Making an Impact: Pharmaceutical Development, from Discovery to Market

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PRESENTATION OUTLINE

- Introduction to Target Product Profile (TPP)
- Preclinical/Toxicology Development
- Regulations/ Clinical Development

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WHO AM I?

- BSc. Pharmacy; MBA

- +30 years of human health technology commercialization,
- Pharma – Regulatory, Product/Franchise Management, Reimbursement
- Capital Markets – Investment analysis / Valuations, fundraising.
- Consultant – Business Development, Executive roles, Board member
- e@UBC L.Sc. EIR

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e@UBC Venture Journeymap

Ideas and innovation of all kinds

Faculty | Students
Alumni | Staff

Courses
e101
Tech entrepreneurship
Masters in Engineering Leadership
New Venture Design

Groups
AMS
Grad Student Society

Hackathons
Tech Meetups
Startup Weekends

UBC On-Campus Resources
ULO
Research Offices

1 Ideation
Building a business model hypothesis

WAYS to ENGAGE
- Open Office
- Workshop
- Lunch & Learn
- Events

2 Business Model Validation
Validating product-market fit

WAYS to ENGAGE
- Open Office
- Lean Launch Pad

3 Company Building
Building the business with hands-on entrepreneurs-in-residence

WAYS to ENGAGE
- Venture Builder Program
- CDL West | Massively Scalable
- HATCH | Tech/product-based ventures

4 Ready to Scale
Business is operational

WAYS to ENGAGE
- e@UBC Impact Fund
- e@UBC Seed Fund
- HATCH

» **e@UBC programs available at all stages:**
startup space, mentor network, professional advisors, workshops and events, and much more

Checkpoints

STAGE 1	STAGE 2	STAGE 3	STAGE 4
Business Model Hypothesis	Committed Team Validated Market	Proven high potential Growing market size	Demonstrated market traction Complete team executing on business model

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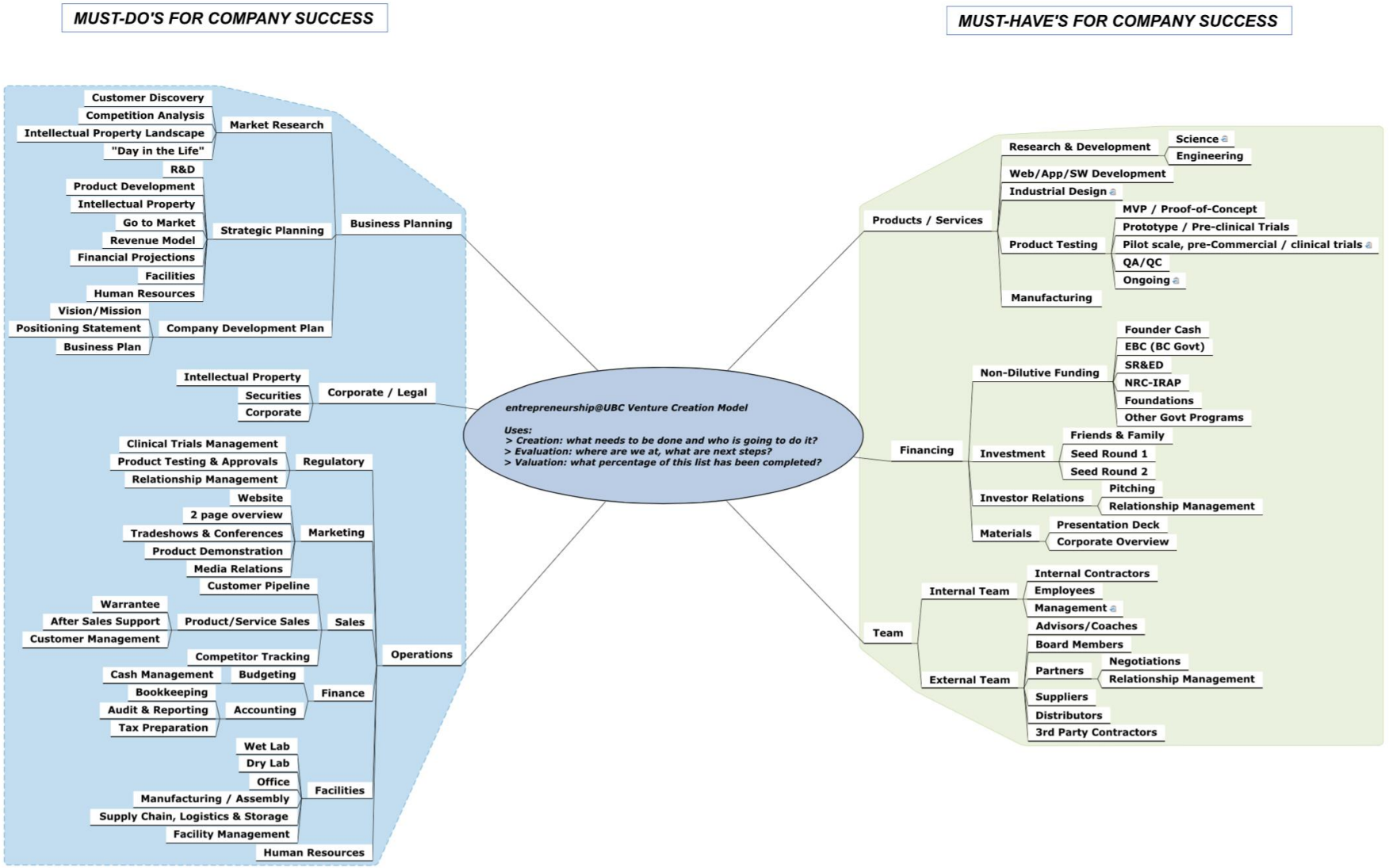
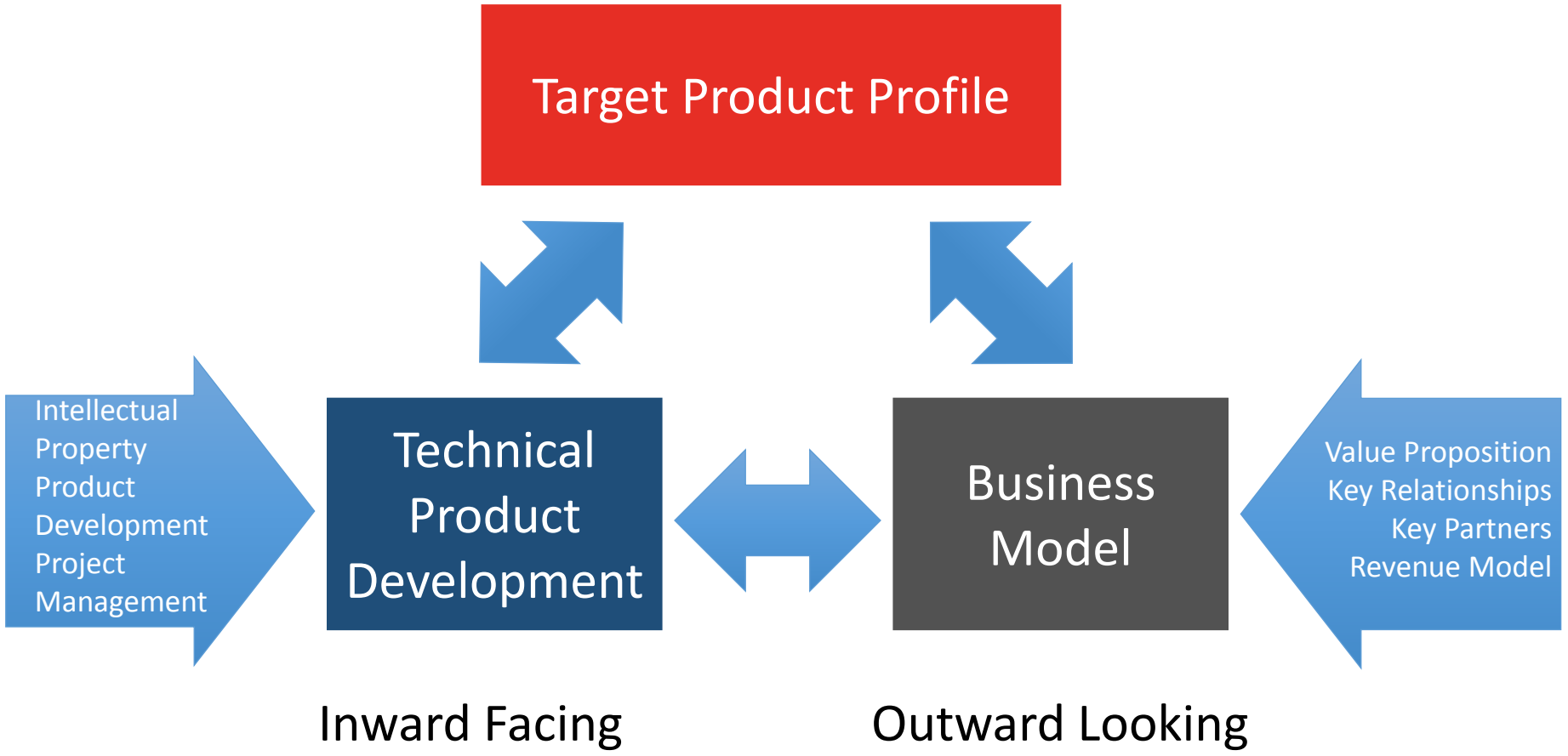
BUILDING A FUNDABLE VENTURE



Development Milestones:

- Financing
- Product Sales
- Partnering
- Other

Parallel Process in Drug Development



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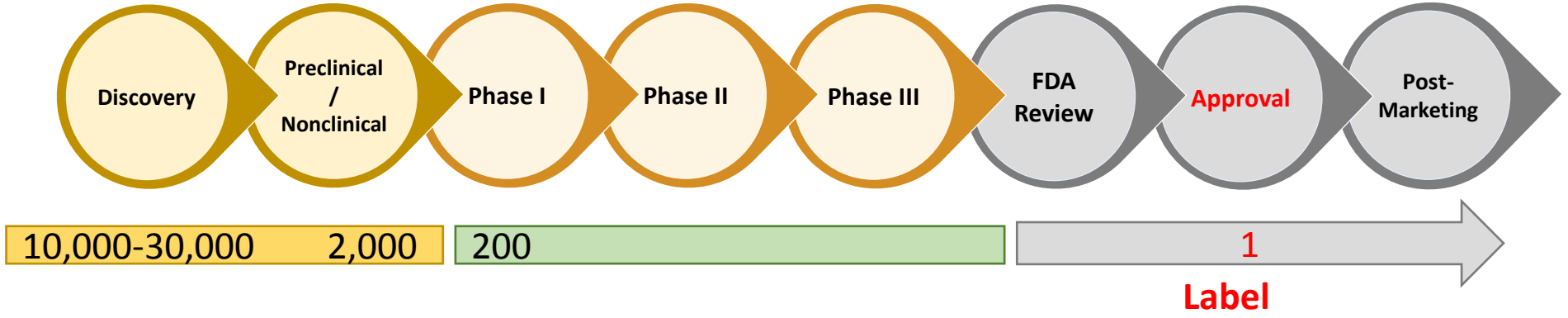
OVERVIEW OF DRUG DISCOVERY AND DEVELOPMENT



Label

1. **Indications and Usage**
2. **Dosage and Administration**
3. **Dosage Forms and Strengths**
4. Contraindications
5. Warnings and Precautions
6. **Adverse Reactions**
7. **Drug Interactions**
8. Use in Specific Populations
9. Drug Abuse and Dependence
10. Overdosage
11. Description
12. **Clinical pharmacology**
13. **Nonclinical toxicology**
14. Clinical studies
15. References
16. **How Supplied/Storage and Handling**
17. Patient Counseling Information

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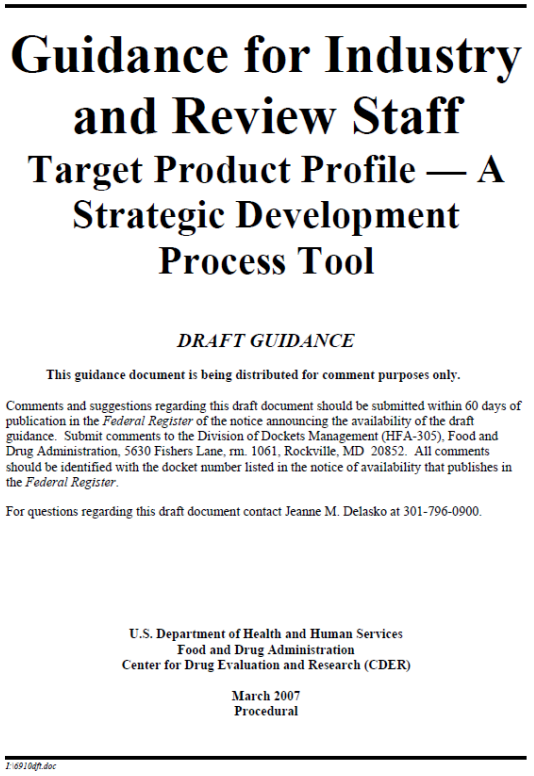
ULTIMATE GOAL: DRUG APPROVAL

For a successful drug discovery and development program, it is critical to identify the desired **end product** i.e., the intended indication and product claims (label**) right from the beginning**.

•FDA recommends using Target Product Profile (TPP) as a strategic development process tool

•**During early discovery and preclinical stages, use simplified templates and WorkbookGuides:** http://www.marsdd.com/mars-library/defining-your-target-product-profile-therapeutics/



Guidance for Industry and Review Staff

Target Product Profile — A Strategic Development Process Tool

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Jeanne M. Delasko at 301-796-0900.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2007
Procedural

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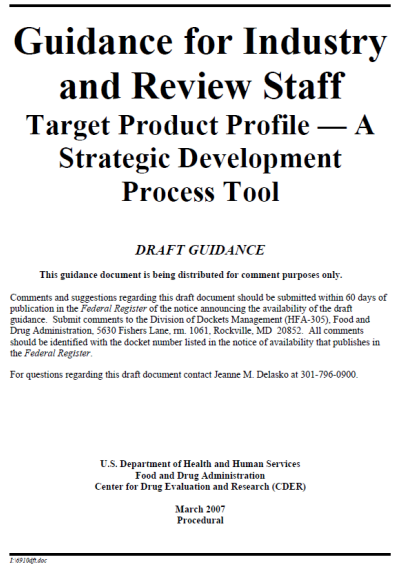
TPP: What is it?

A communication tool with regulatory agencies:

- FDA: “a format for a summary of a drug development program described in terms of labelling concepts”.
- Prepared by Sponsor
- Used to facilitate communication with FDA
- Utilized from pre-IND and up to post-marketing.



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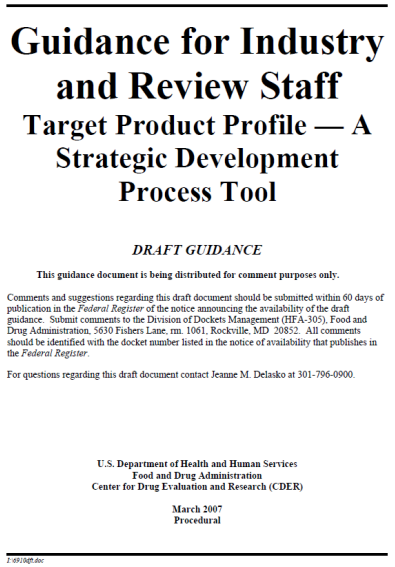
TPP: What is it (cont'd)?

A Strategic Planning Tool for Product Developme

- Define product under development, its indicat and usage
- Identify the "must have" and "nice to have" characteristics (claims) the product will have
- Roadmap to define preclinical, clinical, and manufacturing studies that need to be completed along the drug development path



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TPP: FDA TEMPLATE

1. **Indications and Usage**
2. **Dosage and Administration**
3. **Dosage Forms** and Strengths
4. Contraindications
5. Warnings and Precautions
6. Adverse Reactions
7. Drug Interactions
8. Use in Specific Populations
9. Drug Abuse and Dependence
10. Overdosage
11. Description
12. **Clinical pharmacology (MOA, PD, PK)**
13. **Nonclinical toxicology**
14. Clinical studies
15. References
16. **How Supplied/Storage** and Handling
17. Patient Counseling Information
18. Pricing
19. Intellectual Property

WHO AM I?

- PhD in Pharmacology
- Over 20 years of industrial and academic experience in drug development
- Director/Senior Director of Nonclinical Development
- Launching consulting practice in 2009, focusing on nonclinical toxicology and pharmacology

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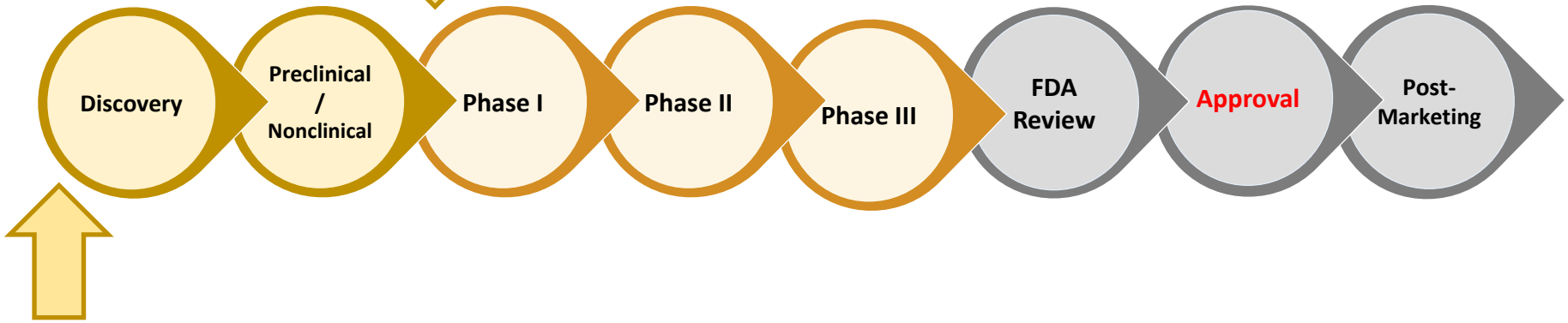
DISCOVERY AND PRECLINICAL DEVELOPMENT

Clinical Candidate Selection



Disease identification; Early screening

- Replacement therapy
- Modification of known drug
- Reformulation of known drug
- Combination of several drugs
- Natural product
- Chemical library
- Rational drug design

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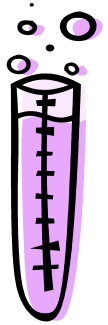
SCREENING AND LEAD IDENTIFICATION

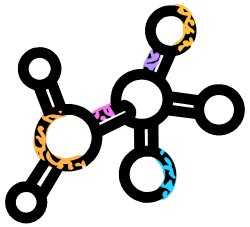
Screening program for drug optimization:

- In vitro testing
  - Molecular
  - Cellular
  - Organ/tissue



- In vivo testing
  - Pharmacodynamics
  - Pharmacokinetics
  - Safety

- Intellectual property
- Chemistry, solubility and stability
- Cost of goods



Review data and select clinical candidate(s)

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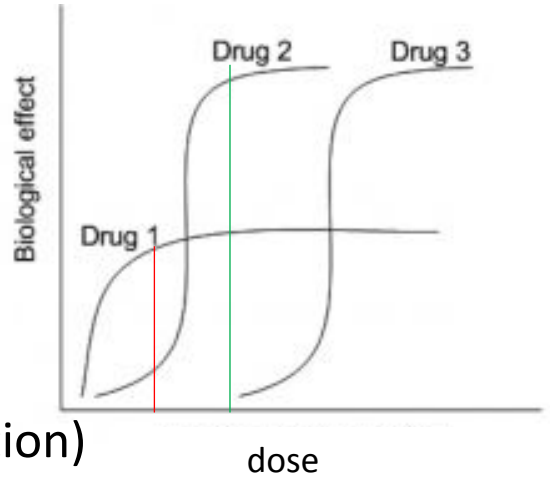
PHARMACODYNAMICS

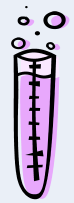
Pharmacodynamics (PD): what a drug does to the body.

Effects of a drug on the body (or on microorganisms/parasites within or on the body) and the relationship between drug concentration and effect

- Understand in vivo models
  - a) how well it reflect human disease
  - b) how well it predicts clinical outcome
- Perform full dose-response characterization
- Use clinical route of administration
- Compare to positive controls (marketed drugs)
- Use appropriate negative controls (vehicle/formulation)
- Demonstrate reproducibility of effects
- Differentiate between pharmacological and non-specific activity
- Recognize difference between statistically significant and clinically relevant.



PRECLINICAL DEVELOPMENT: EXAMPLES

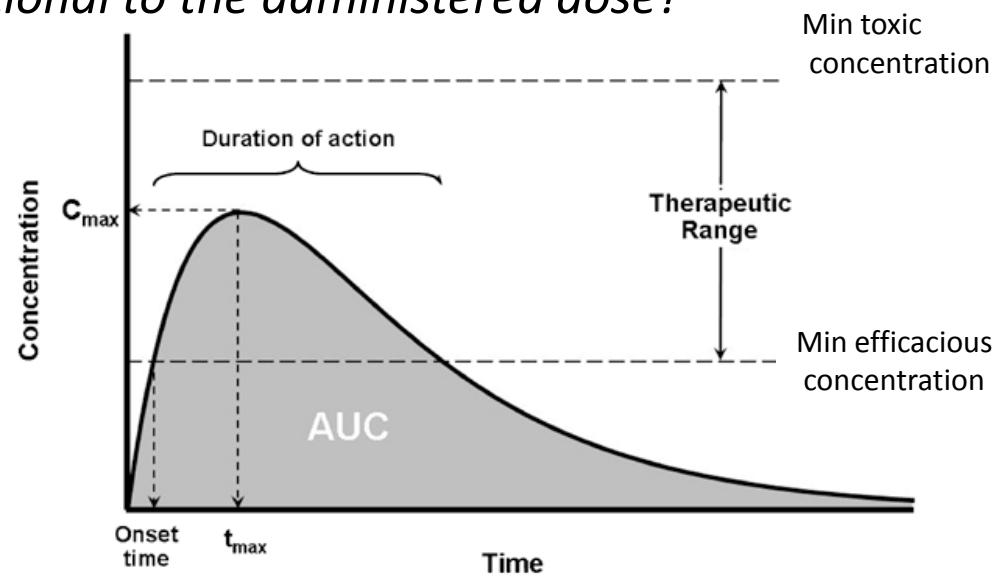
Indications	Skin and soft tissue infection, Pneumonia	Alzheimer disease , Huntington's disease , Amyotrophic lateral sclerosis
Drug	Novel antibiotic	Novel neuroprotective drug
In vitro testing 	Well characterized in vitro and in vivo methods available Known antibiotics can be used as control Regulatory guidance available	Exploratory methods available No or minimally effective control drugs Often no regulatory guidance
In vivo testing 	Well characterized models available Animal models very short (2-7 days) Animal data highly predictive of activity in clinic	Novel (transgenic animals) methods available Very long duration (6-12 months) Poor correlation with clinical activity
Clinical success rate	High	Low

PHARMACOKINETICS

Pharmacokinetics (PK): what the body does to a drug.
Absorption + Distribution + Metabolism + Excretion (ADME)

Key questions:

- *Does the drug reach the target organ?*
- *For how long does the drug persist above the efficacious level?*
- *Is the drug bio-available upon oral administration?*
- *Is systemic exposure proportional to the administered dose?*



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TOXICITY

Dosis facit venenum. (*The dose makes the poison)*

Paracelsus 1493-1541

A 10-year-old boy developed posterior reversible encephalopathy syndrome (PRES) after consuming at least 20 licorice sweets a day for four months, researchers from Italy report. Pediatric Neurol 2014.

- Determine the acceptable safety margin taking your clinical indication into consideration
- Enrich all in vivo efficacy studies with safety end points (body weight, organ weight, observations and clinical pathology)
- Evaluate doses above therapeutic to determine the maximum tolerated dose upon single and repetitive administration
- Animal dose ≠ human dose (alometric scaling is required for small molecules):
  - Human equivalent dose (mg/kg) = mouse dose (mg/kg) : 12.3
  - Human equivalent dose (mg/kg) = rat dose (mg/kg) : 6.2

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LEAD IDENTIFICATION

Lead clinical candidate is identified taking ALL key characteristics into consideration (think target product profile!)

- Mechanism of action
- Pharmacodynamics
- Pharmacokinetics
- Toxicology
- Chemistry and manufacturing
- Intellectual property
- Cost of goods/Pricing

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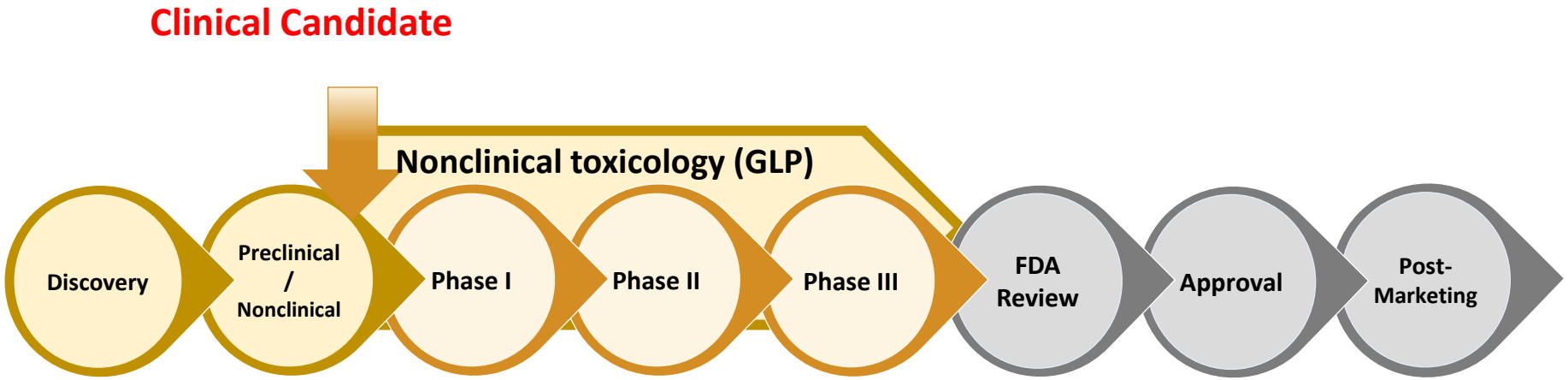
NONCLINICAL (TOXICOLOGY) DEVELOPMENT



NONCLINICAL DEVELOPMENT (SAFETY)

Before Phase I clinical study:

1. Identify target organs of toxicity and provide information for monitoring safety parameters in clinical trials.
2. Determine if toxicity is reversible
3. Determine a safe starting dose for human phase I clinical studies

GLP TOXICOLOGY: BEFORE PHASE I

- Single dose and range-finding repeat dose toxicity: NO LETHAL DOSES! (rodents and nonrodents)
- Repeat dose toxicity[a]: (rodents and nonrodents)
- Toxicokinetic (rodents and nonrodents)
- Genotoxicity panel: Damage to genes & chromosomes (mammalian and nonmammalian cells, rodents)
- Safety pharmacology: respiratory, cardiovascular and CNS (rodents or nonrodents)
- Special studies (irritation, sensitization, blood compatibility, local toxicity, etc.)

a – control and 3 treatment levels from no observed adverse effect level (NOAEL) to toxic levels, route and frequency of administration same as clinical.

Toxicology studies are done under GLP conditions

GLP = Quality **GLP = Good science**

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EXAMPLE: PRE-IND PACKAGE (SMALL MOLECULE)

Study type		US $
Single dose & repeat-dose range finding:	Rodents (rat)	30,000-55,000
	Non-rodents (dog)	40,000-50,000
1-month repeat-dose toxicity & 2 wk recovery:	Rodents (rat)	150,000-200,000
	Non-rodents (dog)	185,00-250,0000
Bio-analytical method development & validation		30,000-55,000/species
TK in rodents (rat):	Sample analysis	10,000-30,000/species
	TK reporting	5,000-12,000/species
Safety pharmacology	hERG	20,000-35,000
	Cardiovascular (dog)	50,000-80,000
	Respiratory (rat)	30,000-35,000
	Central nervous system (rat)	14,000-30,000
Genotoxicity	Ames	8,000-15,000
	Chromosomal aberrations	25,000-35,000
Dose formulation analysis: method development and validation		15,000-45,000
Dose formulation analysis (all GLP studies) per occasion		2,000-4,000
Additional studies (examples)		
In vitro metabolism (liver microsomes or hepatocytes)		5,000 – 10,000
CYP inhibition		3,000-5,000
In vitro target panel (receptors, enzymes, channels)		3,000-10,000
Protein binding (human, rodent and nonrodent)		2,500-30,000

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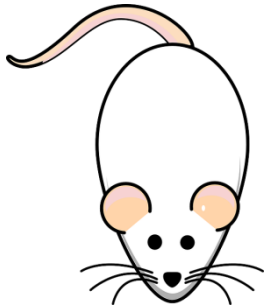
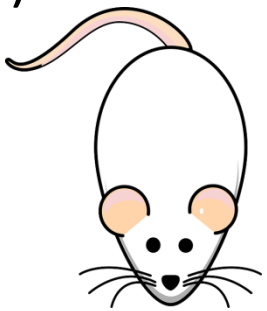
GLP TOXICOLOGY: AFTER PHASE I

After phase I:

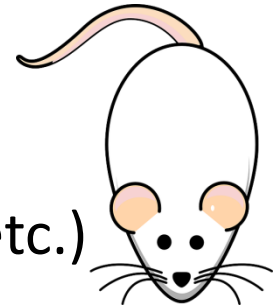
- Reproductive and developmental toxicology
  - Fertility and early embryonic development
  - Embryo-fetal development
  - Peri- and post-natal development



- Absorption, distribution, metabolism and excretion (ADME)
- Toxicity and pharmacokinetics of major metabolites
- Drug interaction studies
  - in vitro Cytochrome P450 (CYP) enzyme inhibition and induction
  - In vitro transporters
  - In vivo PK and/or PD



- Carcinogenicity studies
- Additional repeat dose toxicity studies of longer duration
- Special studies (organ toxicity, irritation, sensitization, phototoxicity, immunotoxicity, dependence, combination, etc.)



WHO AM I?

- Regulatory Affairs Certification since 2006
- MSc in Genetics
- Over 15 years of industry and academic experience clinical development and post-market activities
- Director of Regulatory Affairs & Quality Assurance at CTN and CHEOS
- Regulatory consultant for drug and medical device development

MIGENIX
ADVANCING THERAPY. IMPROVING HEALTH. ENRICHING LIFE!

NOVADAQ
imaging illuminated

QLT Inc.

the CTN
CIHR Canadian HIV Trials Network

le Réseau
Réseau canadien pour les essais VIH des IRSC

CHÉOS
Centre for Health Evaluation & Outcome Sciences

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ROLE OF REGULATORY AGENCIES

Role of modern regulatory agencies is to ensure that medicines and medical devices are both **safe** and **effective.**

Health product and food branch

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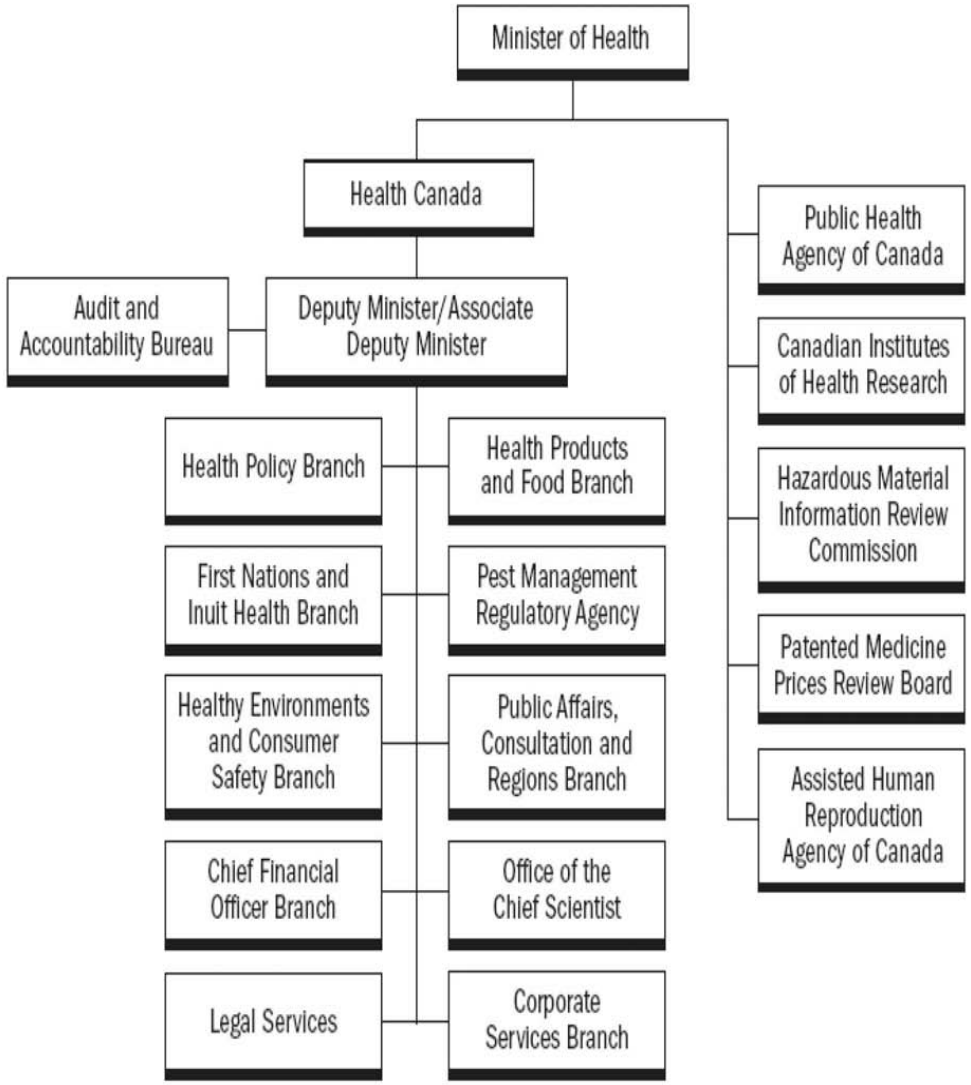
HEALTH CANADA ORGANIZATION



- Federal government legislates what products can be sold, level of control (Rx, OTC, narcotics), issue of drug abuse
- Provincial governments legislate drug distribution and payment for drugs
- HPFB's mandate - management of risks and benefits to health related to health products

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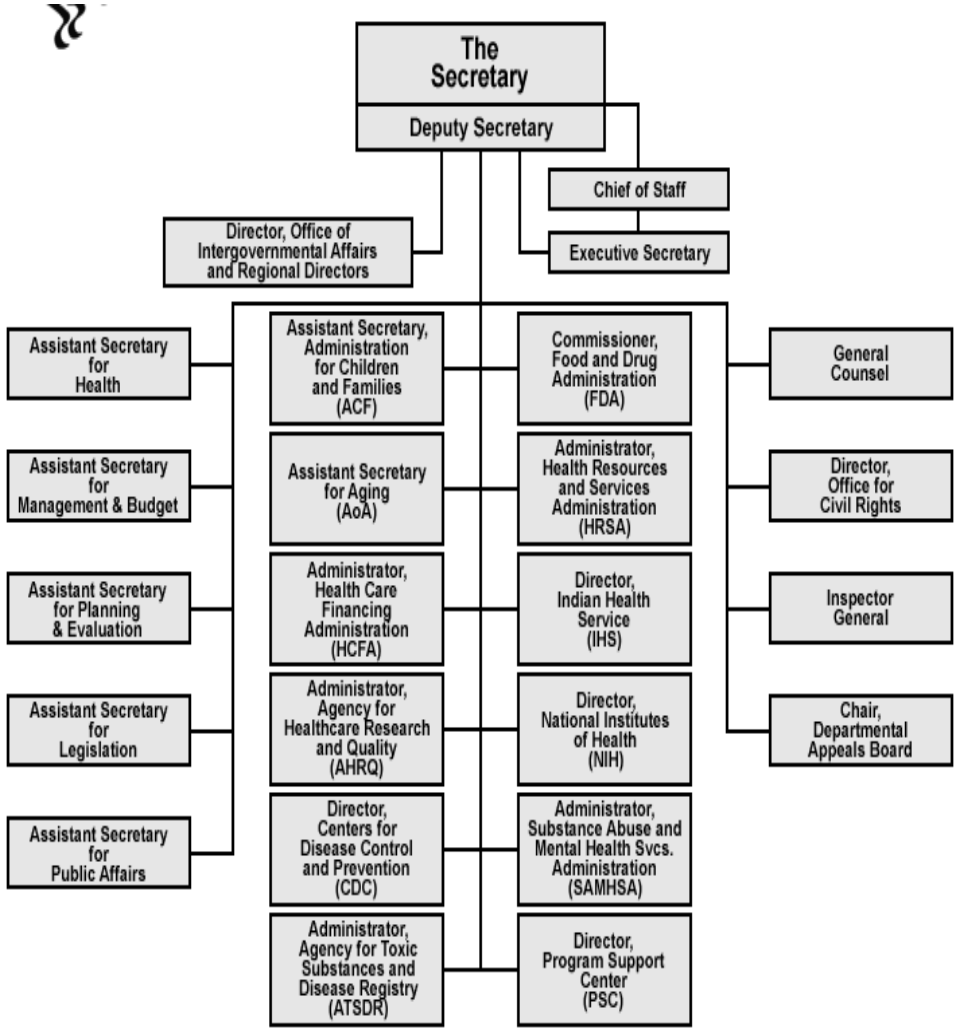
US DEPARTMENT OF HEALTH AND HUMAN SERVICES



- FDA is part of Public Health Service within DHHS; has jurisdiction of products in interstate commerce
- FDA's Mission:
  - review clinical research
  - Ensure safety and efficacy, and proper labeling
  - Collaborate with other countries
  - Consult with experts in science, medicine, public health, consumers and manufacturers

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ACTS, REGULATIONS AND GUIDELINES

- Legislation refers to written laws (Acts or statutes) which are enacted by Parliament

- Regulations are a form of law (subordinate legislation)
  - Define the application and enforcement of legislation.

- Guidelines are departmental documents used to interpret legislation and/or regulation.
  - Describe methods/procedures for complying with law and regulations
  - Do not have the force of law but highly recommended!

GXPs

- Industry term that represent a collection of quality guidelines;
- Most common and important guidelines:
  - Good Laboratory Practices (GLP) - organizational process and conditions under which non-clinical studies are planned, conducted, monitored, recorded and reported.
  - Good Clinical Practices (GCP) - ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials
  - current Good Manufacturing Practices (cGMP) - set minimum requirements for methods, facilities, and controls used in manufacturing, processing, and packing drug products
- Central aspects of GxP:
  - Traceability – reconstructing development history of a drug, medical device or clinical study intervention
  - Accountability – who has contributed what to development and when
- Documentation is a critical tool for ensuring GxP adherence

RECENT RECALLS

Product	Use Years on Market	Cause of Recall and Outcomes
Accutane (Isotretinoin)	Acne 27 years (1982 – 2009)	• Increased risk of birth defects, miscarriages, and premature births when used by pregnant women; inflammatory bowel disease; suicidal tendencies • >7,000 lawsuits, one $10.5 million verdict and two $9 million verdicts
Darvon & Darvocet (Propoxyphene)	Opioid pain reliever 55 years (1955 – 2010)	• Serious toxicity to the heart; >2,110 deaths reported 1981-1999 • UK banned Darvon and Darvocet in 2005. • US FDA was petitioned in 1978 and again in 2006 to ban the drug by the group Public Citizen
Rezulin (Troglitazone)	Antidiabetic / Antiflammatory 3 years (1997 – 2000)	• At least 90 liver failures; at least 63 deaths • ~35,000 personal injury claims were filed against the manufacturer (Pfizer)
Vioxx (Rofecoxib)	OA, RA, acute pain, migraines, cluster headaches 5 years(1999 – 2004)	• Risk of deadly heart attacks and strokes. • Linked to about 27,785 heart attacks or sudden cardiac deaths between 1999 and 2003 • Merck-FDA scandal

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WHERE ARE WE TODAY?

- FDA Enforcement Statistics for FY 2015
  - Warning letters issued: 17232 (majority from Centre for Tobacco Products)
  - Recalled products: CDRH – 2850, CDER – 1822, CBER – 973
- CDRH Quality System Surveillance Inspections in 2015:
  - Domestic – 1484, Foreign – 620
  - Majority of observation in Product production and controls
  - 121 Warning letters issued with QS cited (59 from foreign organizations)
  - Canada: 42 in 2015 vs. 24 in 2014; 6 inspections require official actions to be taken
- Untitled and Warning Letters posted since 2005
  - http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

REGULATORY: REFERENCES

Health Canada: http://www.hc-sc.gc.ca/dhp-mps/index-eng.php

Food and drug administration (FDA), USA: http://www.fda.gov/

European Medicines Agency (EMA), EU: http://www.ema.europa.eu/

Plus regulatory agencies in each European country:
e.g. **UK** Medicines and Healthcare products Regulatory Agency (MHRA):www.mhra.gov.uk

Pharmaceuticals and medical devices agency, PMDA, Japan:
http://www.pmda.go.jp/english/index.html

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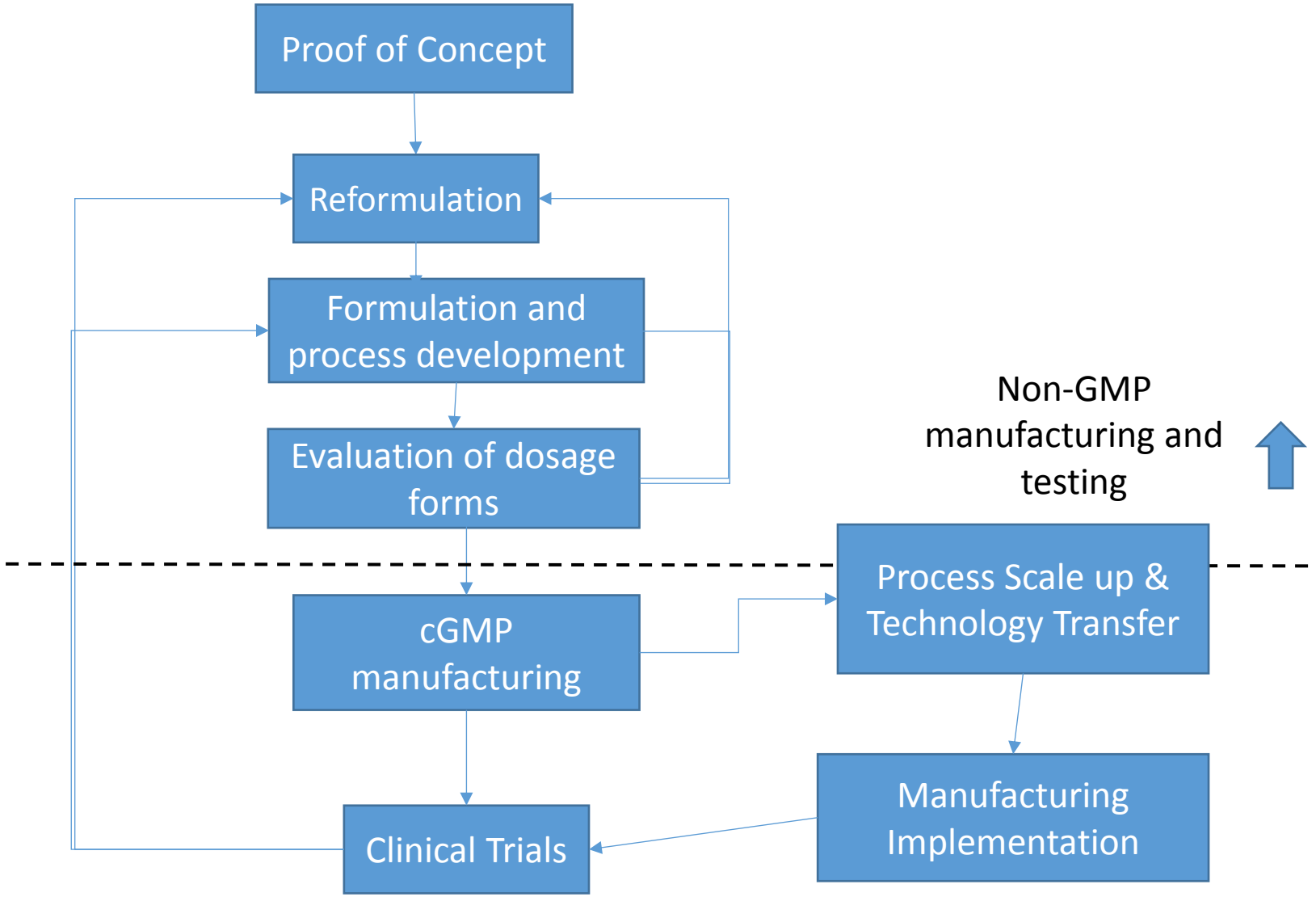
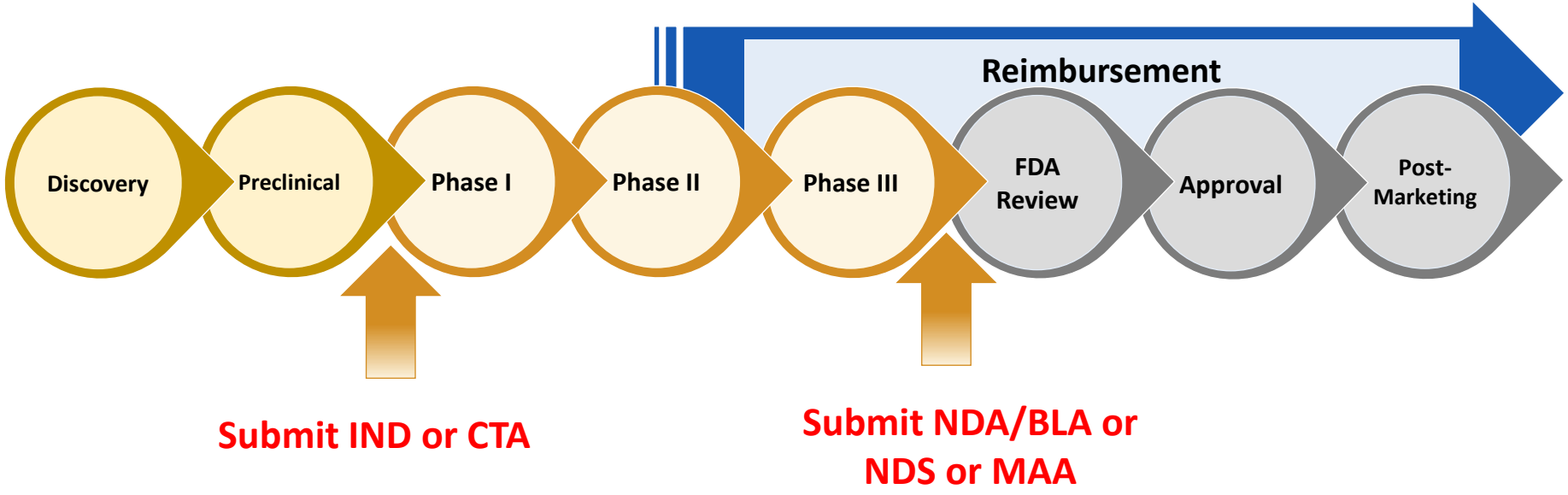
PHARMACEUTICAL MANUFACTURING DEVELOPMENT

- Goal: design a quality product to consistently deliver the intended performance of the product.
- Drug and Method Development
  - establish the physicochemical properties of the new chemical entity: its chemical makeup, stability, solubility
- Formulation Development
  - Choose “ideal” delivery of drug (e.g. solid, semi-solid, immediate or controlled release, tablet, capsule etc.)
- Process Development, Technology Transfer and Scale-up
  - Development and validation of manufacturing and testing methods
  - Account for changes in scale from mg to kg to tons

EXAMPLE: MANUFACTURING DEVELOPMENT STEPS



CLINICAL DEVELOPMENT



- Increasingly complex and demanding phases of clinical testing to support approval for marketing.
- Bench to market usually takes 10-15 years, often costs over $1bln

IND= investigational new drug application
CTA = clinical trial application

NDA – new drug application (USA),
BLA – biologics license application (USA),
NDS-new drug submission (Canada),
MAA – marketing authorization application (EU)

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REGULATORY ASSESSMENT FOR CLINICAL TESTING

- Sponsor is drug company, a cooperative group, physician, or institution
- Regulatory body allows clinical studies to proceed if risk of exposure to product is reasonable
- Risk/benefit determination based on:
  - Data from prior animal or human testing
  - Methods of manufacturing
  - Plans for testing and reporting significant toxicities
  - A well-developed clinical monitoring plan

APPLICATION FOR CLINICAL TESTING

Submit IND or CTA to study drug in clinical trials:*

- Manufacturing (chemistry, stability, manufacturing process, packaging information, etc.)
- Preclinical data (mechanism of action, pharmacology and toxicology)
- Clinical data (if available)
- Clinical development plan and study protocol
- Name and CVs of principal investigators
- Investigator's brochure

*IND – investigational new drug (US), CTA – clinical trial application (Canada)

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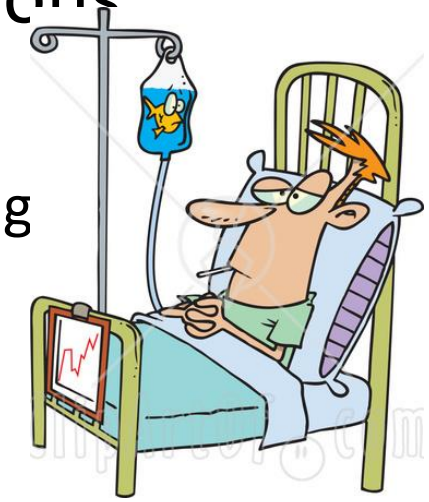
PHASE I: SAFETY

- Usually small numbers (20-100) of healthy volunteers; sometimes patients
- Doses start at very low levels; extensive and careful monitored with dose escalations
- Focus of Phase I is evaluation of:
  - safety and determination of a safe dosag
  - clinical pharmacology (PK and PD)
  - Side effects
  - Sometimes early evidence of effectiveness



PHASE II: PROOF-OF-CONCEPT

- First test of efficacy in patients with target condition
- Up to several hundred participants and last few months to couple years
- Focus:
  - determine the correct dosage
  - identify common short-term side effects
  - Define best regimen and best endpoints for efficacy for use in Phase III pivotal trials

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PHASE III: CONFIRMATORY / REGULATORY PROOF

- Evaluate a product's benefit in a carefully selected patient population with the disease.
  - Confirm efficacy, further evaluate safety and monitor side effects
  - Provide crucial evidence for regulatory evaluations
  - Provide necessary information for product labeling after approval
- Typically consisting of 100s – 1000s of subjects
- Need to meet rigorous requirements for clinical meaningfulness and statistics
- Usually 2 Phase III clinical trials required for approval

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STANDARDS FOR "PIVOTAL" STUDIES

- "Adequate and well-controlled trials" – designed to isolate drug's effects from extraneous factors that might otherwise undermine the validity of the trial's results
- Four criteria to be considered "pivotal":
  - Controlled
  - (ideally) Blinded design
  - Randomized assignment of treatment
  - Adequate size (to ensure statistical power of at least $p<0.05$)

APPLICATION TO MARKET AND SELL NEW DRUG

Submit NDA, NDS or MAA to sell new drug:*

- Chemistry and Manufacturing
- Preclinical (mechanism of action, pharmacology and toxicology)
- Clinical (efficacy, safety and PK
- Proposed labelling

NDA – new drug application (USA),
BLA – biologics license application (USA),
NDS-new drug submission (Canada),
MAA – marketing authorization application (EU).

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POST-APPROVAL REQUIREMENTS

Phase IV studies

- regulators may specify post-marketing study requirements to obtain further info on safety/effectiveness
- Safety surveillance designed to detect any rare or long-term adverse effects in larger patient population over longer time period
  - Harmful effects discovered by Phase IV trials may result in recall or restrictions
- Must be conducted within confines of approved label
  - Does no require IND or CTA

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