



PHARMACEUTICAL COMPANIES
OF *Johnson-Johnson*



THE ANIMAL MODEL FRAMEWORK: A TRANSLATIONAL APPROACH WITHIN SAFETY PHARMACOLOGY

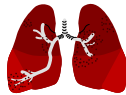
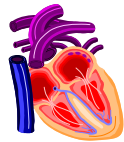
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What is Safety Pharmacology?

- Investigate the potential undesirable effects of a *potential drug* on physiological functions in relation to exposure in the therapeutic range and above
- “*Core battery*” studies: investigate the effects of the *drug* on vital organ functions
 - Cardiovascular, respiratory and central nervous systems



- Supplemental studies: evaluate potential adverse effects on organ system function not addressed by the core battery studies

ICH S7A CPMP/ICH/539/00

Attrition: development & market

- ~ 9 out of 10 *drugs* in clinical development fail
- Safety remains a major reason for drug discontinuation (35-40%)
- Growing focus on drug safety from patients, regulators, health care professionals and payers
- Pharmaceutical industry exploring ways to reduce the high attrition rates

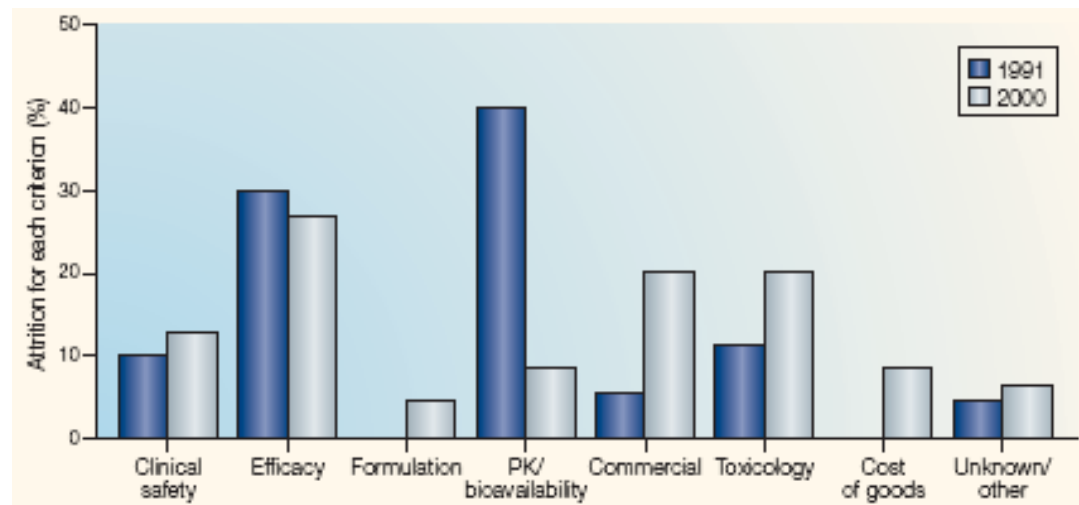
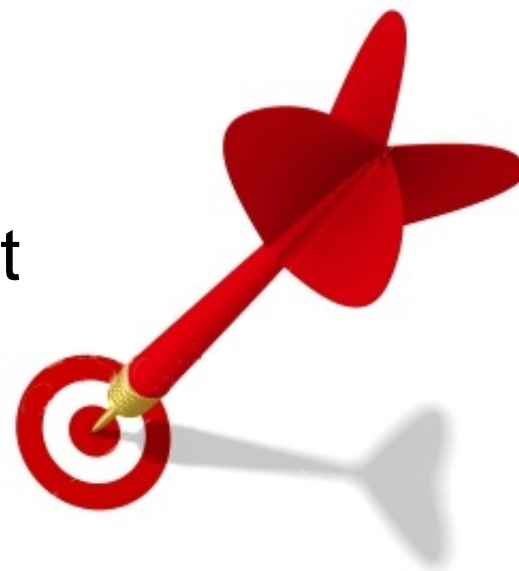


Figure 3 | Reasons for attrition (1991-2000). PK, pharmacokinetics.

Translation – why do it?

- Predict compounds that are “*winners*” thus reducing costly late stage attrition¹
- No dollar or animal cost – extract value from legacy data
- Can lead to potential model refinement
 - eg. Design *more sensitive assays - less animals*
- Concordance can be assessed qualitatively or quantitatively

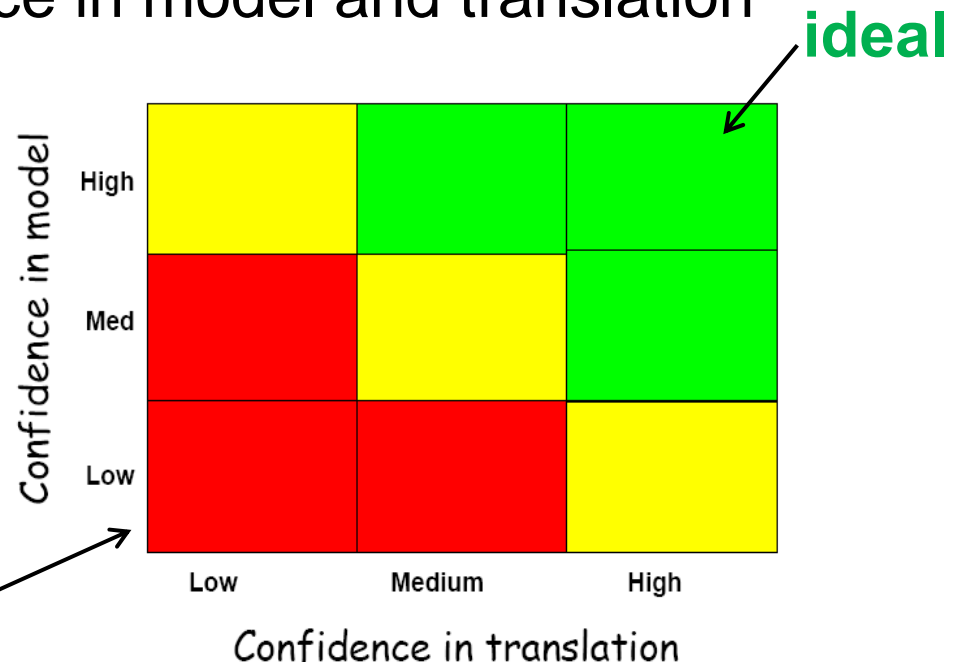


The Animal Model Framework

- Quantitative method to relate preclinical animal data to Phase I clinical trial outcomes
- Two dimensions; confidence in model and translation

Valentin *et al.*, 2009 JPTM 60: 152 - 158

not ideal



- Potential to improve or remove models in the “red”

Model validity: confidence in the model

	Model/Parameter within model		
Score	1	2	3
Matching the clinical end point x2	Cannot or do not measure same end point in animals and human 2	Measure same physiological end point, but not the same measure 4	Measure same end point in humans and animals 6
Matching the pathway/ mechanism (conservation of pathways) x1	Target/pathway not validated or relevant in humans 1	Target/ pathway present in model and hypothesised to be relevant in man 2	Target pathway known and relevant in model and man 3
Matching the physiology x1	Pathway present in model, but relevance to man is unknown 1	Pathway present and functional in model, but unknown direction and magnitude 2	Pathway present and functional in the same direction and magnitude 3

Overall confidence: Low ≤ 6 , Medium 7 to 9, High ≥ 10

Dog Telemetry: QT interval

	Model		
Score	1	2	3
Matching the clinical end point x2			Measure same end point in humans and dogs (eg.QT) (6)
Matching the pathway/ mechanism (conservation of pathways) x1		Close similarity between Ikr ion channels, (2)	
Matching the physiology x1			Similar anatomy and physiology (3)

Overall confidence: High (11)

Rat Telemetry: QT

	Model		
Score	1	2	3
Matching the clinical end point x2			Measure same end point in humans and rats (eg. QT) (6)
Matching the pathway/ mechanism (conservation of pathways) x1	Some similarity between ion channels (1) Eg. Na, Ca, Ito etc but <u>no IKr</u>		
Matching the physiology x1	Repolarisation driven by I _{to} current; physiology dissimilar (1)		

Overall confidence: Medium (8)

Zebrafish larvae: QT surrogate (AV block)

	Model		
Score	1	2	3
Matching the clinical end point x2	Image synchronicity of contraction between atria and ventricle (2)		
Matching the pathway/ mechanism (conservation of pathways) x1		Some similarity between ion channels (based on limited validation data) (2)	
Matching the physiology x1	Anatomy and physiology of the heart different (1)		

Overall confidence: Low (5)

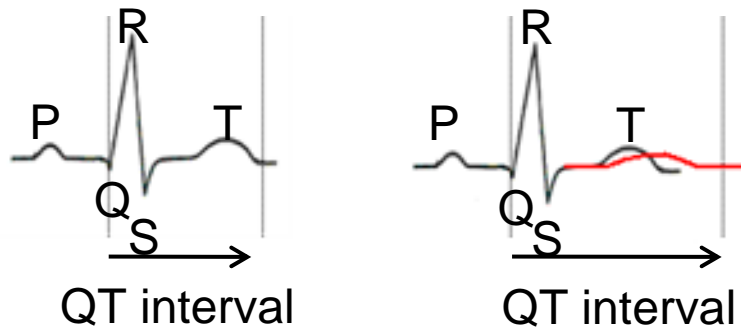
Other factors that could be considered for model validity

- Scientific expertise and knowledge
- Animal welfare (reduce, refine, replace)
- Number of *reference drugs* used in validation & outcome
- Reproducibility of results
- Accuracy of measurements
- Throughput
- Cost of model
- *Convenience*
- *Amount of drug required*

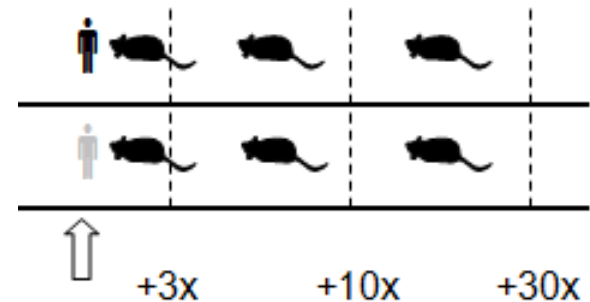


Confidence in translation

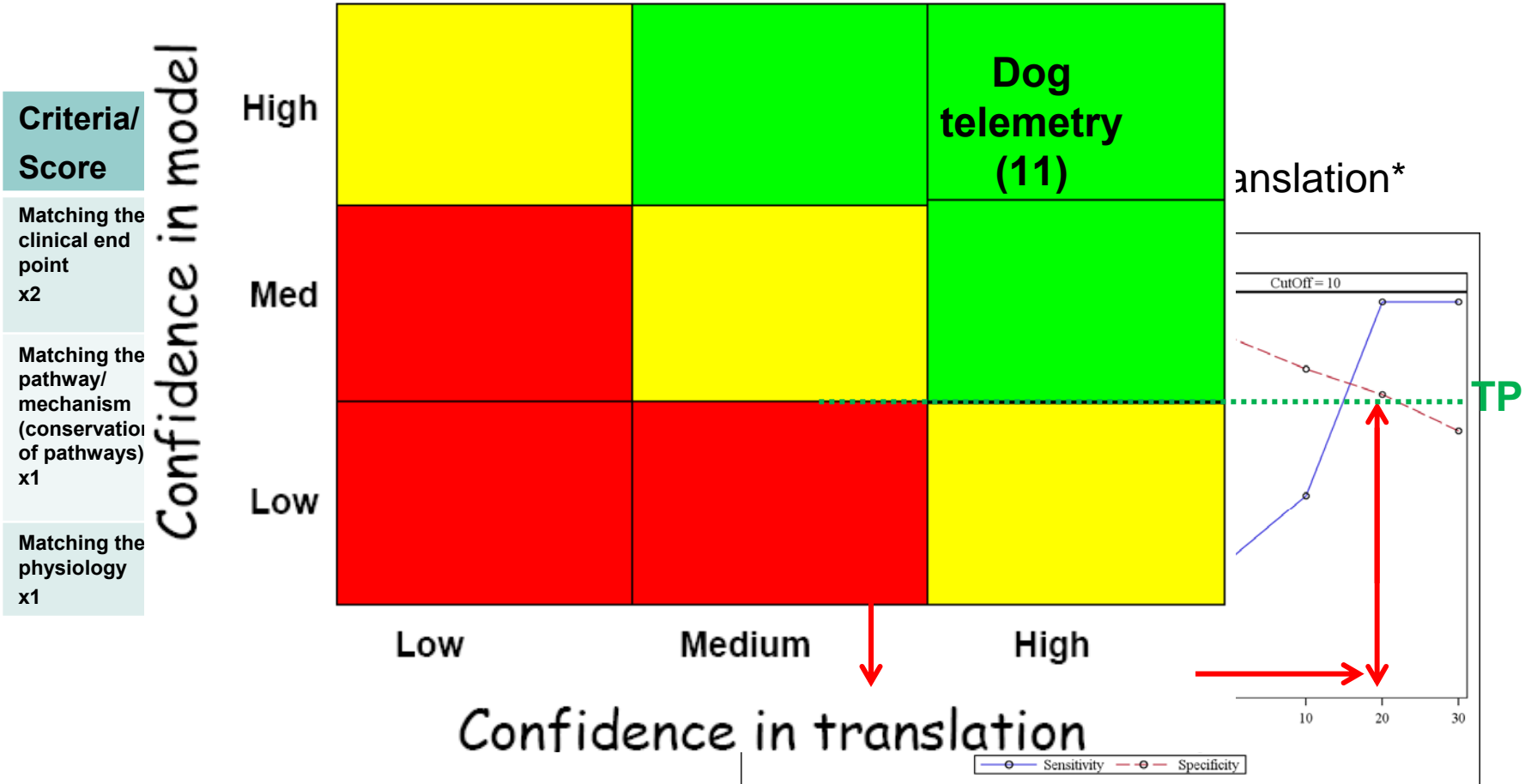
- Pre-clinical magnitude of change
 - Used to assess different thresholds that define an effect
 - 5, 10 or 25% level of change



- Exposure comparison



High confidence in Dog CV Telemetry Model



* Exposures equivalent to human therapeutic dose

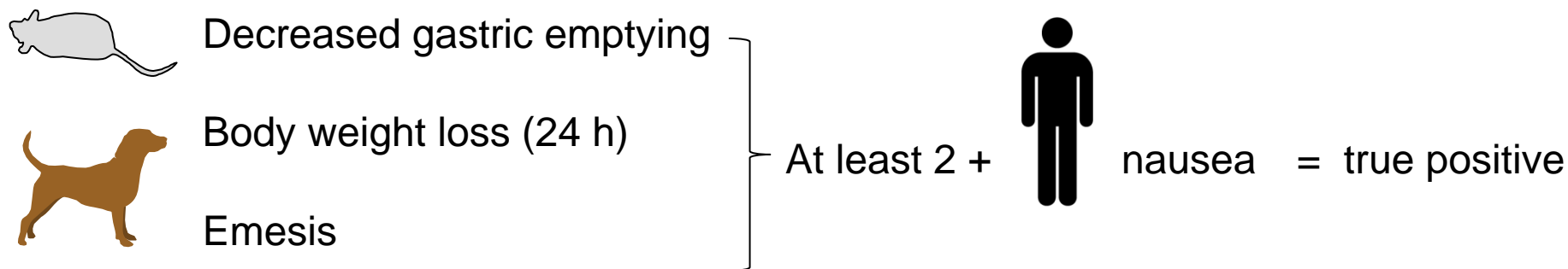
ADR: Drug-induced nausea

Symptom	No. of Cpds	% Total (113)
Headache/migraine	45	40%
Nausea	34	30%
Dizziness/Vertigo	34	30%

- CNS targeted drugs, 68% cause nausea
- No recognised animal model of drug-induced nausea
 - Plausible preclinical correlates (dose-related)
 - emesis in dogs
 - decreased gastric emptying in rodents
 - body weight loss in rodents (24 h)

Integrated risk assessment

- Qualitative approach, using existing data



	TP	FP	TN	FN	Total	Sens.	Spec.	Pred.
Combined	5	7	18	2	32	71%	72%	72%

- Integration of data across organ systems powerful
- Limited by small data set

Potential impact

- Reduction in animal numbers
 - Integrate data from regulatory studies to generate predictions for key adverse events
 - Select only the models that deliver the best translation to man
 - Extend framework to animal models of efficacy
- Scientific refinement
 - Improve sensitivity or specificity of model
 - Positioning within drug discovery process (i.e. high sensitivity/specificity models prior to first time in man)

Summary

- Animal model framework is a cross-company project which aims to reduce costly drug attrition
- Allows quantitative and qualitative assessment of translation
- Potential impact to reduce animal numbers
- Useful for evidence-based decision making
- Potential to influence regulatory bodies

THANKS FOR YOUR ATTENTION

BACK - UP

Sensitivity, Specificity & Predictive Power

		Clinical Outcome	
		-	+
SP model outcome	-	TN <i>True Negative</i>	FN <i>False Negative</i>
	+	FP <i>False Positive</i>	TP <i>True Positive</i>

- **Sensitivity** = $TP / (TP + FN)$
- **Specificity** = $TN / (TN + FP)$
- **Predictive Capacity** = $(TP + TN) / \text{Total}$
 - “Total” number of compounds evaluated = $TN + TP + FN + FP$

Fig. 2. Determination of sensitivity, specificity and predictive capacity of safety pharmacology (SP) models in relation to the clinical outcome. Both the safety pharmacology and the clinical outcome can be either positive (+; an effect observed) or negative (–; no effect observed).

J.-P. Valentin et al / *Journal of Pharmacological and Toxicological Methods* 60 (2009) 152–158