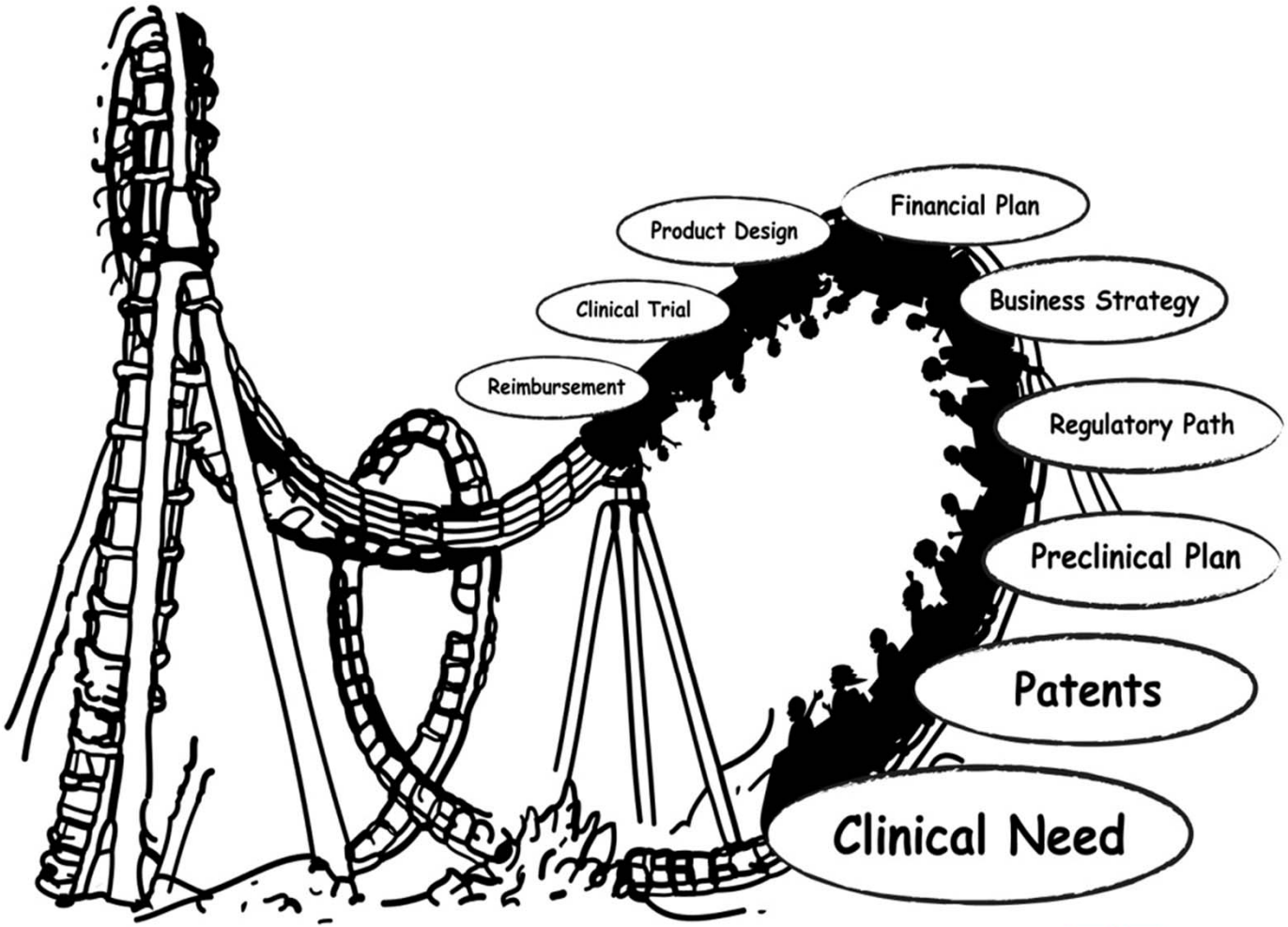
Translational Medicine Symposium 2013:
The Roller Coaster Ride to the Clinic



Meet the
Entrepreneurial Faculty Scholars

TECHNOLOGY
VENTURE DEVELOPMENT
THE UNIVERSITY OF UTAH

Translational Medicine Symposium 2013

Regulatory Pathways

Bench to Business to Bedside:
The Roller Coaster Ride to the Clinic

Introductions

- Moderator:
  - Ronald Weiss (ARUP, U of Utah)

- Panelists:
  - Greg Critchfield (Sera Prognostics)
  - Peter Knauer (LSK BioPartners, BioUtah)

FDA Regulatory Framework

Drugs, Biologics, IVDs and Medical Devices

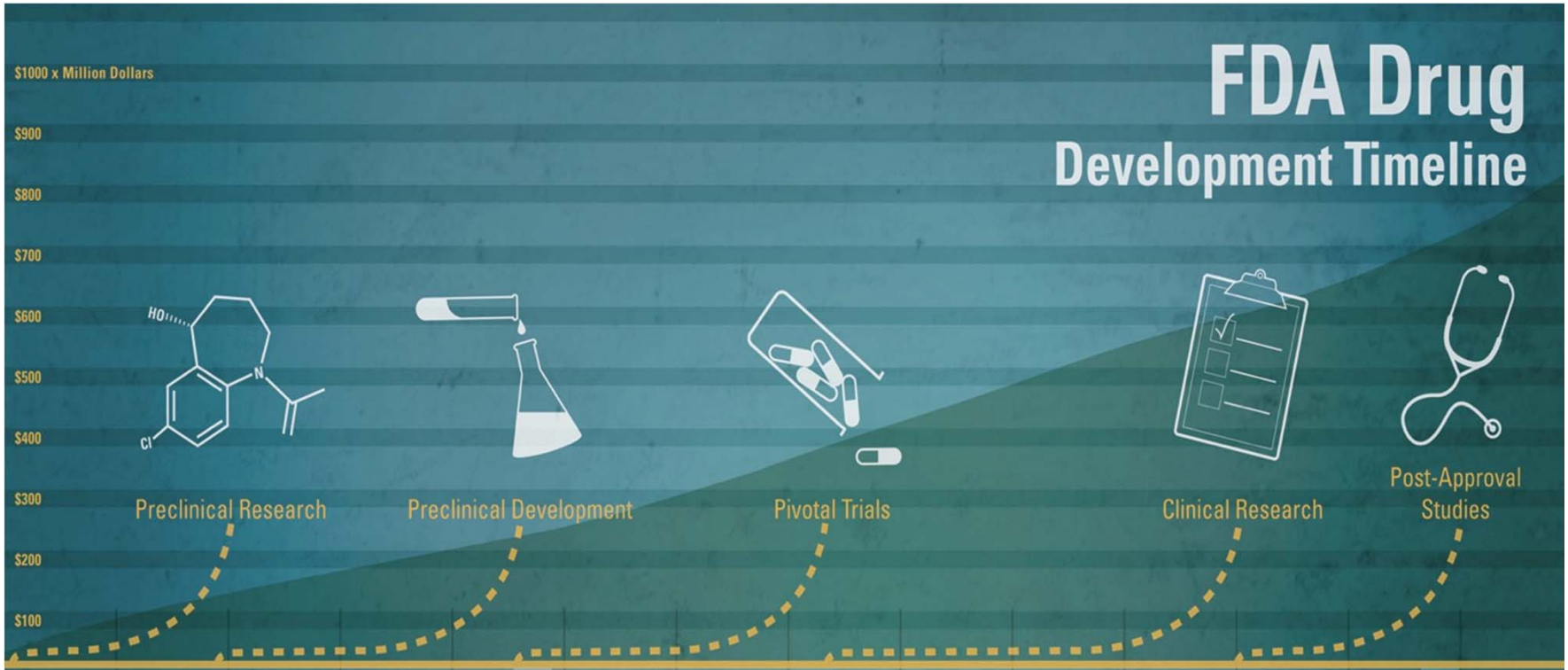
- Center for Biologics Evaluation and Research (CBER)
  - Vaccines, blood products, devices/tests to safeguard the blood supply, biologics/biologic therapies
- Center for Drug Evaluation and Research (CDER)
  - Small Molecule, NCEs, Prescription and OTC drugs
  - Combination Drug/Devices (drug part)
- Center for Devices and Radiologic Health (CDRH)
  - Medical devices (Office of Device Evaluation)
  - IVDs and Laboratory-Developed Tests (Office of In-Vitro Diagnostics)
  - Combination Drug/Devices (device part)

Drugs and Biologics

Peter Knauer

How did this get to you?

FDA Drug Development Timeline



Average Development time:
13 Years
Average cost:
$500 Million - $1 Billion

Phases of a Clinical Trial

Phase I
The drug is tested for safety, dosage and side effects in a small number of healthy volunteers.

Phase II
The drug is tested for safety and effectiveness in a small number of volunteers.

Phase III
The new drug is tested in a large number of volunteers to confirm effectiveness, monitor side effects and compare results with current treatments.

The data collected during the clinical trial is analyzed and then submitted to the FDA for regulatory review, which can take 1-3 years. Once it is approved, the new drug can be prescribed by physicians.

Phase IV
These studies are done after the drug has been approved and is in use. Additional information about risks, benefits and optimal use is collected and analyzed.

PKD FOUNDATION
www.pkdcure.org

Applications

- **IND** – Investigational New Drug
  - Supports the **safety** of a drug in order to move into the clinical
    - Incorporates preclinical research, historical clinical data and information on the chemical compound, manufacturing and controls (CMC)
- **NDA** – New Drug Application
  - Submission application to market a drug for a specific indication based on pivotal Phase 3 trials
    - Includes most of the IND
    - Included are market scale manufacturing, CMC, stability, packaging, pharmacokinetics, carcinogenicity and toxicity studies
    - Most important – Risk/ Benefit profile
    - Demonstrate the **efficacy** & **safety** compared to SOC

Purpose of the NDA?

- Allows the company to market and sell a drug for the approved indication
- **NDA** -Needs to demonstrate a comparable or superior risk/ benefit profile
  - Demonstrate that your compound will offer or fulfill a need
    - Novel chemical entity (NCE) must either be non inferior OR superior to a current Standard of Care
    - Offer a treatment where no current treatment exists
    - No significant safety harm/risk to patient

END GOAL!!!!

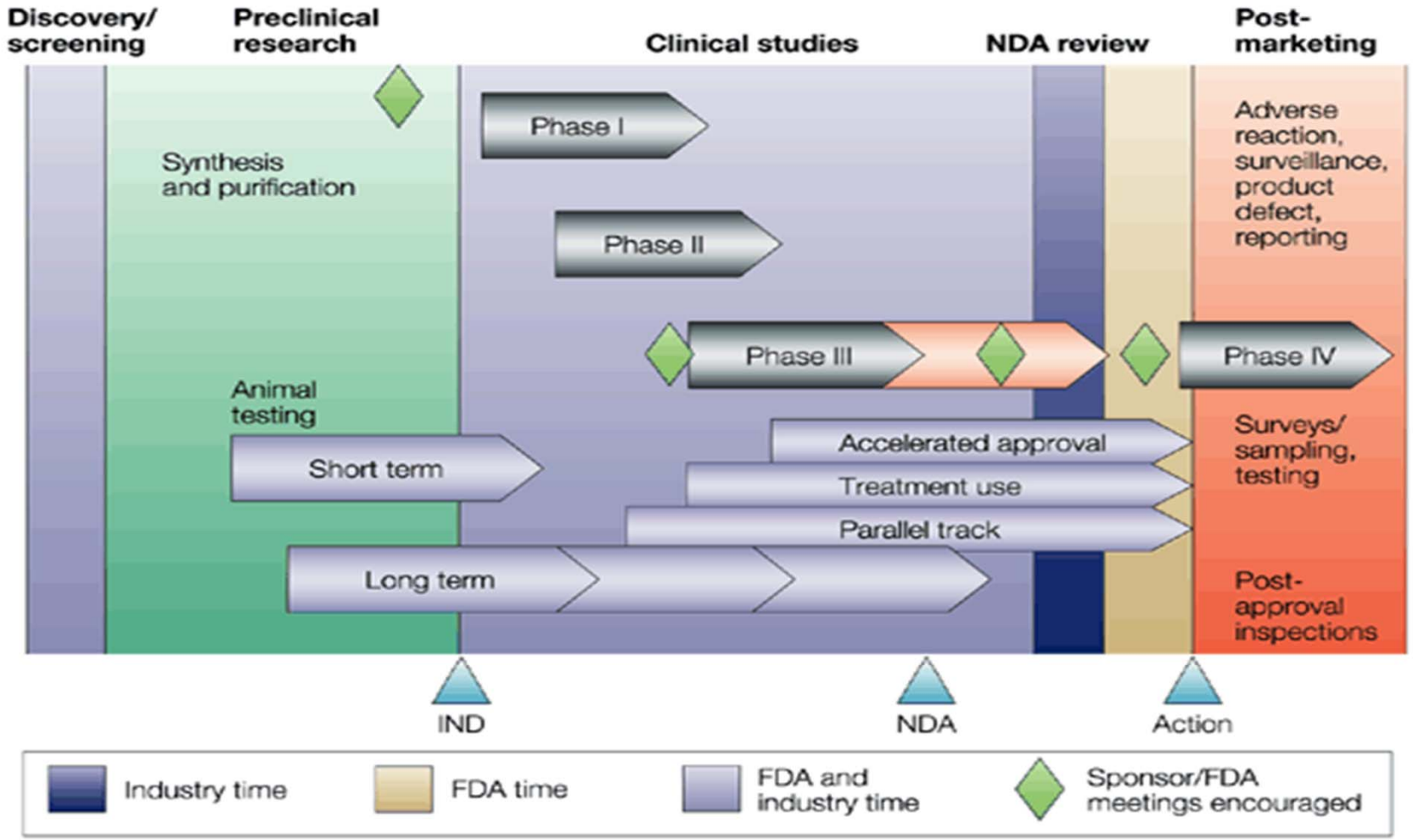
Common Technical Document (CTD)

- Module 1: regional administrative info
- Module 2: Quality Summary, non-Clinical overview, Clinical overview
- Module 3: Quality (CMC)
- Module 4: non-Clinical study reports
- Module 5: Clinical study reports

Interactions with FDA

- Pre IND meeting – propose your preclinical safety toxicology studies, your manufacturing plans and your clinical trial development
  - FIH (first in human) study
  - Single Ascending Dose vs. Multiple Ascending Dose
  - ASK questions
- End of Phase 2 meeting
  - Completed Phase 2b – confirmed your endpoints and your safety/ efficacy
  - Ready to SCALE up

Clinical Studies



Nature Reviews | Drug Discovery

Clinical Trials

- Phase 1 – dose ranging in healthy individuals
  - Access safety & dose in 20-80 normal subjects
    - Open label
    - Systemic and tissue Pharmacokinetics (PK)
- Phase 2a – dose ranging or dose escalation in diseased population of 50 – 100 pts
  - Primary endpoint – assess safety & tolerability, look for efficacy signal as a secondary endpoint
  - Proof of concept study
    - Randomized double (blind) masked prospective study

Clinical Trials

- Phase 2b – larger and longer study (100-300 pts)
  - Statistically powered for an efficacy signal
  - Informs your Phase 3 study design

- Phase 3 –Studies required for filing
  - two large parallel global, randomized control trial (RCT)
  - Primary endpoint - Efficacy in the patients for whom this drug/device will be indicated for
  - Secondary endpoints - efficacy and safety
  - 600 – 900 pts; Millions

Clinical Trials

- Phase 3 – con't
  - more representative of real world (relaxed inclusion criteria)
  - Chronic conditions very often have an efficacy endpoint with a follow on safety extension
- Phase 4 – long term studies, open label, epidemiology, observational studies
  - Evaluate long term safety once a drug is marketed
  - Capture information on a pt population and or for a potential safety issue post NDA approval
  - Very often requested by the regulatory agencies and or country offices (Europe)

Is it suitable for OTC???

- The intended condition is:
  - Self-diagnosable by the public
  - Self-treatable by the public
- The intended drug product must have:
  - Sufficient safety exposures (I.e. marketed to material extent and time)
  - Sufficient safety margin
  - Low patient safety harm/risk

General Conditions for OTC

- Manufactured per cGMP
- Manufacturing establishment is registered and drug product is listed
- Labeled per general guidelines and the OTC drug monograph
- Advertised per label conditions
- Contains suitable inactive ingredients

ANDA (general)

- CDER, Office of Generic Drugs
- RLD-reference listed drug
- Drug products must be same as the RLD
  - Route, dosage form, strength
  - Conditions of use (barring exclusivity)
- Suitability petition

ANDA (data requirements)

- Bioequivalence study
  - Must demonstrate BE to RLD
  - BE study is exempt from IND requirements (under certain conditions 21CFR320.21)
- CMC
  - Complete package (1 batch-pilot scale, $\geq$ 3 mos stability)
  - Comparable dissolution data versus RLD
- Labeling (same as RLD)

In-Vitro Diagnostics & Medical Devices

Ronald Weiss

Medical Devices, IVDs and LDTs

- Regulatory Pathways
  - Risk Classification (I, II and III)
    - Based upon "intended use" claims
  - Exempt from FDA Review
    - Class I devices (General Controls only)
    - Some Class II devices
  - Premarket Notification [510(k)]
    - Class I and II
  - Premarket Approval (PMA)
    - New devices and IVDs
  - Companion Diagnostics
  - Laboratory-Developed Tests
    - Clinical Laboratory Improvement Amendments (CLIA)

Premarket Notification

- 510(k) clearance submissions
  - http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/default.htm
  - For manufacturers seeking new device approval and for FDA to classify that device
    - At least 90 days prior to commercialization
  - ***Substantial Equivalence*** threshold
    - ***Predicate device*** specification

      Same intended use, same technical characteristics or data that demonstrates safety and effectiveness.
  - Labeling, Comparative Information (clinical data sets), Indication for Use, etc.
- De novo 510(k) clearance
  - No predicate device, but no increased risk demonstrated by the manufacturer

Premarket Notification (PMA)

- No substantial equivalence found
- Class III devices
- Investigational Device Exemption (IDE)
  - Pre-clinical studies, clinical trials protocol approvals
- "Safe and effectiveness" demonstration
  - Non-clinical and clinical technical data, device description, intended use claims, manufacturing data, labeling
- http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm
- Humanitarian Use Devices (HUDs)
  - Very low incidence diseases (4000 individual per year or less)
  - PMA, exempt from effectiveness requirement

Companion Diagnostics

- Draft Guidance published July 14, 2011
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf
  - Clearance of an IVD companion diagnostic and therapeutic product
    - Drug usage depends upon use of a diagnostic to meet labeled safety and effectiveness claims
    - Likely Class III device
  - Possible premarket regulatory pathways for each
    - Contemporaneous (preferred); separately
  - Drug labeling identifies an FDA approved/cleared IVD, rather than a specific manufacturer's IVD
  - Example: Roche Zelboraf for melanoma; BRAFV600E mutation

Laboratory-Developed Tests

- Per FDA: Clinical diagnostic test developed by a CLIA-certified clinical laboratory
  - "Non-commercial"
  - Low volume
  - Well-established methods
  - Performed by high complexity laboratories
- FDA's view = LDTs are medical devices
  - Use "enforcement discretion
- Laboratory view = LDTs are medical services

Steps to Market

1. Classify the IVD/medical device
2. Determine the path to clearance or approval
3. Obtain approval to market

- Time to market and cost:
  - 510(k) clearance = months to few years ($$$)
  - PMA = several years ($$$$$)
  - LDTs = months to few years ($$)

Q & A Session