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SÚKL

Non-Clinical Research: Key Milestone in the Drug Development

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Day 1 – 23. 2. 2021

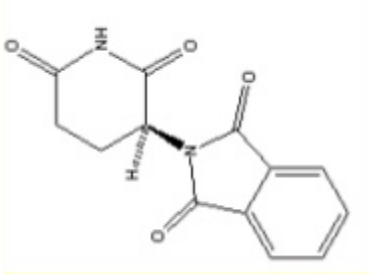
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 825881

Overview of the presentation

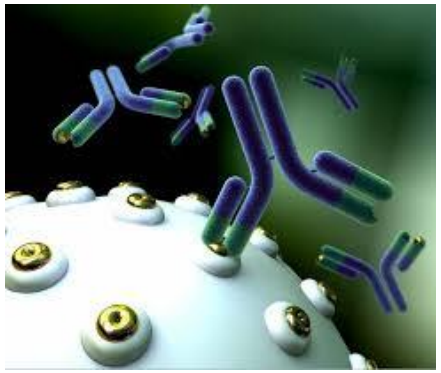
- Relevance of non-clinical studies in the drug development
- Law behind – Directive and Guidelines
- Recommendation for special type IMP and population
- GLP
- Scientific Advice from National Authority

Type of drug product involved in presentation

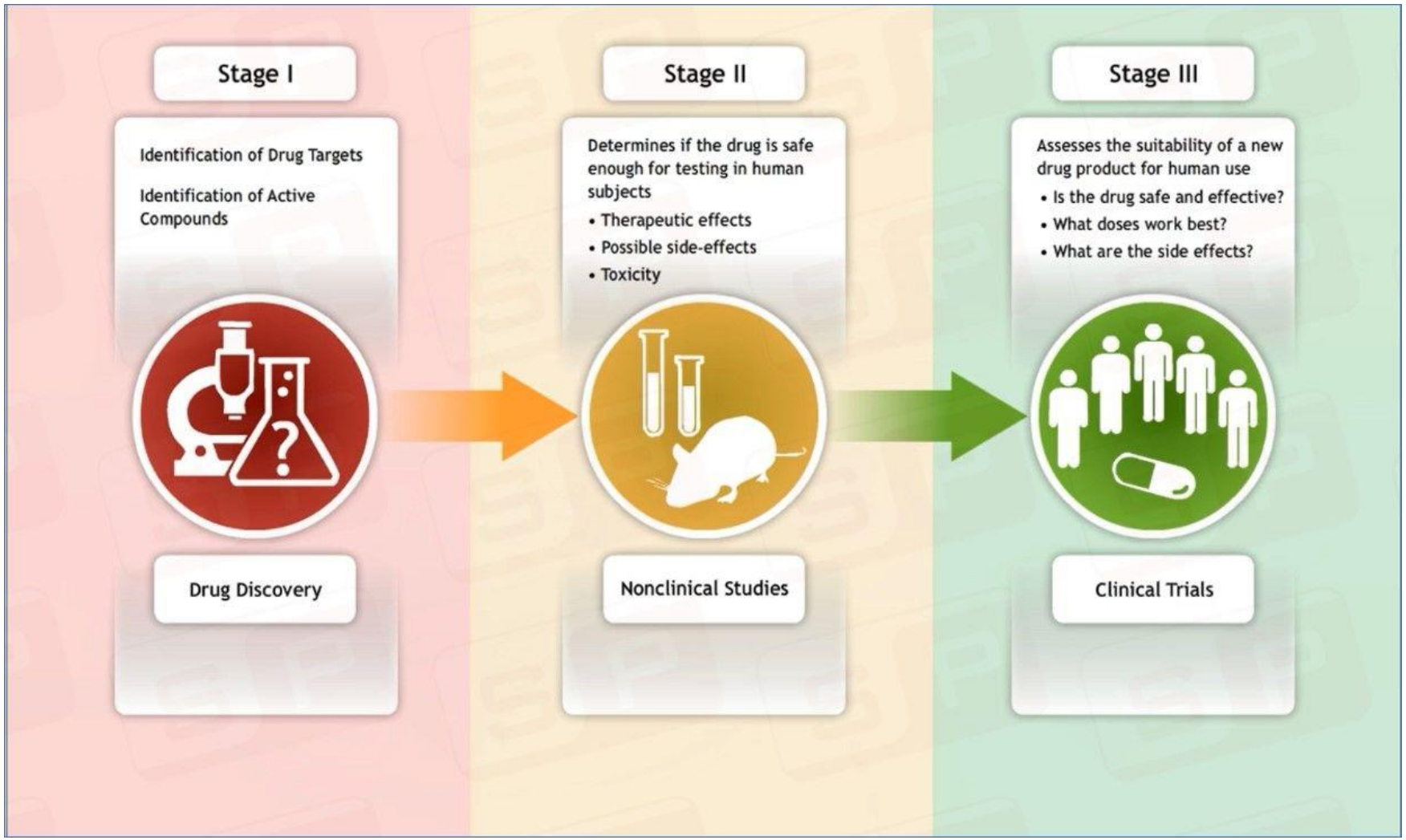
- Small molecules



- Biotechnology products

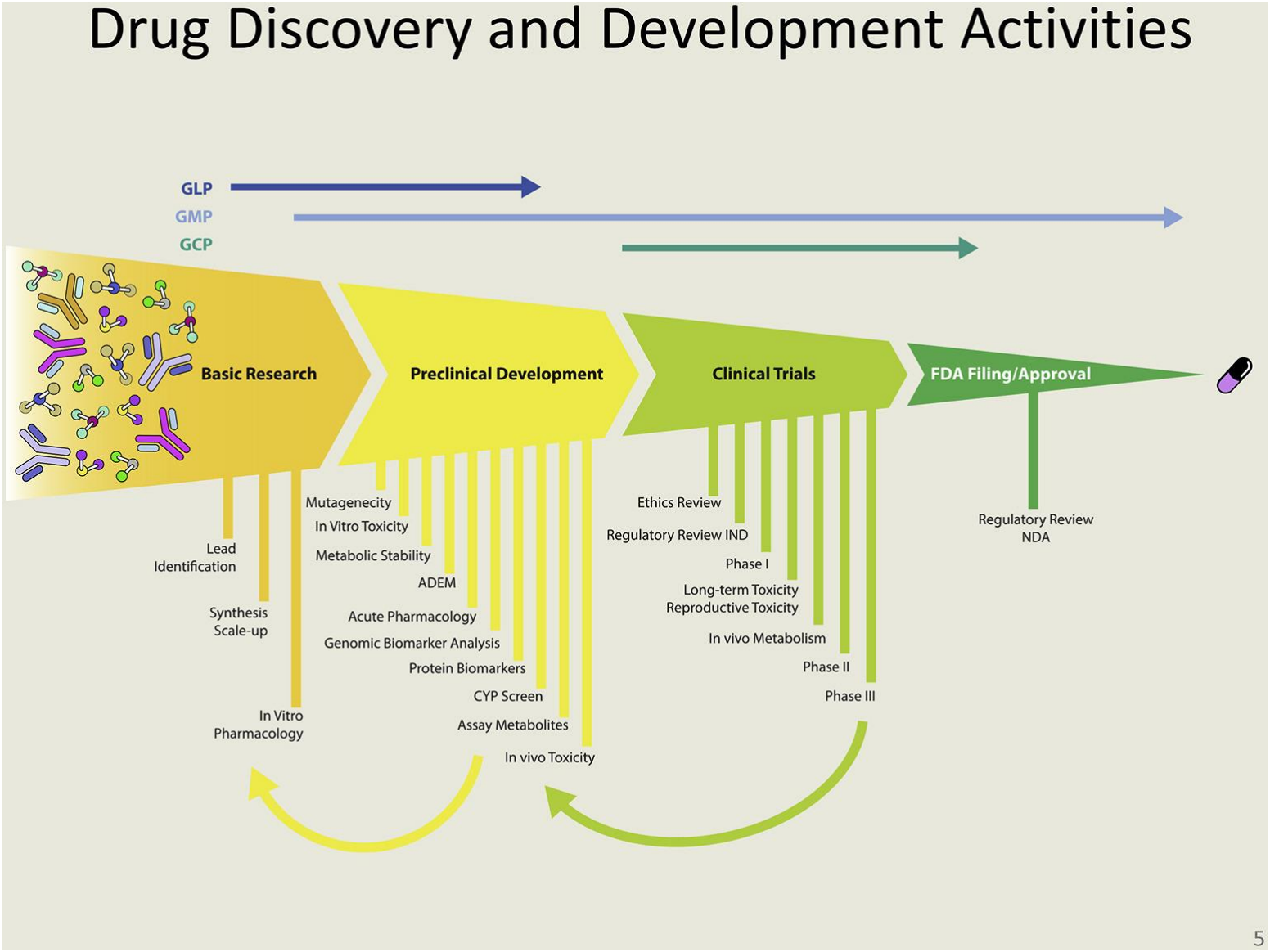


- Advanced Therapy Medicinal Product


Stage I
Identification of Drug Targets
Identification of Active Compounds
Drug Discovery
Stage II
Determines if the drug is safe enough for testing in human subjects
• Therapeutic effects
• Possible side-effects
• Toxicity
Nonclinical Studies
Stage III
Assesses the suitability of a new drug product for human use
• Is the drug safe and effective?
• What doses work best?
• What are the side effects?
Clinical Trials

Skillpad

Drug Discovery and Development Activities



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Relevance of non-clinical studies in the drug development

- EFFICACY: PD (mode of action)
  PK (metabolism)
- SAFETY: toxicological profile and reversibility of AE

- Establish a safe initial dose
- Identify parameters for clinical monitoring of potential adverse effects in clinical trials

Legal Framework

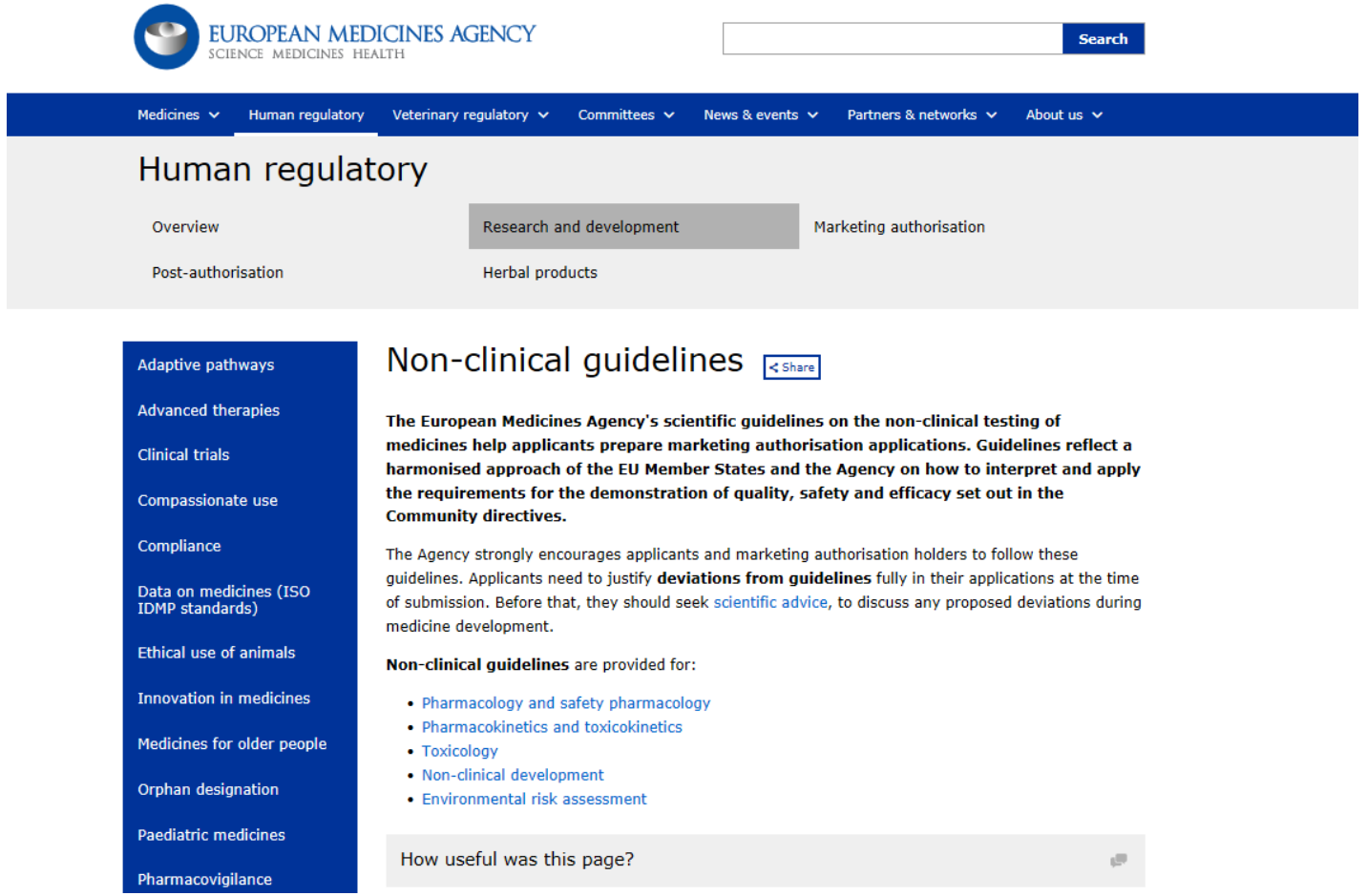
- Directive 2001/20/EC
- **ICH Guidelines:** "Community documents intended to fulfill a legal obligation laid down in the Community pharmaceutical legislation"
- Guidelines are state of the art documents that describe the specific recommendations on how to fulfill the requirements stated by the law
- Guidelines are useful for:

  Harmonisation

  Consistency

  Transparency
- Guidance to academy, industry and assessors
- Justifications are needed if going beyond framework

EMA website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Clinical trials
Compassionate use
Compliance
Data on medicines (ISO IDMP standards)
Ethical use of animals
Innovation in medicines
Medicines for older people
Orphan designation
Paediatric medicines
Pharmacovigilance
Non-clinical guidelines
Share
The European Medicines Agency's scientific guidelines on the non-clinical testing of medicines help applicants prepare marketing authorisation applications. Guidelines reflect a harmonised approach of the EU Member States and the Agency on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in the Community directives.
The Agency strongly encourages applicants and marketing authorisation holders to follow these guidelines. Applicants need to justify deviations from guidelines fully in their applications at the time of submission. Before that, they should seek scientific advice, to discuss any proposed deviations during medicine development.
Non-clinical guidelines are provided for:
Pharmacology and safety pharmacology
Pharmacokinetics and toxicokinetics
Toxicology
Non-clinical development
Environmental risk assessment
How useful was this page?

Timing and extent of NC studies

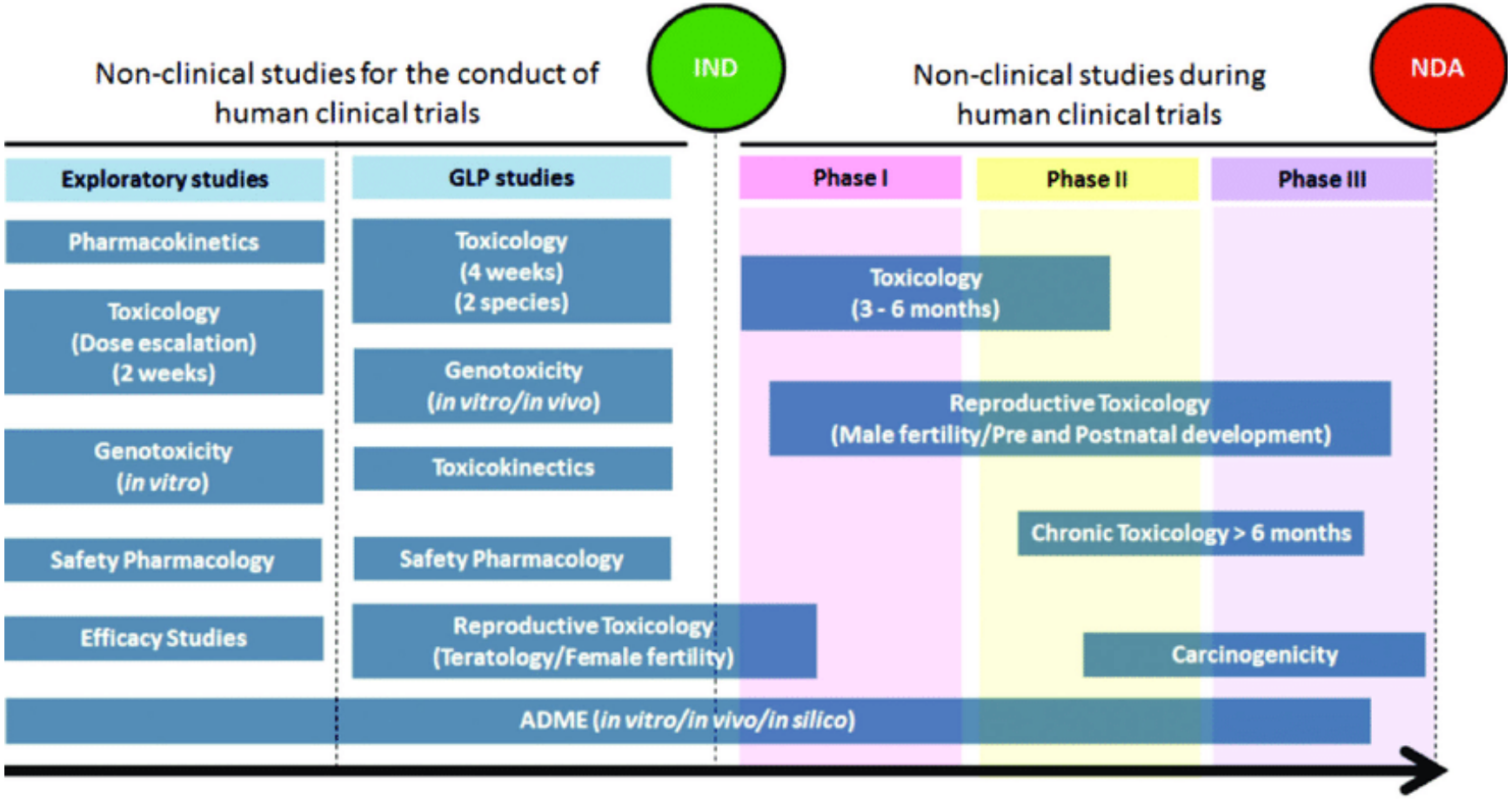
- **ICH M3 (R2)** Non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals
- Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products
- EMEA/CHMP/SWP/28367/07 Rev. 1

1 dead after botched clinical drug trial in France, 5 still in hospital

Man was already brain dead after ingesting painkiller based on a compound similar to cannabis

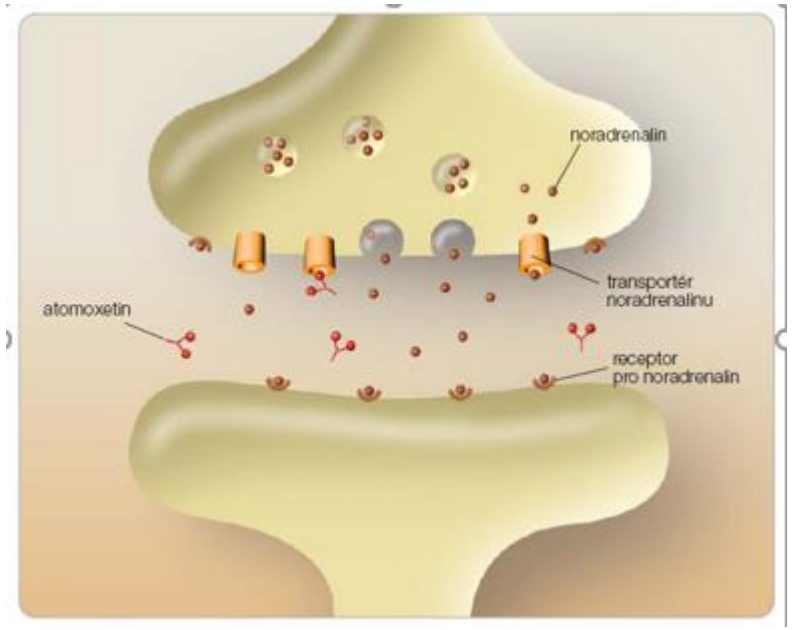
The Associated Press
January 17, 2016

Timing of NC studies



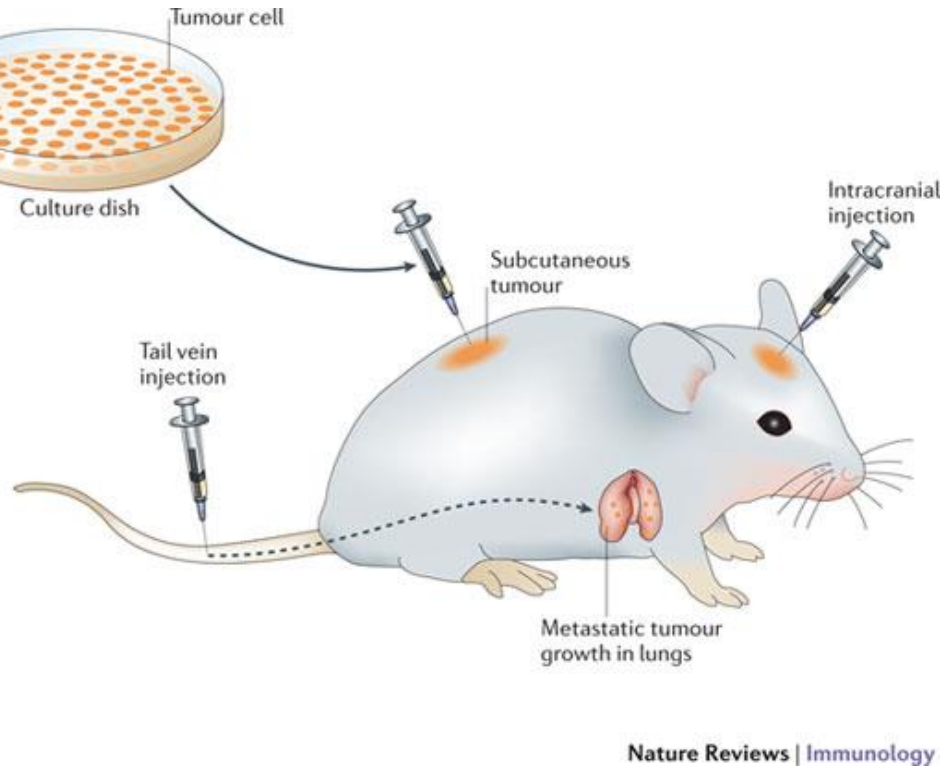
PHARMACODYNAMICS –ICH S7A

- Mechanism of action on molecular, cellular, tissue and body level
- Bound interaction
- Specificity, selectivity
- Ireversibility
- Duration of action

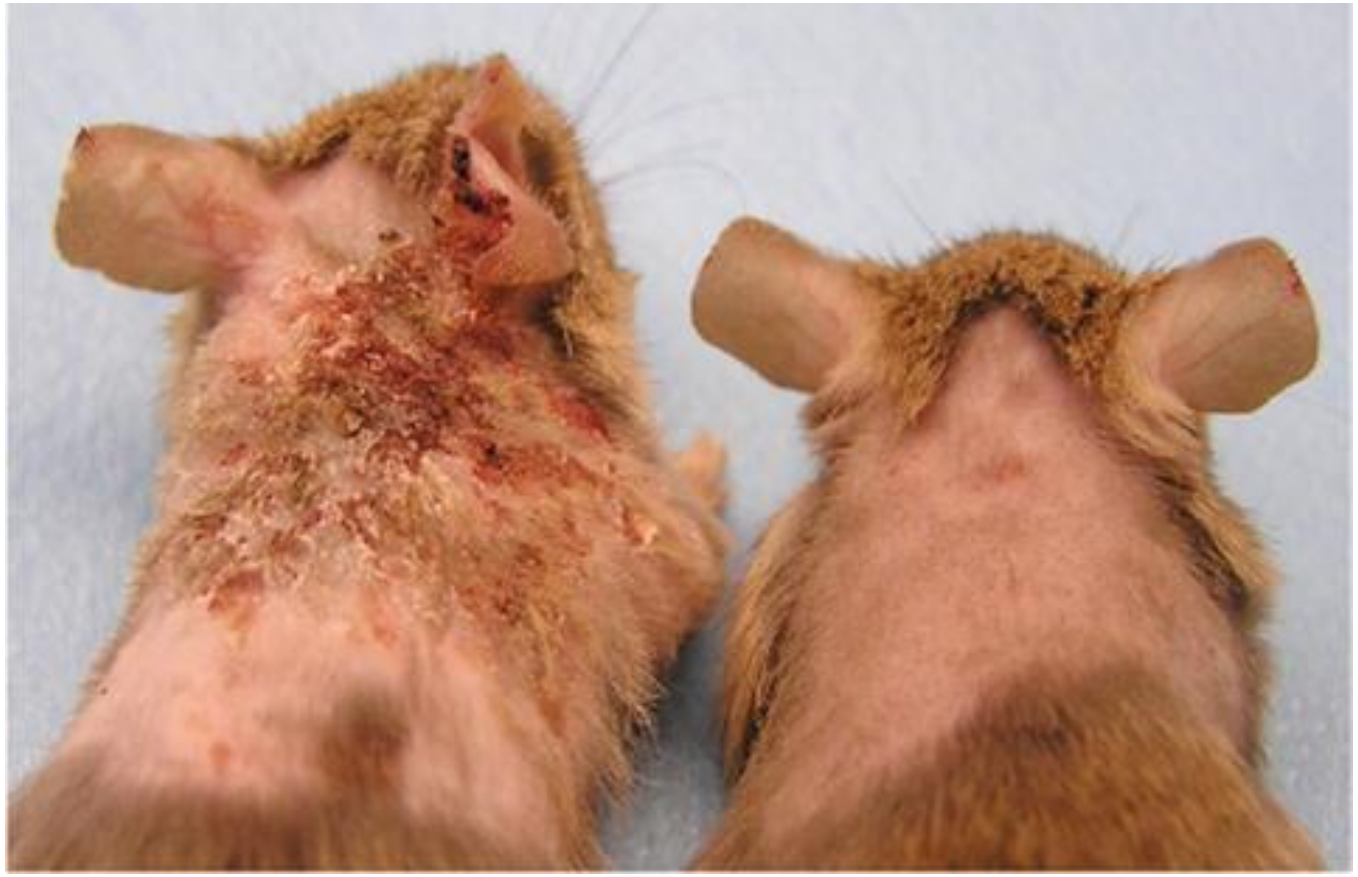


PHARMACODYNAMICS –ICH S7A

- Proof of concept – *in vivo* on **relavant** animal model
- Same target with same potency
- Mechanism of action comparable to human
- Metabolism-PK
- Dosage



Animal model of disease



SECONDARY PHARMACODYNAMICS

- studies on the mode of action and/or effects of a substance not related to its desired therapeutic target.
- Panel of receptors, ion channels, transporters and enzymes, QSAR
- Sildenafilum – vasodilatation (to cure high blood presure x AE? erection)
- Oncology drug – GIT, sperm, hair

SAFETY PHARMACOLOGY ICH S7A, S7B

- CVS (hERG, ECG)
- CNS
- Respiratory
- Liver, kidney – according to composition and mechanism of action

- Could be integrated in toxicology studies

PHARMACODYNAMIC DRUG INTERACTION

Pharmacodynamic Interactions

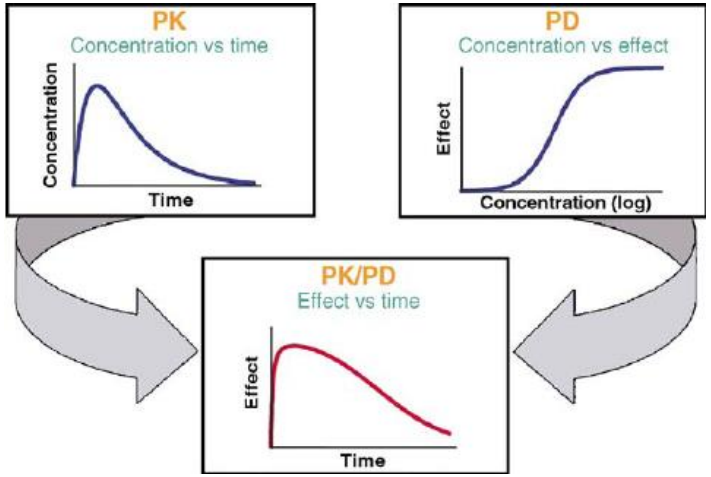
A) Direct Pharmacodynamic Interactions

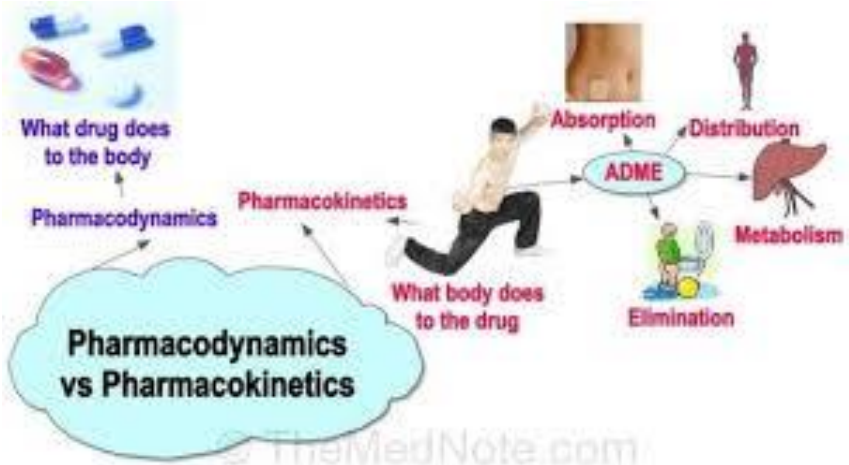
1. Antagonism at same site

- Opiates with Naloxone
- Warfarin with Vitamin K

PHARMACOKINETICS – ICH S3A, ICH S3B

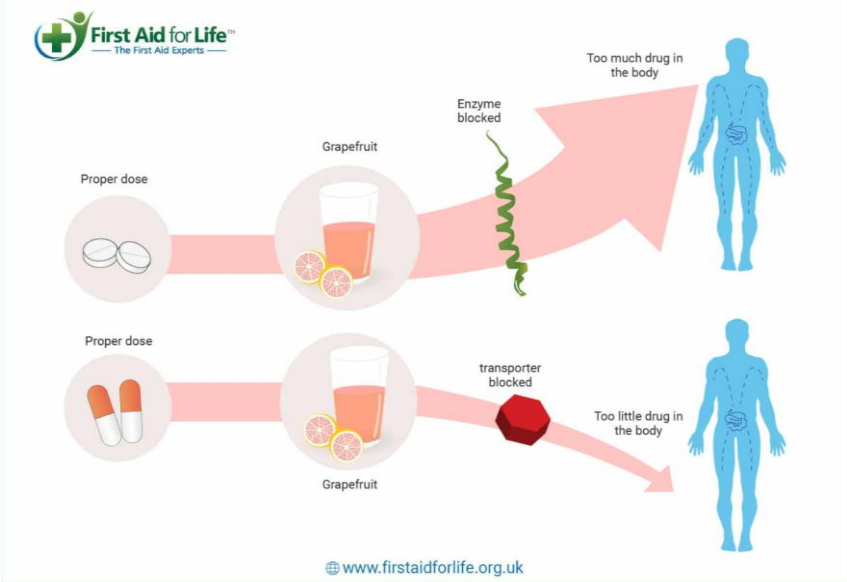
- **A**bsorption – route of administration
- **D**istribution
- **M**etabolism
- **E**xcretion





PHARMACOKINETIC DRUG INTERACTIONS

- Inhibition or induction of enzyme, transporter and co-pathways
- IMP (rifampin), St John‘s wort induce CYP3A4 that metabolise estogens - CONTRACEPTION



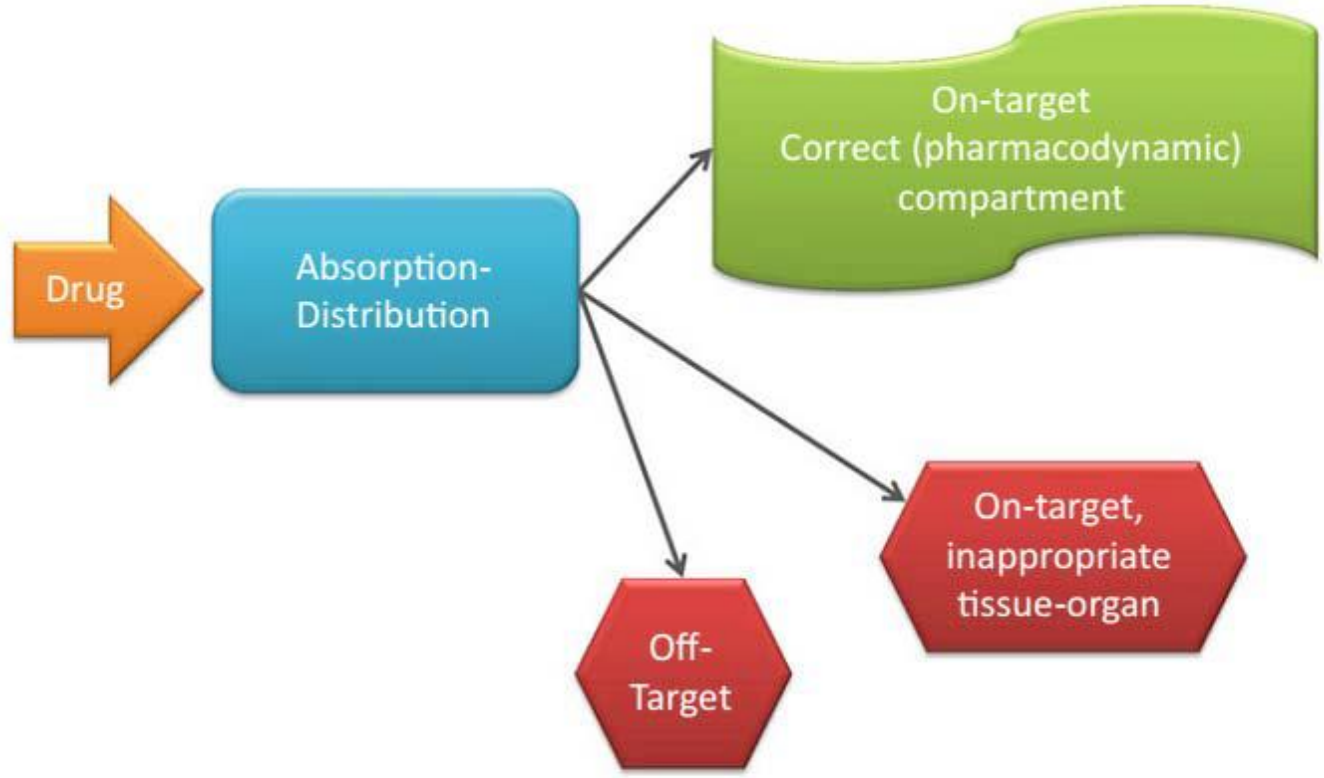
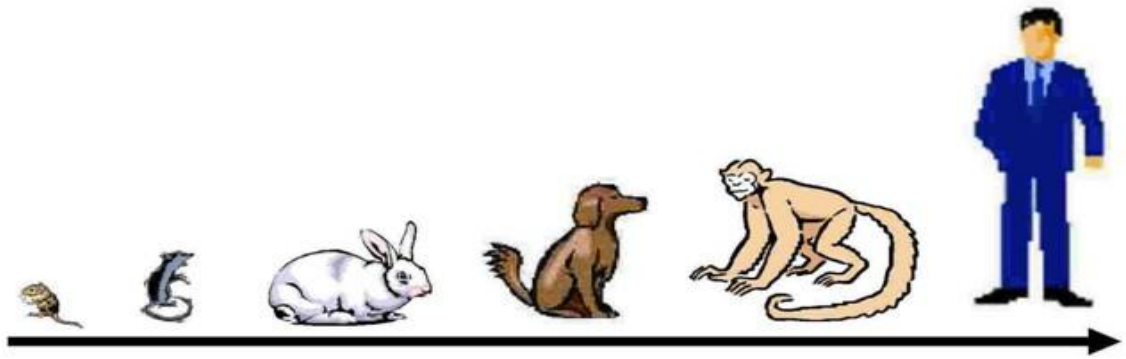


Fig. 3 Tissue–organ distribution in adverse pharmacology. On-target pharmacology can result in adverse effects if engagement of the target is in the wrong or inappropriate tissue

Principles of Safety Pharmacology 2015:pp70

TOXICOLOGY

- Relevant animal species selection
- Comparative physiology (affinity to target, distribution of target)
- ADME – extrapolation of animal data to human



SINGLE DOSE TOXICITY

- Q&A on the withdrawal of the “Note for guidance on single dose toxicity” EMA/CHMP/SWP/81714/2010 Jun 2010

REPEAT-DOSE TOXICITY

- Guideline on Repeated dose toxicity CPMP/SWP/1042/99 Rev. 1 Corr Nov 2010 – List of Tissues

REPEAT-DOSE TOXICITY

LIST OF TISSUES TO BE STUDIED HISTOLOGICALLY IN A REPEATED DOSE TOXICITY STUDY[a]

Adrenal gland	Pancreas
Aorta	Parathyroid gland
Bone with bone marrow[b]	Peripheral nerve
Brain	Pituitary
Cecum	Prostate
Colon	Salivary gland
Duodenum	Seminal veside
Epididymis	Skeletal muscle
Esophagus	Skin
Eye	Spinal cord
Gallbladder	Spleen
Harderian gland	Stomach
Heart	Testis
Ileum	Thymus
Jejunum	Thyroid gland
Kidney	Trachea
Liver	Urinary bladder
Lung	Uterus
Lymph node(s)	Vagina
Mammary gland[c]	Other organs or tissues with gross lesions
Ovary	Tissue masses

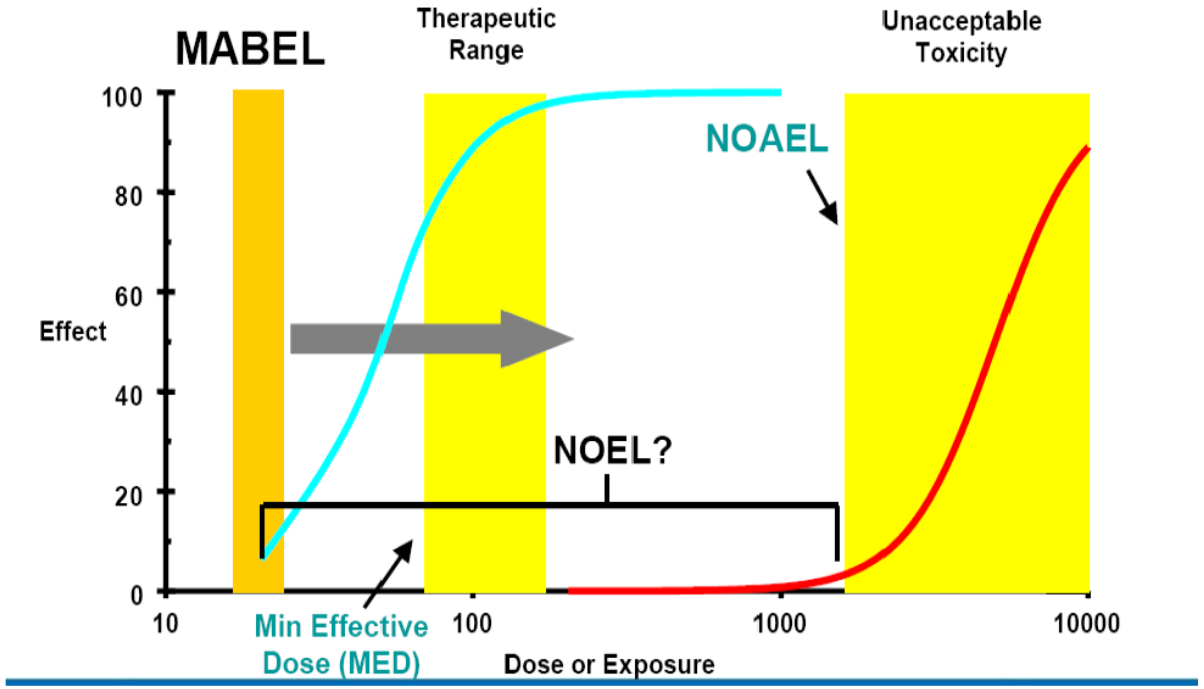
Data from histopathology are unique – couldn´t be obtain in the clinical trials

REPEAT-DOSE TOXICITY ICH M3(R2)

- 2 animal species rodent, non-rodent

Maximum Duration of Clinical Trial	**Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials**	
	Rodents	Non-rodents
Up to 2 weeks	2 weeks[a]	2 weeks[a]
Between 2 weeks and 6 months	Same as clinical trial[b]	Same as clinical trial[b]
> 6 months	6 months[b, c]	9 months [b, c, d]

- Shorter duration – 3 months in ocology IMP



Modified from Jennifer Sims, PhD, *Calculation of the Minimum Anticipated Biological Effect Level (MABEL) and 1st dose in human*

Toxicology

Determine "No Observable Adverse Effect Level" (NOAEL)

Convert NOAEL to a "Human Equivalent Dose" (HED)

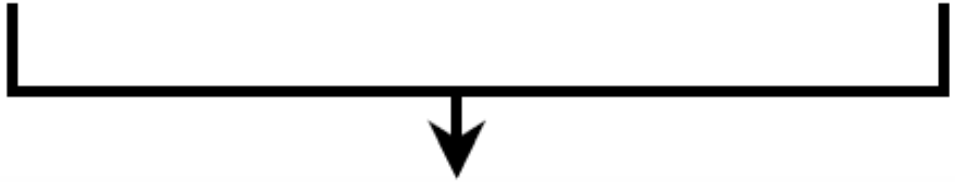
- adjust for anticipated **exposure** in man
- adjust for **inter-species differences in affinity / potency**

Apply ≥10-fold safety factor

Pharmacology

Estimate human "Minimal Anticipated Biological Effect Level" (MABEL)

- **justify based on pharmacology**
- adjust for anticipated **exposure** in man
- include anticipated duration of effect
- adjust for **inter-species differences in affinity / potency**



"Maximum Recommended Starting Dose"

- define anticipated safety window based on NOAEL and MABEL
- appropriate safety factor, if necessary, based on potential risk

NOAEL	calculation	HED
	mg/kg ÷ [k_{baboon}/k_{animal}]	
15 mg/kg in dogs	15 mg/kg ÷ 1.8 =	8 mg/kg
50 mg/kg in rats	50 mg/kg ÷ 6.2 =	8 mg/kg
50 mg/kg in monkeys	50 mg/kg ÷ 3.1 =	16 mg/kg

Table 1: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area

Species	To Convert Animal Dose in mg/kg to Dose in mg/m², Multiply by k_m	To Convert Animal Dose in mg/kg to HED[a] in mg/kg, Either: Divide Animal Dose By	To Convert Animal Dose in mg/kg to HED[a] in mg/kg, Either: 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[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

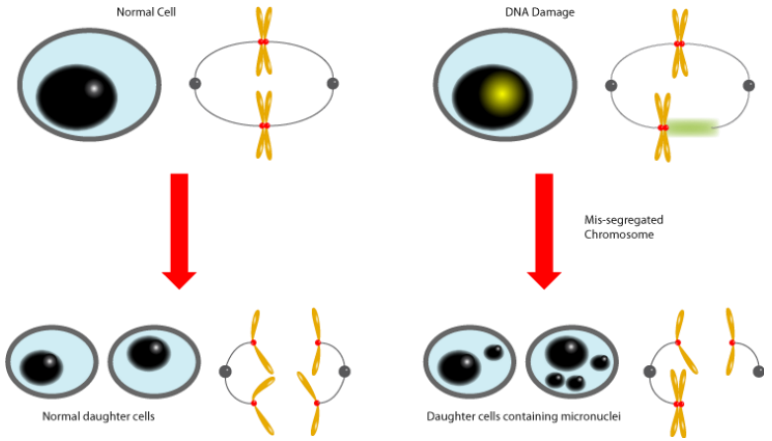
$$MRSD = HED_{dogs}/10 = 0.8 mg/kg$$

IT IS ALWAYS ACCEPTABLE (FROM A SAFETY PERSPECTIVE) TO USE A CLINICAL START DOSE LOWER THAN THE MRSD.

GENOTOXICITY – ICH S2 (R1)

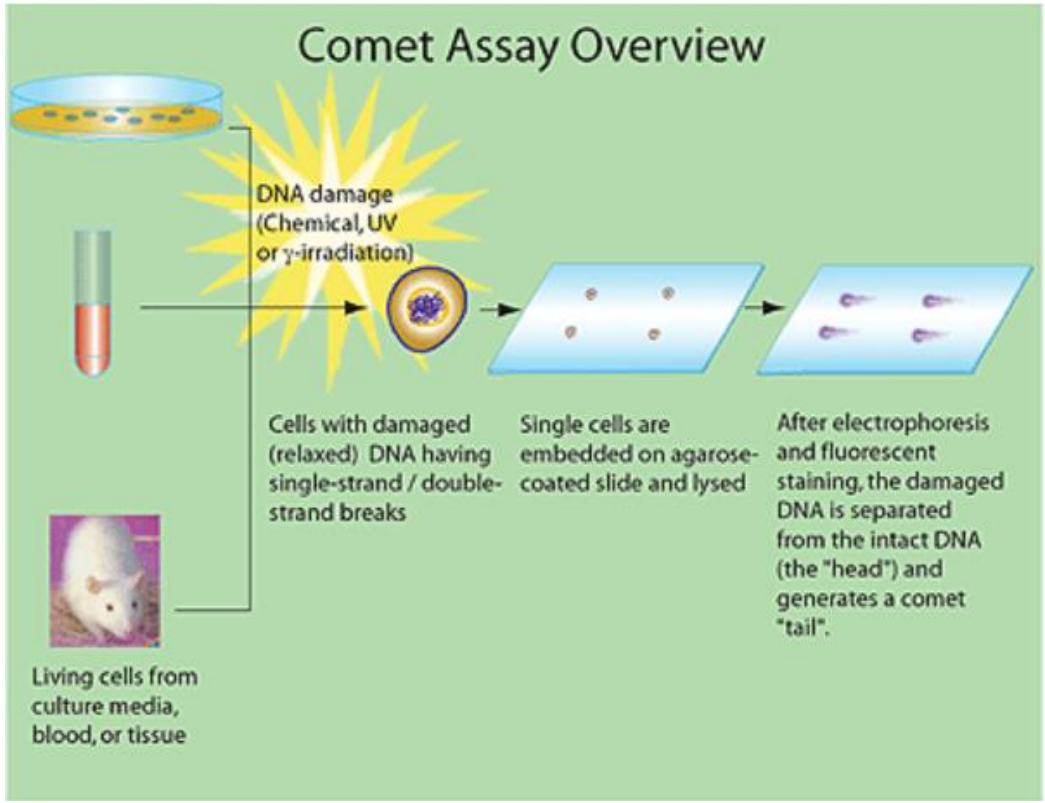
- -/+S9

Type of test/study	Test system
Gene mutations in bacteria	Ames test
In vitro mammalian assay	Chromosomal aberration, micronucleus
In vivo genotoxicity test	Micronucleus assay
Additional assays	



- Could be omitted for oncology drug (alkylating), biotechnology drug, ATB

GENOTOXICITY – ICH S2 (R1)

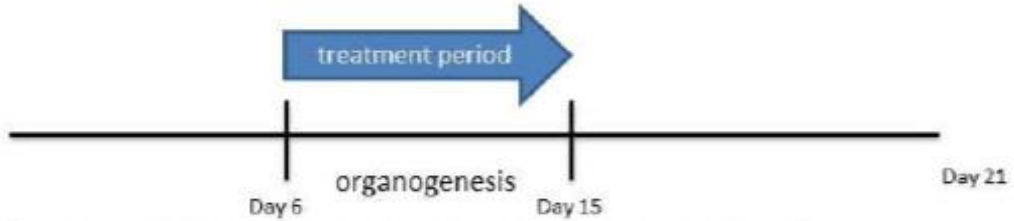


REPRODUCTIVE AND DEVEPOLMENTAL TOXICITY - ICH S5 (R3) - WOCBP

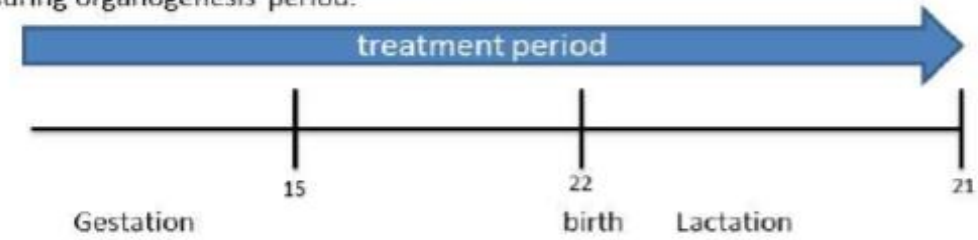
- Fertility and early embryonic development
- Embryo-fetal development
- Prenatal and postnatal development, including maternal function

REPRODUCTIVE AND DEVEPOLMENTAL TOXICITY - ICH S5 (R2)

Phase I. General fertility and reproductive performance.
Measure of pre- and postimplatation death



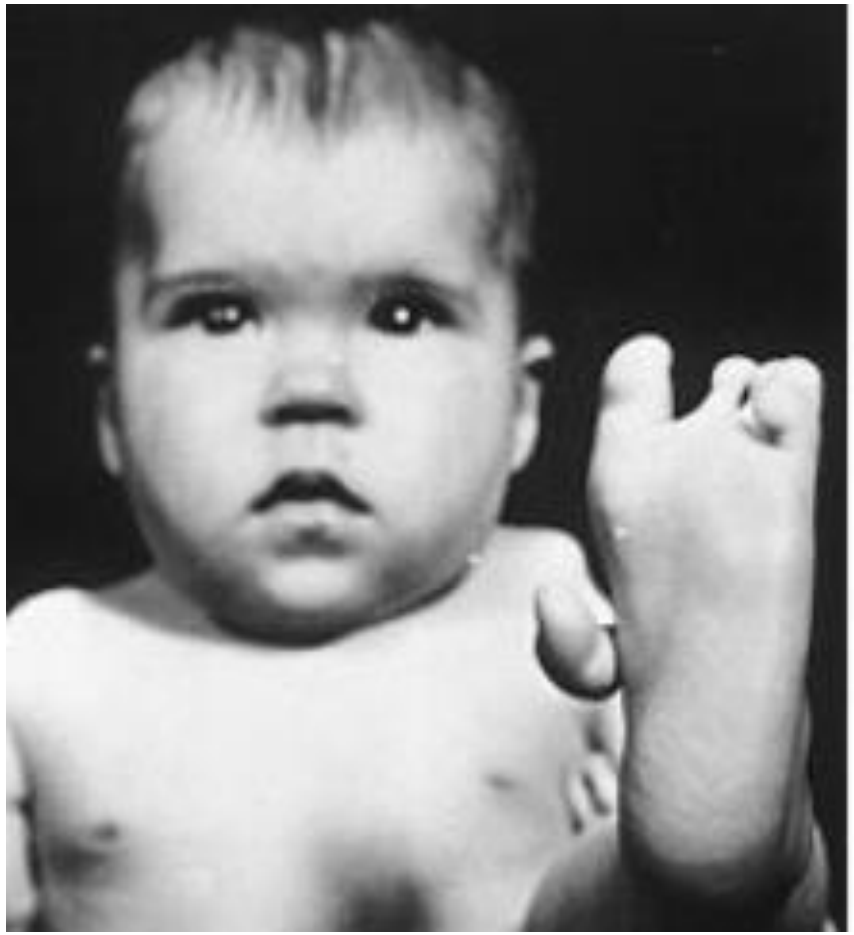
Phase II. Teratology study basic design for mice. 20 insemminated females are treated during organogenesis period.



Phase III. Perinatal/postnatal studies.

THALIDOMIDE

- Thalidomide was first marketed in 1957 available over the counter.
- Promoted for anxiety, trouble sleeping, "tension", and morning sickness in pregnancy.
- concerns regarding birth defects arose in 1961 and the medication was removed from the market in Europe.
- The total number of people affected by use during pregnancy is estimated at 10,000, of which about 40% died around the time of birth. Those who survived had limb, eye, urinary tract, and heart problems.
- Indispensability of comprehensive nonclinical studies



CARCINOGENICITY – ICH S1

- **2 yr rat studies could be waived – Weight-of-evidence factor**
- Knowledge of intended drug target and pathway pharmacology, secondary pharmacology, & drug target distribution in rats and humans.
- Genetic toxicology study results
- Histopathologic evaluation of repeated dose rat toxicology studies
- Metabolic profile
- Immune Suppression
- Results of Non-Rodent Chronic Study
- Evidence of Hormonal Perturbation

Juvenile toxicity studies

- ICH guideline S11 on nonclinical safety testing in support 4 of development of peadiatric medicines - *Draft*
- *Mainly must be evaluated systems that are under development*
- CNS – HEB (*3 years*)
- Skelet (*bone*)

Local tolerance

EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1*

- Topically, by inhalation applied drug product
- Skin and Eye irritation
- Phototoxicity – malanin binding

CNS active IMP

- Drug dependance assay
- Withdrawal potencial

BIOTECHNOLOGY IMP – ICH S6 (R1)

- Complex structural and biological characteristics – require different approaches to their safety evaluation

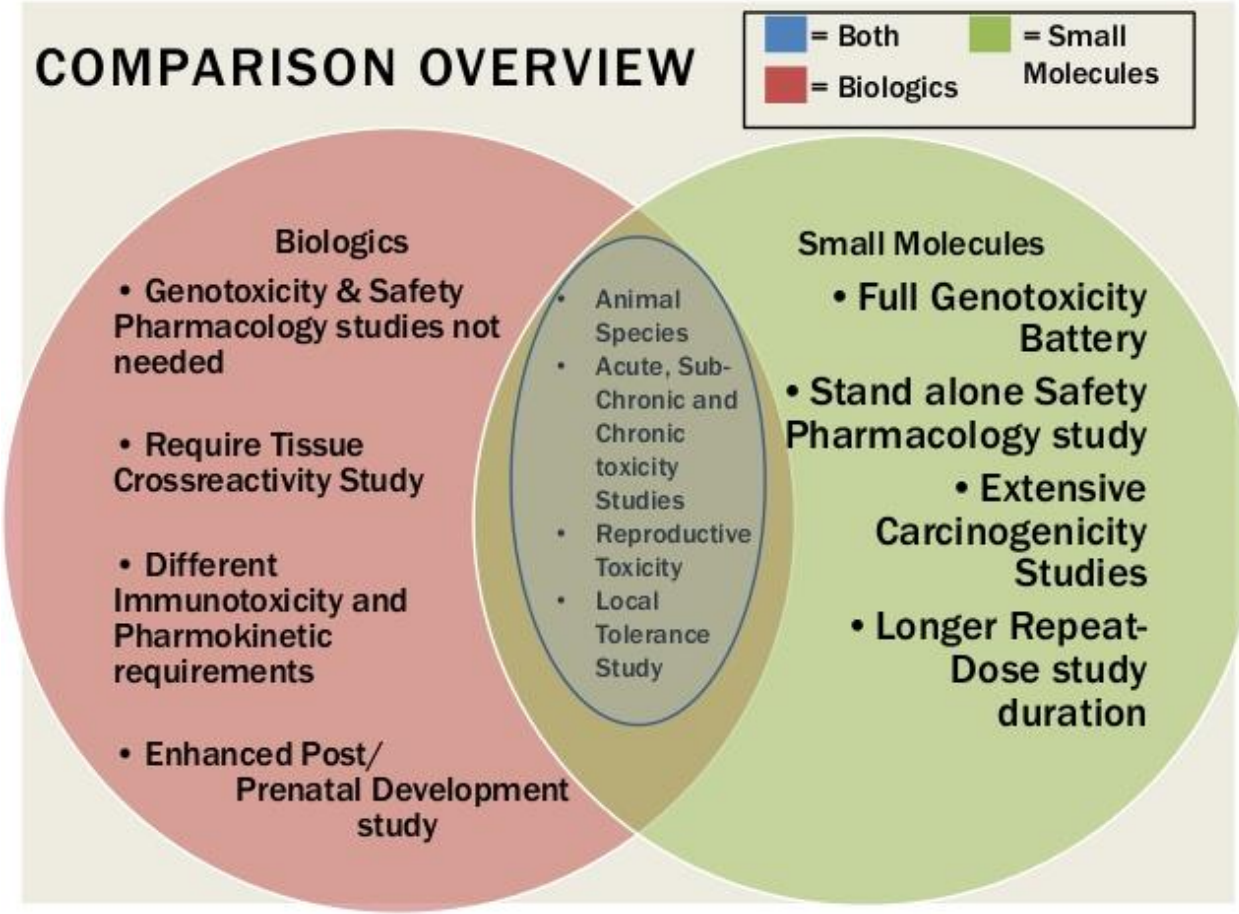
- Homologous molecule
- Transgenic animals
- Nonspecific immunoreaction in animal

Table 3 Monoclonal Antibody Products

Product name	Target	Immunoglobulin	Nature of proof of in vivo pharmacological activity	Indication
Avastin	VEGF	Humanized IgG1	Experiments in nude mice with human tumor xenografts	Colorectal, breast, non small cell lung and renal cancers
Erbitiux	EGFr	Chimaeric IgG1	Experiments in nude mice with human tumor xenografts	Colorectal and head and neck cancers
Herceptin	HER-2	Humanized IgG1	Experiments in nude mice with human tumor xenografts	Breast cancer
Humira	TNFα	Human IgG1	Experiments in transgenic mice expressing human TNFα	Rheumatoid arthritis; psoriatic arthritis
MabCampath	CD52	Humanized IgG1	Experiments in normal cynomolgus monkeys	B cell chronic lymphocytic leukaemia
Mabthera	CD20	Chimaeric IgG1	Experiments in normal cynomolgus monkeys	Non Hodgkin's lymphoma; rheumatoid arthritis
Raptiva	CD11a	Humanized IgG1	Experiments in mice with a	Psoriasis

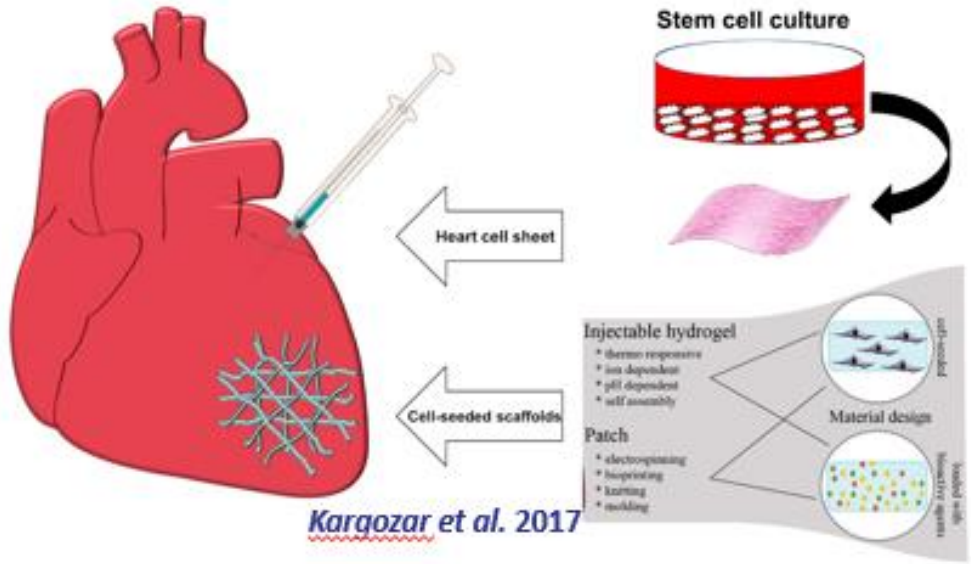
International Pharmaceutical Product Registration, Second Edition

BIOTECHNOLOGY IMP – ICH S6 (R1)



ADVANCED THERAPY MEDICINAL PRODUCTS
EMA/CAT/852602/2018, Directive 2009/120/ES

- Cell based therapy
- Gene therapy
- Tissue engineering



- RELEVANT ANIMAL MODEL!!! Rejection of graft
- Imunocompromised, knockout, transgenic
- Homologous model (from animal to aminal)

ATMP – nonclinical evaluation challange

- Persistence and funcionality of ATMP within the body
- Distribution/Migration
- Proliferation
- Differentiation/fenotype
- Production of bioactive substances
- Adverse effect/target organ of toxicity
- Tumorogenicity
- Imunogenicity
- Viral safety - reactivation

Cell based – stem cells

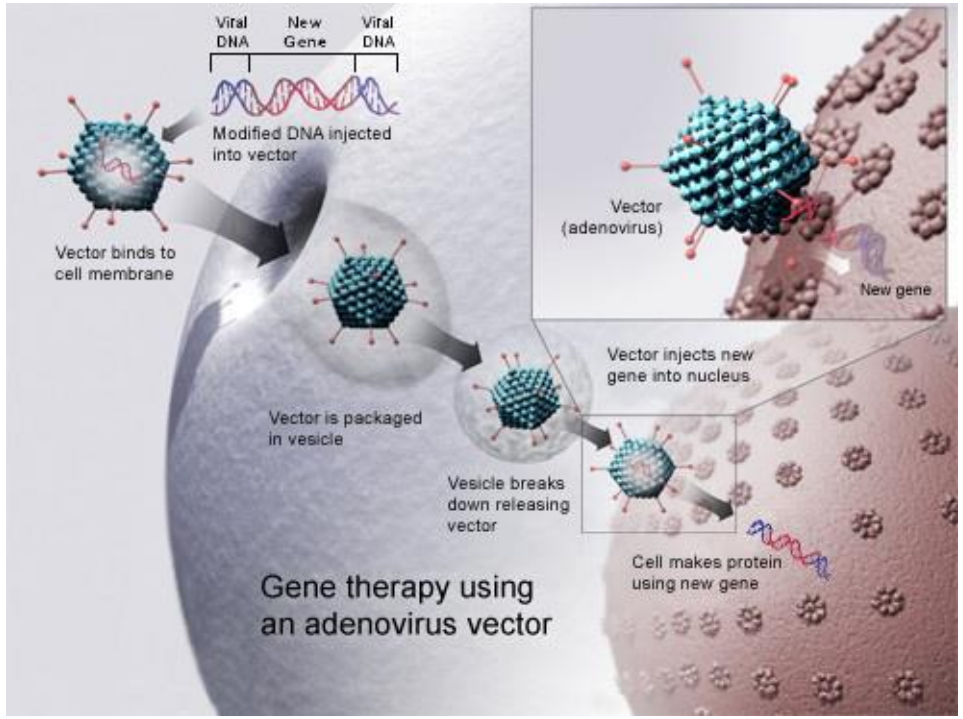
Reflection paper on stem cell-based medicinal products

EMA/CAT/571134/2009

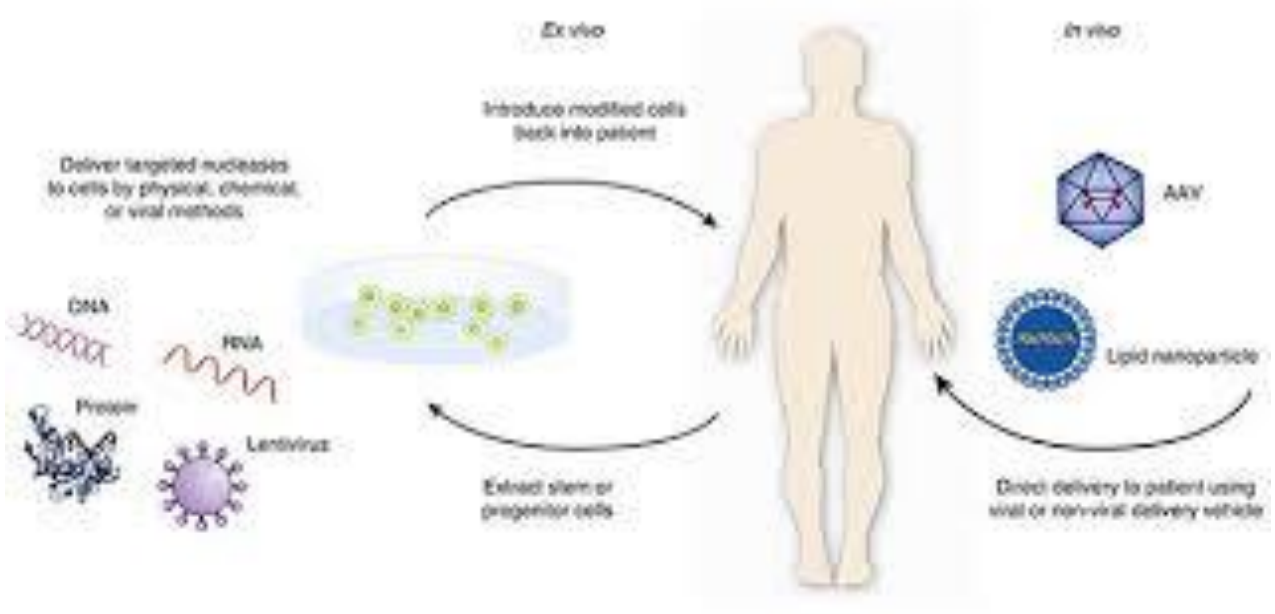
- Source – bone marrow, umbilical cord, adipose tissue…
- Manipulation
- Excipients
- Way of administration
- Indication – proof of concept

GENE THERAPY

- The **intended** action of regulating, repairing, replacing, adding or deleting a genetic sequence should be demonstrated



GENE THERAPY



GENE THERAPY

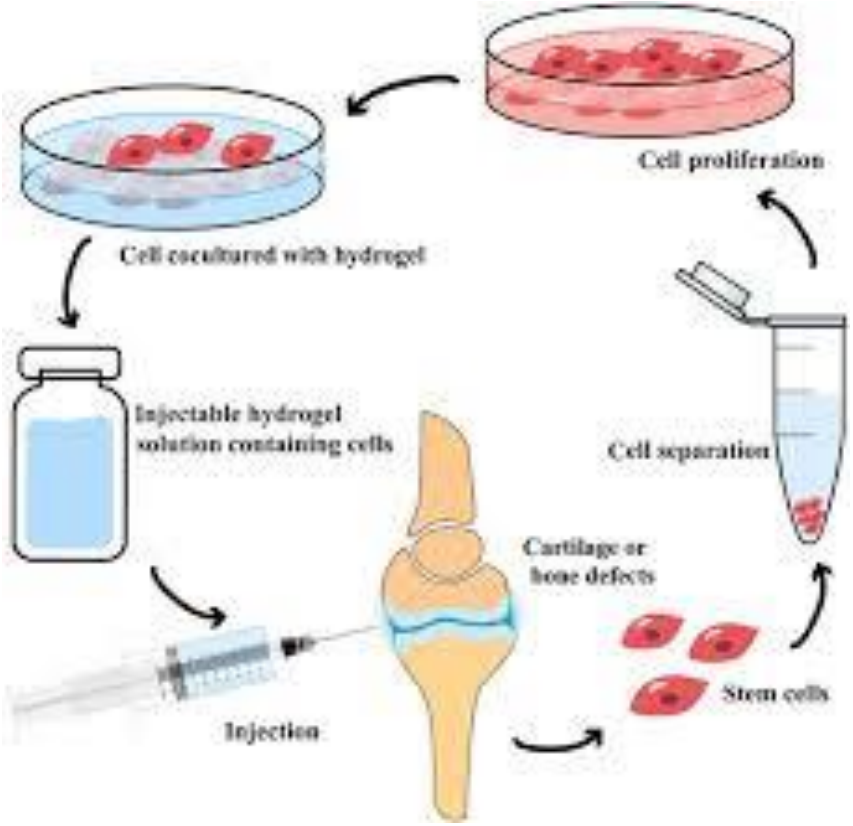
- Quality, Non-clinical and Clinical Aspects of Gene Therapy Medicinal Products – EMA/CAT/80183/2014
- Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors - EMEA/SWP/273974/05
- Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells - CHMP/GTWP/671639/08
- Non-clinical studies required before first clinical use of gene therapy medicinal products – CHMP/GTWP/125459/06

GENE THERAPY

- Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products – CHMP/GTWP/125491/06
- ICH Considerations General Principles to Address Virus and Vector Shedding – CHMP/ICH/449035/09
- Quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors – CHMP/GTWP/587488/07
- ICH Considerations – Oncolytic Viruses – CHMP/GTWP/607698/08

TISSUE ENGINEERED PRODUCT

- Reflection paper on in-vitro cultured chondrocyte containing products for cartilage of the knee EMA/CAT/568181/2009
- Proof of principle – in vitro 3D methods, scaffold - biomechanical properties, strucure integrity
- Small animals – migration
- Bigger animals – higher orthopedic conformity



GOOD LABORATORY PRACTICE

- **DIRECTIVE 2004/10/EC**
- GLP should be applied to the non-clinical safety testing of test items contained in pharmaceutical products
- Comparable quality of test data forms the basis for the mutual acceptance of data among countries OECD MAD.
- **define a set of rules and criteria for a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, reported and archived.**
- promote the development of quality test data
- **GLP laboratories are inspected by National Authorities**

GOOD LABORATORY PRACTICE ATMP

If a pivotal non-clinical safety study has not been conducted in conformity with the GLP principles, a proper justification should be submitted. This justification should also address the potential impact of the non-compliance on the reliability of the safety data (26 January 2017).

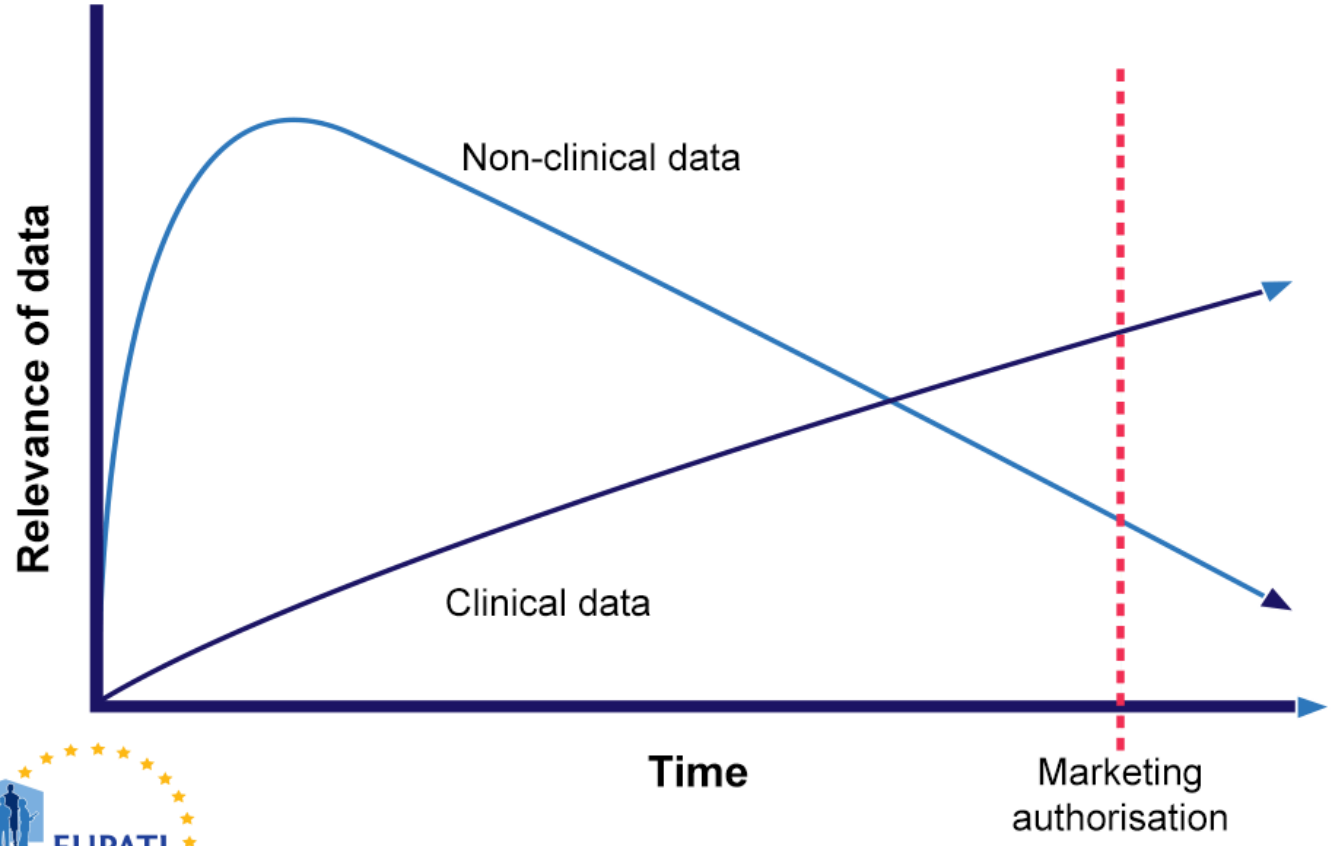
3R – reduce/refine/replace

- *In vitro, in silico* (computer modeling, human-on-a- chip)
- Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes.
- Replacement of animal studies by in vitro models CPMP/SWP/728/95 Feb 1997 – Under Revision to include 3Rs developments

Scientific Advice

- With national authorties or EMA
- Could help guide scientics during drug development to follow legal frame
- Could help optimalised non-clinical research – minimal animal amount with maximum data mining

Relevance of non-clinical studies in medicines development



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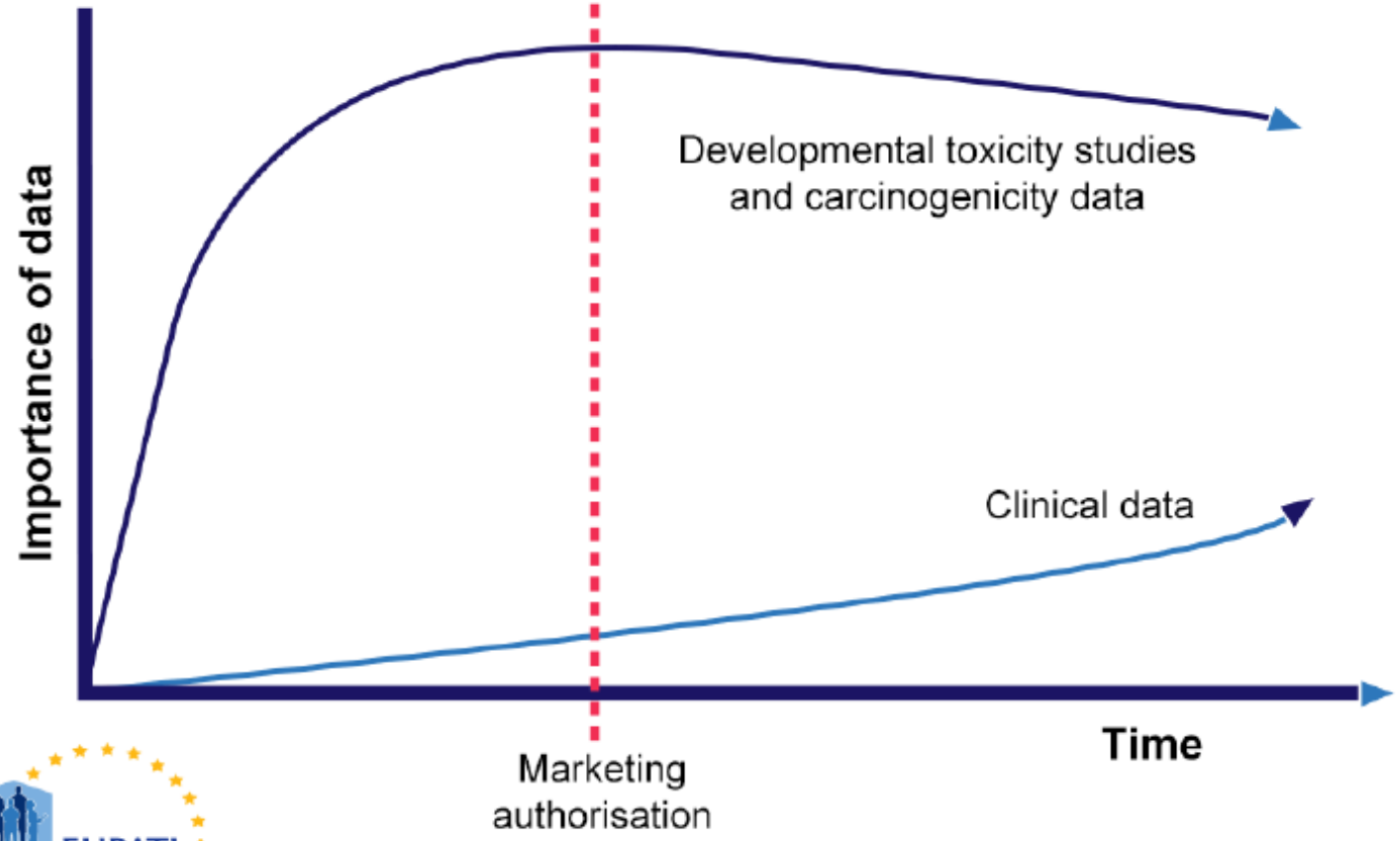
Adapted from Nieto-Guiterrez, M. (2011) *Non-clinical assessment requirements.* London: European Medicines Agency.

Importance of developmental toxicity and carcinogenicity data vs clinical data



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