Preclinical and CMC Development

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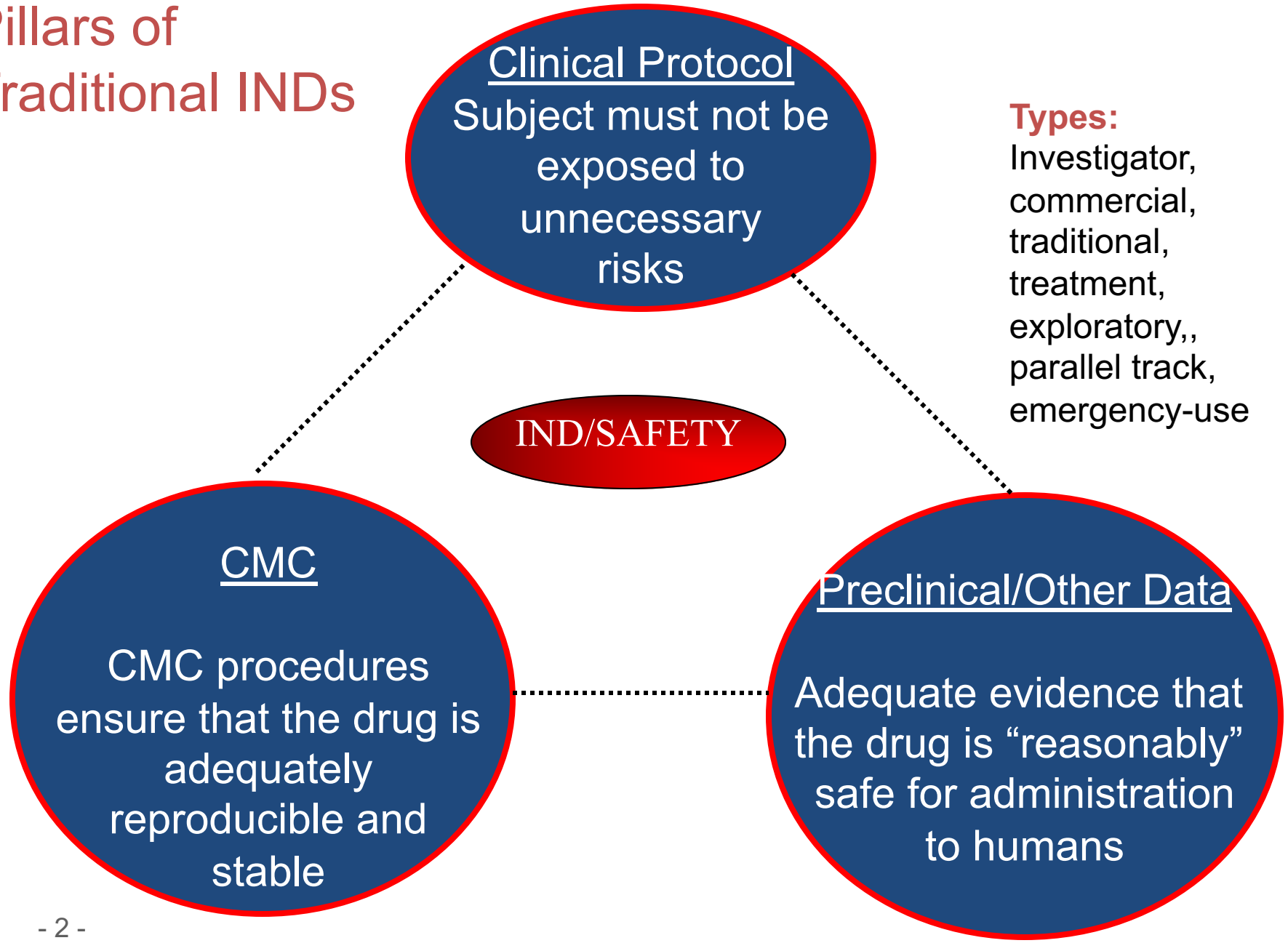
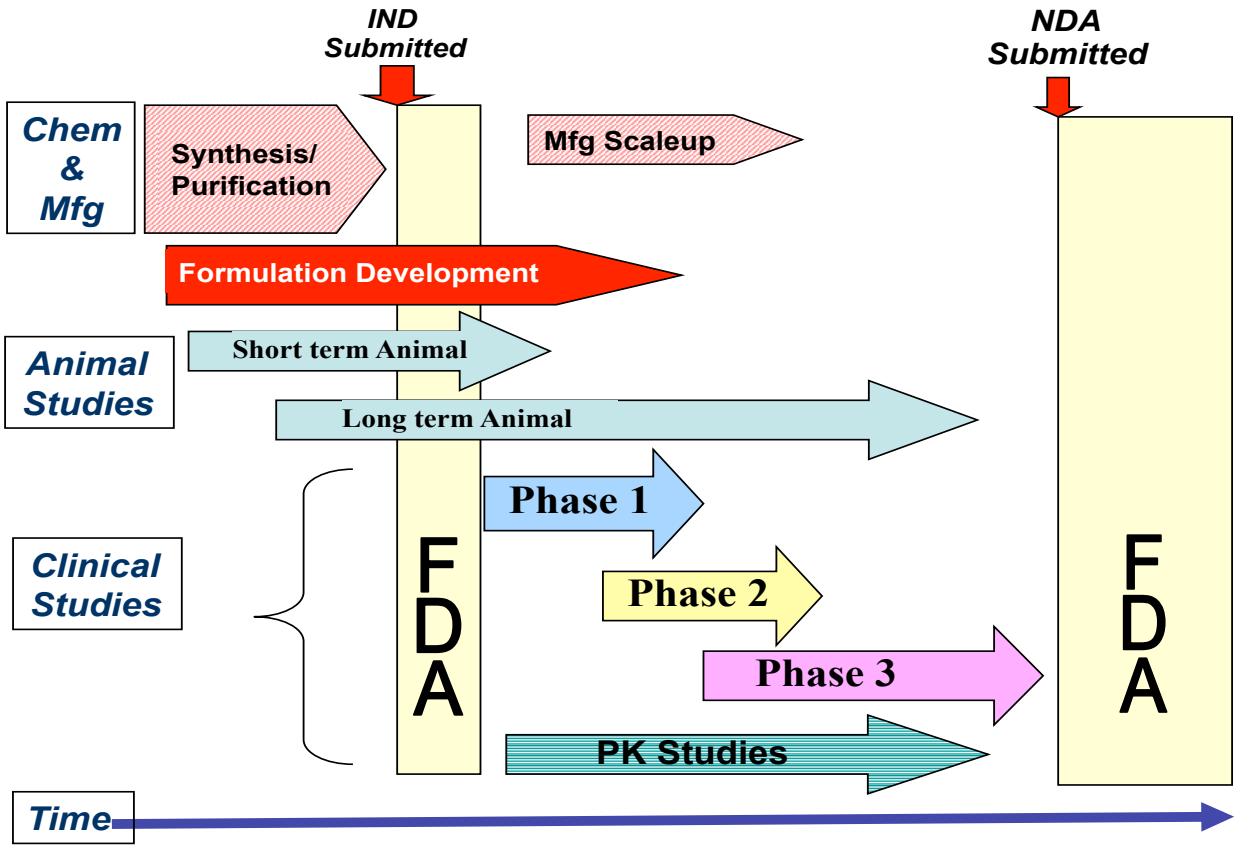
Pillars of Traditional INDs



Types:
Investigator, commercial, traditional, treatment, exploratory,, parallel track, emergency-use


IND Submitted
NDA Submitted
Chem & Mfg
Synthesis/ Purification
Mfg Scaleup
Formulation Development
Animal Studies
Short term Animal
Long term Animal
Clinical Studies
Phase 1
Phase 2
Phase 3
PK Studies
FDA
FDA
Time

Timeline

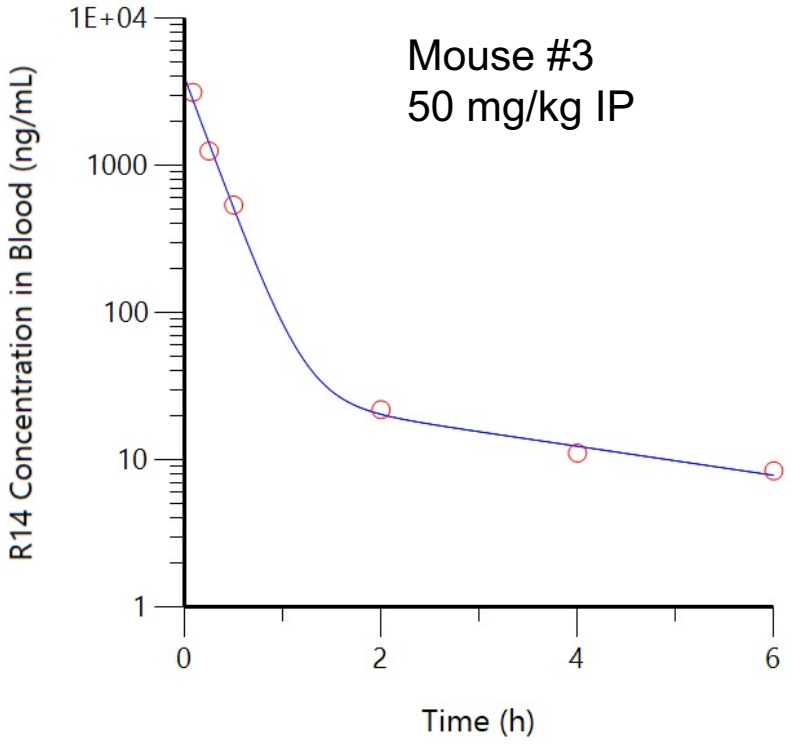
- **When do I need to consider a dosage formulation of my novel compound? Do I file patent protection for my formulation?**

- **When do I need to evaluate ADME in vitro? Why bother with PK? What information would PK/PD studies provide? To what extend do I need to do PK, mouse, rat, primates?**

- **What and when do I prepare Chemistry, Manufacturing and Control (CMC)?**

Case #1 – Dosage Formulation Matters

	Mouse 3 (new formulation	Mouse 1 (original formulation)	Mouse 2 (original formulation)
5 min	3130	114	1050
15 min	1250	24.9	51.9
30 min	537	-	-
45 min	-	18.6	29.5
2h	21.9	n.d.	31.3
4h	11.1	157	n.d.
6h	8.41	n.d.	34.7



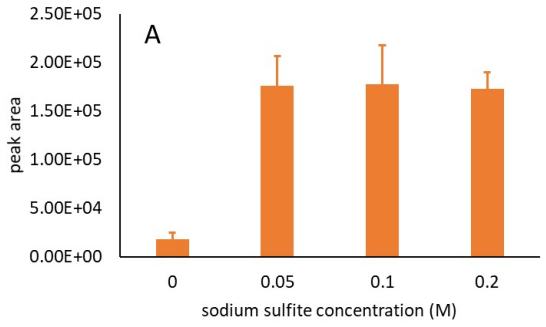
Original Formulation: Drug precipitates in aqueous media
New Formulation: Co-solvent, drug soluble in aqueous media

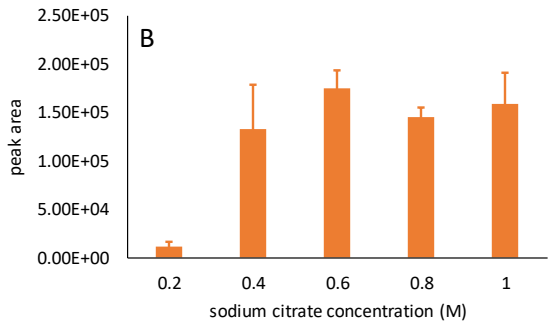
Case #2 – Drug Stability

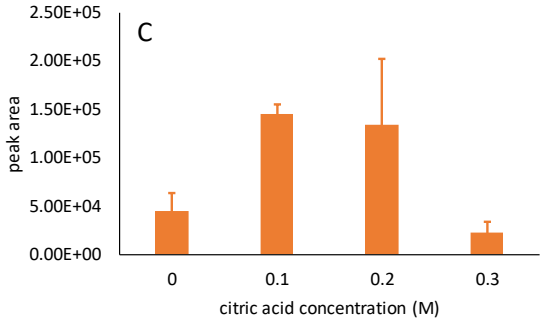
- Development an stability indicating LC-MS/MS assay for PK studies

PK blood samples were stored at -70°C freezer

Nominal concentration (ng/mL)	With preservative (n=3)	Without preservative (n=3)
	Observed concentration (mean ± SD)	Observed concentration (mean ± SD)
3	3.32±0.26	<1
50	50.63±2.19	5.52±1.18
800	832.75±58.49	114.8±30.3



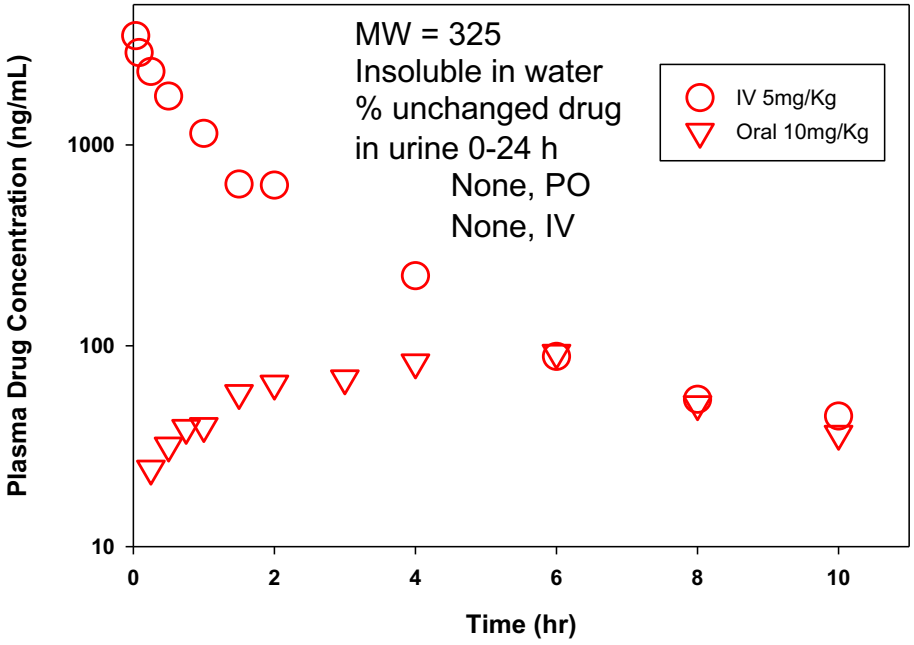




Preservative: 0.2 M sodium sulfite, 0.8 M sodium citrate, and 0.1 M citric acid

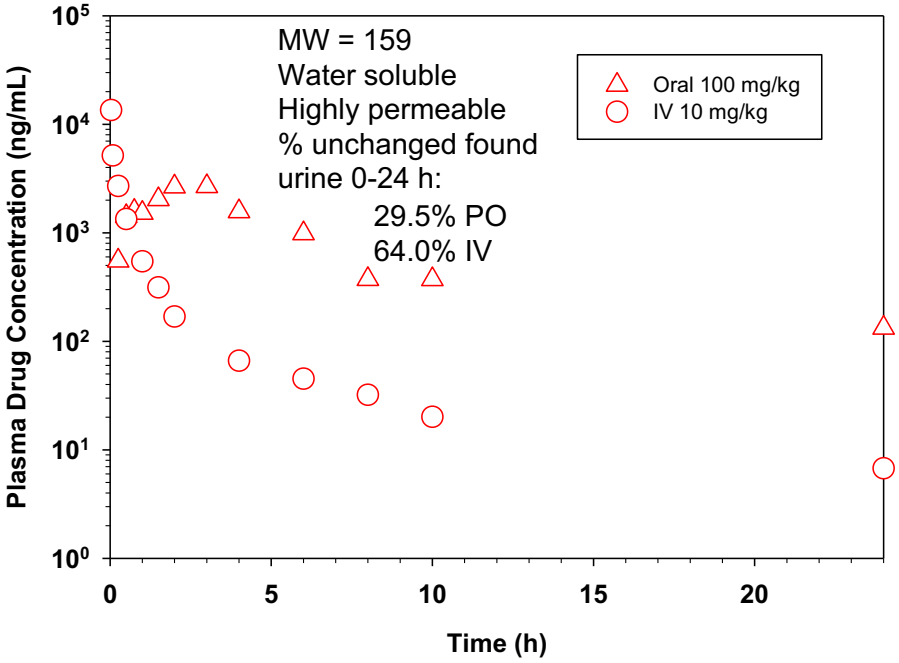
Case #3: Oral Bioavailability

Compound A



$F_{absolute}$ = 9.3%

Compound B



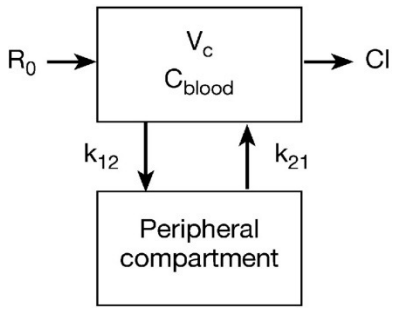
$F_{absolute}$ = 58.4%

Recommendation: go or no-go?

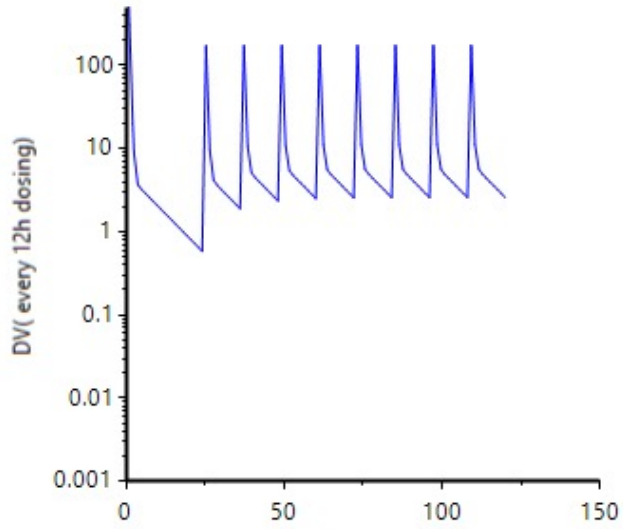
Case #4 - PK in Early Development Phase

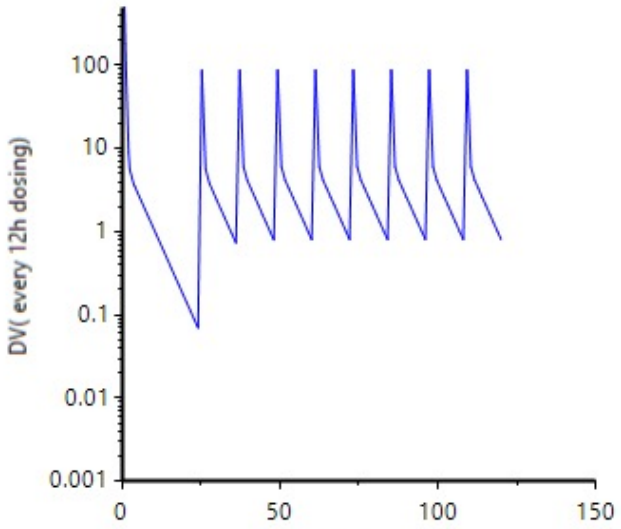
	5 days treatment				24 hour treatment			
Sampling time	M4 (ng/mL)	M5 (ng/mL)	M6 (ng/mL)	Mean±SD	M1 (ng/mL)	M2 (ng/mL)	M3 (ng/mL)	Mean±SD
15min	2048	3680	3464	3064±887	2616	2912	2128	2552±396
1 HR	221	241	122	195±64	132	221	266	206±68
2 HR	37.7	26.1	14.2	26±12	25.8	7.97	37.3	24±15
4 HR	5.97	5.36	6.68	6±0.7	3.1	3.97	9.85	5.6±3.7
8 HR	1.76	1.94	1.97	1.9±0.1	2.17	1.56	1.75	1.6±0.3
24 HR	0.61	0.63	0.6		ND	ND	ND	

Parameter	Units	CIDD150184 _5Day	CIDD150184 24hour
Number of Mice		3	3
AUC	hr*ng/ml	1765 ± 526	1682 ± 417
C_{max}	ng/ml	5600 ± 3154	5420 ± 2515
Alpha_HL	hr	0.24 ± 0.08	0.23 ± 0.06
Beta_HL	hr	7.60 ± 0.87	4.39 ± 0.74
CL	ml/hr	341.3 ± 120.7	345.4 ± 75.4
V_c	ml	130.9 ± 86.6	119.3 ± 53.5
V_2	ml	127.6 ± 91.0	58.6 ± 32.3
K_{12}	1/hr	0.09 ± 0.02	0.08 ± 0.02
K_{21}	1/hr	0.1 ± 0.01	0.17 ± 0.03

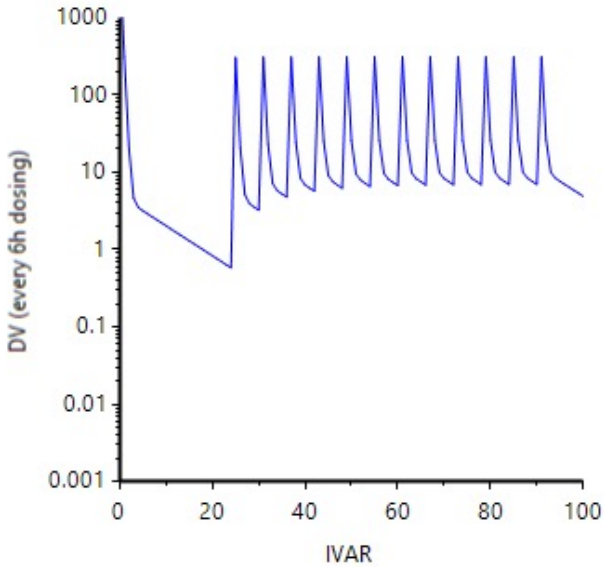


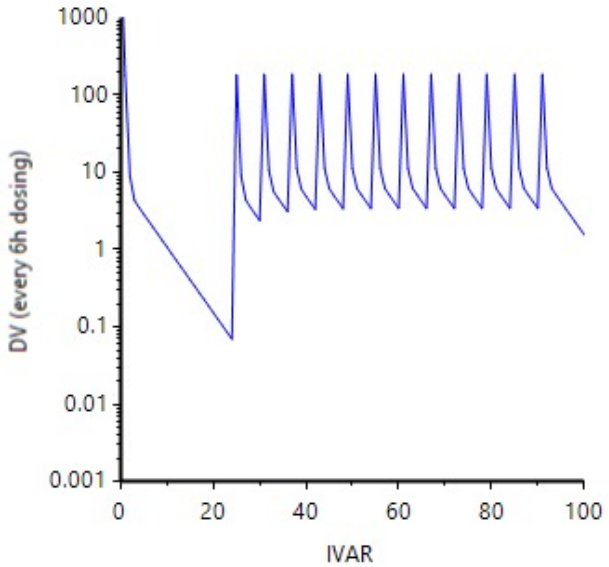
Steady-State Prediction





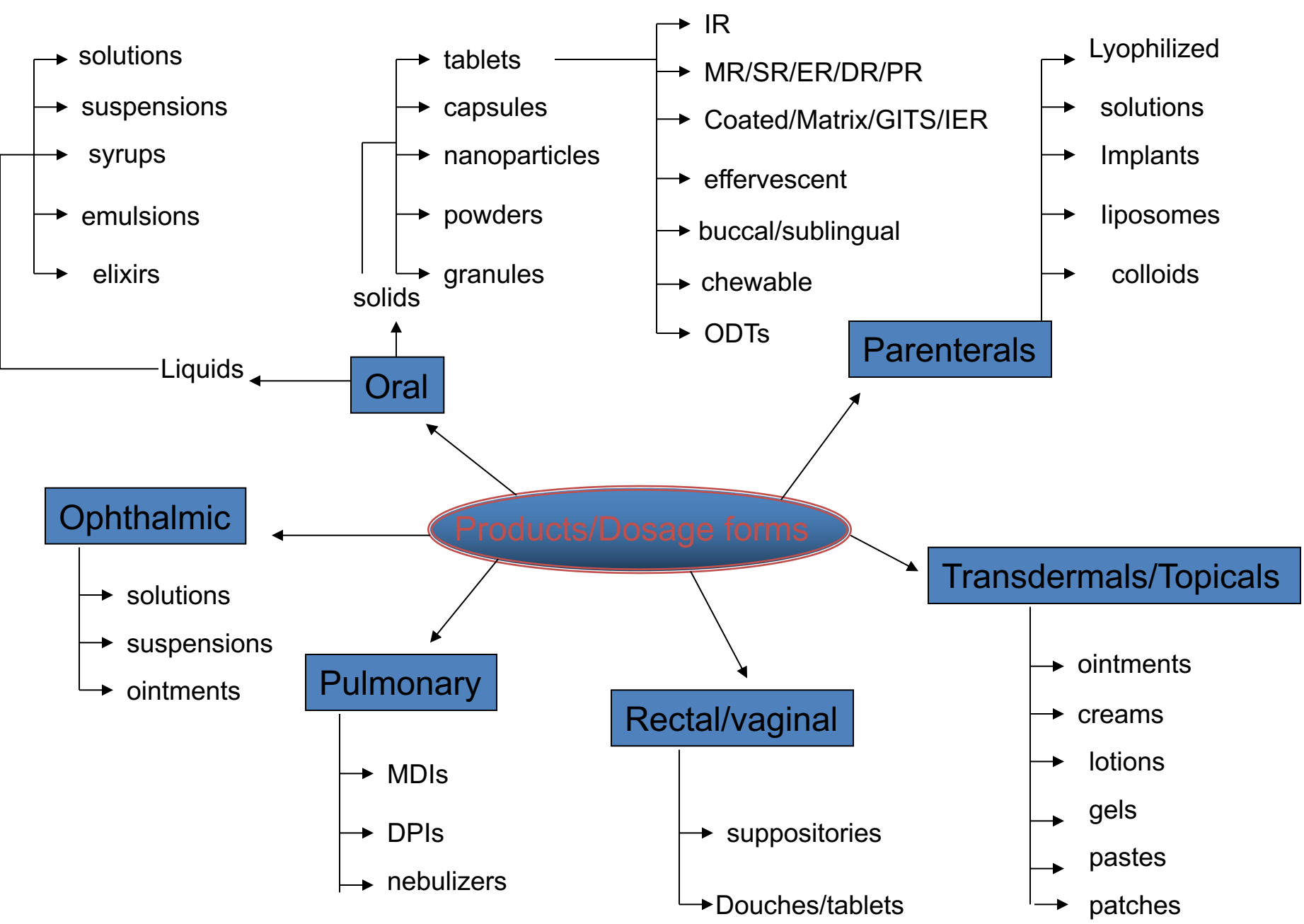
Dosed every 12 h



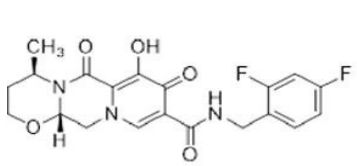


Dosed every 6 h

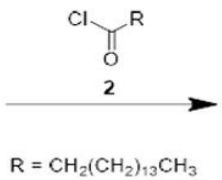
Target blood concentration = 400 ng/mL
Decision: Look for other analogs

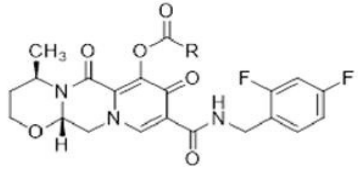

Products/Dosage forms
Oral
solids
tablets
IR
MR/SR/ER/DR/PR
Coated/Matrix/GITS/IER
effervescent
buccal/sublingual
chewable
ODTs
capsules
nanoparticles
powders
granules
Liquids
solutions
suspensions
syrups
emulsions
elixirs
Parenterals
Lyophilized
solutions
Implants
liposomes
colloids
Ophthalmic
solutions
suspensions
ointments
Pulmonary
MDIs
DPIs
nebulizers
Rectal/vaginal
suppositories
Douches/tablets
Transdermals/Topicals
ointments
creams
lotions
gels
pastes
patches

Prodrug Synthesis and Microparticles Preparation



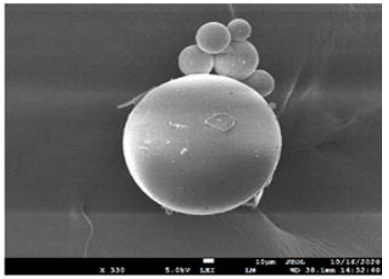
Dolutegravir





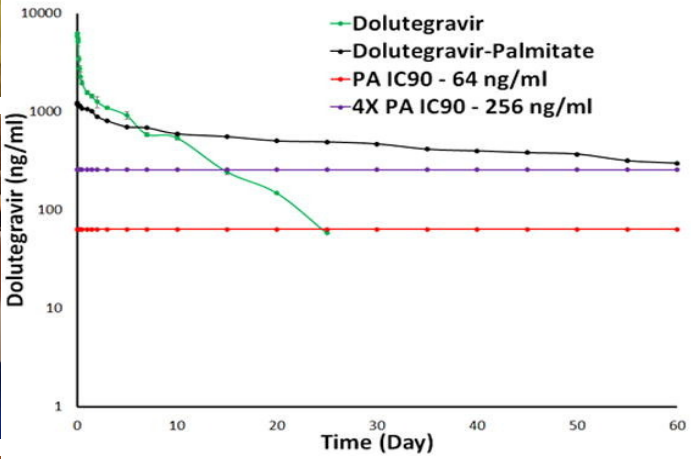
Dolutegravir-Palmitate

Encapuslation in biodegrdable microparticles

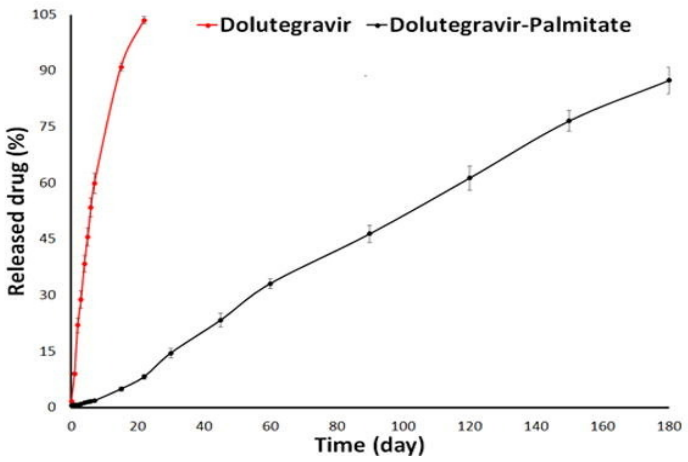


Microparticles

Pharmacokinetics



In-vitro release from microparticles



Enhancing solubility

Maximum Solubility of Gallium Maltolate at 37°C, after which it precipitates

Solvent	Ratio	Amount (mg)	Volume (mL)	Solubility (mg/mL)
EOH: water	(1:1)	145.9	4	36.5
EOH: water	(2:1)	113.8	3	37.9
EOH: water	(1:2)	115.2	3	38.4
PG: EOH: water	(1:1:1)	123.3	3	41.1
PG: EOH: water	(1:2:1)	165.6	4	41.4
PG: EOH: 0.1 N NaOH	(1:1:1)	109.5	3	36.5

Approaches used to enhance solubility: Micro/nanosizing, surfactants, cosolvents, inclusion compounds, and others