



Venn Life Sciences

part of Open Orphan plc

Challenges in early phase formulation development

Are dogs old-fashioned?

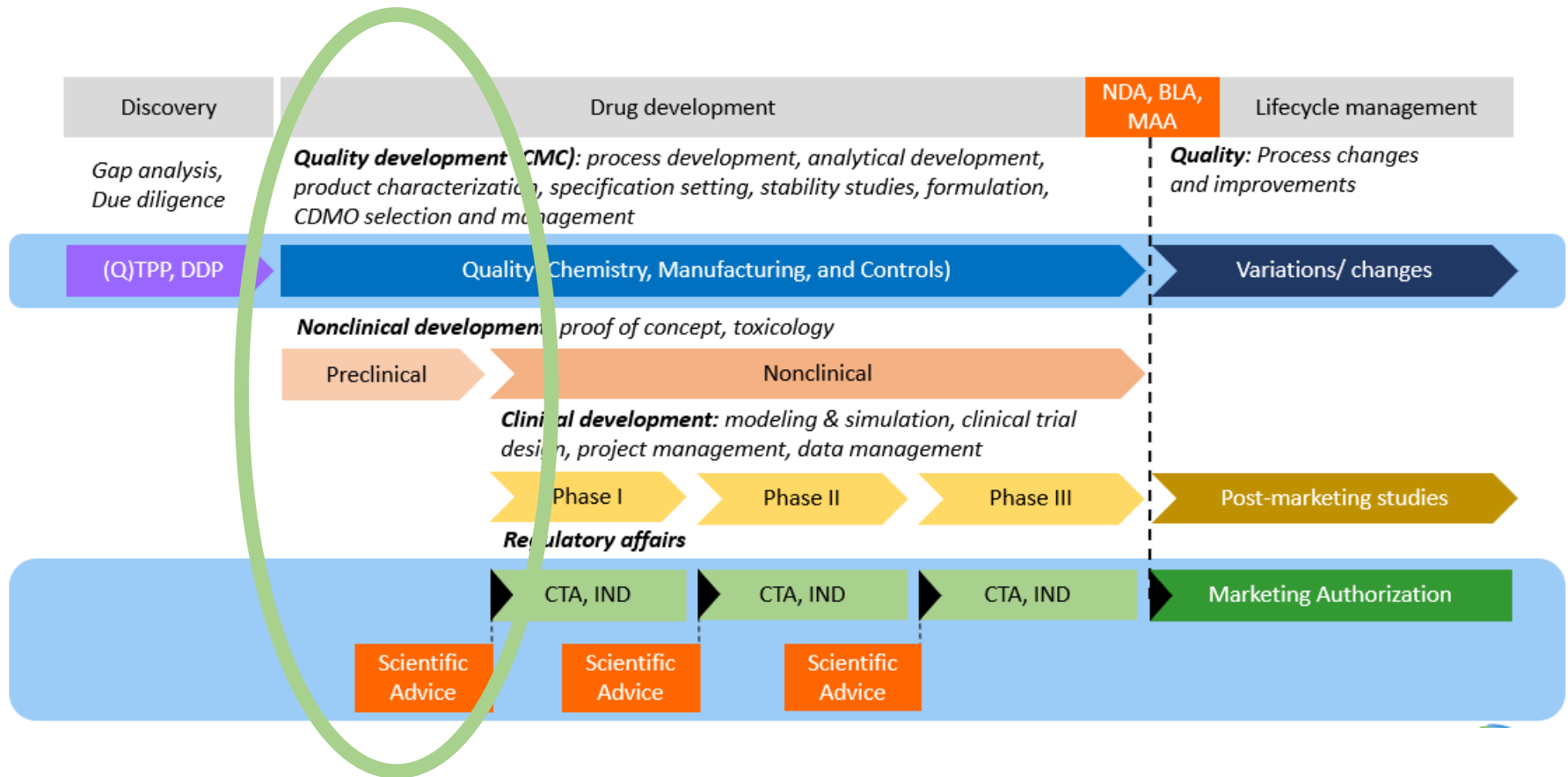
Clinical Supplies Forum

April 23, 2021

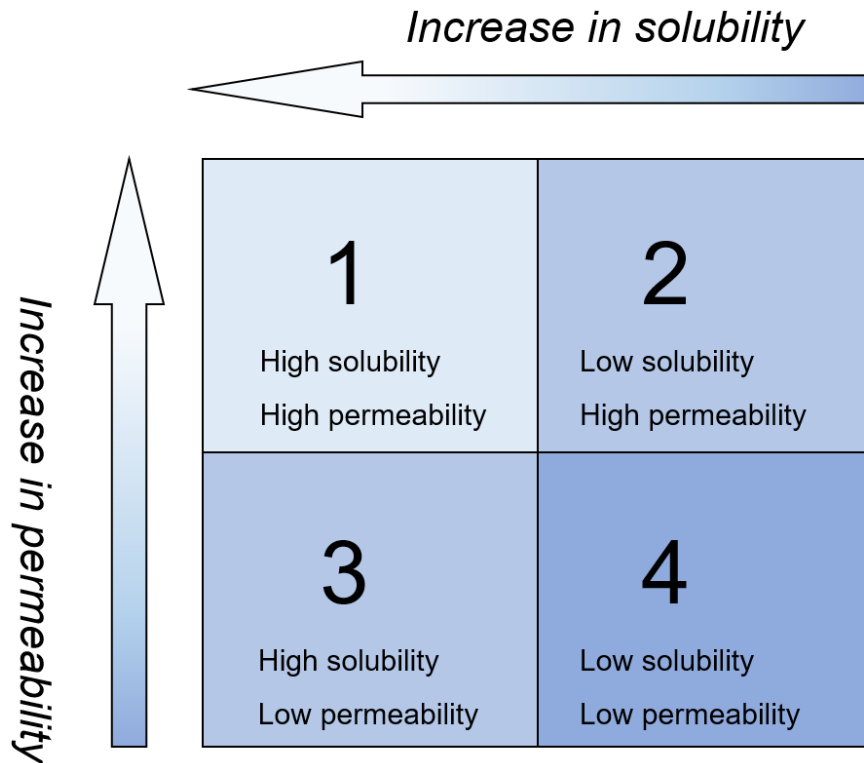
Sabien van der Schoot – Venn Life Sciences

Susann Bellmann – The TIM Company

Phases in drug development



Small molecules

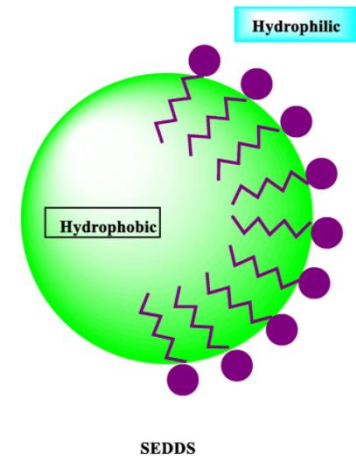


- From BCS class 1 to 4:
Increasing complexity
- Formulation most
challenging for BCS 2 & 4



Formulation development

- Solubilization improved by e.g.
 - Increasing surface area
(e.g. nanomilling or wetball milling)
 - Amorphization API
(e.g. amorphous solid dispersions)
 - Emulsification
(e.g. SEDDS/SMEDDS/SNEDDS)
 - Complexation
(e.g. use of cyclodextrins)
- Formulation screening
 - In vitro dissolution using FaSSGF & FaSSIF
 - In vivo testing (dogs)

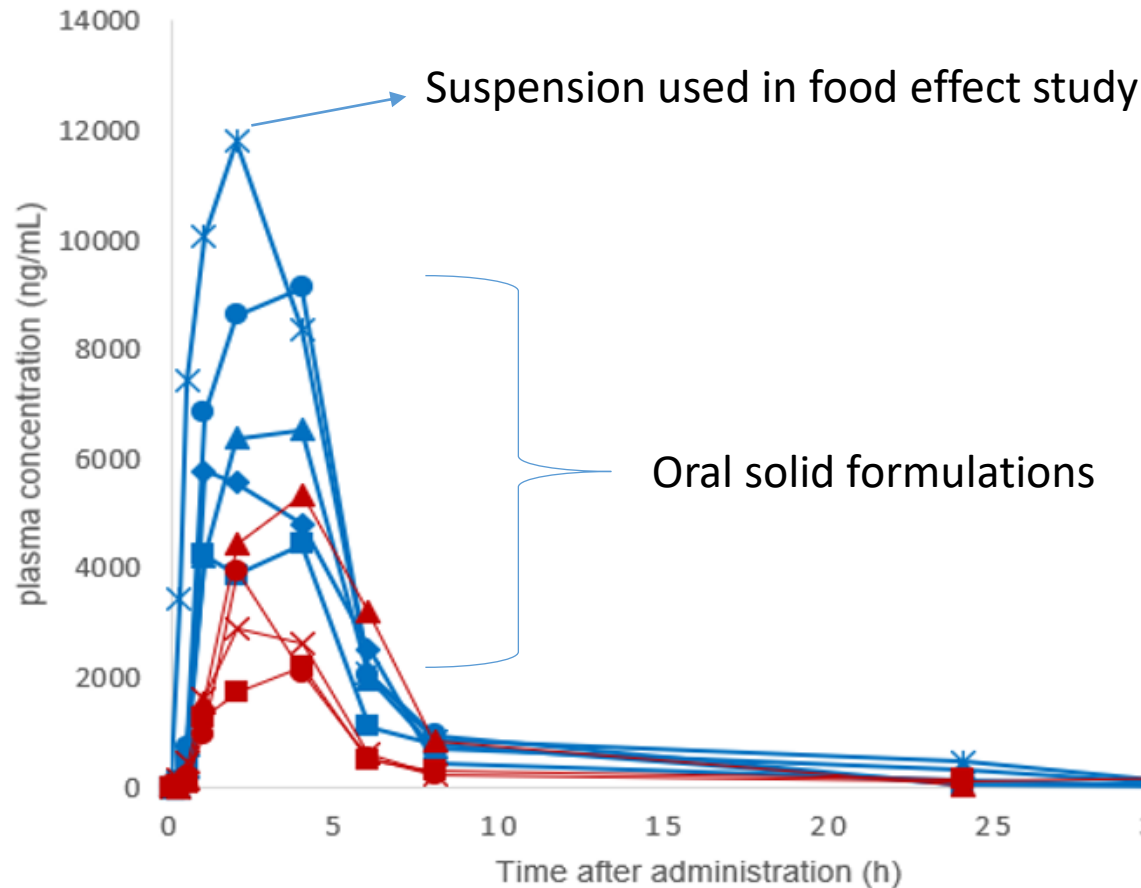


[AAPS PharmSciTech](#)
volume 20, Article: 129 (2019)



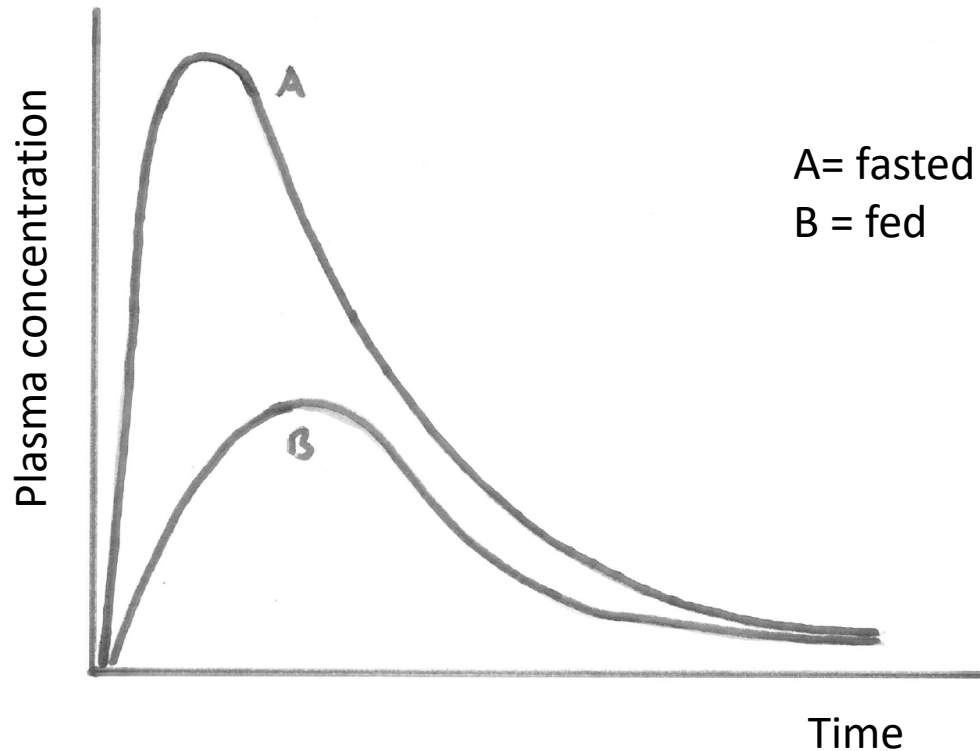
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Testing formulations in fasted dogs of API BCS class 2 or 4

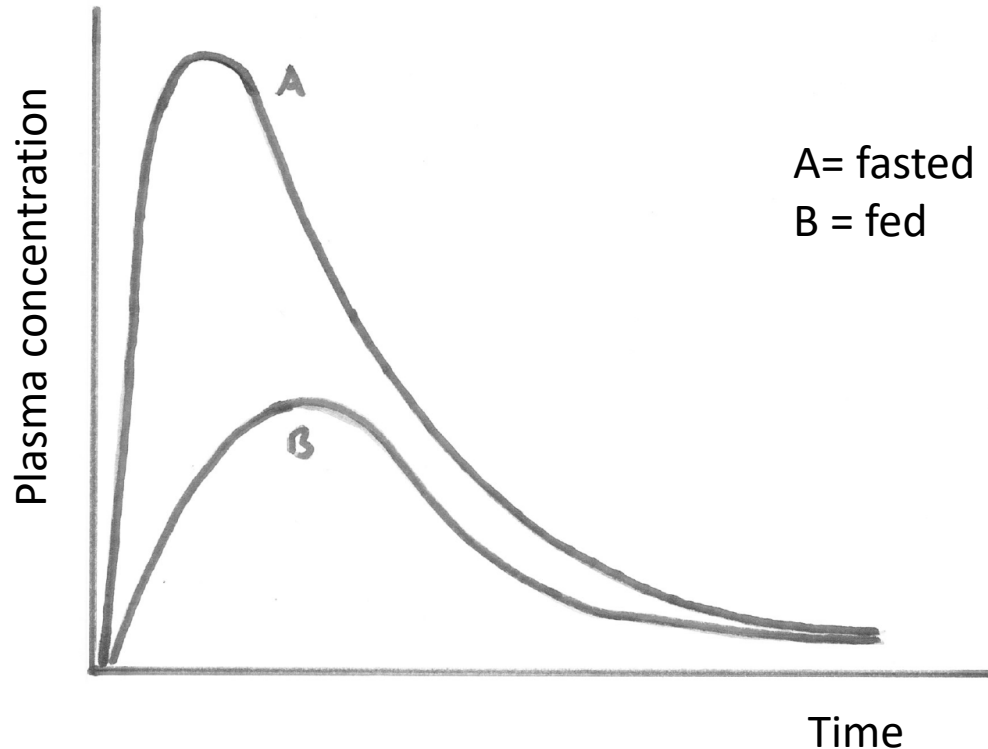


Food effect study

For more than half of subjects below was seen:



Food effect study

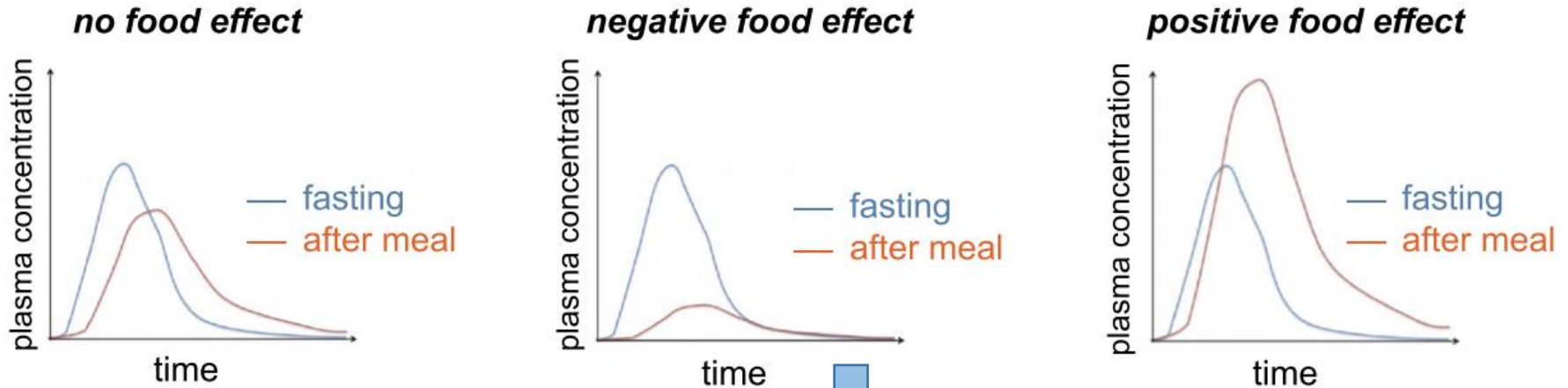


→ A negative food effect

(Formulation has delayed release in fasted state)



Food effect



Adapted from Koziolk et al. Adv Drug Del Rev 2016;101;75-88



Can be due to

- Binding of drug with food components.
- Reduced diffusivity in the viscous contents especially in combination with a small absorption window.

Interesting article on food drug interactions: Koziolk et al., J. Pharm.Sci. 2019;134;31-59



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More investigation needed...

Because:

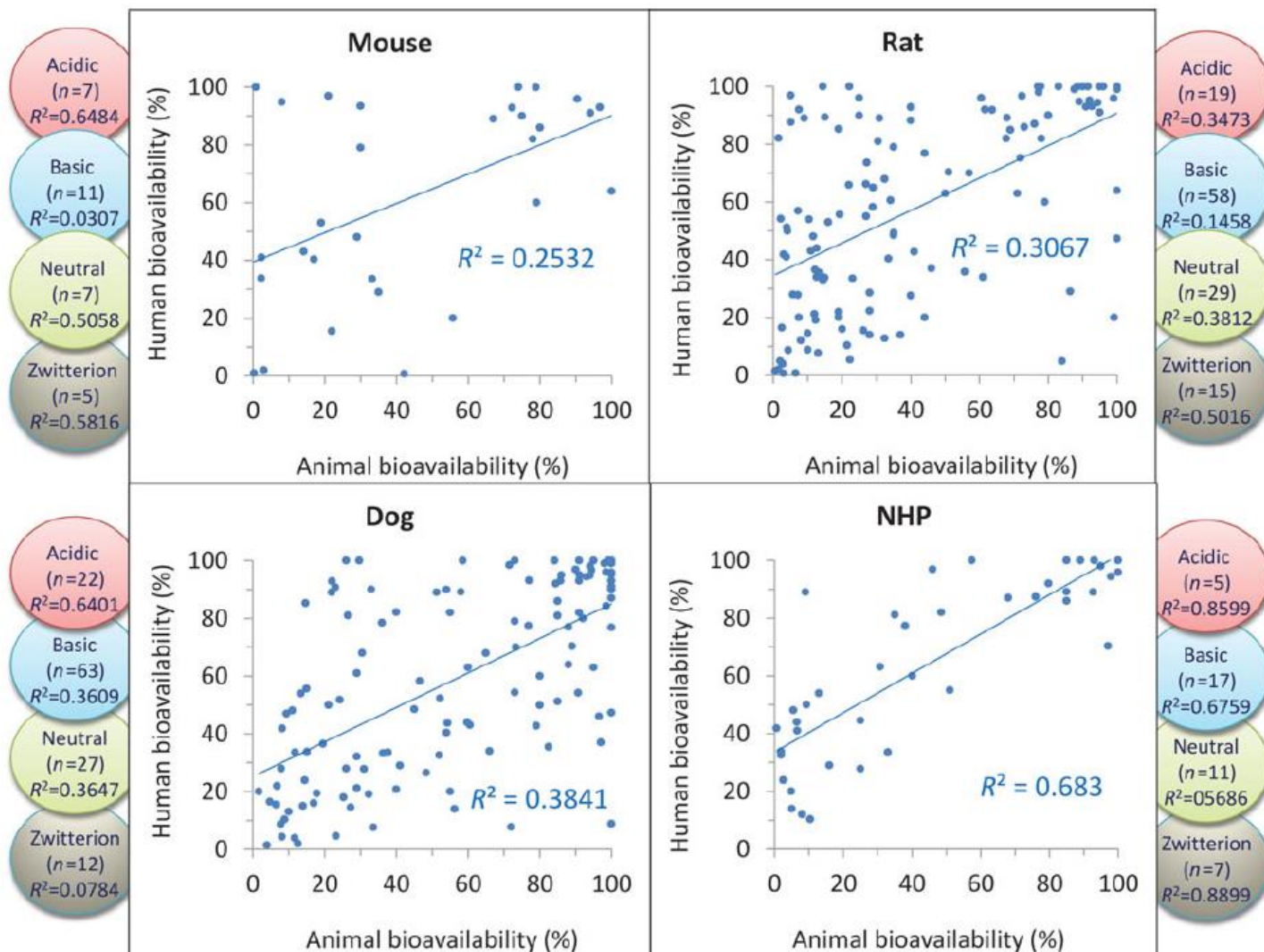
- BSC class 4 compounds normally show no or positive food effect.
- Dog results showed opposite BA than expected based on biorelevant dissolution data

→ More investigation needed.

→ Dog maybe not the best model?



Human BA vs animals





The TIM Company

Food Effects

TIM – TNO Intestinal Models



TIM Systems are computer-controlled *in vitro* systems simulating the dynamic luminal conditions of the stomach, small intestine and large intestine

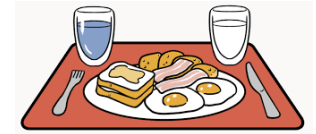
- For nutritional and pharmaceutical applications
- De-risking human intervention trials
- Replacement of animal trials (3R principle)



Tiny-TIMsg 2017

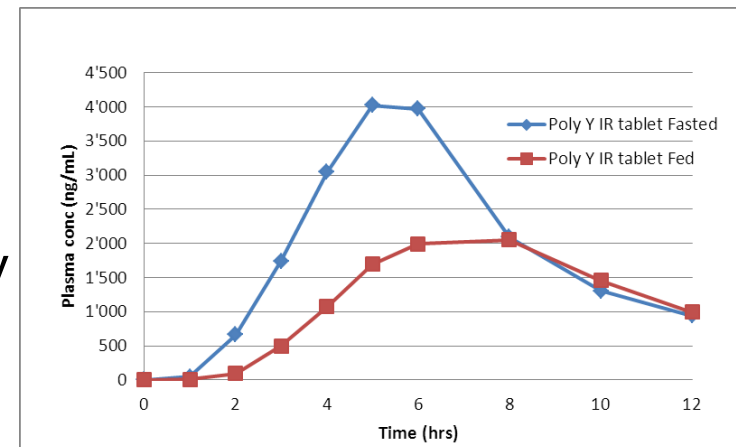
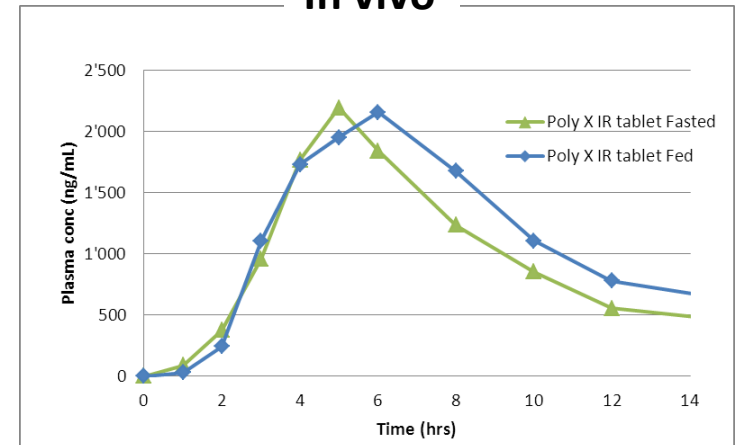


- One API in two amorphous forms, same dose level
- Studied during simulation of fasted and fed state

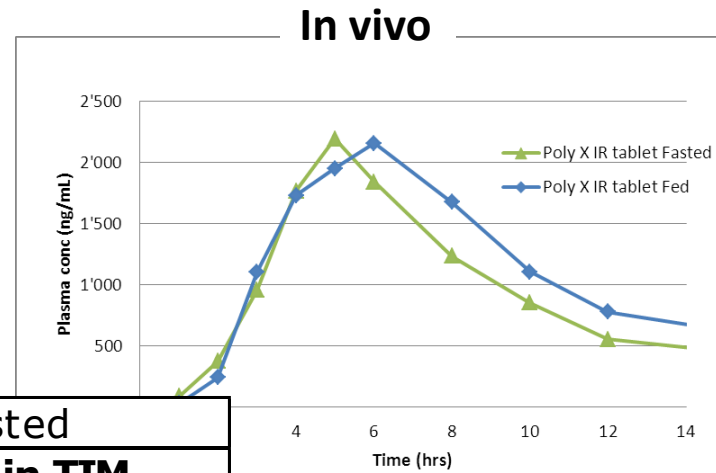
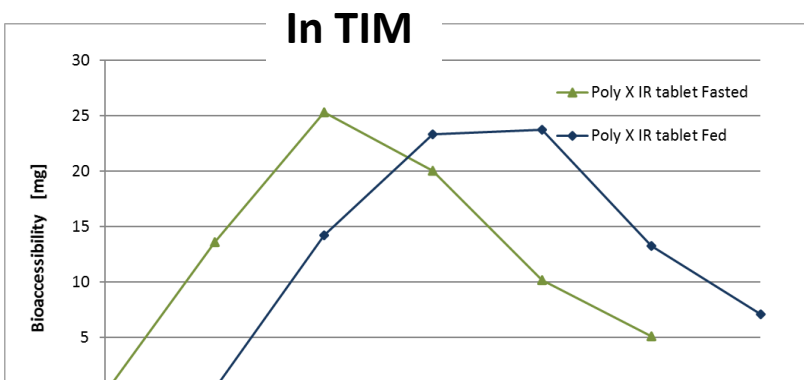


- Polymorph X showed no food effect
 - same bioavailability
-
- Polymorph Y showed a positive food effect
 - Fed state: two fold increased bioavailability

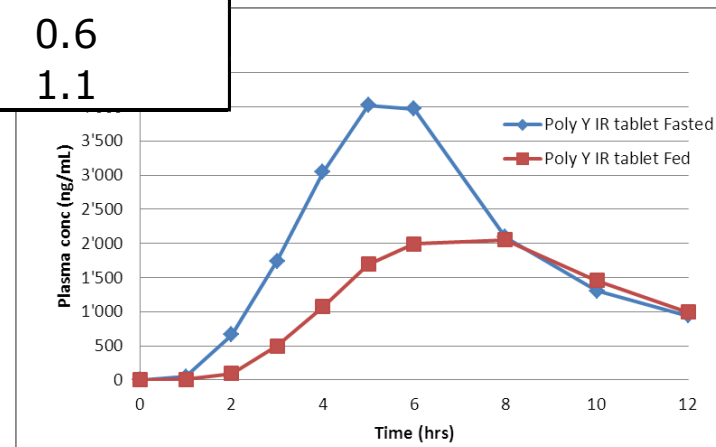
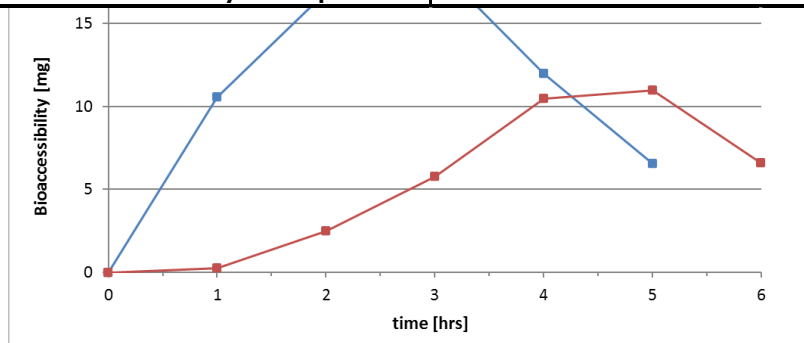
In vivo



- TIM sample X-ray analysis showed structure changes of polymorph forms during transit through the GI tract and explained the presence and absence of a Food Effect.

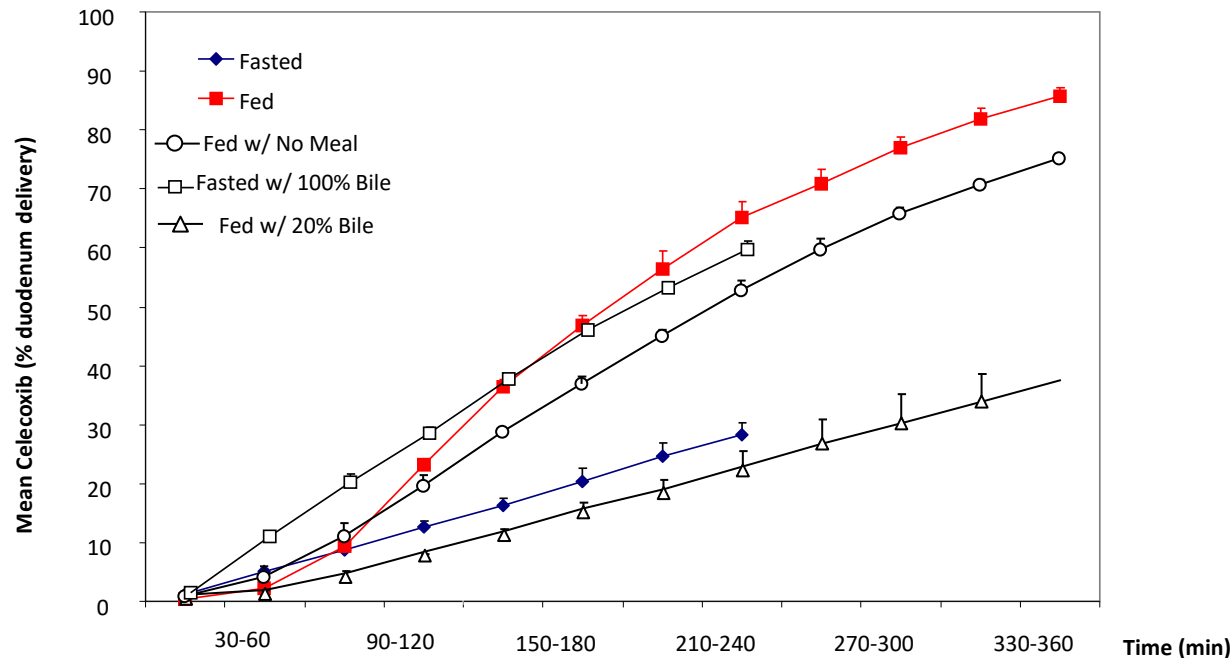


Formulation	ratio fed / fasted	
	in vivo	in TIM
150 mg IR tablet Polymorph Y	0.7	0.6
150 mg IR tablet Polymorph X	1.2	1.1



Bioaccessibility of Celecoxib

- 1200 mg Celecoxib, solubility water 3.3 mg/L, LogP 3.9; Positive food effect *in vivo* (10-20% ↑ of AUC)
- What impacts the food effect the most?



Lyng et al., 2016

THE TIMES | Saturday January 8 2011

It might look like a dog's dinner, but this artificial stomach will save (canine) lives

Mark Henderson Science Editor

An artificial human digestive system has allowed a leading pharmaceutical company to reduce the use of animal experiments to evaluate drugs.

AstraZeneca has closed a dog research facility at its laboratories in Macclesfield, Cheshire, after replacing animal experiments with a synthetic intestinal tract. The network of glass tanks, plastic tubes, filters and valves has been shown to replicate the conditions of the human stomach and so accurately that the company has all but abandoned the use of dogs in the stage of its research.

Between three and 12 animals were previously used for each new drug, to examine how well its active compounds were dissolved after being taken orally and then absorbed through the gut.

"Four or five years ago, we were maintaining a colony of about 30 dogs, just for formulation studies," said Paul Dickinson, the principal scientist for drug absorption at AstraZeneca. "We

have reduced our usage and ... completely closed the facility. We very rarely use dogs now."

The advance shows how it can be possible to reduce the number of animals required for some kinds of medical research, and occasionally to replace them altogether with good in-vitro models of human organs.

As well as reducing unnecessary animal suffering, this can also save money. "If you have a good understanding of the system you're trying to model, you can sometimes remove the need for animal experimentation," Dr Dickinson said. "Maintaining animal colonies is very expensive, so there's a big cost saving there."

For oral drugs to be absorbed into the body they must first be dissolved, and many modern agents are poorly soluble in water. "Some modern drugs are much less soluble than older ones, 1,000 if not 20,000 times less so than paracetamol. A lot of drugs are less soluble than marzipan," Dr Dickinson said. The solubility and absorption rates of different drug formulations must

therefore be tested to ensure that they can get into the bloodstream to have a therapeutic effect. This can be done through testing on human volunteers, but it is impossible for some drugs, particularly cancer drugs, because they are too toxic. Dogs are therefore generally used as an alternative.

"Their gastro-intestinal physiology is similar to that of humans," Dr Dickinson said. "It's similar enough to make

good predictions: how a drug behaves in dogs is usually similar to how it behaves in people."

Troy Seidle, director of research and toxicology at the Humane Society International, welcomed the development. "This new use of the intestinal model in drug testing is a fantastic example of how innovative technologies can replace animal experiments and improve medical research at the same time," he said.

The Times January 8, 2011

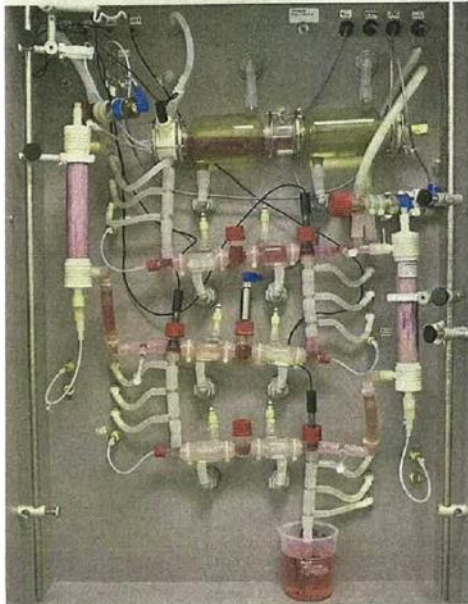
Interview Paul Dickinson of AstraZeneca

'We were maintaining a colony of about 30 dogs for formulation studies.

We have reduced our usage and ... completely closed the facility.'

- Understanding mechanisms, that can't be simulated in a living organism

- Why to use a dog as model if there is a model that simulates the human situation?





Poll questions

Poll questions

Poll end of Slide 3:

What type of formulation is not suited for BCS class 4?

- a) Solid Amorphous dispersion
- b) Micronized API in capsules
- c) SEDDS/SMEDDS
- d) Nanomilled API

Poll end of Slide 6:

What do you see here?:

- a) Negative food effect
- b) No food effect
- c) Lower dose was given
- d) Positive food effect

• Poll end of Slide 15:

Which parameter has the biggest impact on the food effect:

- A: the FDA recommended high fat meal
- B: the bile levels
- C: transit time

