

Enabling Technologies for Key Decision-Making in Early Clinical Trials

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Why are new approaches to pharmaceutical development needed?

- **Development costs may exceed \$800 million per compound and require up to 10 years**
- **Fewer than 1 in 10 compounds entering clinical trials will succeed**
- **More targets (genome project) and drug candidates (high throughput screens) have been identified than can be developed**
- **Greatest potential therapeutic benefits come from compounds that carry the greatest development risks for failure**
- **Safer and less expensive drugs are sought**

Value of Novel Paradigms

Earlier differentiation of promising compounds

- Reduced time, facility, and personnel expenditure
- Reduced API requirements
- Reduced overall costs to eliminate 'losers'

Expose human subjects to compound

- Avoid discontinuation of program due to non-translation between animal and human data

Target specific compound-related questions

- Fewer studies and animals required
- Reduced time frame to POC

Potential Benefits Derived from Investment in Exploratory Research

Novel Mechanism

- Biomarker assessment of target modulation/disease process
- Investigate PK/PD relationship

Precedented Mechanism

- Differentiation based on:
 - ✓ Safety profile
 - ✓ PK (QD dosing)
 - ✓ Potency/specificity

Alternative Approaches to Gain Confidence in Investment

- Exploratory IND
 - ✓ Microdosing (PK and Imaging)
 - ✓ Pharmacologically relevant doses
 - ✓ MOA related to efficacy
- Single Dose IND
- Pharmacologically Active Dose (PADs) – CHMP Concept

Comparison of FIH Strategies

	IND	PADS (CHMP Concept)	Microdosing	MOA Related to Efficacy	Pharmacologic Endpoint
Clinical Outcome	Tolerance, PK, PD	PK, target modulation with biomarker	PK	Target modulation	PK, Target modulation
Clinical Dosing	Multiple dose Full dose profile to MTD	1 – 2 doses Low pharmacologic	Single dose Subpharmacologic (dependent upon ultrasensitive analytics)	≤ 7 days Pharmacologically active	≤ 7 days Pharmacologically active
Nonclinical Studies	2 species, 2 weeks by clinical route Genetic toxicity Safety Phm	2 species, 2 weeks by the clinical route Genetic toxicity Safety Phm	1 species, single dose by clinical route with extended observation period	2 species, modified pharmacologic and safety studies with mechanistic endpoints	1 species (rat), 2 weeks by clinical route Validation study in nonrodent Genetic toxicity Safety Phm
API (nonclinical)	1 – 3 Kg	500 – 1500 g	1 – 50 g	100 – 1000 g	10 – 300 g
Preclinical (Lead compd to IND)	9 – 18 months	8 – 16 months	3 – 6 months	6 – 10 months	3 – 6 months

expIND

expIND Principles

- Intended for investigation of pharmacologic and pharmacokinetic endpoints in a multidose clinical trial
- Multiple compounds tested under a single expIND
- Restricted clinical dosing range and duration
- Compound sparing nonclinical program

Clinical Study Designs for an explIND

- **Single dose studies - subpharmacologic or escalating to a pharmacologic dose to determine kinetics and/or other appropriate markers**
- **Multiple dose studies - up to 7 days at dose levels achieving pharmacologic activity**
- **Normal volunteers and minimally diseased subjects allowed**

Nonclinical Studies Required for an expIND

General Toxicology Testing

Objective: Primary expIND enabling study

Design: 2-week repeat dose study with toxicokinetics in a single sensitive species

- Usually rodent based on metabolic and target receptor sensitivity
- Routine toxicological assessments (including clinical pathology and histopathology)
- Identify target organ toxicity and NOAEL
- GLP

Nonclinical Studies Required for an expIND

General Toxicology Testing

Objective: Establish the primary species as adequately sensitive

Design: Multiple dose study (up to 7 days) in nonrodent (e.g. 3-4, single sex) at a single dose that approximates the rodent NOAEL on a body surface area or exposure basis (need not identify target organs or general toxicity)

(The repeat dose phase would be \geq the number of days of clinical dosing, and not to exceed 7 days)

Nonclinical Studies Required for an expIND

Genetic Toxicology

- Two appropriate *in vitro* assays or one *in vitro* and one *in vivo*

Drug Metabolism

- Toxicokinetics, *in vitro* metabolism (test species and human)

Safety Pharmacology (i.e. CV, CNS, Respiratory)

- Relevant endpoints incorporated into design of supporting general toxicology studies - or - evaluated specifically on a need basis

Safety of the approach was established using a PhRMA dataset

Data on INDs filed over the previous 3 years were requested from PhRMA member companies

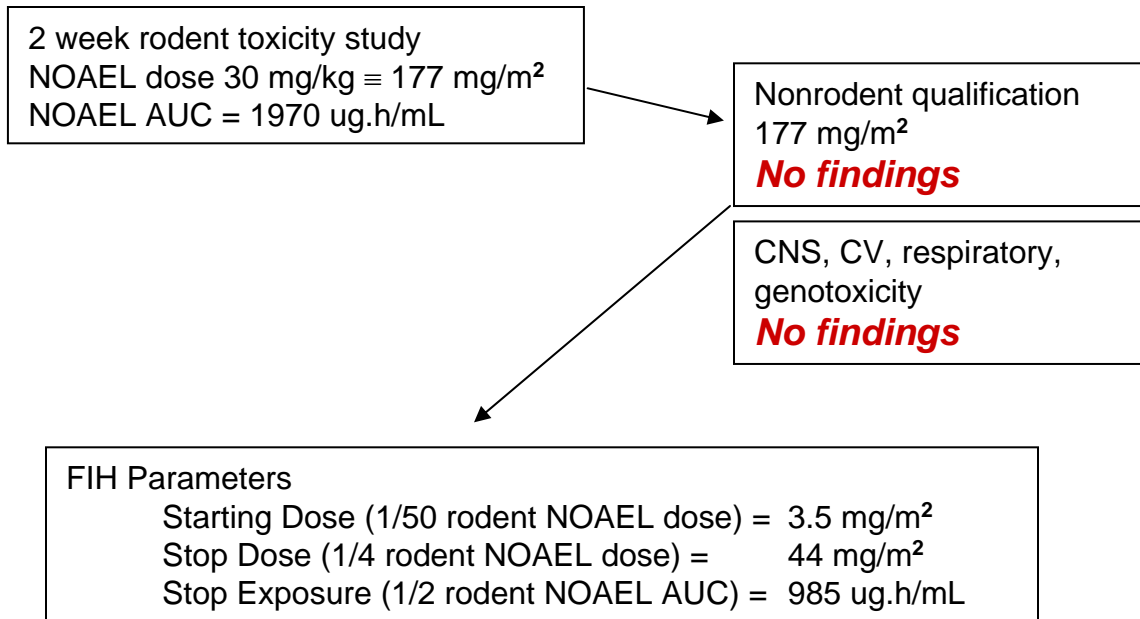
- Rodent and non-rodent NOAEL dose, duration of treatment and exposure in definitive, IND-enabling studies
- Phase 1 entry and stop doses with exposures, dosing regimen and reason for stop dosing
- Principal toxicity observed during nonclinical studies in rodents, nonrodents and results of the CV assessment in nonrodents

explIND Clinical Dosing Guidelines

- A starting dose of 1/50 the NOAEL dose in rodents will safely initiate the clinical trial as designed
- The trial will be stopped safely based on whichever of the following criteria occur first:
 - Clinical dose equivalent to $\frac{1}{4}$ NOAEL dose in rodents
 - Clinical exposure equivalent to $\frac{1}{2}$ NOAEL exposure in rodents
 - If AUC in nonrodents is significantly lower than in rodents at equivalent doses, then the nonrodent AUC will serve as the clinical stop dose target
 - Occurrence of clinical effects in humans (AE or pharmacologic target modulation)

How would a simulation of the expIND concept appear in a situation where both dose and AUC criteria were met

Compound #8 from the dataset



Experimental Data

NR NOAEL Dose = 360 mg/m²
AUC = 3450 ug.h/mL

Start dose = 31 mg/m²
Stop dose = 555 mg/m²
Stop exposure = 4660 ug.h/mL
Dose-limiting headache

Outcome

Trial stops at 44 mg/m² w/o effects. Further escalation only upon consultation with FDA.

How would a simulation of the expIND concept appear in a situation where the nonrodent species was sensitive

Compound #42 from the dataset

2 week rodent toxicity study
NOAEL dose 2000 mg/kg \equiv 11,800 mg/m²
NOAEL AUC = 40 ug.h/mL

Nonrodent qualification
11800 mg/m²
**CNS, respiratory,
hepatic and GI effects**

CNS, CV, respiratory,
genotoxicity
CV effects (QTc and HR)

FIH Parameters

Starting Dose (1/50 rodent NOAEL dose) = 236 mg/m²
Stop Dose (1/4 rodent NOAEL dose) = 2950 mg/m²
Stop Exposure (1/2 rodent NOAEL AUC) = 19.9 ug.h/mL

Experimental Data

NR NOAEL Dose = 60 mg/m²
AUC = 1.2 ug.h/mL

Start dose = 0.185 mg/m²
Stop dose = 31 mg/m²
Stop exposure = 0.61 ug.h/mL
Dose-limiting somnolence

Outcome

Toxicity in the NR at the rodent NOAEL dose either terminates the program or triggers additional studies leading in all likelihood to a conventional IND

How would a simulation of the expIND concept appear in a situation where bioavailability in the nonrodent species was low

Example #49 from the dataset

2 week rodent toxicity study
NOAEL dose 40 mg/kg \equiv 236 mg/m²
NOAEL AUC = 2.75 ug.h/mL

Nonrodent qualification
236 mg/m²
Low exposure relative to rodent

CNS, CV, respiratory,
genotoxicity
No findings

FIH Parameters

Starting Dose (1/50 rodent NOAEL dose) = 4.7 mg/m²
Stop Dose (1/4 rodent NOAEL dose) = 59 mg/m²
Stop Exposure (NR AUC) = 0.3 ug.h/mL

Experimental Data

NR NOAEL Dose = 200 mg/m²
AUC = 0.3 ug.h/mL

Start dose = 6.2 mg/m²
Stop dose = 27.8 mg/m²
Stop exposure = 0.62 ug.h/mL
Dose-limiting nausea/vomiting

Outcome

Exposure in the NR is lower than in the rodent at the NOAEL equivalent dose. The NR exposure becomes the AUC target for capping dosing and the trial is stopped at a safe dose.

Drug substance required to support FIH studies

(Rodent and nonrodent equally sensitive)

Full IND Requirements		Proposed Exploratory IND Requirements	
Study	CPD (g)	Study	CPD (g)
DRF + 2-wk GLP rodent	55	DRF + 2-wk GLP rodent *	55
DRF + 2-wk GLP nonrodent	700	7-day nonrodent	5
CV Safety Pharm	12	CV Safety Pharm	12
CNS Safety Pharm	5	Mutagenicity	2
Pulm Safety Pharm	5		
Mutagenicity	2		
Clastogenicity	2		
Total	781		74

• Assume 500 mg/kg MTD and 50 mg/kg NOAEL in rodents

* Includes in vivo micronucleus assessment on study animals

DRF = dose range-finding



The expIND will accelerate discovery and development of new pharmaceutical agents

	Conventional IND	expIND
API	1 – 3 Kg	10 - 300 g
Preclinical Resources	<ul style="list-style-type: none"> • 9 – 12 studies • 220 rodent and 38 NR • 9 – 18 months 	<ul style="list-style-type: none"> • 5 – 6 studies • 170 rodent and 6 NR • 3 – 6 months
Comparison	<ul style="list-style-type: none"> • Full toxicology profile • MTD targeted in Ph1 • Progression directly to Ph2 • Late and costly attrition • Comprehensive, costly preclinical development • Program delays and BU strategy 	<ul style="list-style-type: none"> • Single species profile • Restricted dosing • IND required prior to Ph1 • Early and less costly attrition • Faster progression to clinical trials • Better development decisions made more quickly