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Non-clinical Assessment of New Medicinal Products for Safety Pharmacology

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She is involved in conducting and planning of short term and long-term studies like, sub-acute, sub-chronic, neurotoxicity, toxicokinetic / pharmacokinetic and safety pharmacology studies. Also, actively works for new validation studies. She has professional experience of more than 5 years in CRO industries.

WHAT IS SAFETY PHARMACOLOGY?[1,2]

The nonclinical safety assessment of a new chemical entity (NCE) or drug chemical is acquired by the combination of data generated during preclinical phase like data from toxicological studies, pharmacological studies and in silico studies.

During non-clinical study phase there are three different types of pharmacology studies are conducted i.e., primary, secondary and safety pharmacology studies. Primary and secondary pharmacology studies are performed to confirm the mode of action of candidates and its effects related or non-related to the therapeutic target, respectively. Safety Pharmacology studies are investigating undesirable pharmacodynamic effects of a drug on physiological processes when exposed at therapeutic levels or above.

Data generated from safety pharmacology can help in making decisions at each stage of the preclinical drug development process i.e.

01 To aid in the choosing of series and compounds

02 To determine the prospective of clinic failure owing to adverse events

03 To identify probable adverse drug reaction so that clinical pharmacologist can focus on them

04 In humans to determine a therapeutic window for acute dose

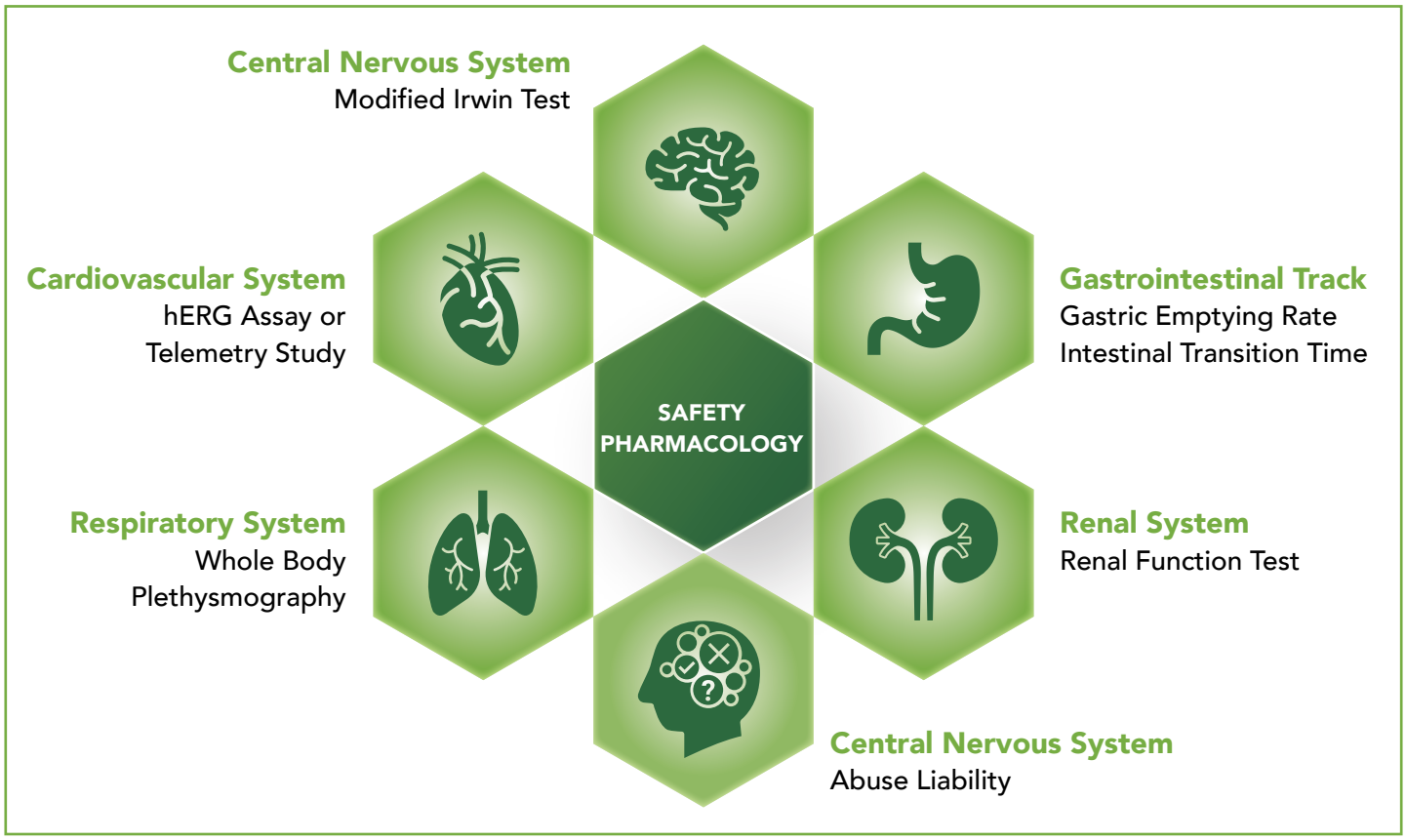

Figure 1: Type of Safety Pharmacology Studies

ATTENTIVENESS OF PHARMACOLOGY[1]

Safety pharmacological studies are currently considered as one of the most necessary battery of studies those help to understand secondary pharmacological of new drug molecules. In the general nonclinical safety assessment of an NCE, safety pharmacology studies are increasingly regarded as a vital technique.

The following are some of the most important points of interest:

- Good predictive values for Human (CVS, QT)
- Most of the trials are conducted early on, with a single dose, short term design, and little amounts of product
- Studies do not require large number of laboratories
- The possibilities of noninvasive methods like imaging, telemetry, invitro models etc
- Providing a dynamic approach compared to the toxicological studies, more rigid and less flexible
- Good cost/informative prospective ratio

SAFETY PHARMACOLOGY RISK ASSESSMENT[3]

The risk assessment involves the stepwise and comprehensive evaluation of results generated from the nonclinical studies. Physiological function data of safety pharmacology studies are also integrated with other non-clinical data for the purpose of risk assessment as well as management in humans during clinical trial studies. Safety pharmacology provides a direct correlation between findings and risk in both animals and humans by using different biomarker eg. QT prolongation. Data generated from such studies help for risk associated with different phases of drug development. These safety pharmacology studies when performed at early development stages help to screen the compound early stage and reduce drug failure at clinical phase based appropriate evaluation of parameters and findings. For the safety pharmacology data matrix type approach has been proposed to simplify and standardize its contribution in early risk assessment (Table 1).

Table 1: Safety Pharmacology integrated risk assessment matrix[4]

Therapeutic Target	Existing Therapy	Severity of Safety Pharmacology Outcome		
		Minor	Moderate	Major
		100x, 10x, 1x	100x, 10x, 1x	100x, 10x, 1x
Minor/Moderate	Good	X		
	Partially effective	X		
	Poor/None	X		
Debilitating	Good		X	
	Partially effective		X	
	Poor/None		X	
Life threatening	Good			X
	Partially effective			X
	Poor/None			X

PROPHETIC VALUE OF SAFETY PHARMACOLOGY TESTING[1,5]

It has been noticed in the last few decades that the major cause of drug attrition is non-clinical and clinical safety during drug development. There are many clinical hazards predicted from the non-clinical safety studies in the past. In case of safety pharmacology testing, a new different approaches and model have been developed to predict the safety of human in involved in trials and getting treated with medicines for disease. Safety pharmacology studies have helped to reduce later drug attrition by detecting drug-induced safety-relevant effects early on.

Following are the few examples of effect that are detected with help of non-clinical safety pharmacology studies.

- Clonidine's sedative effects in many animal species and humans
- Propensity of cisapride to prolong ventricular repolarization
- Morphine's respiratory depressing effects
- Nephrotoxic effect of cyclosporine
- Gastrointestinal effects of erythromycin

The data presented in table also indicates some examples of SP testing model for its sensitivity, predictivity.

Test System	Species	Experimental condition	Clinical endpoint	Number of compounds	Sensitivity%	Specificity%	Predectibility%	References
Optometry	Zebra fish	*In vivo*	Visual acuity	37	71	78	73	Richards et al. (2008)
Speed and distance travelled	Zebra fish	*In vivo*	Seizuer	25	76	63	72	Winter et al. (2008)
hERG	Human	*In vitro*	QT interval prolongation	19	82	75	79	Wallis R. (2007)
QT interval prolongation	Dog	*In vivo*	QT interval prolongation	19	83	86	85	Wallis R. (2007)
Screenit	Rabbit	*In vitro*	Torsades de Pointes	64	65	89	75	Lawrence et al. (2006)

References:

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