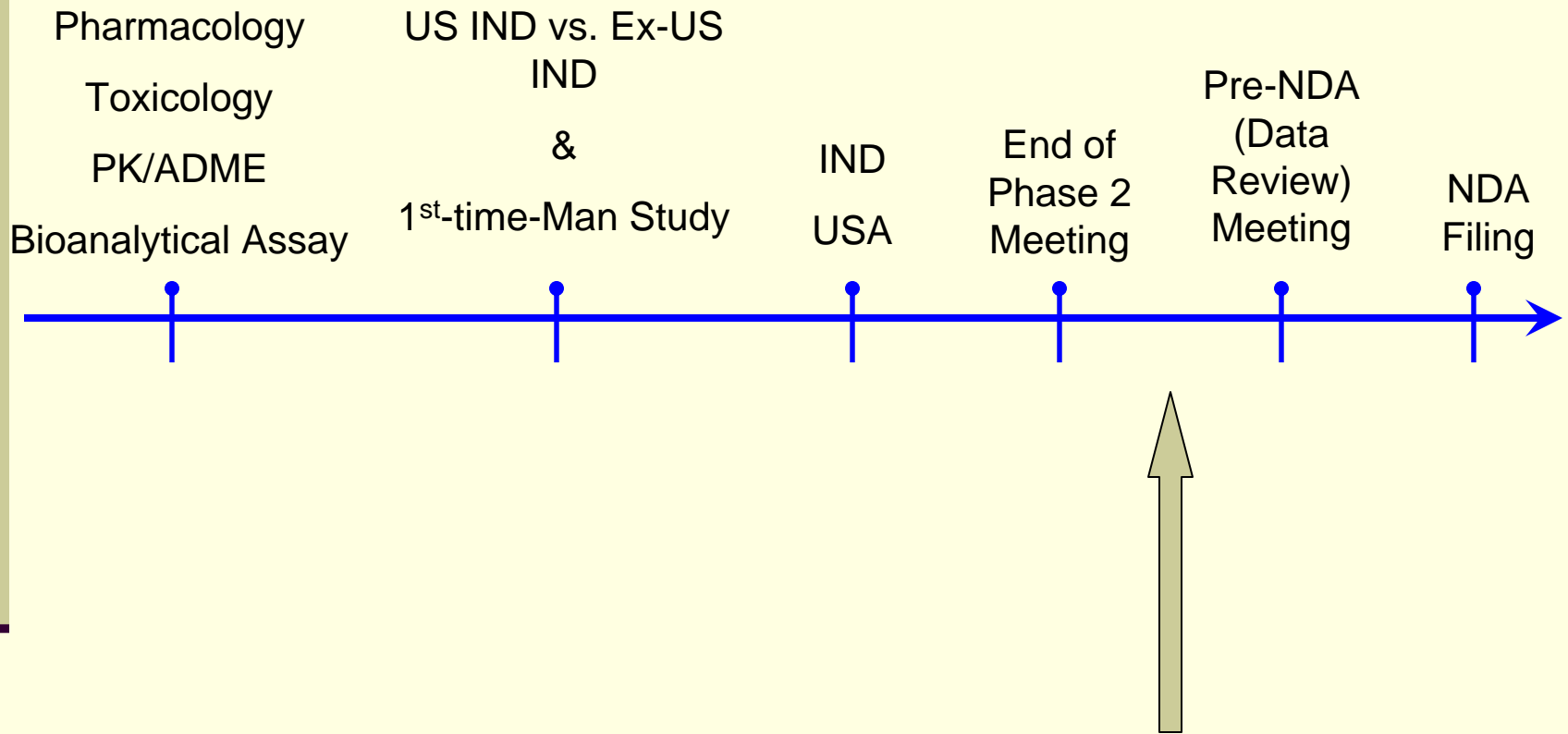
Partner/Out-License Options



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Thank You!

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