IN VIVO FAST PK SCREENING: A CRO PERSPECTIVE

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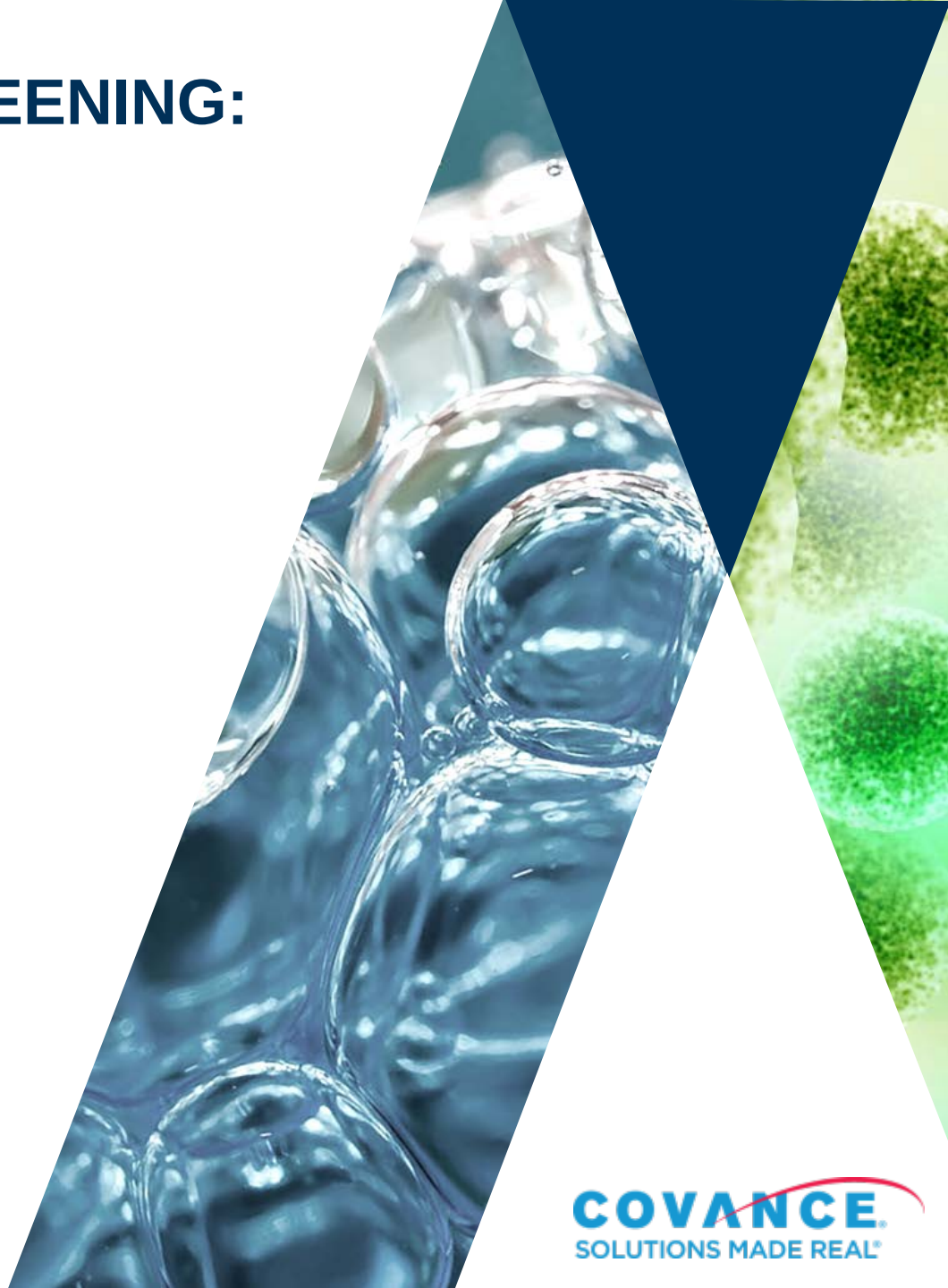
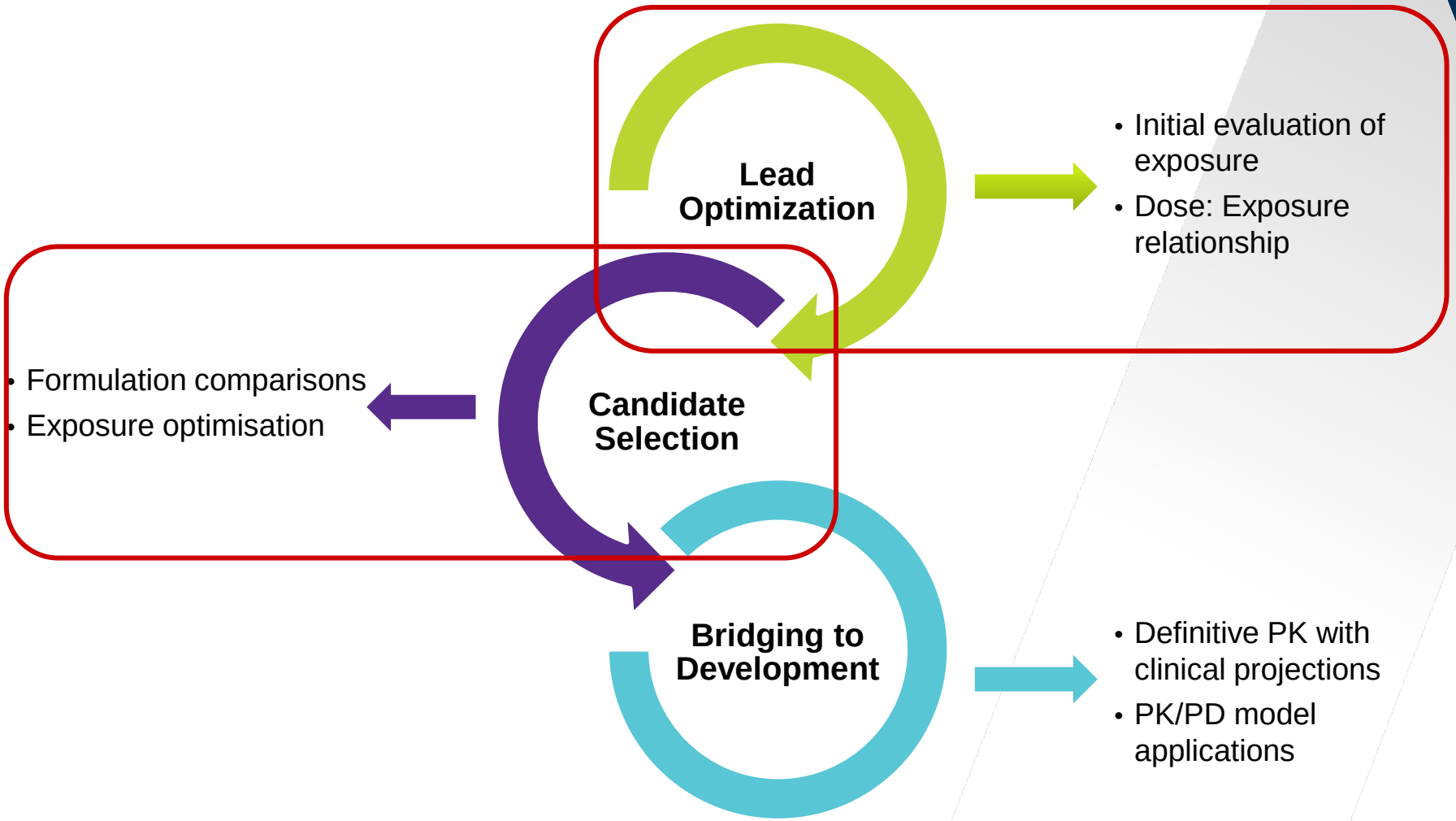


COVANCE
SOLUTIONS MADE REAL®

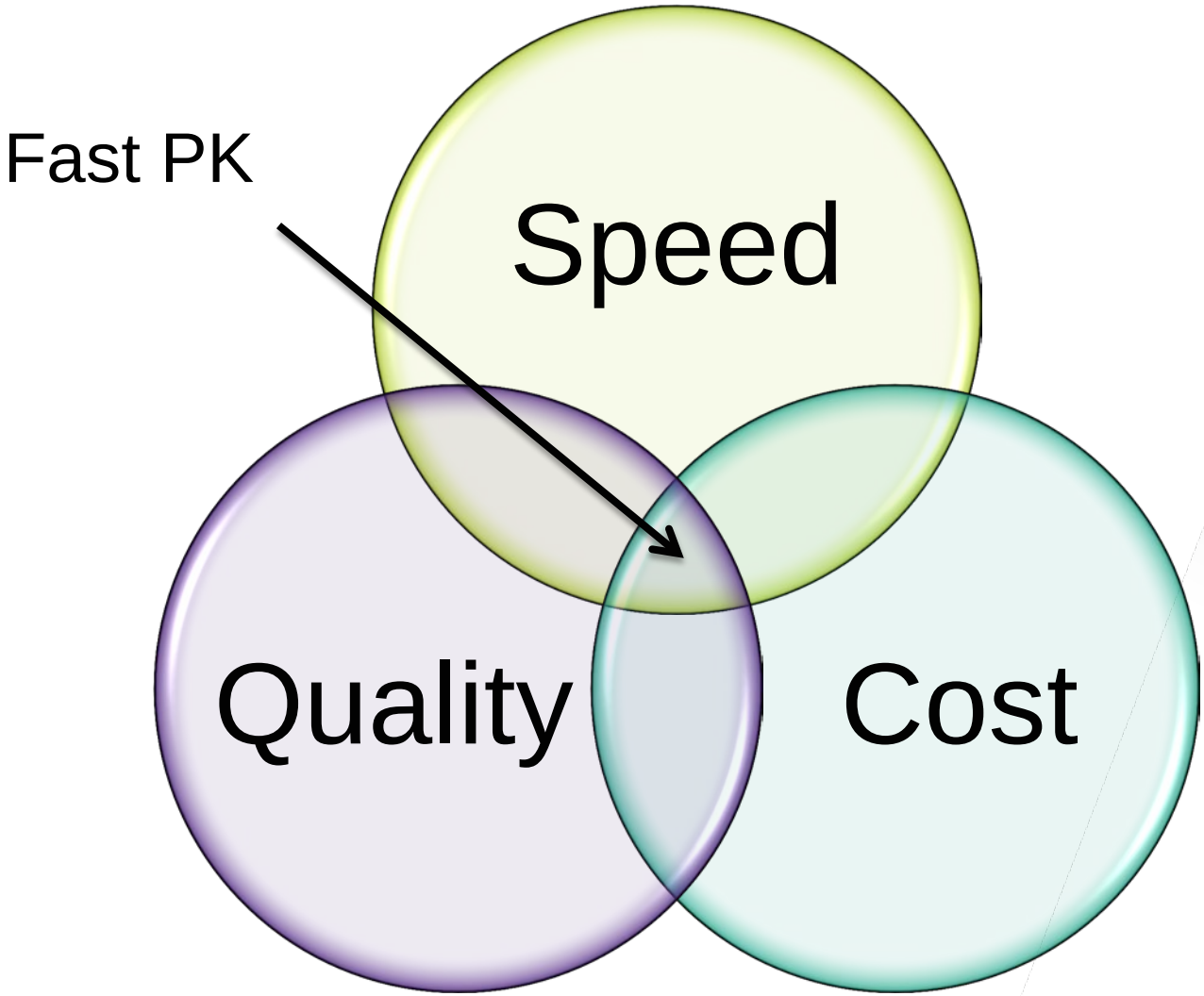
Introduction

THE MANY FACES OF PHARMACOKINETICS



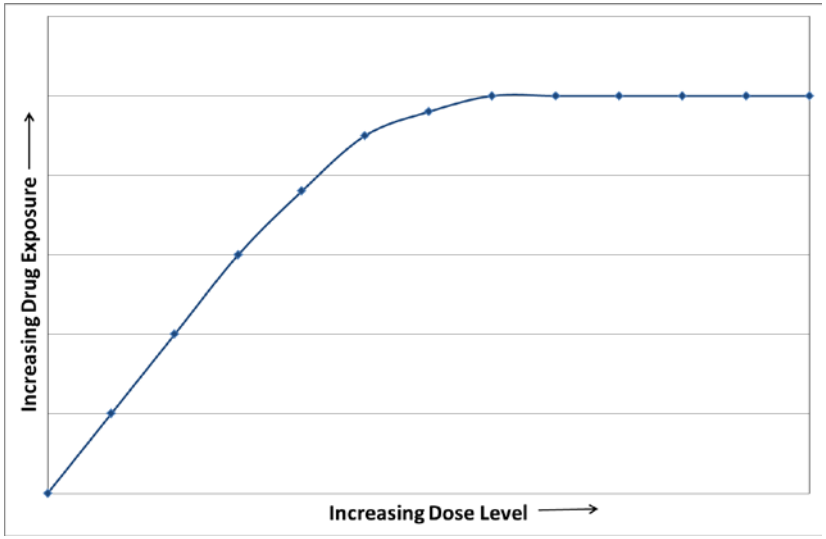
Finding Synergy Between Speed, Cost & Quality

THE BEST OF ALL THREE

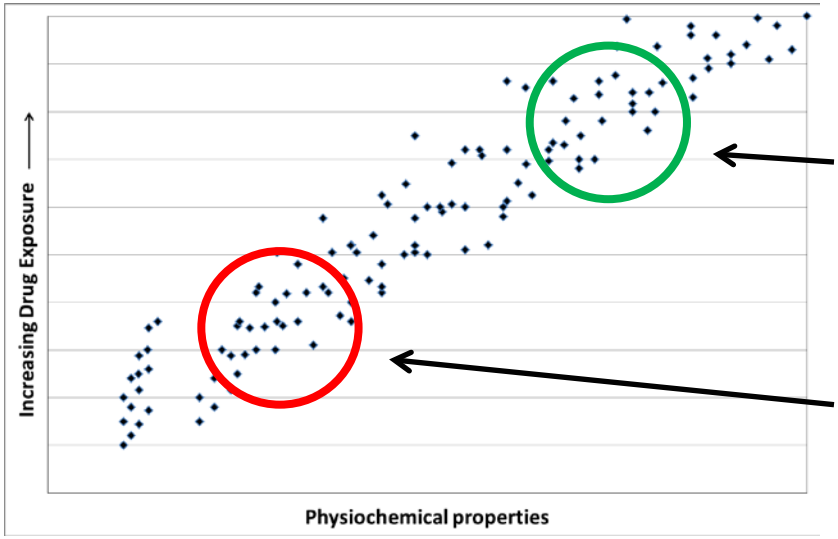


Why Fast PK?

WHAT QUESTIONS ARE WE LOOKING TO ANSWER



- Is drug exposure linear with increasing dose?
- Is target exposure (e.g. organ) limited?
- How do different formulation preparations impact exposure?

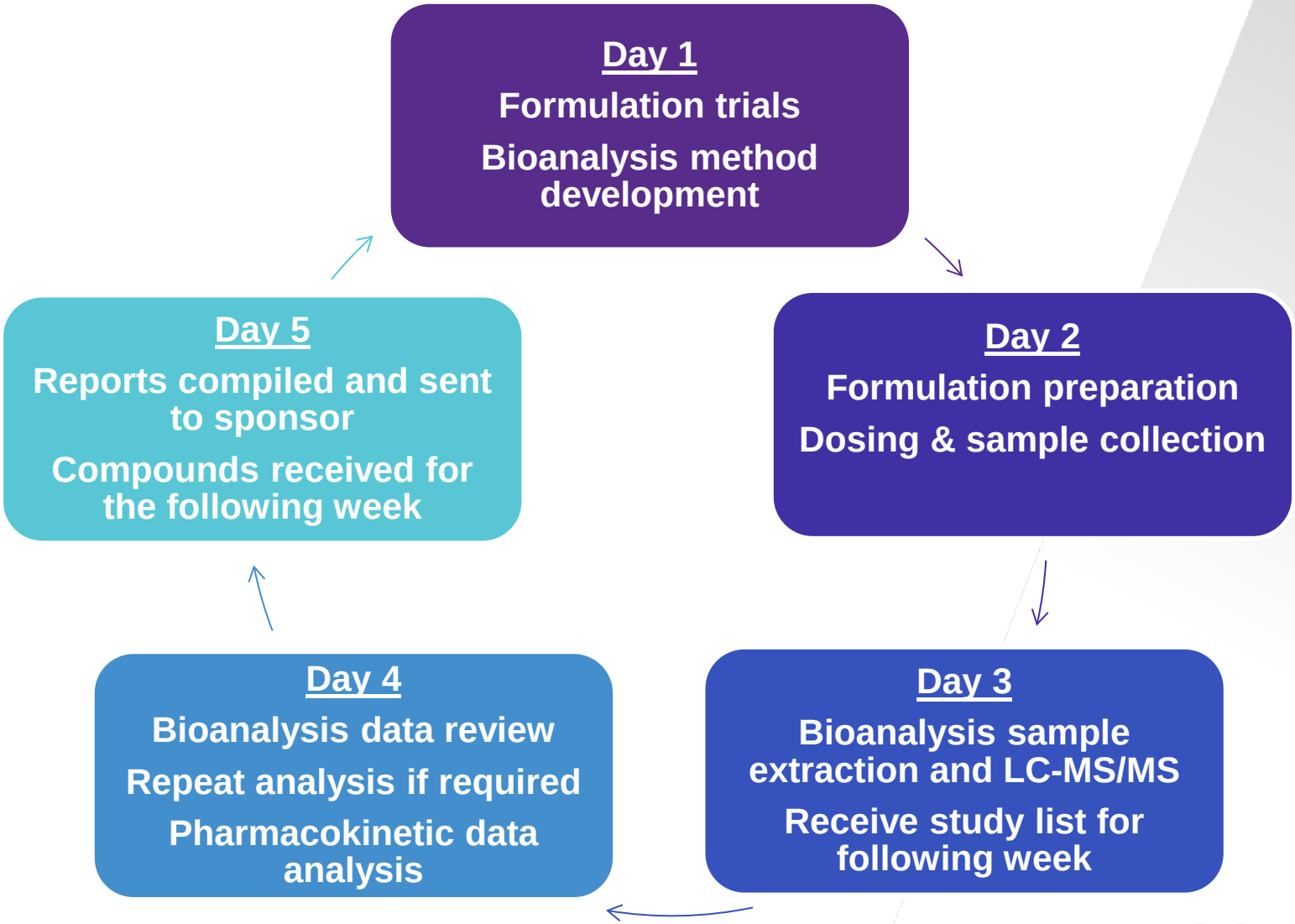


Good exposure – physical/chemical properties to emulate in lead optimization

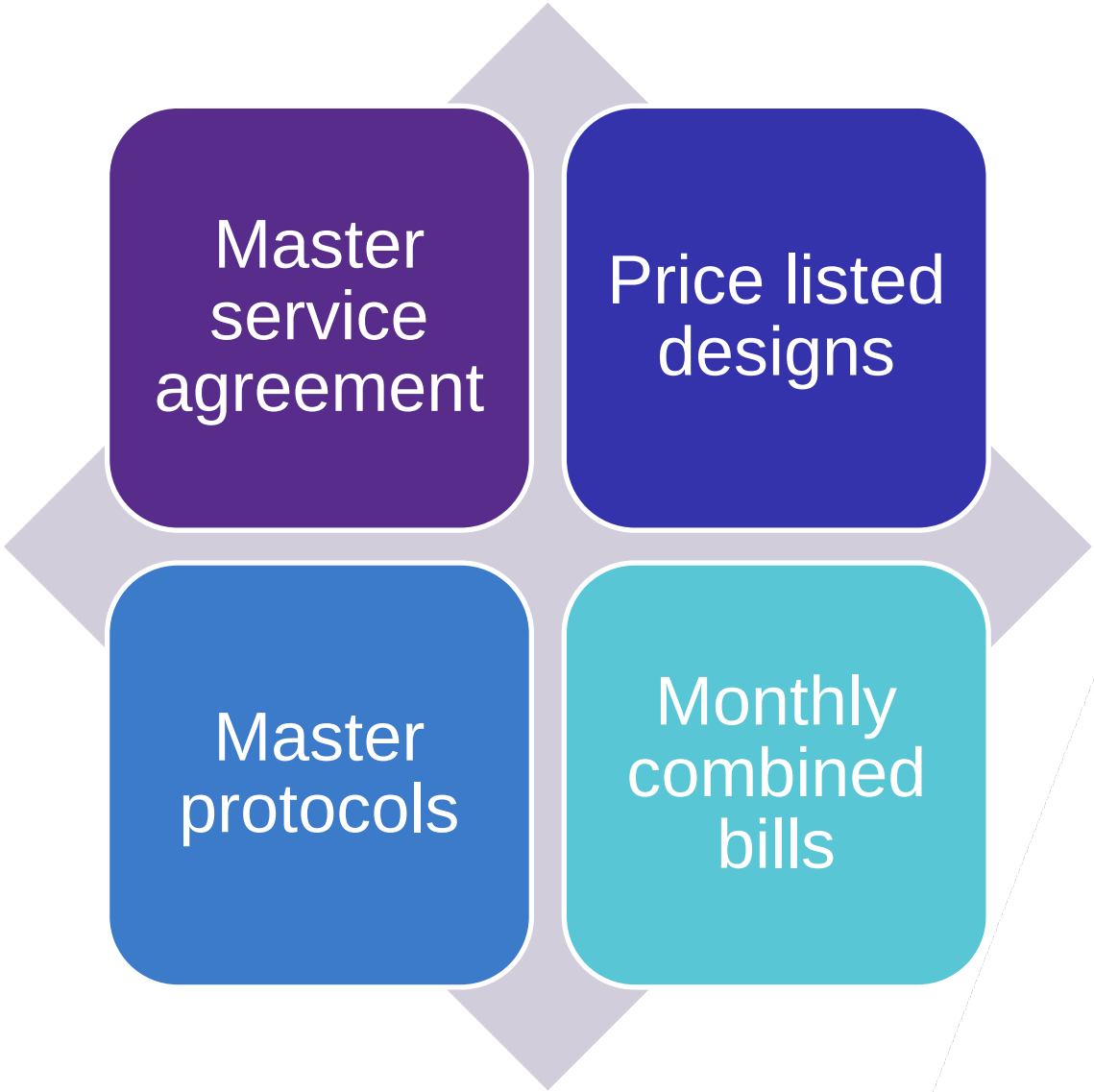
Poor exposure – physical/chemical properties to avoid with future lead optimization

What is Fast PK?

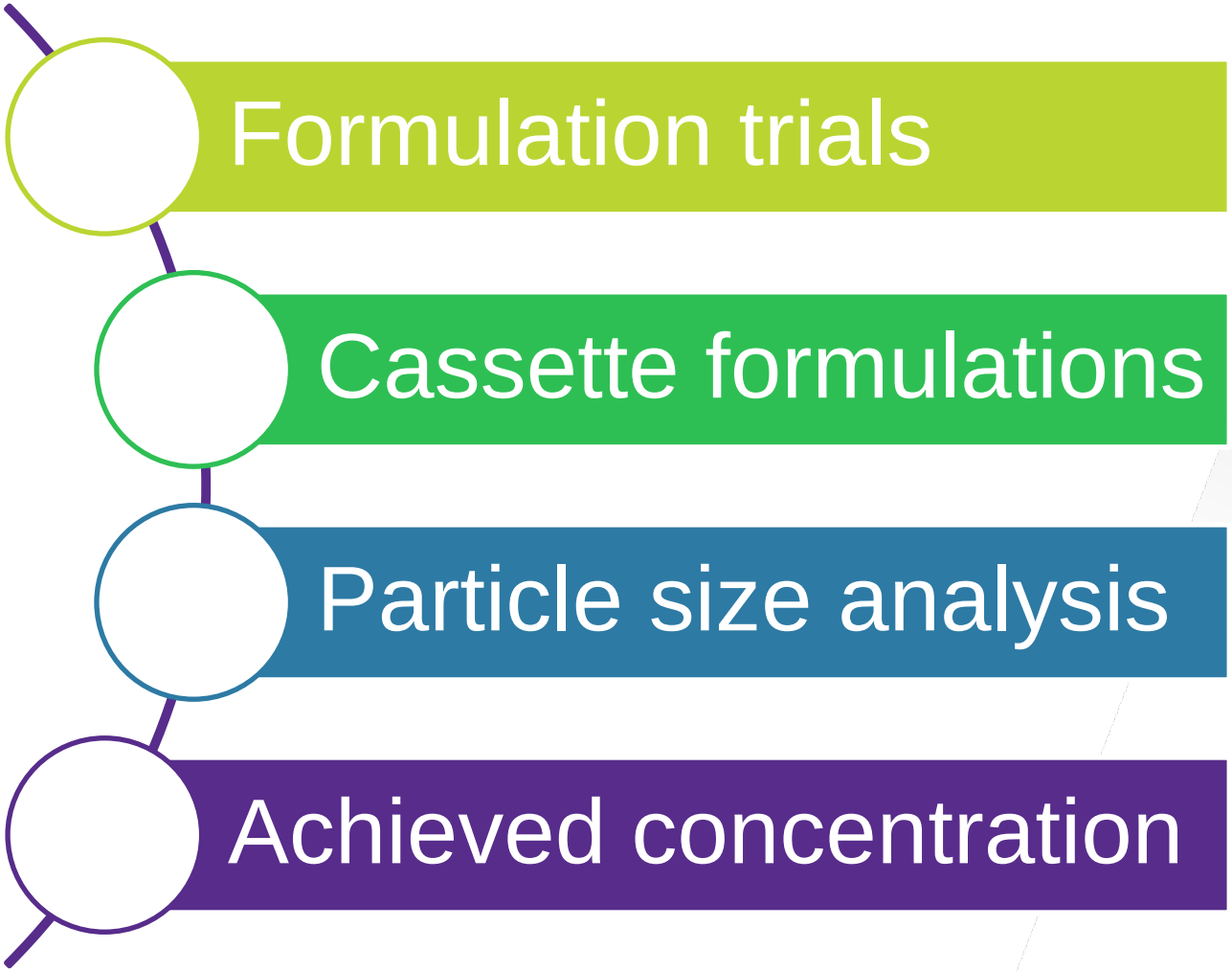
How Does it Work?



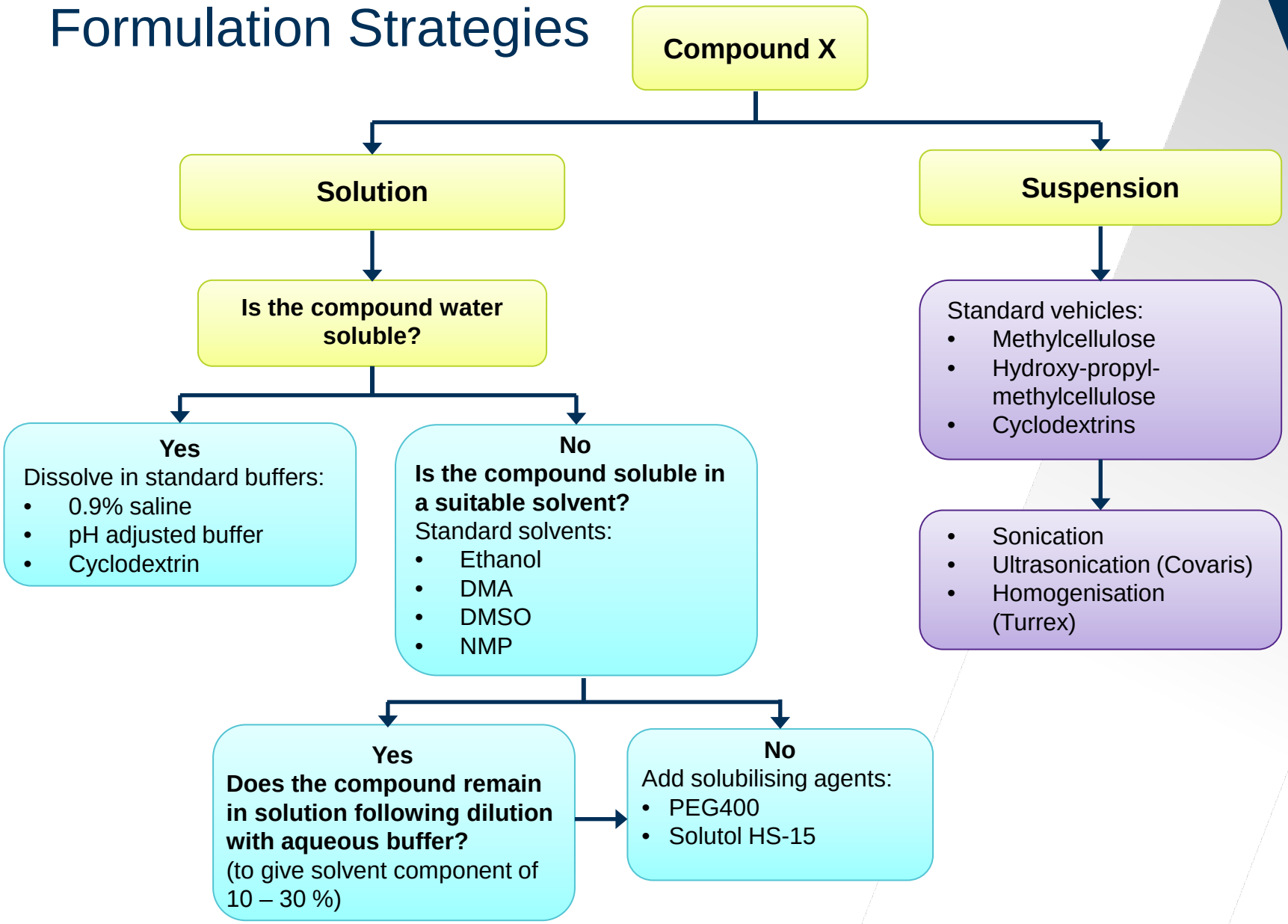
Study Initiation



Formulation Development

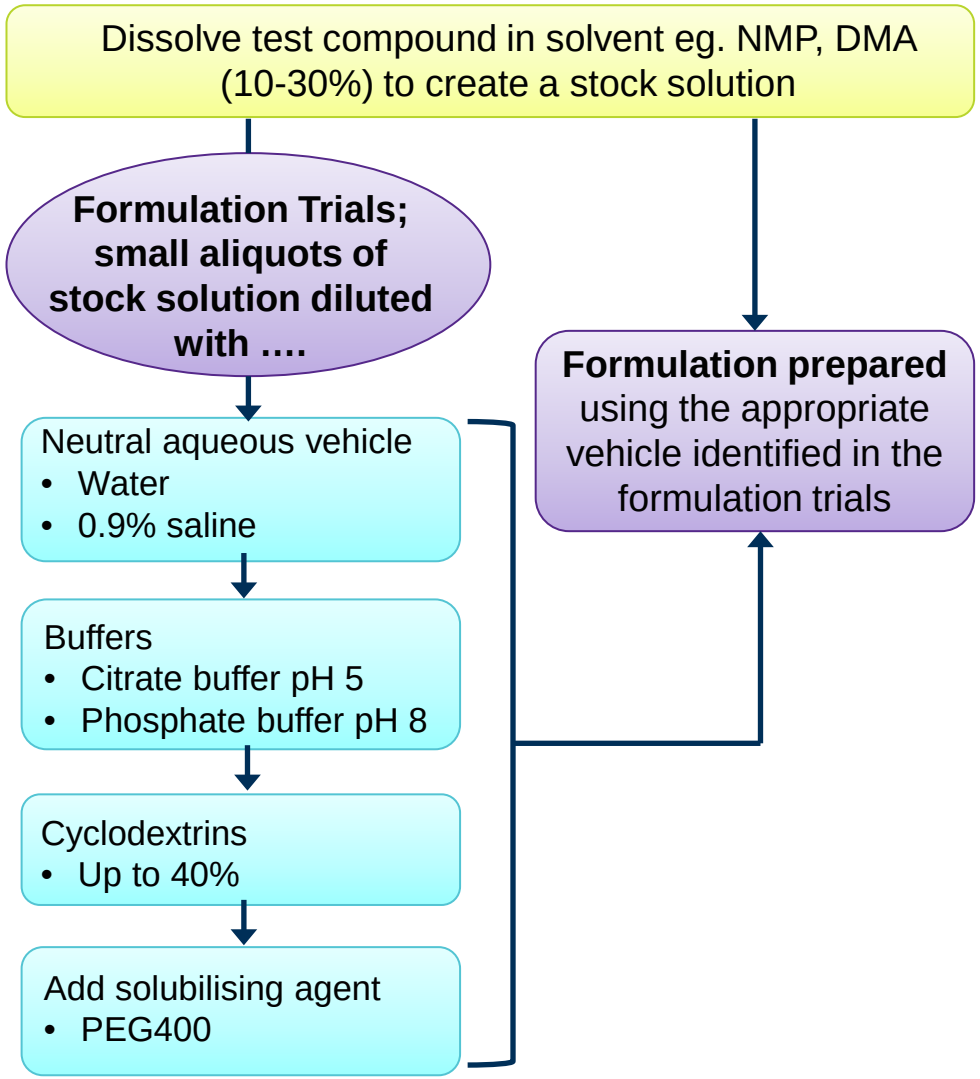


Formulation Strategies



Fast PK Formulation Strategy

Solution (single administration, rodents)



Pros

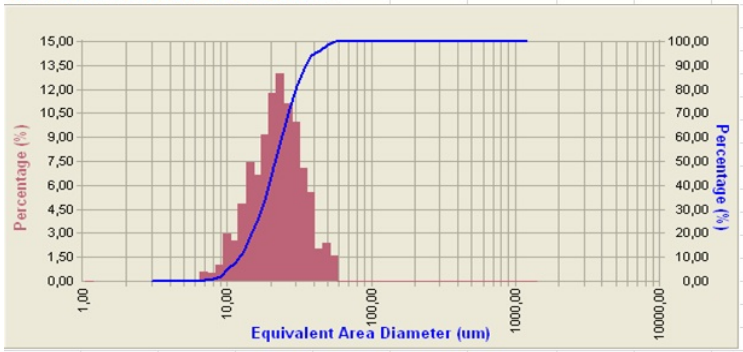
- Saves time on developing individual formulations.
- Conserves test compound.
- Checks for cassette interactions.
- Effective for *ca* 95% of test compounds.

Cons

- Insoluble compounds only identified immediately prior to dosing.
- Postpones administration of these compounds.
- Tailored formulation development still required for large animal and repeat dose studies.

Particle Size Analysis

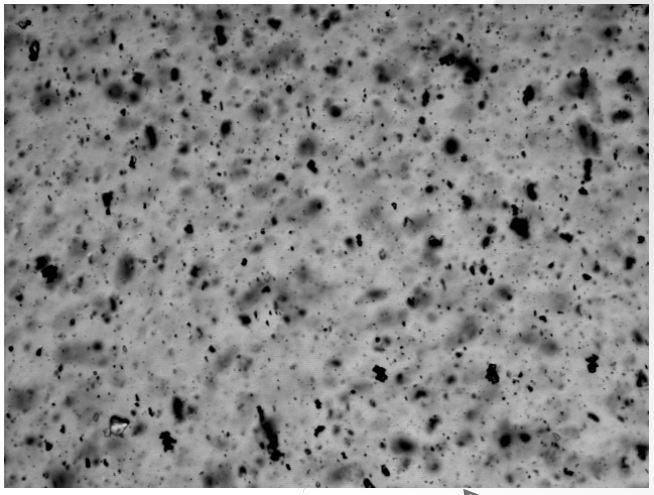
Volume Histogram and Cumulative Undersize
Parameter: Equivalent Area Diameter Group: ALL (15000) (Full scale)
Mean: 22.98 um STD: 9.38 um Conf.: 100.00 %
D10 : 12.09 um D50: 21.78 um D90: 35.55 um



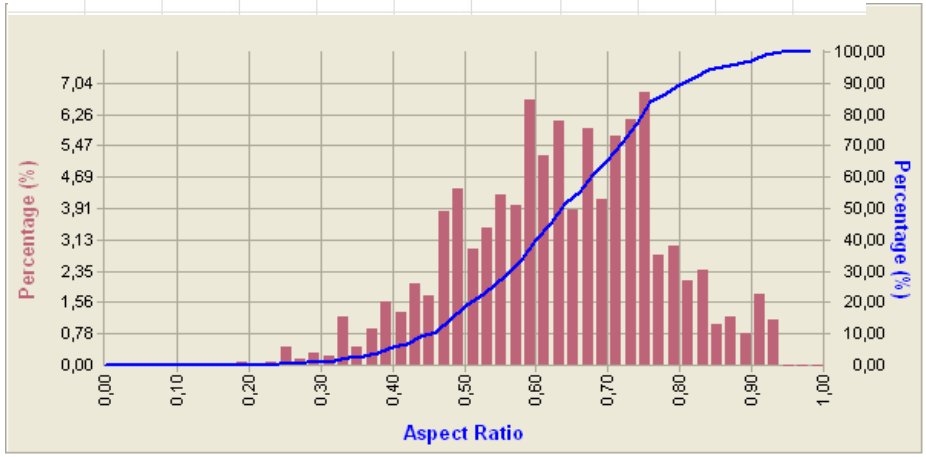
Volume Equivalent Area Diameter Percentage Table (ID#:129) (#Particles Percentage) (Status: Full scale)

Under(%)	Size (um)	Under(%)	Size (um)	Under(%)	Size (um)	Under(%)	Size (um)
0.00	5.46	30.00	17.19	60.00	23.82	90.00	35.55
10.00	12.09	40.00	19.23	70.00	26.88	100.00	54.93
20.00	15.15	50.00	21.78	80.00	30.45		

Combination of graphs and statistics to break down the analysis



Live image capture



Aspect ratio indicates the shape of the particles in the formulation

Achieved Concentration Analysis

LC-MS/MS

- Analyse alongside plasma samples
- Requires only a small volume of formulation
- Estimation / confirmation of concentration only

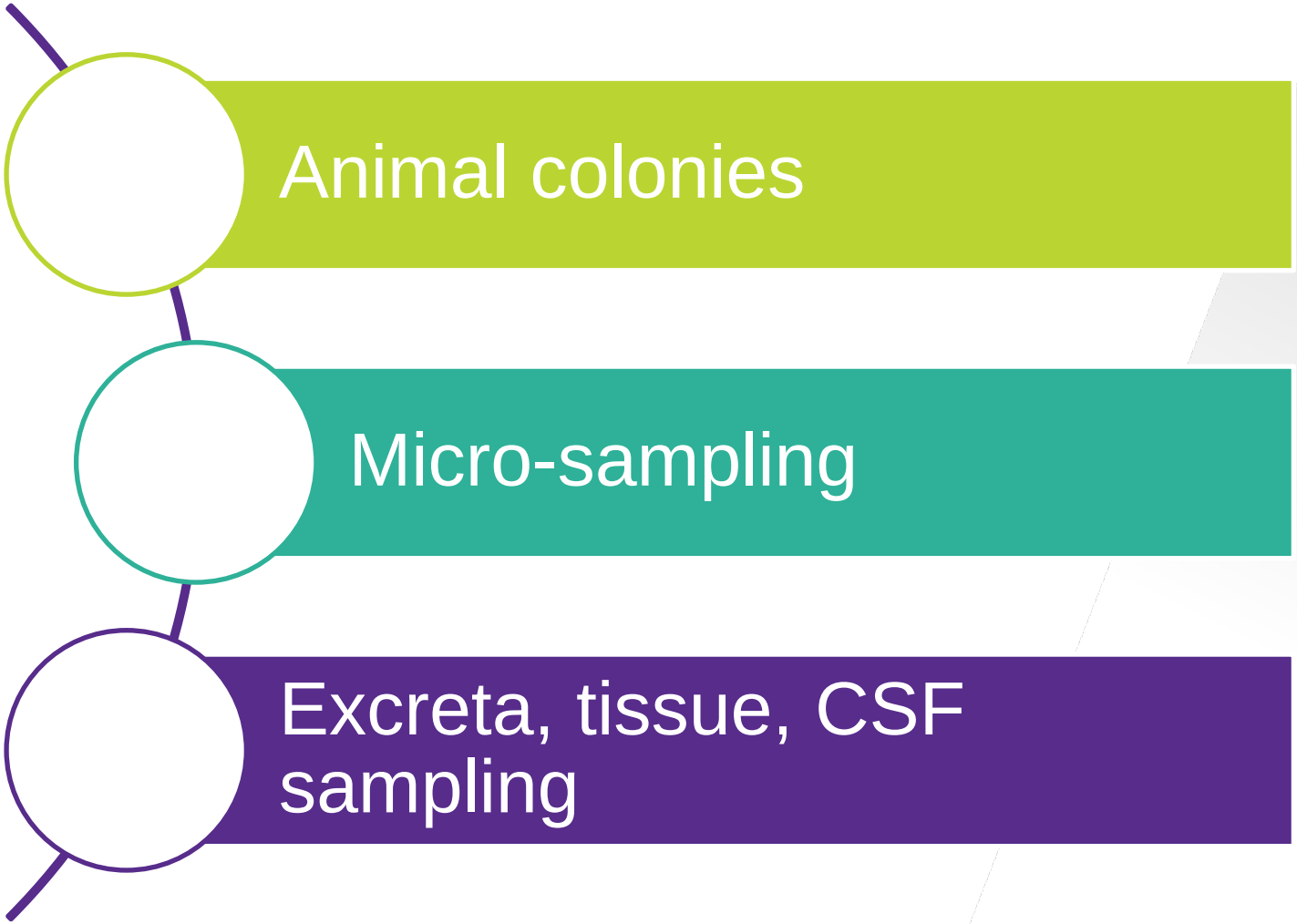
HPLC

- Validated methods using calibration curves
- Qualified methods using bracketed standards
- Requires only a small volume of formulation

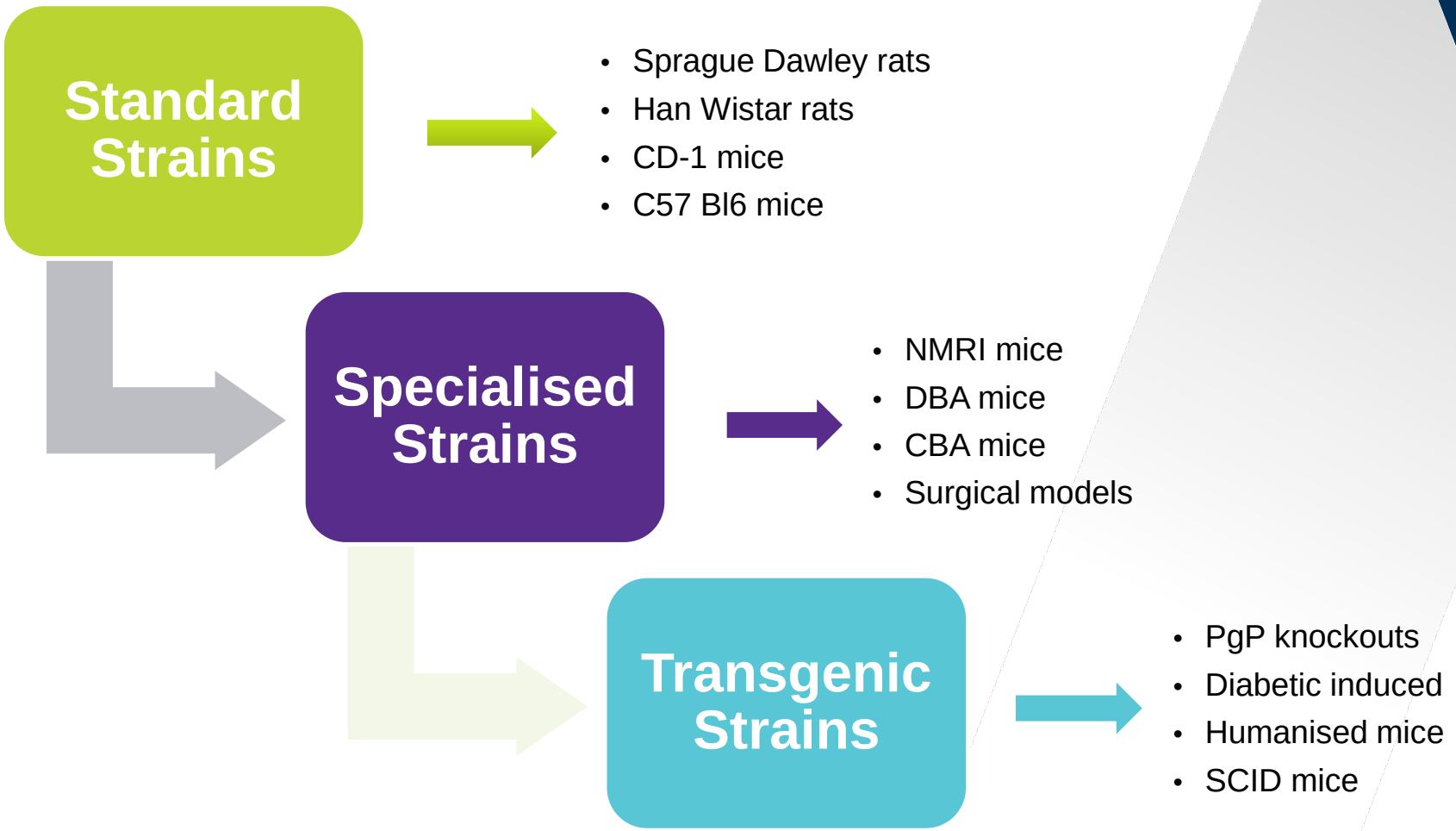
UV

- Fast measurements
- Requires validated / qualified methods
- Requires large volumes of formulation and vehicle

In-life



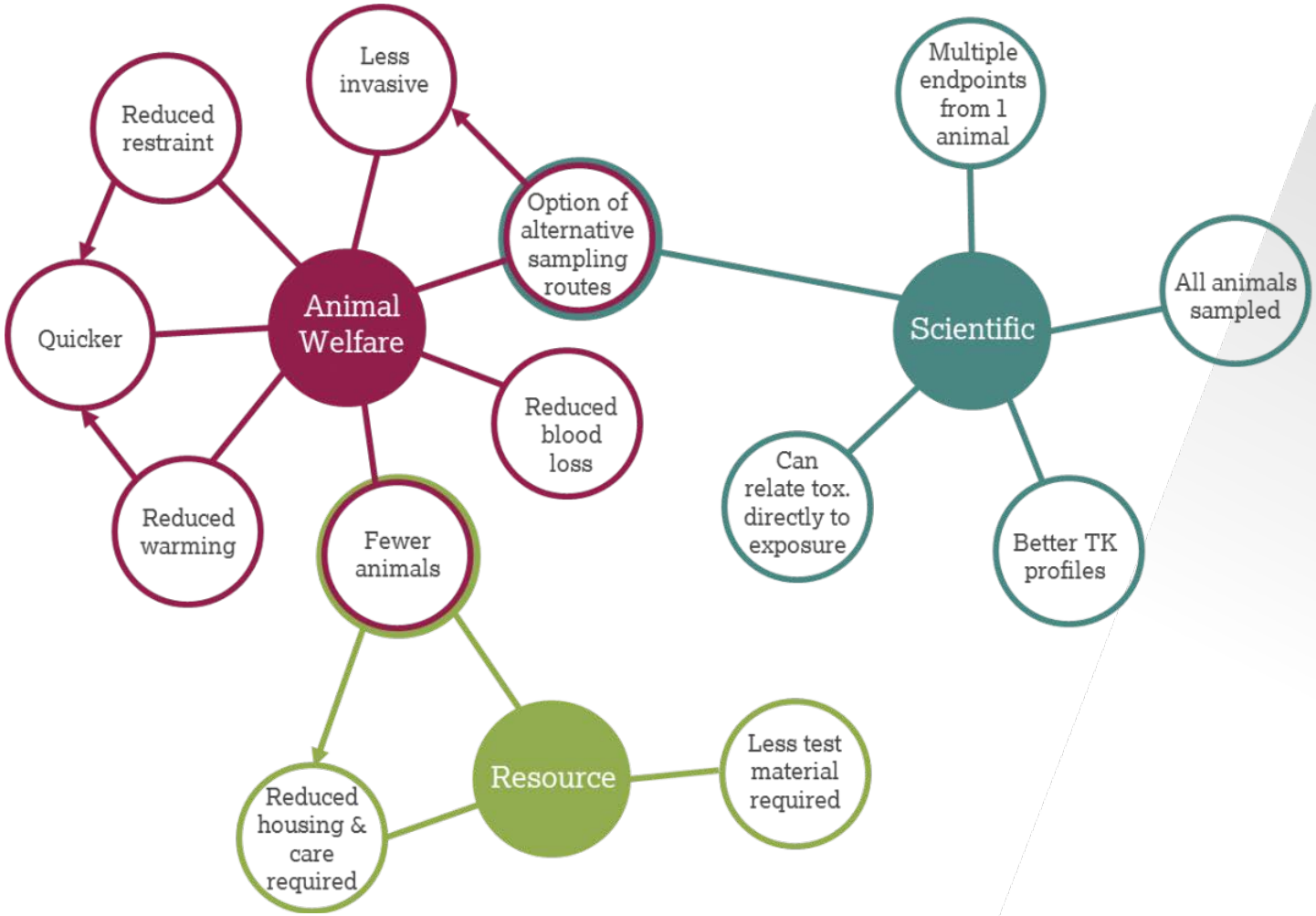
Rodent Colonies



Non-rodent Colonies

Covance colonies	• No ongoing management costs to sponsor • Study requests placed in the general schedule
Sponsor colonies	• Available when required • Re-use the same animals on multiple linked projects
Ethical re-use	• Weekly dosing • Treatment free week after three successive uses • Monitor animal health and blood volume limits
Acclimatisation and training	• Extended training and familiarisation of animals and technicians • Train primates to extend arm for blood sampling (future development)

Benefits of Micro-sampling



Source: NC3R's Microsampling Resource, https://www.nc3rs.org.uk/microsampling, Accessed 24 July 2018

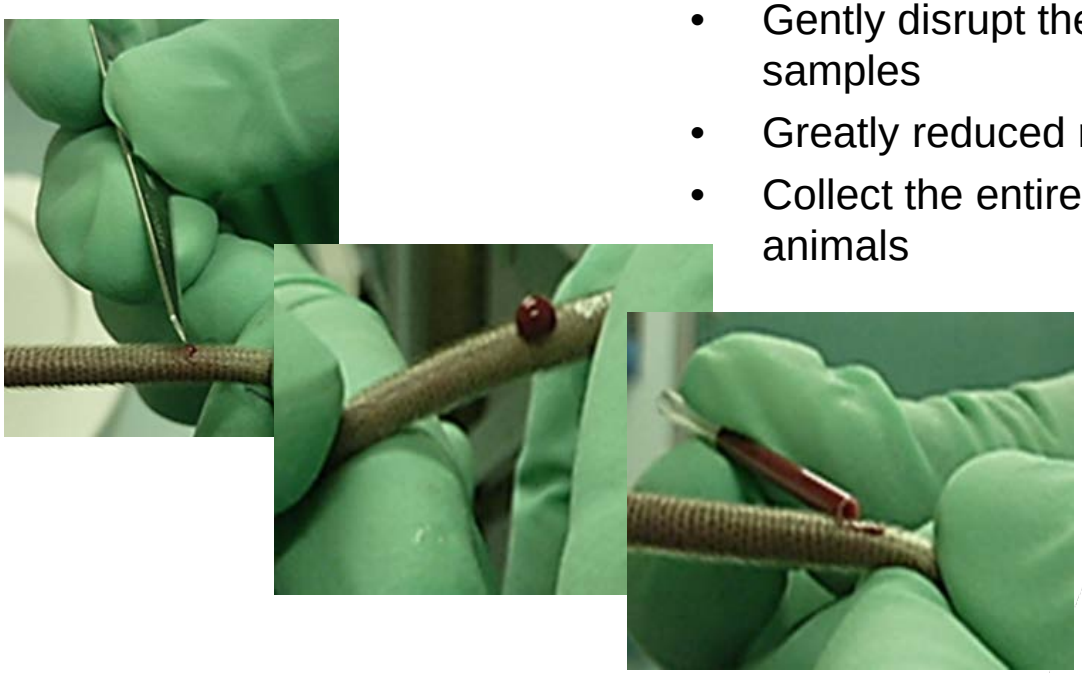
Mouse Tail Nick Sampling

Previous model

- Tail vein venepuncture
- Extensive warming of animals
- Bruising to the tail
- Multiple cohorts of animals
- *ca* 3 samples/animal

New model

- Superficial transection of the lateral tail vein
- Gently disrupt the healing to collect subsequent samples
- Greatly reduced requirement to warm the animals
- Collect the entire profile from a single cohort of animals



Rat Blood Sampling

Jugular Vein Venepuncture

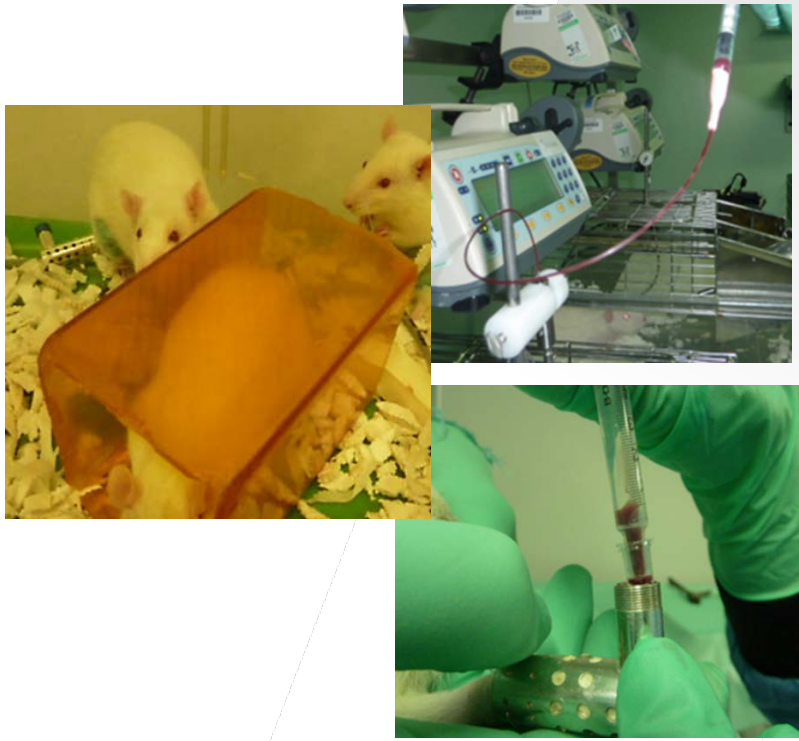
- No requirement to warm the animals
- Rapid sampling
- Good for larger sample volumes
- Invasive when taking multiple samples

IV/PO Cross-over

- Surgically cannulated animals (femoral & jugular)
- iv and po doses to same animals
- 24h wash-out between each phase
- No intra-animal variability
- Absolute bioavailability from same animals

Tail Vein Venepuncture

- Minimally invasive
- Requires animals to be pre-warmed
- Not ideal following IV dosing



Dog and Primate Micro-Sampling

Previous model

- Jugular (dog) or femoral (primate) venepuncture
- Effective for large volume collections
- Repeat sampling invasive
- Difficult to collect small volumes

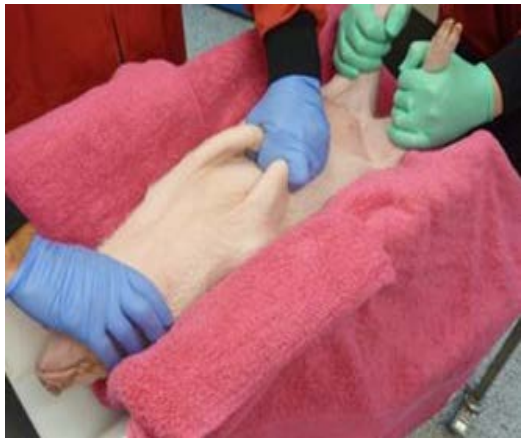
Future model

- Micro-sampling *via* more easily accessible veins (cephalic, saphenous, tail vein)
- Closed system capillaries for sampling accurate volumes
- Quick, minimally invasive sampling
- Reduction in volume of blood sampled

Re-use of Minipigs

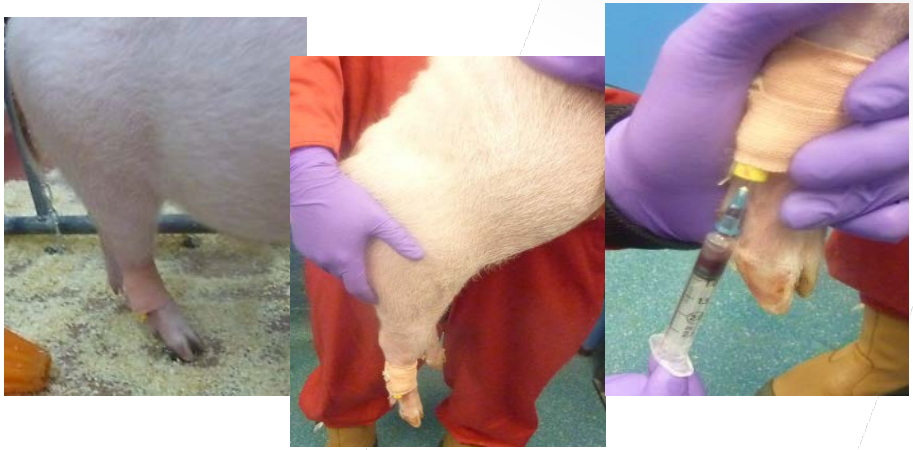
Previous model

- Re-use was limited to animals which had had mild or one moderate procedure
- Single iv/po study per animal (2 phases), then termination



New model

- Saphenous vein cannulation for sampling
- Mild/Moderate procedure under anaesthesia
- Potentially no further needle insertions
- Re-use with 10 days between phases



Additional Samples

Cannulation models	• Bile duct (rats, dogs, primates) • Intestinal (rats) • Vascular (femoral, jugular, portal vein)
Terminal tissue sampling	• Rodents • With or without perfusion
Biopsies from non-rodents	• Skin biopsies (pigs) • Liver biopsies (dog and primate) • Muscle (primates)
CSF	• Terminal (rats and mice) • Serial (rats, dogs and primates)

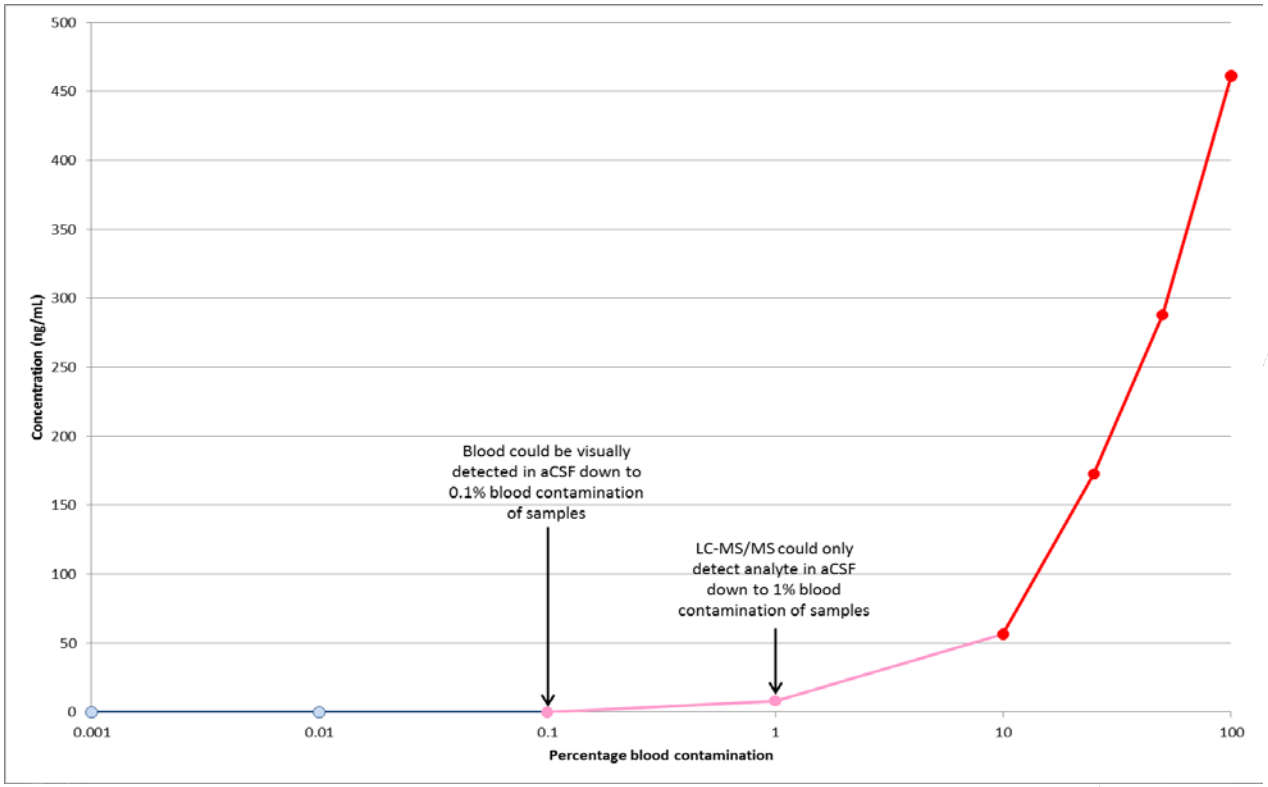
Mouse CSF Sampling

Success rate = 80% ✓

Achieved in albino CD-1 and pigmented C57 mice (based on visually clear CSF appearance)

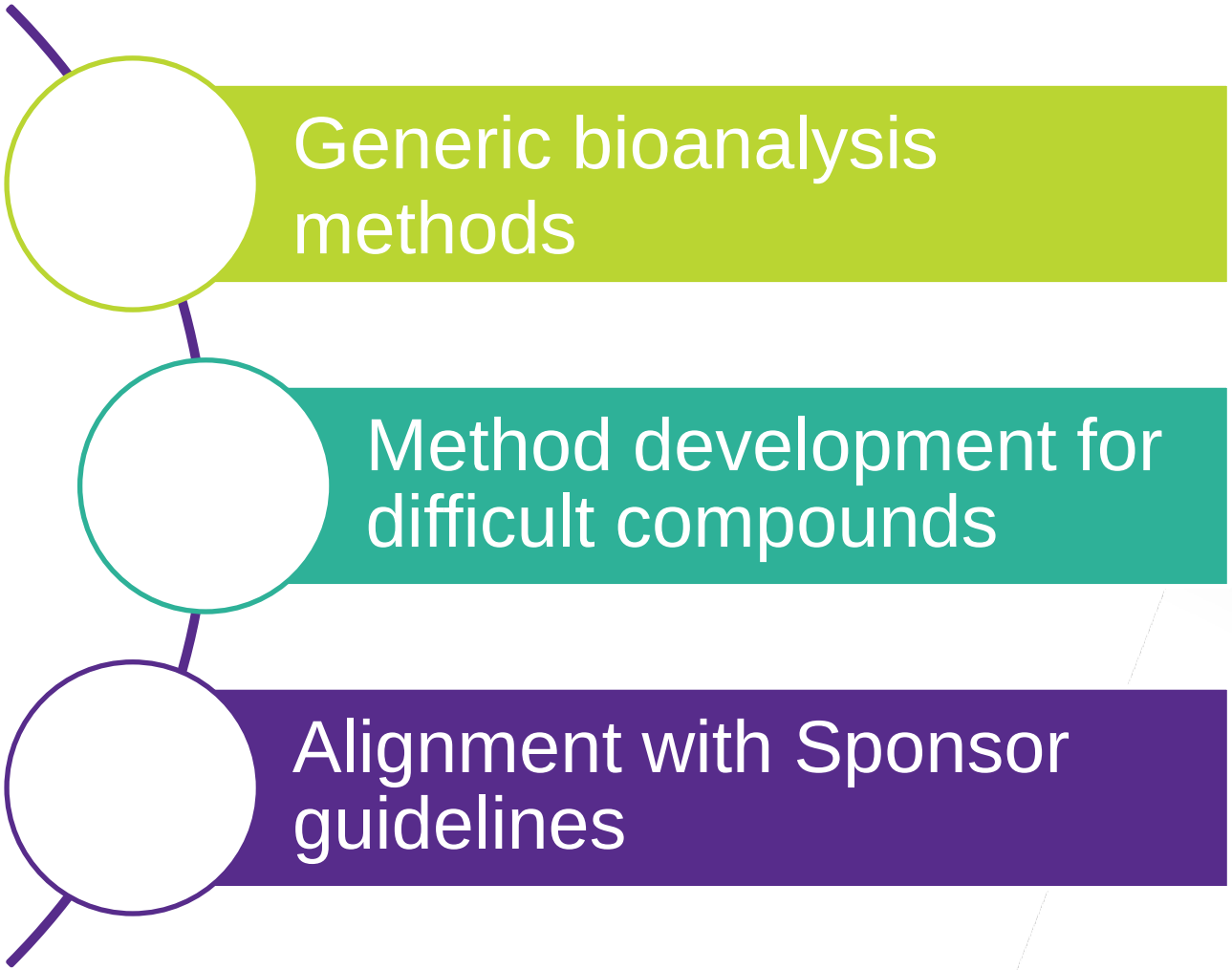
Average volume = 5µL ✓

1:4 dilution with plasma for bioanalysis

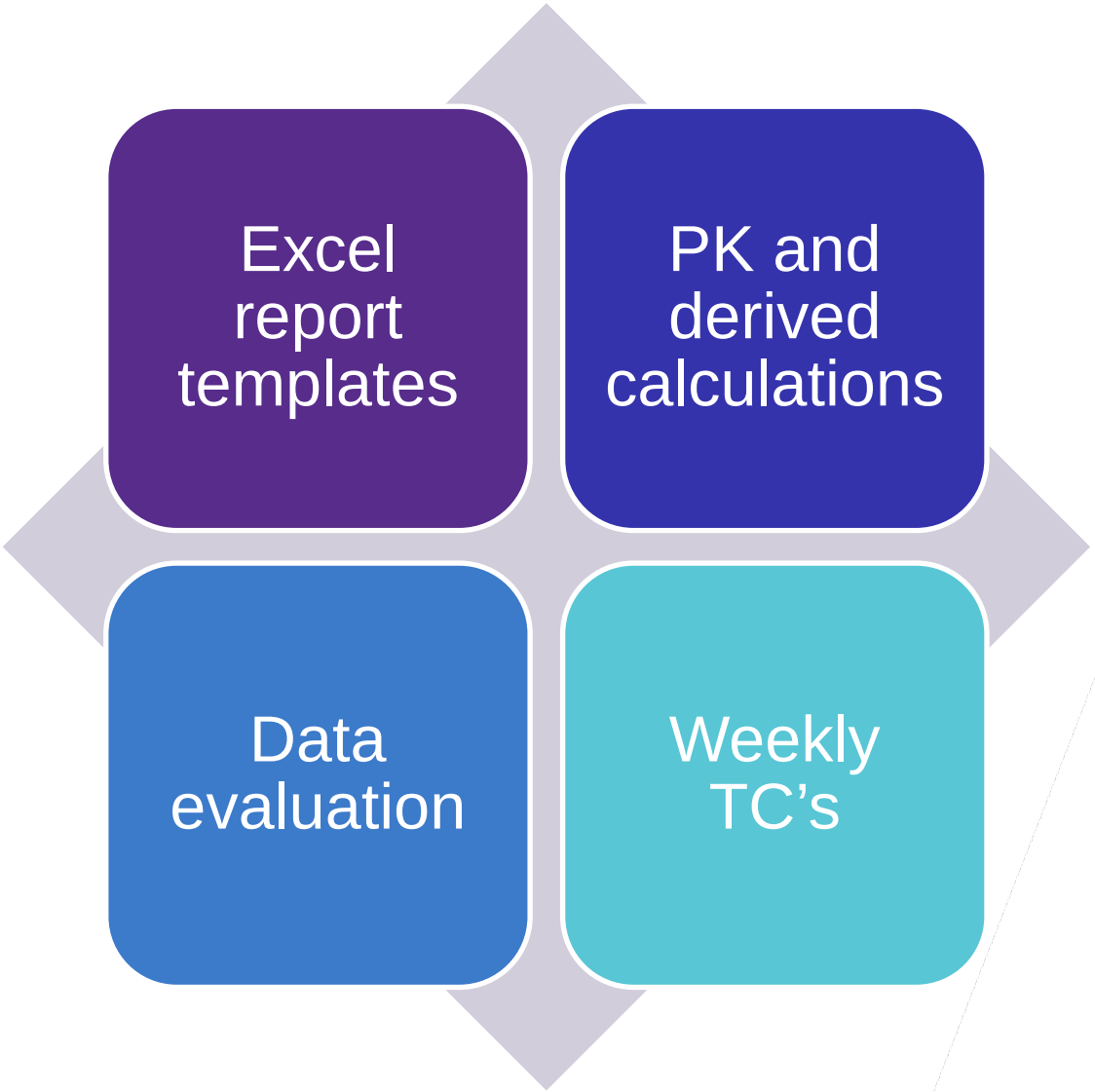


Visual assessment of the CSF samples for blood contamination is sufficiently sensitive for robust data

Bioanalysis



Reporting



Fast PK Reporting

CONCISE REPORTING

Dose Group	Species	Strain	Route of Administration	Formulation Vehicle	Appearance	Particle Size (µm)	Animal Number	Bodyweight (g)	Dose Administered (mL)	Dose Level (mg/kg)
1	Rat	Male, HanWistar	Oral	1% methylcellulose	White suspension	5.3 - 28.9	101M	314	1.54	10
							102M	335	1.65	10
							103M	329	1.62	10

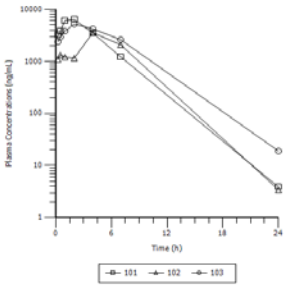
Analyte Concentrations (ng/mL)

Animal	101M		102M		103M		Mean		SD	
Timepoint (h)	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood
0.25	3330	2400	1090	790	2380	1670	2270	1620	1124	806
0.50	3790	2730	1330	965	2930	2060	2680	1920	1250	891
1.00	6110	4410	1210	877	3830	2690	3710	2660	2450	1770
2.00	6400	4620	1150	834	5200	3650	4250	3040	2750	1970
4.00	3500	2530	3560	2580	4220	2960	3760	2690	400	235
7.00	1230	888	2080	1510	2610	1830	1970	1410	700	479
24.0	3.87	2.79	3.41	2.47	18.9	13.3	8.74	6.19	8.84	6.16

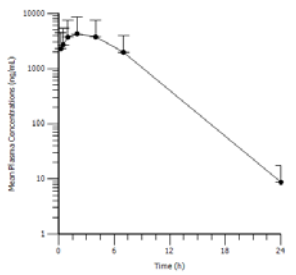
Plasma PK Parameters

	101M	102M	103M	Mean	SD
Cmax (ng/mL)	6400	3560	5200	5050	1430
Tmax (h)	2.0	4.0	2.0	2.67	1.15
Half-life (h)	2.04	1.84	2.50	2.13	0.342
MRTinf (h)	3.69	5.62	5.19	4.83	1.01
AUCinf (ng.hr/mL)	29800	20700	35600	28700	7490
AUClast (ng.hr/mL)	29800	20700	35500	28700	7460
Clast (ng/mL)	3.87	3.41	18.9	8.74	8.84
Tlast (h)	24	24	24	24	NA

Individual Plasma Concentrations



Mean Plasma Concentrations



Fast PK Reporting

FULL EXTRACTION AND LC-MS/MS METHOD

Working Std. Prep

WStd.	Conc. (ng/mL)	Std	Vol. (uL)	Reagent Vol. (uL)	Total Vol. (uL)
Cal B	100,000	A	100	900	1000
Cal C	90,000	A	90	910	1000
Cal D	50,000	A	50	950	1000
Cal E	20,000	A	20	980	1000
Cal F	4,000	Cal E	200	800	1000
Cal G	1,000	Cal E	50	950	1000
Cal H	200	Cal E	10	990	1000
Cal I	40	Cal G	40	960	1000
Cal J	20	Cal G	20	980	1000
QCB	500,000	A	100	100	200
QCC	80,000	A	80	920	1000
QCD	7,500	QC B	15	985	1000
QC Int	6,000	QC C	75	925	1000
QCE	60	QC Int	10	990	1000

Cal Prep

Cal	Cal. Conc. (ng/mL)	WStd.	WStd. Conc. (ng/mL)	WStd. Vol. (uL)	Matrix (uL)	Total Vol. (uL)
11	5,000	Cal B	100,000	10	190	200
10	4,500	Cal C	90,000	10	190	200
9	2,500	Cal D	50,000	10	190	200
8	2,250	**Cal D**	50,000	**18**	**382**	400
7	1,000	Cal E	20,000	10	190	200
6	600	**Cal E**	20,000	**12**	**388**	400
5	200	Cal F	4,000	10	190	200
4	50	Cal G	1,000	10	190	200
3	10	Cal H	200	10	190	200
2	2	Cal I	40	10	190	200
1	1	Cal J	20	10	190	200
DQC	25,000	QCB	500,000	10	190	200
HQC	4,000	QCC	80,000	10	190	200
MHQC	2,000	**QCC**	80,000	**10**	**390**	400
MQC	375	QCD	7,500	10	190	200
LQC	3.00	QCE	60	10	190	200

Mass Spectrometer Sciex 5500

Ionisation Interface and Temperature TISP 650

Analyte	Precurson ion (m/z)	Product Ion (m/z)	Polarity
Compound X	192.1	106.0	+
ISTD1	268.0	159.0	+

Mobile Phase A 10mM Ammonium Acetate (aq): Ammonia (100:0.5 v/v)

Mobile Phase B Methanol

Injection Volume 5uL

Analytical Column Acquity UPLC HSS C18 1.8 µm 2.1 x 50 mm

Column Temperature 40°C

Flow Rate 0.6

Sample Temperature 5°C

Gradient Profile

Time (min)	% Aqueous Phase
0	80
2.50	2
3.00	2
3.10	80
4.00	80

Plasma sample preparation

1. Transfer a 10uL aliquot into a clean 2mL 96-well collection plate.
2. Add 25 uL IS-B (500ng/mL). Add 25uL MeCN to all blanks.
3. Mix Plate ~30 seconds.
4. Add 100uL of MeCN to all samples Mix well (~30 seconds).
5. Centrifuge 2000g for 10mins at 5°C.
6. Transfer a 20uL aliquot into a clean 1.2mL 96-well collection plate.
8. Dilute with 180uL 10mM Ammonium Acetate (aq): Ammonia (100:0.5 v/v)
9. Mix well (2mins) and centrifuge 2000g for 5mins at 5°C
10. Submit for analysis by LC/MS-MS

Fast PK Reporting

AUTOMATED CAL AND QC CHECKING

Compound X Run 3 Standard Summary

Standard Sample Data

Harrogate NRG Study:Mouse PK Run 3
Plasma, Concentration of Compound X (ng/mL)
Assay Compound X

Sample No.	Nom Conc	Wgt	Area	IntStd Area	Response Value	Conc Found	%Bias
7	2.000	0.250000	277.2	594565.8	0.000466	2.195	9.8
8	4.000	0.0625000	391.8	599694	0.000653	3.298	-17.6
9	20.00	0.00250000	1911.1	600111.2	0.003185	18.23	-8.9
10	100.0	0.000100000	9507.2	588354.9	0.016159	94.75	-5.3
11	400.0	0.00000625000	40948.4	591761.3	0.069197	407.7	1.9
12	1200	0.000000694444	124475.4	590278	0.210876	1245	3.8
13	2000	0.000000250000	216484.4	587202.3	0.368671	2179	9.0
14	4500	0.0000000493827	497399.2	581044	0.856044	5079	12.9
15	5000	0.0000000400000	531596.9	599257.6	0.887092	5264	5.3
16	9000	0.0000000123457	896321.9	593475.3	1.510294	9003	0.0
17	10000	0.0000000100000	890728.8	595465.1	1.495854	8916	-10.8

Model: Response = A * (Concentration**2) + B * Concentration + C

Curve Parameters:

A =	-0.000000000205
B =	0.000170
C =	0.0000938
Quadratic Limit =	414200
R-Squared =	0.9898

Response Type = Area Ratio

BLQ - Concentration Found is Less than 2.000 (Lowest Standard)
ALQ - Concentration Found is Greater than 10000 (Highest Standard)

Compound X Run 3 QC Summary

QC Sample Data

Harrogate NRG Study:Mouse PK Run 3
Plasma, Concentration of Compound X (ng/mL)
Assay Compound X

Sample No.	Nom Conc	Area	IntStd Area	Response Value	Dilution Factor	Conc Found	%Bias	Mean Conc	Mean %Bias
21	6.000	779.1	599090	0.001300	1	7.113	18.6	6.671	11.2
57	6.000	651	565988.4	0.001150	1	6.228	3.8		
22	100.0	11113.1	573275.9	0.019385	1	113.8	13.8	115.0	15.0
58	100.0	10999.3	555646.7	0.019795	1	116.2	16.2		
23	750.0	85711.8	580545.7	0.147640	1	871.0	16.1	878.1	17.1
59	750.0	85673.6	571041.9	0.150030	1	885.1	18.0		
24	4000	440954.4	590031.5	0.747340	1	4430	10.8	4741	18.5
60	4000	475117.1	557968.6	0.851512	1	5052	26.3		
25	8000	710033.9	573102	1.238931	1	7371	-7.9	8751	9.4
61	8000	956935.3	563681.6	1.697652	1	10130	26.6		

Fast PK Reporting

RAW DATA EXPORT

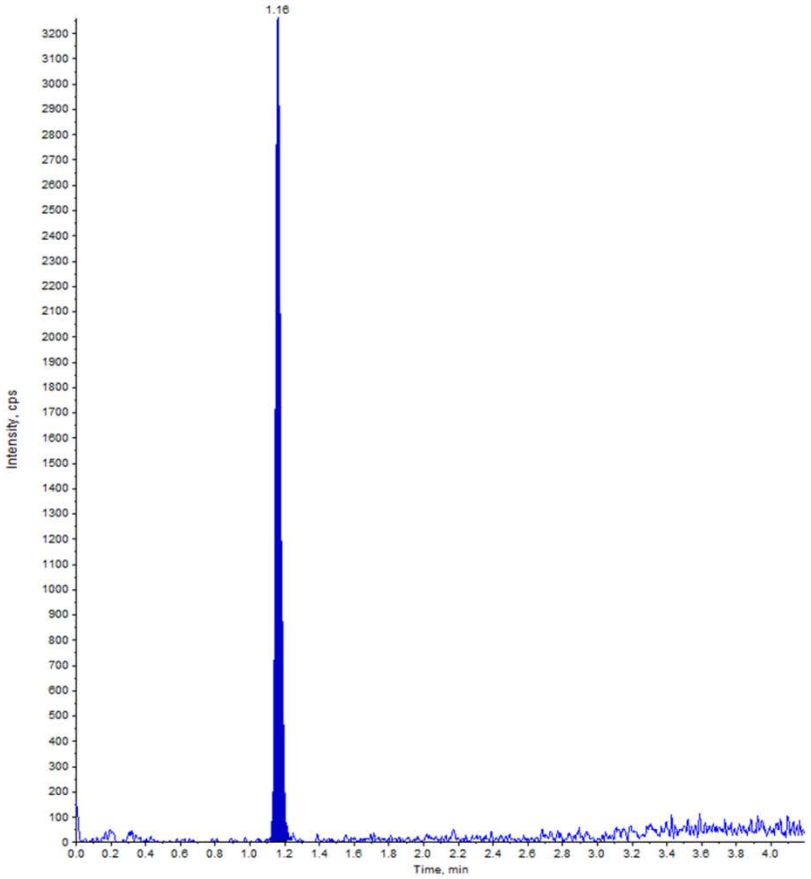
Raw Data Report

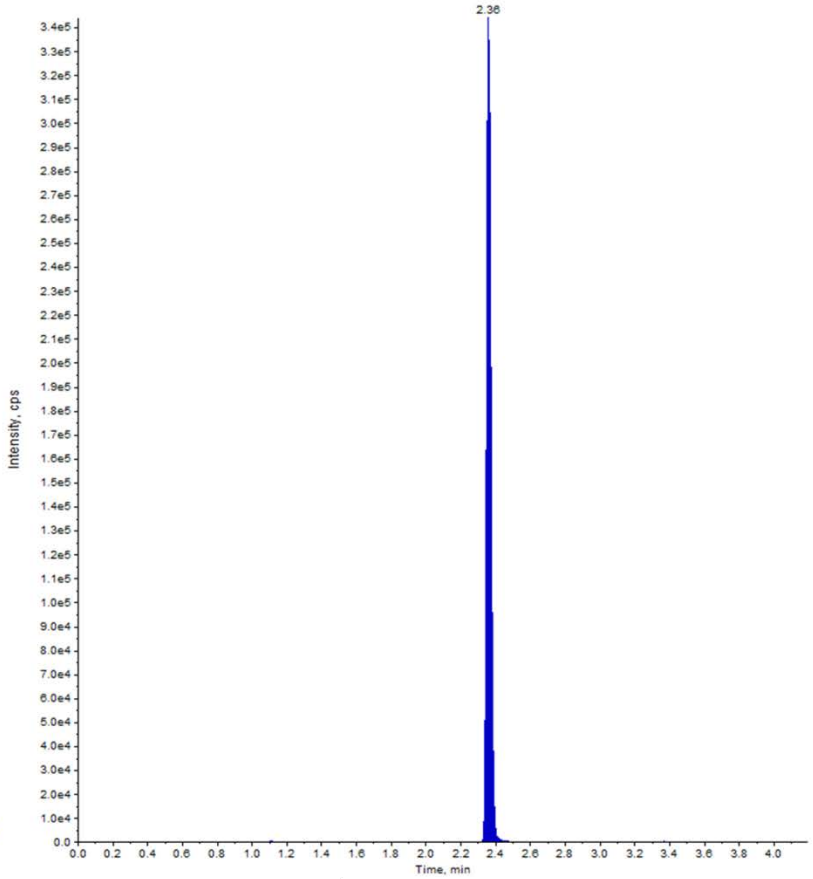
Raw and Concentration Results from Analytical Run 3 analyzed 23-May-2018
using Assay Compound X on Instrument Sciex Analyst (Study Mouse PK)

Analyte	Seq. Number	Sample Name	Theoretical Value ng/mL	% Bias	Area	Ret Time	IS Area	IS Ret Time	Instrument Response	Assay Date/Time	File Name	Dilution Factor	Internal Standard	Conc. (ng/mL)
Compound X	1	Mouse PK SES-LLOQ			194.2	1.16	601250.5	2.36	0.000323	23-May-2018 03:26:44	use PK_Run_3_Group1.w	1	ISTD1	BLQ[1.352] 2.000
Compound X	2	Mouse PK SES-ULOQ			921303	1.16	612945.1	2.36	1.503076	23-May-2018 03:31:41	use PK_Run_3_Group1.w	1	ISTD1	8960
Compound X	3	Mouse PK SES-BLK			71.4	1.16	0	0.00		23-May-2018 03:36:37	use PK_Run_3_Group1.w	1	ISTD1	BLQ 2.000
Compound X	4	Mouse PK BLK-RGT			84	1.21	0	0.00		23-May-2018 03:41:32	use PK_Run_3_Group1.w	1	ISTD1	BLQ 2.000
Compound X	5	Mouse PK BLK-MTX			56.7	1.21	0	0.00		23-May-2018 03:46:28	use PK_Run_3_Group1.w	1	ISTD1	BLQ 2.000
Compound X	6	Mouse PK BLK-CTRL 0			18.9	1.15	583683.9	2.35	0.000032	23-May-2018 03:51:23	use PK_Run_3_Group1.w	1	ISTD1	BLQ[-0.3644] 2.000
Compound X	7	Mouse PK CAL 1 1	2.000	9.8	277.2	1.16	594565.8	2.36	0.000466	23-May-2018 03:56:18	use PK_Run_3_Group1.w	1	ISTD1	2.195
Compound X	8	Mouse PK CAL 2 1	4.000	-17.6	391.8	1.16	599694	2.36	0.000653	23-May-2018 04:01:16	use PK_Run_3_Group1.w	1	ISTD1	3.298
Compound X	9	Mouse PK CAL 3 1	20.00	-8.9	1911.1	1.16	600111.2	2.36	0.003185	23-May-2018 04:06:12	use PK_Run_3_Group1.w	1	ISTD1	18.23
Compound X	10	Mouse PK CAL 4 1	100.0	-5.3	9507.2	1.16	588354.9	2.36	0.016159	23-May-2018 04:11:08	use PK_Run_3_Group1.w	1	ISTD1	94.75
Compound X	11	Mouse PK CAL 5 1	400.0	1.9	40948.4	1.16	591761.3	2.36	0.069197	23-May-2018 04:16:03	use PK_Run_3_Group1.w	1	ISTD1	407.7
Compound X	12	Mouse PK CAL 6 1	1200	3.8	124475.4	1.16	590278	2.36	0.210876	23-May-2018 04:20:58	use PK_Run_3_Group1.w	1	ISTD1	1245
Compound X	13	Mouse PK CAL 7 1	2000	9.0	216484.4	1.16	587202.3	2.36	0.368671	23-May-2018 04:25:53	use PK_Run_3_Group1.w	1	ISTD1	2179
Compound X	14	Mouse PK CAL 8 1	4500	12.9	497399.2	1.16	581044	2.35	0.856044	23-May-2018 04:30:50	use PK_Run_3_Group1.w	1	ISTD1	5079
Compound X	15	Mouse PK CAL 9 1	5000	5.3	531596.9	1.16	599257.6	2.36	0.887092	23-May-2018 04:35:46	use PK_Run_3_Group1.w	1	ISTD1	5264
Compound X	16	Mouse PK CAL 10 1	9000	0.0	896321.9	1.16	593475.3	2.36	1.510294	23-May-2018 04:40:40	use PK_Run_3_Group1.w	1	ISTD1	9003
Compound X	17	Mouse PK CAL 11 1	10000	-10.8	890728.8	1.16	595465.1	2.36	1.495854	23-May-2018 04:45:36	use PK_Run_3_Group1.w	1	ISTD1	8916
Compound X	18	Mouse PK BLK-MTX-CO			63.5	1.17	0	0.00		23-May-2018 04:50:34	use PK_Run_3_Group1.w	1	ISTD1	BLQ 2.000
Compound X	19	Mouse PK BLK-MTX-Add			21	1.22	0	0.00		23-May-2018 04:55:30	use PK_Run_3_Group1.w	1	ISTD1	BLQ 2.000
Compound X	20	Mouse PK BLK-MTX-Add			56.7	1.15	0	0.00		23-May-2018 05:00:26	use PK_Run_3_Group1.w	1	ISTD1	BLQ 2.000
Compound X	21	Mouse PK LQC 1	6.000	18.6	779.1	1.16	599090	2.36	0.001300	23-May-2018 05:05:21	use PK_Run_3_Group1.w	1	ISTD1	7.113
Compound X	22	Mouse PK LMQC 1	100.0	13.8	11113.1	1.16	573275.9	2.36	0.019385	23-May-2018 05:10:17	use PK_Run_3_Group1.w	1	ISTD1	113.8
Compound X	23	Mouse PK MQC 1	750.0	16.1	85711.8	1.16	580545.7	2.36	0.147640	23-May-2018 05:15:13	use PK_Run_3_Group1.w	1	ISTD1	871.0
Compound X	24	Mouse PK MHQC 1	4000	10.8	440954.4	1.16	590031.5	2.36	0.747340	23-May-2018 05:20:09	use PK_Run_3_Group1.w	1	ISTD1	4430
Compound X	25	Mouse PK HQC 1	8000	-7.9	710033.9	1.16	573102	2.36	1.238931	23-May-2018 05:25:05	use PK_Run_3_Group1.w	1	ISTD1	7371
Compound X	26	Mouse PK BLK-MTX-Add			32.5	1.18	0	0.00		23-May-2018 05:30:01	use PK_Run_3_Group1.w	1	ISTD1	BLQ 2.000
Compound X	27	Mouse PK BLK-MTX-Add			22.5	1.11	0	0.00		23-May-2018 05:34:58	use PK_Run_3_Group1.w	1	ISTD1	BLQ 2.000
Compound X	28	Mouse PK BLK-MTX-Add			47.7	1.16	0	0.00		23-May-2018 05:39:54	use PK_Run_3_Group1.w	1	ISTD1	BLQ 2.000
Compound X	29	Mouse PK 101 IP Day 1 8h PLM-1			6748.1	1.16	574742.2	2.36	0.011741	23-May-2018 05:44:51	use PK_Run_3_Group1.w	1	ISTD1	68.69
Compound X	30	Mouse PK 102 IP Day 1 8h PLM-1			7787.5	1.16	573223.9	2.36	0.013585	23-May-2018 05:49:47	use PK_Run_3_Group1.w	1	ISTD1	79.56
Compound X	31	Mouse PK 103 IP Day 1 8h PLM-1			11228.8	1.16	575763.5	2.36	0.019502	23-May-2018 05:54:43	use PK_Run_3_Group1.w	1	ISTD1	114.5
Compound X	32	Mouse PK 101 IP Day 1 4h PLM-1			53209.6	1.16	577864.9	2.36	0.092080	23-May-2018 05:59:39	use PK_Run_3_Group1.w	1	ISTD1	542.8
Compound X	33	Mouse PK 102 IP Day 1 4h PLM-1			32471.4	1.16	569448	2.36	0.057023	23-May-2018 06:04:36	use PK_Run_3_Group1.w	1	ISTD1	335.8
Compound X	34	Mouse PK 103 IP Day 1 4h PLM-1			51380.6	1.16	566104.8	2.36	0.090762	23-May-2018 06:09:32	use PK_Run_3_Group1.w	1	ISTD1	535.0
Compound X	35	Mouse PK 101 IP Day 1 2h PLM-1			115594	1.16	575893.2	2.36	0.200721	23-May-2018 06:14:28	use PK_Run_3_Group1.w	1	ISTD1	1185
Compound X	36	Mouse PK 102 IP Day 1 2h PLM-1			97439.8	1.16	572823.8	2.36	0.170104	23-May-2018 06:19:23	use PK_Run_3_Group1.w	1	ISTD1	1004
Compound X	37	Mouse PK 103 IP Day 1 2h PLM-1			123058.4	1.16	569655.5	2.36	0.216022	23-May-2018 06:24:20	use PK_Run_3_Group1.w	1	ISTD1	1275
Compound X	38	Mouse PK 101 IP Day 1 1h PLM-1			197718.4	1.16	572995.4	2.36	0.345061	23-May-2018 06:29:16	use PK_Run_3_Group1.w	1	ISTD1	2039
Compound X	39	Mouse PK 102 IP Day 1 1h PLM-1			25609.2	1.17	81696.2	2.36	0.313469	23-May-2018 06:34:14	use PK_Run_3_Group1.w	1	ISTD1	1852
Compound X	40	Mouse PK 103 IP Day 1 1h PLM-1			161462.3	1.16	580132.9	2.36	0.278320	23-May-2018 06:39:10	use PK_Run_3_Group1.w	1	ISTD1	1644
Compound X	41	Mouse PK 101 IP 30 mins / Day 1 0.5h PLM-1			147366.8	1.16	570496.6	2.36	0.258313	23-May-2018 06:44:05	use PK_Run_3_Group1.w	1	ISTD1	1525
Compound X	42	Mouse PK 102 IP 30 mins / Day 1 0.5h PLM-1			144656.8	1.16	566199.9	2.36	0.255487	23-May-2018 06:49:03	use PK_Run_3_Group1.w	1	ISTD1	1509
Compound X	43	Mouse PK 103 IP 30 mins / Day 1 0.5h PLM-1			178173.2	1.16	565018.1	2.36	0.315341	23-May-2018 06:53:59	use PK_Run_3_Group1.w	1	ISTD1	1863
Compound X	44	Mouse PK 101 IP 15 mins / Day 1 0.25h PLM-1			232581.8	1.16	577060.5	2.36	0.403046	23-May-2018 06:58:56	use PK_Run_3_Group1.w	1	ISTD1	2383
Compound X	45	Mouse PK 102 IP 15 mins / Day 1 0.25h PLM-1			205848.5	1.16	563212.6	2.36	0.365490	23-May-2018 07:03:52	use PK_Run_3_Group1.w	1	ISTD1	2160
Compound X	46	Mouse PK 103 IP 15 mins / Day 1 0.25h PLM-1			220215.6	1.16	561922.9	2.35	0.391896	23-May-2018 07:08:49	use PK_Run_3_Group1.w	1	ISTD1	2317
Compound X	47	Mouse PK 101 IP 7 mins / Day 1 0.117h PLM-1			233057.5	1.16	582031	2.36	0.400421	23-May-2018 07:13:45	use PK_Run_3_Group1.w	1	ISTD1	2367
Compound X	48	Mouse PK 102 IP 7 mins / Day 1 0.117h PLM-1			208330.7	1.16	581783.9	2.36	0.358089	23-May-2018 07:18:43	use PK_Run_3_Group1.w	1	ISTD1	2116
Compound X	49	Mouse PK 103 IP 7 mins / Day 1 0.117h PLM-1			122500.9	1.16	566560.8	2.36	0.216218	23-May-2018 07:23:41	use PK_Run_3_Group1.w	1	ISTD1	1276
Compound X	50	Mouse PK BLK-MTX-Add			0	0.00	0	0.00		23-May-2018 07:28:38	use PK_Run_3_Group1.w	1	ISTD1	BLQ 2.000

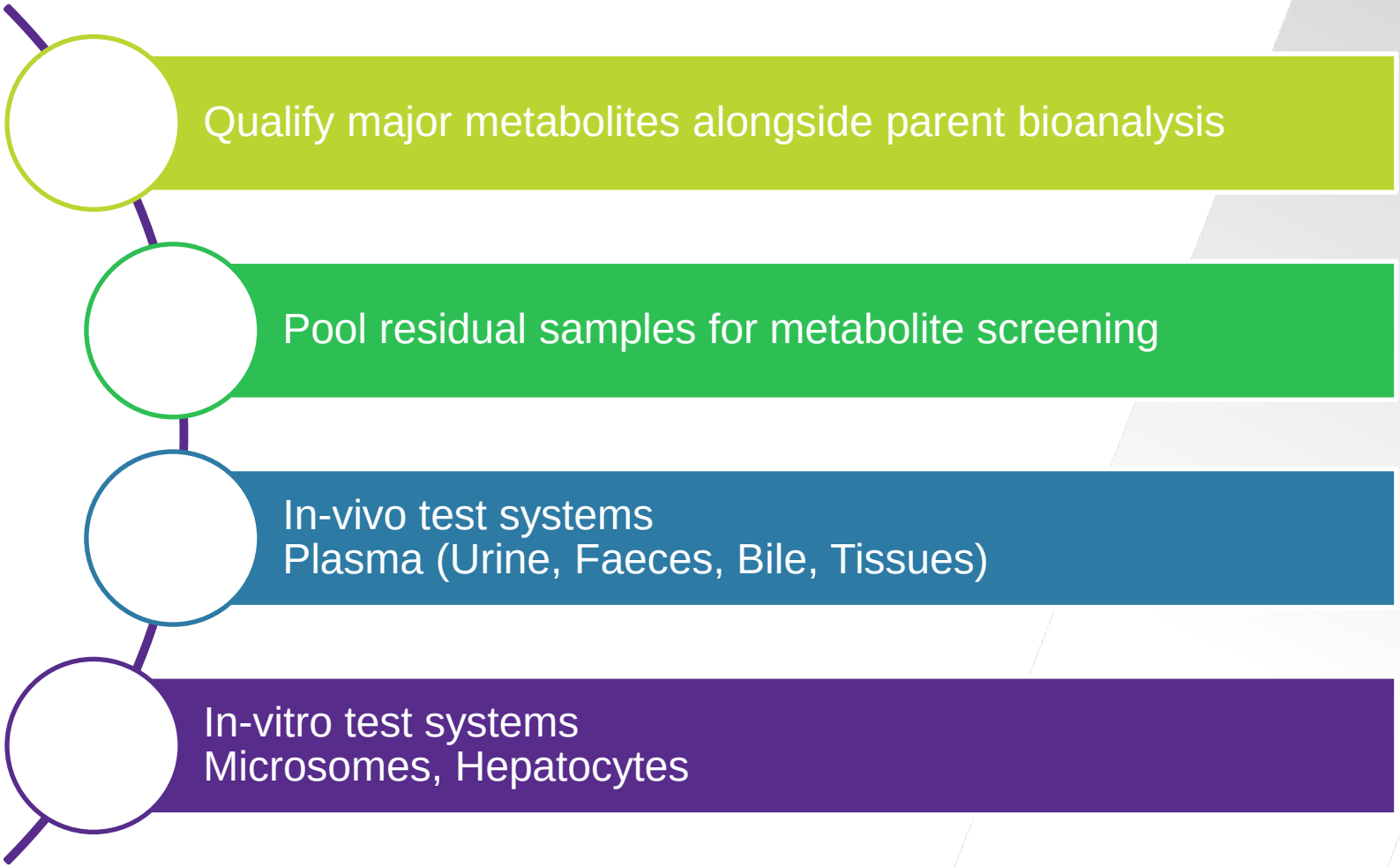
Fast PK Reporting

EXAMPLE CHROMATOGRAMS





Early Metabolite Characterization



PBPK Modeling

Simulates the concentration of a drug over time in tissue(s) and blood, by taking into account the rate of its absorption into the body, distribution in tissues, metabolism and excretion (ADME) on the basis of **interplay among critical physiological, physicochemical and biochemical determinants**.

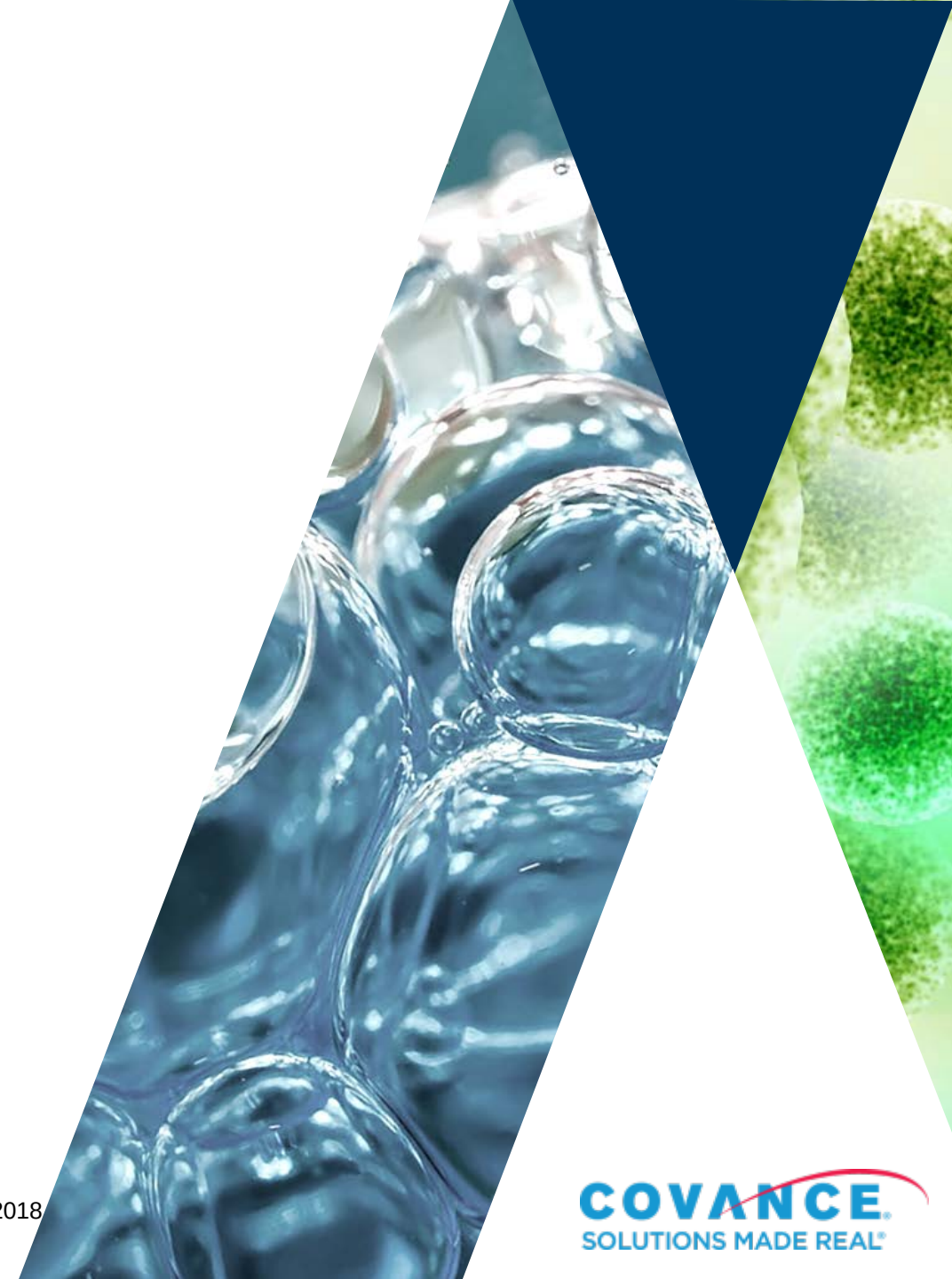
Multi-compartment approach that takes the anatomy and physiology of the system into consideration

Includes the physiochemical parameters of the drug (structure, LogP, pKA, solubility)

Includes the physiological parameters of the body (permeability, perfusion, flow rates, organ volumes)

Includes the parameters of drug-body interaction (protein binding, enzyme kinetics, transporters, DDI)

THANK YOU



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