Pharmacological Approaches

•Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery.

Drug Development Process:

1- Screening of thousands of active compounds by means of biological assays ALS F STP
2. Choice of the lead compound
3. Synthesis and physico-chemical characterization of the lead compound
4- Formulation of the drug product consisting of the drug substance, excipients and delivery system
5- Scale-up of production and quality control
6. Toxicology
7. Preclinical pharmacology, composed of pharmacokinetics and pharmacodynamics.

#Pharmacological Approches:

Pharmacological studies fall into two categories:
1. Research pharmacological studies
2. Safety pharmacological studies

1-Research Pharmacological Studies:

- Mainly conducted at the start of a drug development Program
- They do not need to be performed at GLP standard

There are two types:

1. Primary research pharmacological studies
2. Secondary research pharmacology studies

Primary research pharmacological studies:

- Primary actions are related to proposed therapeutic-use
- These studies focus on the mechanism of action of drug and can be conducted in vitro and in vivo.
- Studies conducted in vitro include radioligand binding studies and focus on drug action on specific receptor site.
- Studies conducted in vivo investigate the pharmacological action of the drug in animal models.
- This study is useful in predicting potential safety

issues, drug interaction and other undesired effects.

Secondary research pharmacology studies

- Secondary actions focus on the overall pharmacological activity of the drug compound
- And also relates to the actions that occur which is not directly related to the proposed therapeutic use
- This can be concluded in vitro and in vivo. --- In vitro studies investigate the binding of drug molecule with the non-target receptors.
- In vivo studies investigate the general pharmacological actions in animal models.

Safety Pharmacological Studies:

- Safety pharmacological studies investigate potentially undesirable effects of the drug compound
- They are conducted in animal models
- These are single dose studies using intended

therapeutic dose

- They focus on functional changes in major organ systems within the body
- These studies investigate the undesirable effect on the functioning of CNS, CVS and respiratory system.

Eg: CNS	CVS
Skeletal muscle tone	BP
locomotion	H.R
reflexes	ECG changes

Respiratory system

rate and depth of breathing

□ Estimating the Maximum recommended Starting Dose (MRSD) in Clinical Trials for A NEW DRUG in Adults Healthy Volunteers:

Introduction:

- Maximum recommended starting dose (MRSD) for first-in-human

- clinical trials of new molecular entities in adult healthy volunteers

The goals of this guidance are to:

- Establish a consistent terminology for discussing the starting dose
- Provide common conversation factors for deriving a human equivalent dose (HED)
- To derive a strategy for selecting the MRSD for adult healthy volunteers, regardless of the projected clinical use.

Glossary

Body surface area conversion factor (BSA-CF): A factor that converts a dose (mg/kg) in an animal species to the equaling dose in humans (also known as the human equivalent dose), (HED) based on differences in body surface area.
-A BSA-CF is the ratio of the body surface areas in the tested species to that of an average human.

Human equivalent dose (HED): A dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose.

- In this guidance, as in many communications from Sponsors, the term HED is usually used to refer to the human equivalent dose the NOAEL.

K: A dimensionless factor that adjusts for differences in the surface area to weight ratio of species because of their different body shapes.

K_m: Factor of converting mg/ml dose to mg/m^2 dose

Maximum recommended starting dose (MRSD):

The highest dose recommended as the initial dose in a clinical trial. In clinical trials of adult healthy volunteers the MRSD is predicted to cause no adverse reactions.

- The units of the dose (e.g mg/kg or mg/m^2) may vary depending on practices employed in the area being investigated.

• No observed adverse effect level (NOAEL): The highest dose tested in an animal species that does not produce a significant increase in adverse effects in comparison to the control group. Adverse effects that are biologically significant, even if not statistically significant, should be considered in determining an NOAEL.

• Safety factors (SF): A number by which the HED is divided to introduce a margin of safety b/w the HED and the maximum recommended starting dose. MRSD = HED/SF

Human Equivalent Dose Calculation

Conversation Based on Body Surface Area

• An analysis of the effect of the allometric exponent (b) on the conversion of an animal dose to the HED was conducted.

HED = animal NOAEL x (W animal/W human)$^{(1-b)}$

Based on this analysis and on the fact that correcting for body surface area increases clinical trial safety by resulting in a more conservative starting dose estimate, it was concluded that the approach of converting NOAEL doses to an HED based on body surface area correction factors (i.e., WO.67) should be maintained for selecting starting doses for initial studies in adult healthy volunteers.

Conversion of Animal Doses to Human Equivalent Doses (HED) Based on Body Surface Area
(only for reference)

Species	To convert Animal Dose in mg/kg to Dose in mg/m2, multiply by km	To Convert Animal Dose in mg/kg to HED in mg/kg, either:	
		Divided Animal Dose By	Multiply Animal Dose By
Human	37	---	---
Child(20 kg)b	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel	7	5.3	0.19
monkey	20	1.8	0.54
Baboon			
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

ONLY FOR REFERANCE

Most appropriate species selection

Factors that can influence:

- Differences in the absorption, distribution, metabolism, and excretion(ADME) of the therapeutic between the species.
- Class experience that may indicate a particular animal model is more predictive of human toxicity. Selection of the most appropriate species for certain biological products (e.g. human protein)

APPLICATION OF SAFETY FACTOR (SF)

- To provide a margin of safety for protection of human subjects receiving the initial clinical dose.

- This safety factor allows for variability in extrapolating from animal toxicity studies to studies in humans resulting from:
- Uncertainties due to enhanced sensitivity to pharmacologic activity in humans V.S animals.
- Difficulty in detecting certain toxicity in animals (e.g. headache, myalgia, mental disturbances)
- Differences in receptor densities or affinities
- Unexpected toxicities interspecies differences in ADME of the therapeutic.
