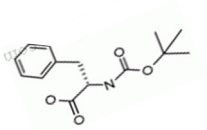
Non-clinical challenges of novel medicinal products

Dr. Gundel Hager • 7th International VPM Days, Hannover 2013

Pharmacology • Toxicology • Analytics

Novel medicinal products

Small Molecules



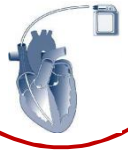
Biologics

- Peptides
- Proteins
- Hormones
- Antibodies
- Biosimilars
- RNA & DNA
- Cell therapy
- Vaccines

Your Compound

Herbal Extracts
Phytopharmaceuticals

Medical Device



Non-clinical development of novel medicinal products

From development candidate to marketed product

CTA/IND

MAA

Pharmacodynamics

Clinical trials

ADME-PK

Toxicity & Safety testing

Bio-Analytics

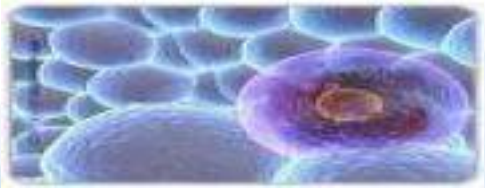
Development Strategy

Elements of Safety Assessment

Goal:

Investigate expected and identified risks and protect from unexpected risks

- Target organs for toxicity
- Markers for toxicity in clinical studies
- (Highest free dose)
- NOAEL / MTD / toxic dose
- Local reactions
- Systemic toxicity reactions
- Mode of toxicity
- Cancerogenicity / tumorigenicity
- Acute life threatening risks for vital organ systems (safety pharmacology)
- ....



Screening approach versus risk based approach

Screening approach:

A panel of safety test covering different fields of toxicity is tested.

- Genotoxicity
- Repeated dose toxicity
- Local tolerance
- DART
- Cancerogenicity
- Ecotoxicology
- …

Risk based approach = tailor made approach:

- Define fields of concern
- To which risk group does my test item belong?
- Find appropriate models
- Develop testing strategy

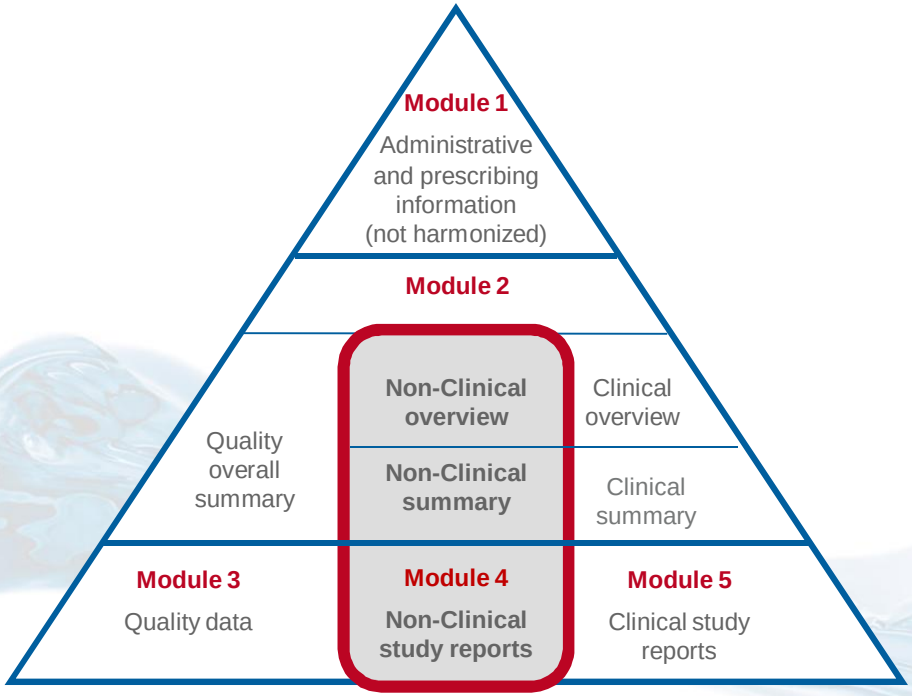
➡ **Problems:**

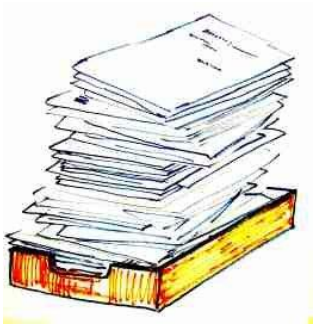
What is about unknown or unexpected risks?
Fields of concern might be defined by the grade of knowledge?

➡➡ **Solution:**

Check risk based approach on the basis of the approach for conventional toxicity testing.

Non-clinical testing of medicinal products - CTD





Driving projects forward

Testing to identify the Most Human-Like Species

***In vitro* Metabolism** *(Basis: Established bioanalytical methods)*

- Interspecies comparison of *in vitro* metabolism,
- Investigation of *in vitro* metabolic stability,
- Analysis of plasma protein binding,
- Metabolite profiling using liver microsomes or hepatocytes
- Screening of metabolic enzymes

Tissue Cross-Reactivity (TCR)

to compare the binding of the test substance in tissues of different species, including human (for biologicals, i.e. for MABs).

General Toxicity and Safety Pharmacology

Genotoxicity – to assess mutagenicity and chromosomal aberrations (*in vivo / in vitro* tests).

Single-Dose Toxicity / Dose-Range Finding – to determine the feasible dose for the start of the safety programme.

Repeated Dose Toxicity – where the test substance is administered on a regular and repeated basis by one or more routes over a certain period of up to 1 year. Determination of a specific design is based on the intended clinical use of the test substance.

Main goals are to:
- identify the toxicological targets,
- characterize the toxicological profile of the substance,
- define the NOAEL,
- assess the MTD,
- define the dose, plasma, or tissue levels at which toxicological effects are to be observed,
- assess the toxicokinetics,
- understand basic mechanisms of identified toxicities.

General Toxicity and Safety Pharmacology

Toxicokinetics/Bioanalytics

to estimate the systemic exposure achieved at different dose levels, establish a dose *versus* exposure relationship, correlate the exposure achieved with the toxicological findings and assess their relevance for clinical safety.

PK/PD Modeling Studies

to correlate systemic exposure and efficacy.

Safety Pharmacology

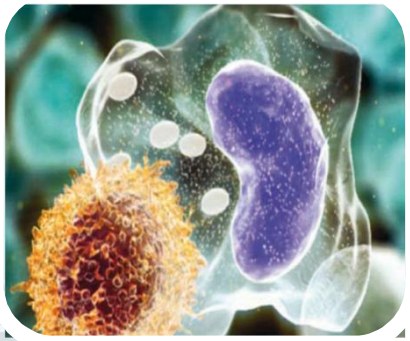
to assess the acute side effects on vital organ systems when administered at doses in the therapeutic range (or higher). A standard set of assays, assessing cardiovascular and central nervous systems and respiratory effects are considered the *core battery studies*.

Particular Toxicity Testing

Immunotoxicity

The initial screen comes from the general toxicity.
If immunotoxicity is an issue, further testing is required for:

- unintended immunosuppression,
- unintended immunostimulation (rather a general dysregulation of the immune system),
- immunogenicity,
- induction of hypersensitivity,
- induction of autoimmunity,



Hepatotoxicity

Phototoxicity (Photoallergy, Photogenotoxicity, Photocarcinogenicity):

- *in vitro*, 3T3 NRU test (OECD 432),
- *in vivo*, grading of skin reaction.

Local Tolerance and Irritation

to assess the short-term hazard of test substances in the immediate region of their application or during false applications.

Particular Toxicity Testing

DART (Development and Reproductive Toxicity)

Studies of fertility and early embryonic development to implantation:

- premating to conception,
- conception to implantation.

Studies for effects on pre- and postnatal development, including maternal function:

- implantation to closure of the hard palate,
- closure of the hard palate to the end of pregnancy,
- birth to weaning,
- weaning to sexual maturity.

Juvenile Studies

assess toxicity of a drug substance in developing organisms.

Carcinogenicity

identifying the potential of a substance to induce or to facilitate the formation of tumors.

Particular Toxicity Testing

Drug–Drug Interaction

to characterize potential additive, potentiating, or antagonistic effects of compounds when used together, and to identify potential toxicity unique to the combination, not previously seen for the substances administered alone.

Impurities

to identify and qualify impurities.



Safety program NCE for first into men *(minimalistic)*

Genotoxicity

Dose range finding

- Single and repeated dosing in two species

Repeated dose toxicity

- Duration and administration scheme depending on clinical trial design

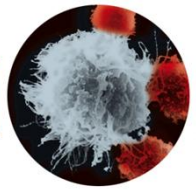
Toxicokinetics

Local tolerance *(depending on administration route)*

- Single or repeated dosing

Safety pharmacology "Core battery"

- CNS (rat, e.g. Irwin test, modified FOB)
- CVS (dog/minipig/NHP, e.g.telemetry)
- RS (rat, e.g. whole body plethysmography)



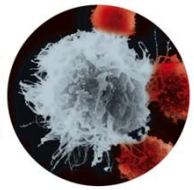
Challenges for non-clinical assessment

Diversity & specificity ➡ no one fit for all strategy and study design for testing

Combine:
- scientific expertise
- technical experience
- regulatory understanding

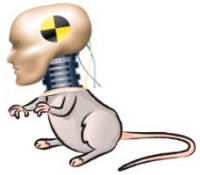
to :
- identify relevant animal models for *in vivo* efficacy and safety data
- consider country specific requirements
- evaluate specific risk for specific patient populations

➡ **Submission of the safety assessment strategy and study designs to regulatory authorities <u>prior</u> starting the regulatory safety animal studies**



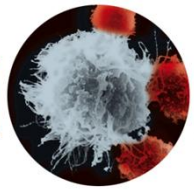
Efficacy testing goal

- assessment of
  - → specific immune response
  - → survival
  - → pathogen clearance / tumor resorption



- challenge of
  - → animal model(s): identify (all possible) relevant species
  - → doses (volumes!)
  - → schedules and intervals
  - → combination therapies

- test best routes of administration (im , id, iv, it ?)



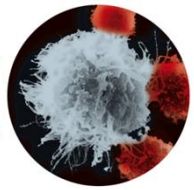
Obstacle

➡ Appropriate animal model

- some vaccine are highly human specific
  - → use humanized mice: e.g. HLA2 tg or human PBMC xenotransplant
  - → use NHP
  - → use of surrogates (mouse specific antigen, antibodies, etc…)
- evaluate and qualify relevant PD biomarker in the POC species
- consider the species as possible species for toxicity testing




Non-clinical assessment of Vaccines / Immunotherapies

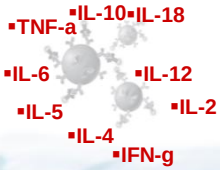


Safety ➡ which studies do you really need to perform?

Novel Vaccine/Adjuvant? → YES → General toxicity studies

+

May affect physiological parameters? → YES → Safety pharmacology studies



Novel adjuvant, or excipient? → YES → General toxicity studies

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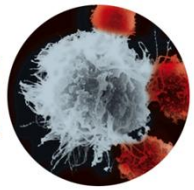
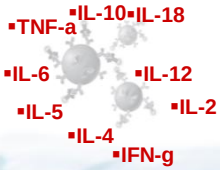
Novel **synthetic** adjuvant, excipient or preservative? → YES → Genotoxicity studies

Non-clinical assessment of Vaccines / Immunotherapies



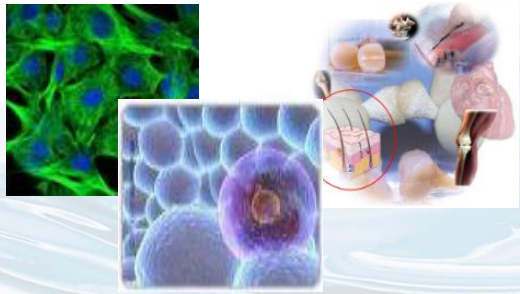
Safety ➡ which studies do you really need to perform?

Does vaccine contains nucleic acids, viruses, cells?	YES	Biodistribution study
+		
Cell (gene)-based immunotherapy?	YES	Tumorigenicity study
Is vaccine for women of childbearing potential or pregnant women?	YES	DART studies
Specific adverse effect of vaccine for intended indication/route	YES	De-risking strategy



Non-clinical assessment of regenerative ATMPs

- **Pharmacodynamics / POC *** *Non-GLP*
- **Biodistribution: migration & persistence ?** *Non-GLP / GLP*
- **Tumorigenicity ?** *GLP*
- **Short & long term Toxicity *** *GLP*



Submission of the non-clinical testing strategy and study designs for approval to regulatory authorities <u>prior</u> starting the studies

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