Early BioPharm Risk Assessment in Discovery

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PCF9

17th September 2010, Barcelona

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Outline

- Background
- Why?
- How?
  - cMAD and early absorption simulation
- Case Studies & Examples
- Summary

Poor Solubility

- **increased risk, cost and time to development**

- incomplete absorption may be expected
- enabling technologies may be required
- bridging between formulations adds complexity to clinical program

- **Increased Bio.Pharm risk**

Why do we need early Bio.Pharm. Risk Assessment?

- Better informed choice of short-list candidates
- Identify projects/chemical series where Bio.Pharm. risk is likely to delay project delivery &/or complicate (pre)clinical program

???

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Maximum Absorbable Dose (MAD)

- A drug must be in solution to be absorbed
- MAD is a composite parameter of solubility and permeability
- If MAD < Dose incomplete absorption may be expected

Solubility	Permeability
Biorelevant media (FASSIF or HIF) Aqueous buffer Measured value at pH 6.5 or pH extrapolation from pH 7.4 solubility	Approx Ka / min^{-1} (rat perfusion) Typical Values low = 0.001 moderate = 0.03 high = 0.05

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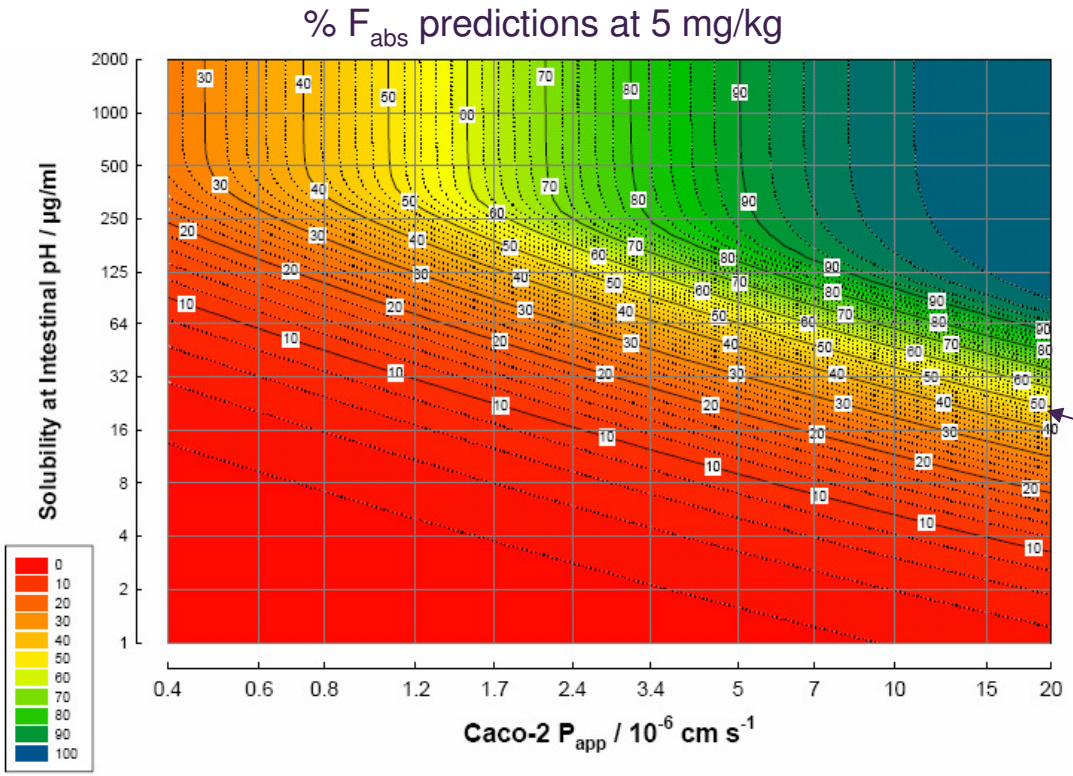
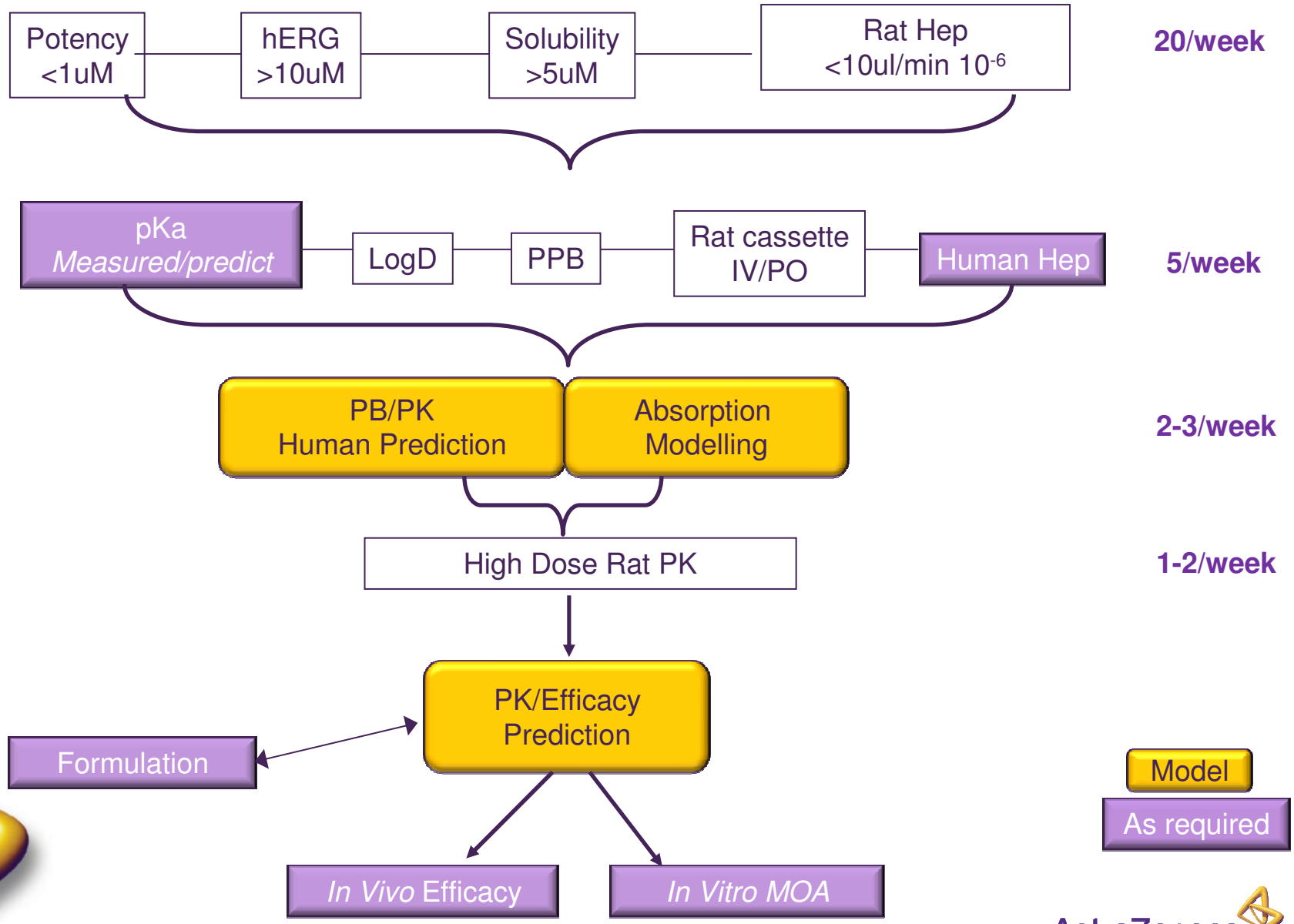
MAD, Solubility & Permeability



Fabs = 50%

- A highly permeable drug is OK if solubility is low
- For a moderately permeable drug, a solubility of around 60 µg/ml (120 µM) is needed to reach F_{abs} of 50 %

Project X Screening Cascade



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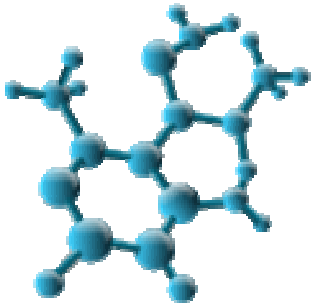
Project X: Options to Substitute Cpd 1

	Cpd 1	Cpd A	Cpd B
In vivo efficacy	YES	YES	YES
Buffer Solubility (pH 7.4 μM)	8	530	41
Predicted Dose (mg) BID	500	240	500
Predicted MAD (mg)	60	3407	802

- A and B matched Cpd 1 efficacy in disease model
- Top predicted human dose < 500 mg
- MAD > Top predicted human dose
- CPD1 substituted by CPDA and CPDB

Early Dose Prediction (DMPK)



potency

in-vitro clearance

protein binding

PK parameters

eD2M

measured

model

Spot winners early!

Ken Page, DMPK, Alderley Park. In press.

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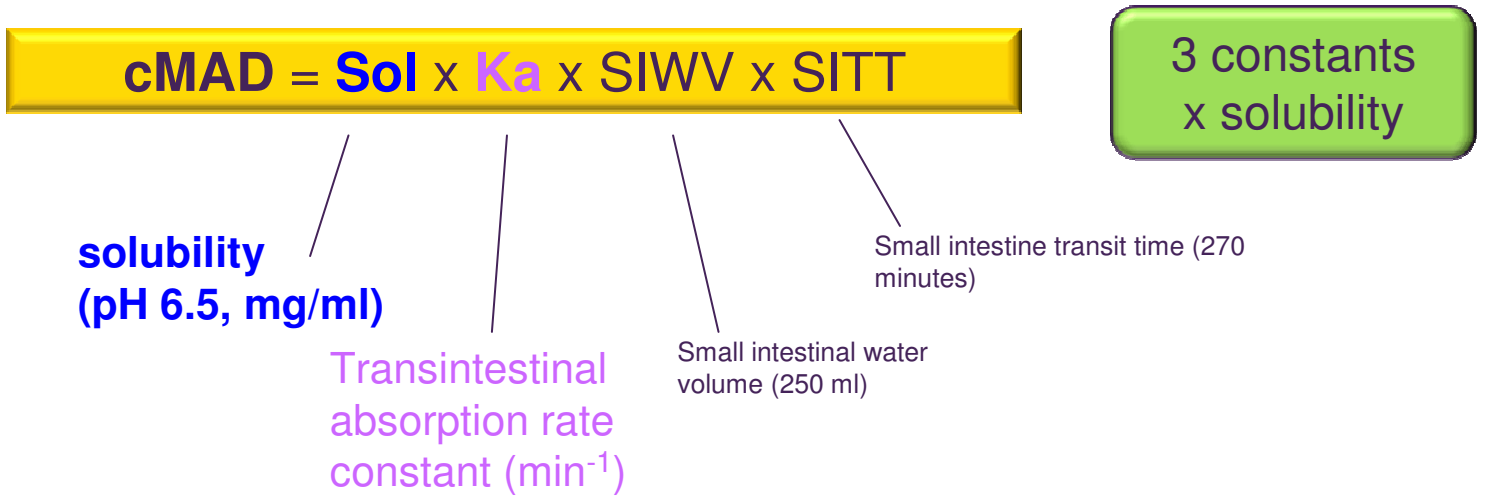
Early MAD

- Measured buffer solubility (shake flask pH 7.4, 25℃)
- Measured or predicted pKa
- Assume moderate/high permeability
  - Unless chemical space or measured permeability suggests otherwise

- **cMAD**
  - All compounds with measured solubility
  - Rank compounds within a project or chemical series
- **Early Absorption Simulation**
  - More complex model for key project compounds

cMAD (Curatolo MAD Calculation)

- **cMAD is the quantity of drug that could be absorbed if the small intestine could be saturated for 4.5 hours**



- A simple tool to assess solubility in the context of dose
- Allows ranking of compounds within chemical series
- Does not replace more complex absorption models

W Curatolo, PSTT, *1*, (9), **1998**: Physical chemical properties of oral drug candidates in the discovery and exploratory development settings

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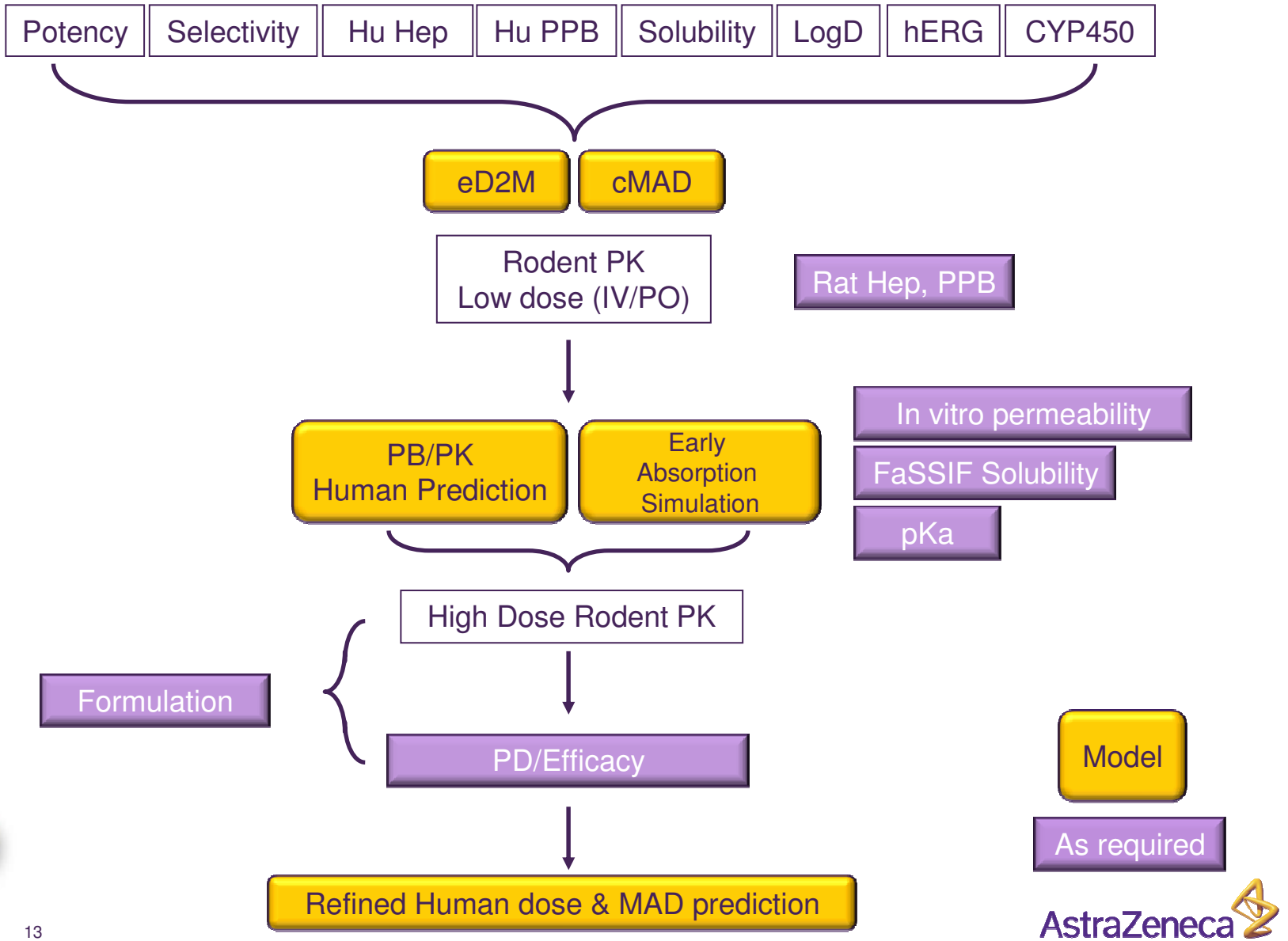
cMAD & Early Absorption Simulation

Early Absorption Simulation	cMAD
9 compartment model Inputs Equilibrium Sol in buffer (mg/mL) pKa Mod/High permeability (no transporter effect) pH gradient Accounts for supersaturation	Single tank Inputs Equilibrium Sol in buffer (mg/mL) Extrapolation to pH 6.5 Mod/High permeability (no transporter effects) Fixed pH No supersaturation or precipitation **Conservative Estimate**

Typical Screening Cascade



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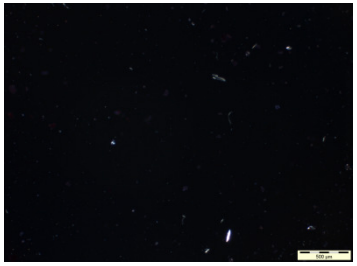
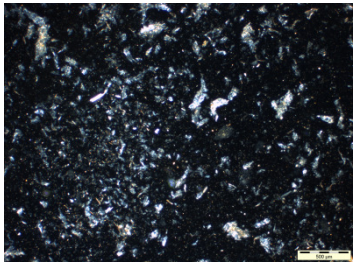
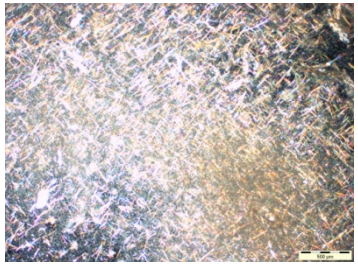
Solubility Assessment

- Equilibrium solubility in aqueous buffer (pH 7.4) is measured from solid material
- Final form is assessed by polarised light microscopy (PLM)
- Samples classified as crystalline, semicrystalline or amorphous and results uploaded to database
- PLM data helps contextualise solubility result

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A project snapshot

Compound	Final Crystallinity (PLM)	Sol pH 7.4 (uM)	eD2M (mg/kg)	eD2M (mg)	cMAD (mg)	Early Abs. Pred. MAD (mg)
1		871	3.8	266	4386	6227
2	Amorphous	12	0.34	23.8	67	410
3	Semicrystalline	625	0.72	50.4	3000	5729
4		59	1.34	93.8	306	1504
5	Semicrystalline	21	0.61	42.7	112	629
6	Semicrystalline	125	1.67	116.9	628	265
7			4.15	290.5		
8	Crystalline	2	4.9	343	13	93
9	Crystalline	5	9.04	632.8	28	195
10	Semicrystalline		6.62	463.4		
11	Semicrystalline	2	11.65	815.5	12	
12	Semicrystalline	14	10.61	742.7	28	268
13	Crystalline	2	28.88	2021.6	4	23
14	Crystalline	3	13.55	948.5	14	106
15		145	31.05	2173.5	705	274
16	Semicrystalline	41	16	1120	195	104
17			20.86	1460.2		
18	Semicrystalline	2	496.5	34755	8	59
19	Semicrystalline	148			568	1964

MAD > Dose
Reduced BioPharm Risk

MAD < Dose
Increased BioPharm Risk

Solubility (pH 7.4) & PLM (final form)

Early Human Dose Estimate

cMAD
(Curatolo eqn)
Extrapolated sol (pH 6.5)
Ka 0.024 min^{-1} (Mod/High)

Early Absorption Simulation
From pH 7.4 buffer sol, pKa, LogD & Mod/High Perm

Use Early MAD in conjunction with early Dose Estimate

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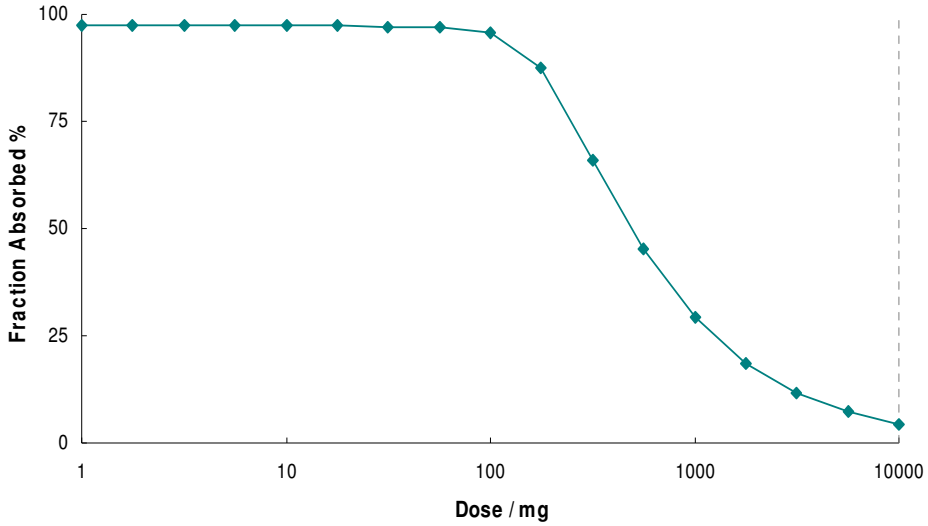
Early Absorption Simulation (Pharm. Dev)

More complex absorption modelling has been employed to provide better understanding of BioPharm risks for long-list compounds



Dose / mg	% Fabs Colon Off	Amount absorbed (mg)
1.00	97.35	0.97
1.78	97.35	1.73
3.16	97.35	3.08
5.62	97.34	5.47
10.00	97.32	9.73
17.78	97.28	17.30
31.62	97.18	30.73
56.23	96.88	54.48
100.00	95.76	95.76
177.83	87.48	155.56
316.23	65.82	208.14
562.34	45.12	253.73
1000.00	29.50	295.00
1778.28	18.74	333.25
3162.28	11.68	369.35
5623.41	7.19	404.32
10000.00	4.38	438.00

Dose (g)	%Fabs
0.5	49
1.0	30
2.5	14
5.0	8

MAD 438mg

Nick Stainforth, AstraZeneca, Pharm. Dev.

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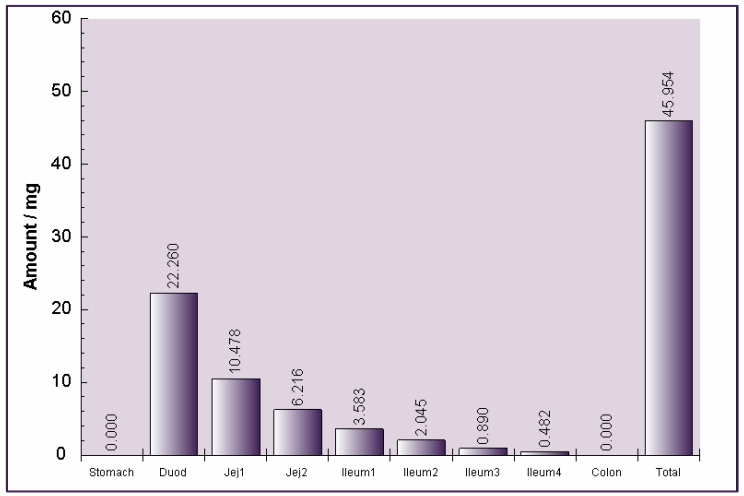
Early GISim Compound X

- MAD << Predicted Human Dose

Method	MAD (mg)	Comment
cMAD (mod/high permeability, buffer sol)	10	Conservative estimate
Early Absorption Simulation (permeability range, buffer sol, pKa)	44-124	Little change in MAD over time
Absorption Simulation (Pharm. Dev) (caco2 permeability and FaSSIF sol)	110	Dose prediction increased



Early Absorption Simulation

9 compartment model simulates absorption profile through GI tract

Accounts for enhanced solubility at low pH and potential supersaturation effects upon gastric emptying

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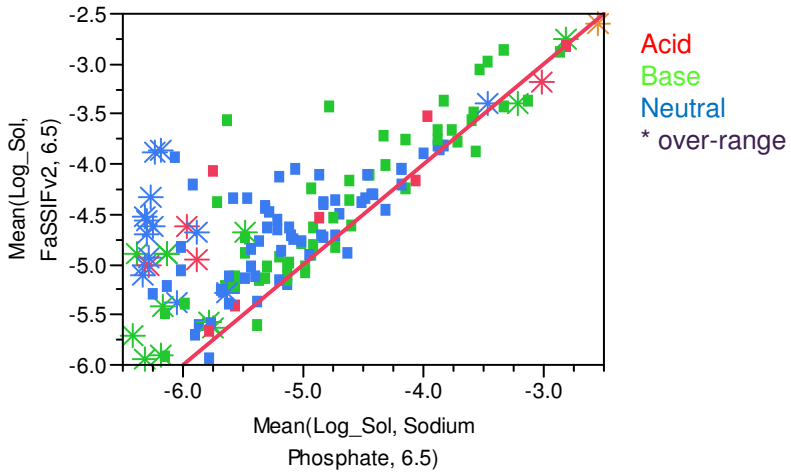
FaSSIF vs Buffer Solubility



- Buffer solubility is generally not predictive of FaSSIF solubility
- Greater solubility enhancement in FaSSIF is generally seen for poorly soluble compounds

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Biorelevant Solubility

- Buffer solubility may underestimate absorption potential (Dressman/Amidon lit)
- FaSSIF or HIF media generally accepted as standard for early absorption modelling
- Pharm. Dev. Measurements are low throughput & require stable crystalline form

- HT FaSSIF solubility assay for discovery
- Data previously only available for short-list & development compounds
- Enables early MAD evaluation with biorelevant solubility data

FaSSIF solubility measurements

Discovery FaSSIF	Pharm. Dev. FaSSIF
Media from Pharm.Dev group	
Samples from collection Ideally crystalline material	Well characterised solid state, usually stable crystalline form
Tecan Automation (96 well format) Single shot 24 h timepoint 37°C Centrifugation Single point calibration PLM assessment of final form Results in discovery database Facilitates SPR analysis	Single compound Duplicate 1 and 24 h timepoints 37°C Ultracentrifugation Multiple LC calibration stds

AP FaSSIF Solubility Method

- Modified standard shake flask solubility protocol

- ~1.5 mg solid (ideally **crystalline material**)
- 1 mL buffer or biorelevant media
- 24h agitation at 37℃
- Separation of undissolved solid by centrifugation
- PLM assessment of final solid form
- Analysis by gradient LCUVMS vs single point standard in DMSO solution

AP FaSSIF Solubility Strategy

- Access to biorelevant solubility measurements for wide range of chemistries
- Use to refine early MAD estimations
- Assess likely BioPharm risk for chemical series/project
- SPR learning
- Informed selection of short-list compounds with reduced BioPharm risk

- Identify projects where further evaluation is required
  - Consultation with BioPharm experts
  - More detailed studies: dissolution/precipitation, alternative media, may require alternative formulation for safety/efficacy…

Summary

- Early human dose estimation and MAD assessment allows early Bio.Pharm risk assessment using discovery data
- Influence Med.Chem. design

- Discovery FaSSIF solubility
- Refined MAD analysis
- Influence short-lists
- SPR analysis

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