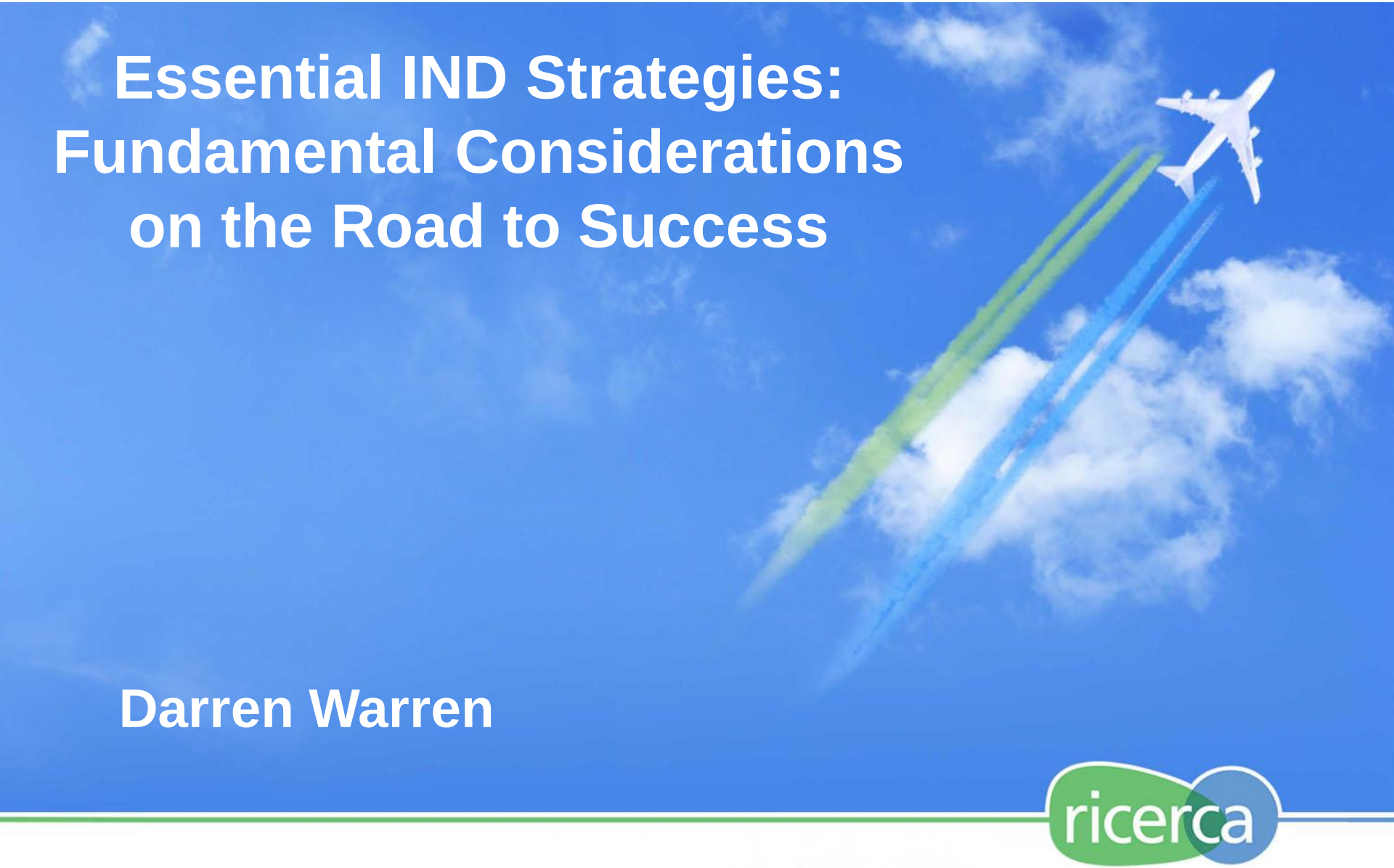
Essential IND Strategies: Fundamental Considerations on the Road to Success



Darren Warren

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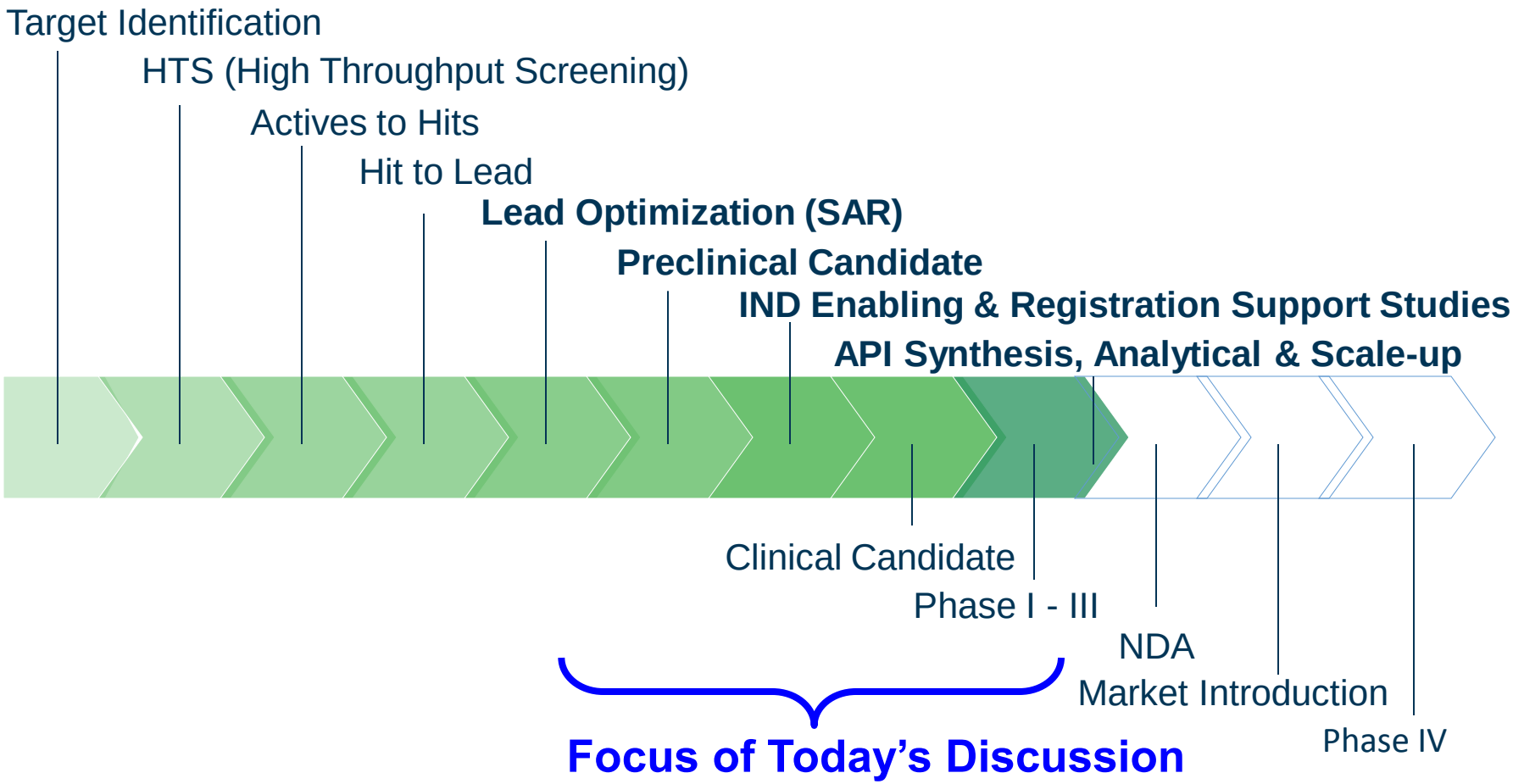
Drug Discovery & Development



Early Clinical Goals & Regulatory Strategy

1) **Define drug development goals:** Identify target patient population, rationale for clinical need, & initial region for clinical development. *Goal should not simply be to file an IND, rather develop a drug therapy*

2) **Initial clinical trials designed to characterize:** Human DMPK, safety, pharmacologic activity & proof of concept

3) **Understand regulatory guidelines and precedented approaches for similar drugs (same chemical class & indication or relevant)**

4) **Chemical development strategies:** Develop robust API synthetic route that yields appropriate physical/chemical properties; clinically suitable drug formulations, with well characterized impurity profiles.

5) **IND-enabling pharmacology, DMPK & toxicology studies:** Need to align with clinical route of administration, dose schedules, & duration of treatment. Design to identify: PK/PD responses, target organs, dose response, exposure multiples & safety margins

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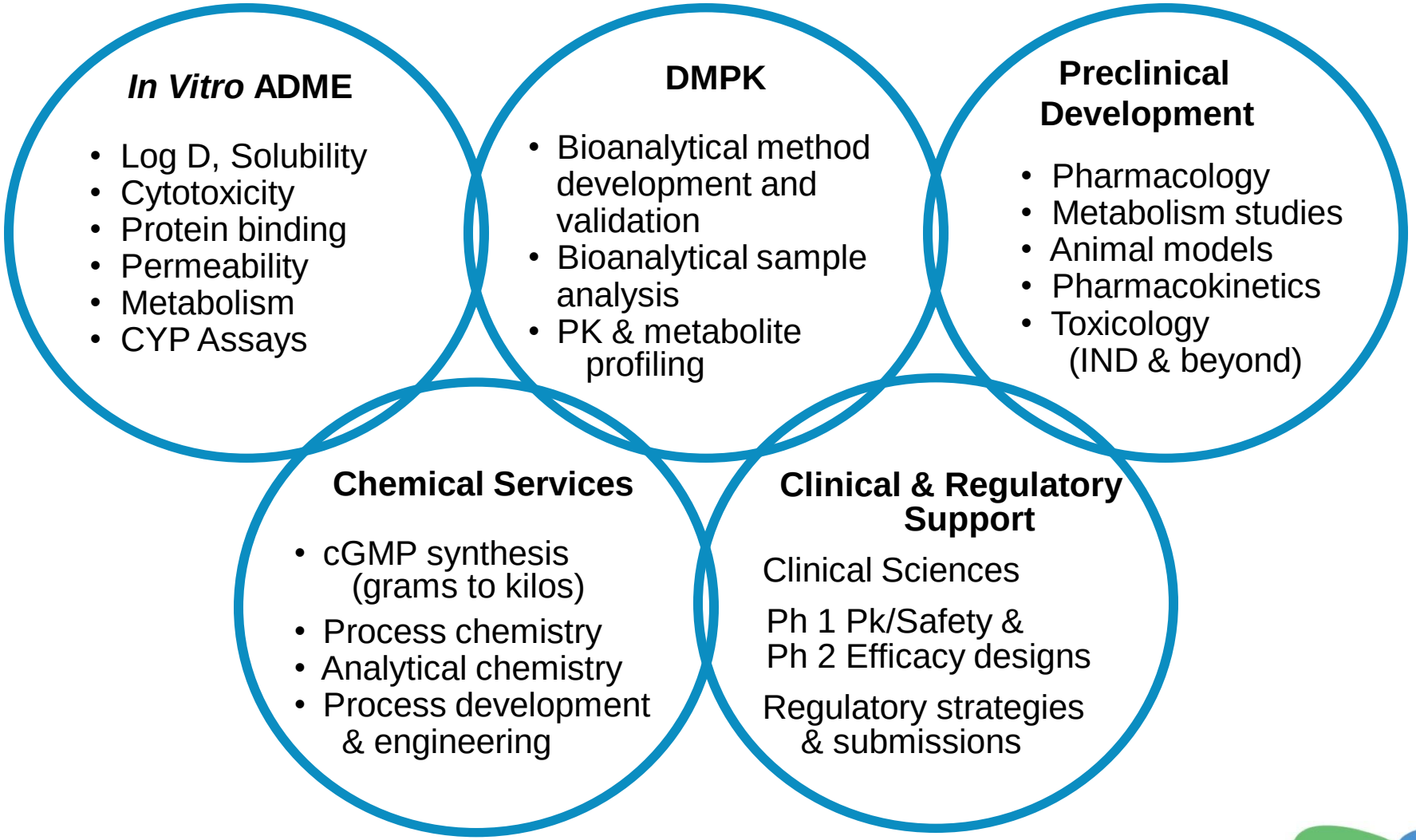
Drug Development….Highly Integrated Process



Pitfall #1: The Rush to First Dose

Task	Duration	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14
	weeks									
Project Accepted										
CRM Procurement - Lab Work	3									
Benchmarking/Scale-Up Changes	12									
API Sample Preparation - 200 g	6									
Analytical Methods Work	12									
API Demo Lot Preparation - 2.5 kgs	13									
Storage Stability Study - 6 months	Start									
RS Prep & Characterization - 50 g	3									
CRM Procurement - Production	8									
cGMP-grade API Production - 25 kgs	11									
Release Testing & QA Review	3									
Storage Stability Study - 36 months	Start									

Manufacture of test article, development of analytical and bioanalytical methods, development of appropriate dosing formulations and as necessary preformulation work all occur before first dose.

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API Supply Targets

Item	Pre-Clinical		Phase I
	Range-Finding	GLP Toxicology	
API Needed	50 - 200 grams	0.20 - 2.0 kilograms	2 - 10 kilograms
Process Status	Discovery route	Upgraded to scaleable and reliable	Upgraded to scaleable and reliable
Preparation Scale	5 - 12 liters	50 liters	200 - 400 liters
API Purity	> 95%	97%	NLT 98%
Analytical Methods	ID/purity - TAN	Purity - TAN Related substances - TAN Solvents - total	Purity - weight-based Related substances - TAN Residual Solvents - ICH Guidelines Counter ion Process residues

Map out your API Supply

API Need For	Amount, grams
Dose Range Finding Studies	100
Salt Screen	10
Polymorph Screen	10
GLP Toxicology Studies	1,000
Formulations research	100
Reference Standard	50
Phase I	3,000
Stability Study	25
ST	4,295
Program Contingency @ 25%	1,074
ST	5,369
Mass Contingency @ 25%	1,342
Program Total	6,711

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Map out your API Supply

Target = Requirement * (1 + (MC/100))

Process Status	Amount Prepared grams	Mass Contingency, % (MC)
Discovery Route	< 10	100 - 200
Some Process Research	> 100	50
Process research/Scale-Up Changes	> 250	25

Typical API Specification – Phase I

Property/Attribute	Method	Specification
Appearance	Visual	Off-white powder
Identity	H NMR	Matches reference standard
	C NMR	Matches reference standard
	Mass Spectrum	Matches reference standard
Elemental Analysis		Consistent with structure
Purity	HPLC	NLT 98.0%(w)
Impurity Profile	HPLC	No single impurity > 0.5%
		Total impurities NMT 2.0%
Form	XRPD	Report result
Melting Range	DSC	Report Result
Residual Solvents	GC	Conforms to ICH Limits
Heavy Metals	Titration	NMT 20 ppm
Residual Palladium	ICP	NMT 10 ppm
Residue on Ignition	Combustion	NMT 0.2%
Moisture	Karl Fischer	NMT 0.5%

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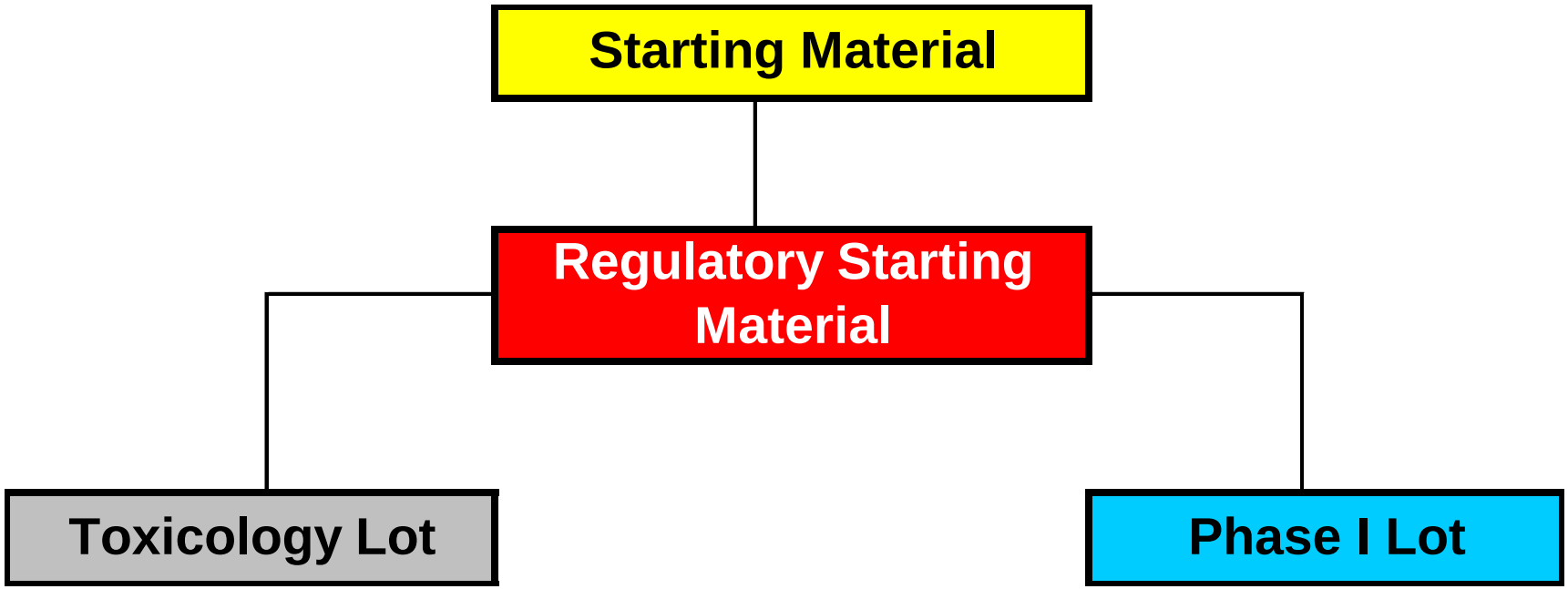
API Preparation Strategies

Model C

Dose Range-Finding Lot – Toxicology/Phase I Lots



API Preparation Strategies

Model C

Dose Range-Finding Lot – Toxicology/Phase I Lots

Advantages

- Utilizes dose range finding data to set needs
- Can control impurity profile difference between Toxicology and Phase I lots
- Balances scale-up risk and preparation time

Disadvantages

- May have slight delay in Toxicology lot delivery
- Complete process run more than 2 times

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API Supplies – Program Progression

Item	Pre-Clinical	API for Clinical Trial Materials			Commercial
		Phase I	Phase II	Phase III	Production
API Amount, kilograms	0.1 - 3	1 - 10	50 - 200	> 200	>1,000
Process Status	Discovery Route	Process Scaleable and Reliable	Process Intended for Commercial Use	Process Developed and Validated	Process Locked for Routine Production
Preparation Scale, liters	1 - 50 - Kilo-Lab	50 - 400 Small Pilot Plant	2000 - Pilot Plant	> 2,000 - Semi-Works	> 8,000
Analytical Methods	TAN-based HPLC Purity	Weight-based purity, related substances residual solvents, and other methods are developed and validated in proportion to the clinical phrase			Methods fully developed, validated, and locked for production support
API Characterization	Rudimentary	Characterization becomes more complete as process knowledge and experience increases		Comprehensive using validated methods	Routine Quality Control testing for production support and API release
API Purity, %	95	98	98+	98+	98+
Specifications	ID and purity	Specifications refined and tightened as process			Locked
cGMP Controls	None	Required = application rigor increases with process knowledge and experience and phase			Full routine compliance

API Preparation Planning – Capacity Model

CAPACITY MODEL	BATCH SEQUENCING PLAN

Step	Step Product	MW	Yield	Amount Required		Process	Total	Reactor Specifics			Batches	Cycle	Run
			%	kg-moles	kgs	Output	Working	Size	Usage	MOC		Time	Time
						g/l	Volume	liters	%			days	days
							liters						
S-1	C3	452.90	70.0	0.0113	5.14	79.0	65.0	50	65.0	Glass	2	3.0	6.0
S-2	C4	351.00	80.0	0.0091	3.18	75.0	42.5	40	53.1	Glass	2	3.0	6.0
S-3	API	424.00	65.0	0.0059	2.50	75.0	33.3	50	66.7	Glass	1	4.0	4.0
	Overall		36.4				140.8				5		16.0
Step	Custom RM	MW	Usage	Amount Required									
			m/m	kg-moles	kgs								
S-1	C1	222.00	1.00	0.0162	3.60								
S-1	C2	248.90	1.00	0.0162	4.03								

DMPK & Early Development

- In Vitro Metabolism
  - Plasma stability
  - Protein binding
  - Blood compatibility
  - Microsomal/Hepatocyte stability & metabolism
  - Species comparison in microsomes & hepatocytes
  - Define metabolic pathway and major metabolites; metabolite structure elucidation
- Pharmacokinetics (PK) & Toxicokinetics (TK)
  - Lead & Formulation selection, pilot PK
  - Bioavailability & complete PK profiles
  - In vivo metabolite profiling & ADME studies (using cold or radio-labeled compound). Conducted preclinically or early Phase 1.

Critical for Non-clinical Species Selection & Prediction of Human DMPK Responses

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DMPK & Early Development

- Drug-Drug Interaction (DDI)
  - **CYP Assays:** Consider patient population & co-therapies
  - **Inhibition** (cocktail & individual assays, IC50 and Ki)
    - Mechanism based inhibitor (MBI) determination
  - **Induction**
    - In vitro induction in hepatocytes
    - Toxicology/TK data can provide early indicators of induction
    - Ex vivo induction in liver from treated animals
  - Reporter gene assays for induction of CYP1A2 & CYP3A4
  - UGT enzyme inhibition
- Cell Transport
  - Drug Transporters
  - Permeability (Caco2, uni- and bidirectional)
  - MDR1-MDCK bidirectional permeability (P-gp)
  - Uptake transporter assays

Critical for predicting Drug-Drug Interactions; interpreting PK & tox outcomes; & prediction of human PK profiles

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Pharmacokinetics & Metabolism

- Pharmacokinetics
  - Define Active Drug Concentration & PK profiles (major & relevant metabolites)
    - AUC, C_{max}/C_{min}, T_{max}, $T_{1/2}$, Vd, & Cl
    - Characterize over range of dosages, including expected clinical and toxicology dosages (1x-10x efficacious dosages)
    - Single & Repeat-dose PK (3-7 days)

Defines saturation of absorption, metabolism, clearance/excretion, accumulation, gender and species differences

- ADME
  - Not generally required for IND
  - Will need to identify and characterize major/relevant metabolites
  - Helpful to understand primary routes of excretion & tissue distribution

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Drug Safety

Non-GLP & GLP Toxicology & Safety Pharmacology Studies

- GLP vs non-GLP
  - Any study can be conducted in accordance with GLP
  - GLP incurs increased cost and timelines
  - GLP (only) required for extrapolation to humans

- Species Selection
  - Selection based on in vitro metabolism and PK data
  - Major metabolites must be expressed in tox species
  - Rodent (mice, rats)
  - Non-Rodent (dogs, nonhuman primates)
    - Gottingen mini-pigs, rabbits, etc. as justified
  - Requirement for two species may be waived (ex. no pharmacology in rodent species for biologics)

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Drug Safety

Non-GLP & GLP Toxicology & Safety Pharmacology Studies

- Dose Administration & Schedule
  - Should be the same as intended clinical route & schedule
  - Dose schedule: daily (or multiple daily) vs. cycle dosing
    - Oral: gavage, nasogastric route, oral tablet/capsule or solution
    - Parenteral: intravenous, continuous intravenous infusion, subcutaneous, intramuscular, intraperitoneal
    - Topical: dermal, ocular
    - Regional treatment: intra-tendon, intra-articular and intra-vitreal
  - Characterize dose-response relationship
    - Minimum of 3 dosages
    - Good separation between dosages to avoid exposure overlap
    - Dose to toxic effect or maximum feasible limit

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Drug Safety

Toxicology Studies

- Pilot Toxicology Studies
  - Initial toxicity readouts (single and multiple dose)
  - Required in each species, non-GLP
  - Tolerability - define the Maximum Tolerated Dose (MTD): single dose; morbidity/mortality, GI distress, severe CNS effects, respiratory distress, immune reactions
  - Repeat Dose Range-Finding Toxicity: repeat dose 5-14 days; identify dose & exposure responses, target organ toxicity; major organ system pathology; dose-limiting toxicities; repeat-dose TK
  - A go/no-go decision often follows: Toxicity profile? PK profile? Dose limitations? Off target tox?

Pitfall: not considering your formulations carefully
Pitfall: not conducting complete / robust pilot tox studies

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Drug Safety

Toxicology Studies

- IND-enabling (pivotal) GLP
  - Typically 14-28 day repeat dose to support SAD & MAD Ph I clinical studies
  - Intended as survey studies. Expected to include endpoints relevant to molecular class, anticipated toxicity, PD identification
  - Dose selection intended to elicit toxicity
  - Primary endpoints are clinical pathology & anatomical pathology assessments with TK profile correlates
  - Goals: Identify target organ toxicity/pathology, translational predictive safety biomarkers, assess reversibility or progression, assess local tolerance, determine adverse effects with NOAEL & exposure ratios
  - Basis for selecting initial clinical doses & escalation.

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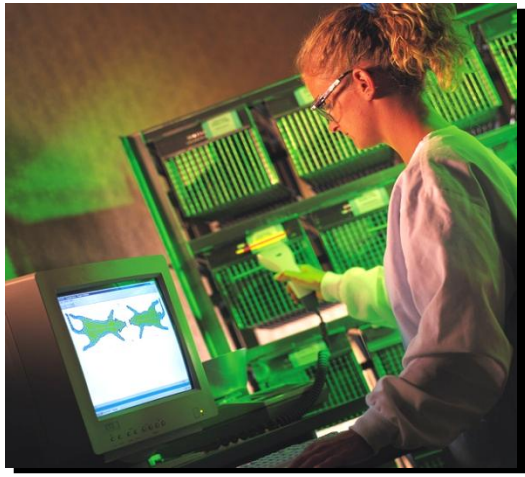
Drug Safety

IND-Enabling Toxicology

- Specific assessments as indicated
  - Local effects (ex. injection or application site)
  - Specific safety biomarkers as appropriate (clinical pathology or specialty assay)
  - Immunogenicity as warranted (anti-drug antibody)
  - Immune suppression or cytokine storm
- Common concerns / issues
  - Blood volume limitations for large animals
  - TA consumption substantial
  - TA preferred same batch as Ph I
  - Maintain purity of purpose = IND enabling. Avoid discovery investigations; pitfall for including unneeded endpoints



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Drug Safety

Genetic Toxicology

- Hazard Identification for DNA damage in form of mutations or chromosomal damage
- Pre-IND requirement for 2 in vitro assays: AMES & Mammalian in vitro Chromosomal Aberration assay
- Registration Requirement for in vivo Chrome Ab assay (Micronucleus Test)
  - Prudence in conducting all 3 assays pre-IND
- Additional clarification assays as needed (example to show epigenetic or mechanism based effects)
- Does not address potential genotoxic impurities in API

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Drug Safety

Safety Pharmacology

- Requirements
  - ICH Core Battery:
    - CNS & Respiratory (generally rat) and Cardiovascular (generally canine or non-human primate)
    - In vitro cardiovascular ion channel assessment
  - GI, Renal, others as target organs dictate
- Purpose and Designs
  - Determine potential for untoward pharmacology
  - Single dose pharmacology study, top dose near MTD
    - Small molecule – commonly stand alone studies
    - Biological – incorporate endpoints into non-rodent tox study
    - Oncology (end stage) – waived

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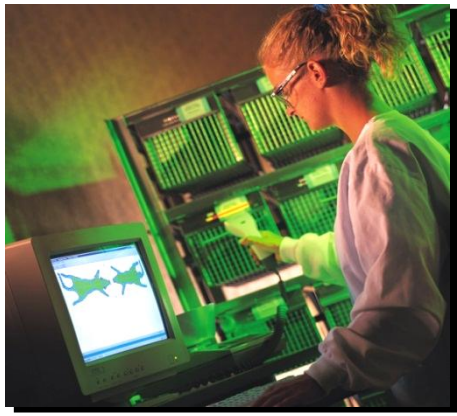
Drug Safety

Core Safety Pharmacology Studies

- Cardiovascular Assessments
  - In vitro hERG (minimum, other ion channel assay as indicated)
  - In vivo telemetry cardiovascular functional evaluations: blood pressure, heart rate, and ECG waveform analyses
- Respiratory Functional Assessments
  - In vivo respiratory assessment in rodents
    - Plethysmography measuring respiratory rate, tidal volume, and minute volume
- CNS Functional Assessments
  - In vivo central nervous system functional assessment in rodents
    - Functional observational battery
    - Motor & behavioral activity



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Development Timelines and Resources

Elements	Ballpark Price ($, 000)
In Vitro metabolism	Various
Bioanalytical method validation (per analyte, two species)	65 - 80
PK (per study)	10 – 20
MTD / DRF (two species)	100 – 130
Genetic toxicity	85 - 100
Safety pharmacology	135 - 160
28 Day: Rat Dog Monkey	200 – 300 250 – 350 400 – 600
+ Candidate API supply + BA Internal standard synthesis + Formulations development + IND preparation / publication	?? ?? ?? ??

Development Timelines and Resources

- Chemical Development (6 - 8 months)
  - Synthetic process improvement & production of gram batches
  - Chemical synthesis process development for 1-10 Kg batch
  - API characterization and stability established
  - Initial non-clinical & clinical formulations developed
  - Drug product characterization supporting early clinical use
- Drug Safety and Metabolism (8 – 10 months)
  - In vitro DMPK studies
  - Pilot pharmacokinetic & toxicology studies
  - Drug safety IND-enabling toxicity studies (14 - 28 day rodent and non-rodent)
  - Genotoxicity assays
  - Safety pharmacology profile

The above are required elements, there are no real short-cuts

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Development Timelines and Resources

- Program Outcome
  - IND filed 10 - 12 months after lead selection, barring any technical or safety issues. Requires parallel activities including IND preparation and clinical plan determination (15-18 months for biologics)
  - Commercially-viable prototype API process developed and demonstrated
  - Total project cost = $ 2.5 – 4.0 million (biologics can be more)
- Clinical entry with a well characterized molecule