MEETING REQUIREMENTS FOR CLINICAL TRIALS AND MARKETING AUTHORISATION

REPROTOXICITY

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This presentation concerns general recommendations

For certain types of products e.g.

- biopharmaceuticals
- anticancer
- vaccines

alternative approaches may be more relevant

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Reprotoxicity testing to reveal *any* effect on mammalian reproduction

- Drugs can cause reproductive toxicity by acting on
  - the father
  - the mother
  - the foeto-placental unit
  - the foetus directly

- Postnatal development can also be affected by
  - maternal behaviour
  - changes in the quality or quantity of breast milk

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Main guidelines agreed

- **ICH S5:**
  - Reproductive toxicology: Detection of Toxicity to Reproduction for Medicinal Products
  - Toxicity to male fertility
- **ICH M3:**
  - Non-clinical studies for conduct of human clinical trials for pharmaceuticals

  Under revision!
- **EMEA/CHMP/203927/05**
  - Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling

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Reproductive Toxicity (ICH S5A and B)

Exposure of mature adults during **all stages of development** - before mating through sexual maturity.

* Fertility and early embryonic development
* Embryo-foetal development; ‘teratogenicity’
* Pre - and post natal development including maternal function

If an effect is seen, further mechanistic studies may be needed

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Before starting

- Relevance of animal models
  - Pharmacological response
  - Basic info on PK in selected species (ICH S3A)
    - E.g. from earlier tox studies in non-pregnant animals
    - For adjustment of choice of species, study design
      - e.g. metabolites, degree of absorption, T½
- Dose-finding (rabbit) useful for assessment of maternal toxicity and basic PK
- Value of info on placental transfer, transfer to milk
- Same species as in other tox studies desirable!

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Embryo-foetal development

- From **implantation** to **closure of hard palate**
- Normally in **two** species, of which one non-rodent (rabbit).
  - Typically 16-20 litters/study
  - Doses to cover minimal maternal toxicity, but not too high
  - Desirable to determine a NOAEL

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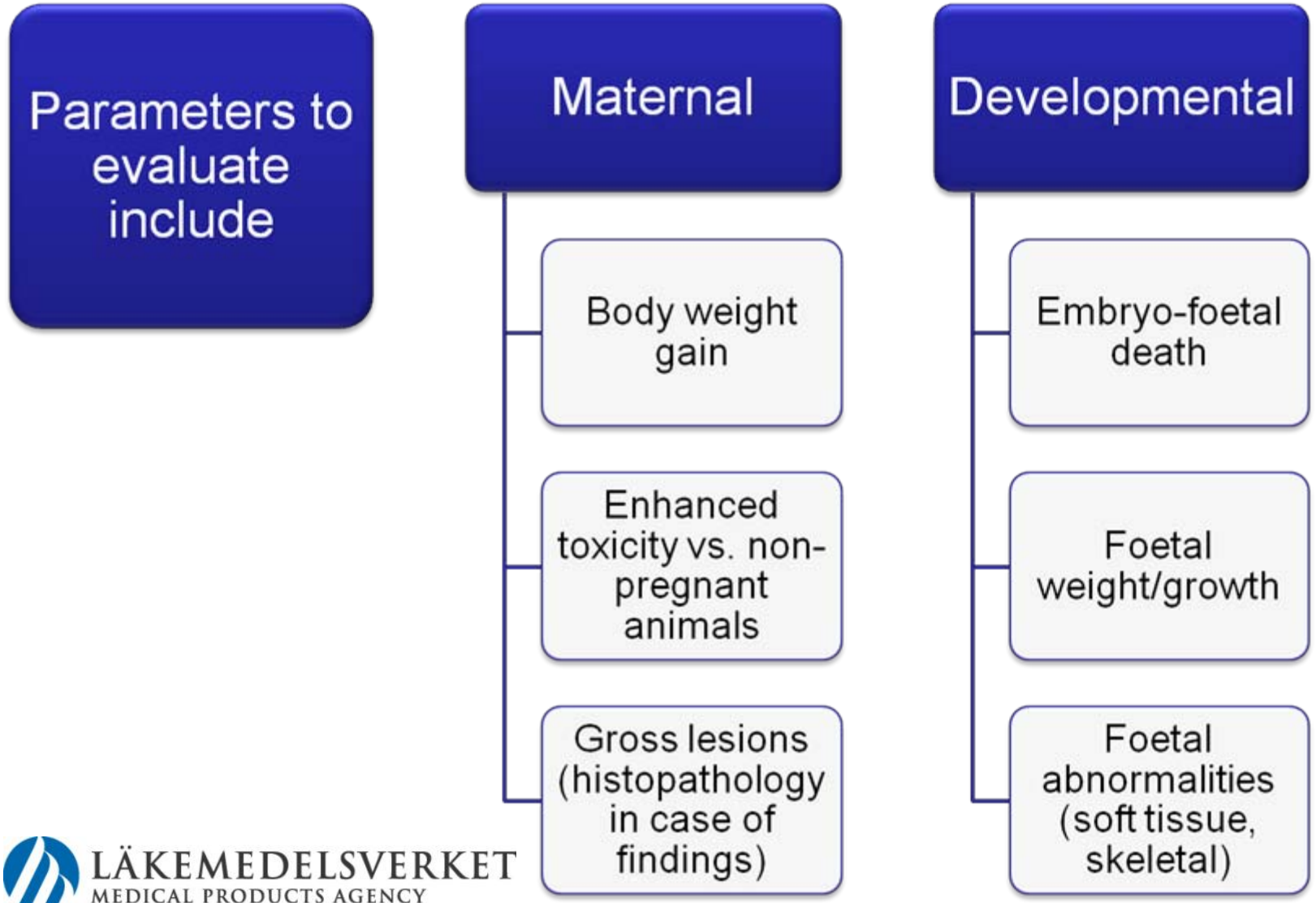
Embryo-foetal Development



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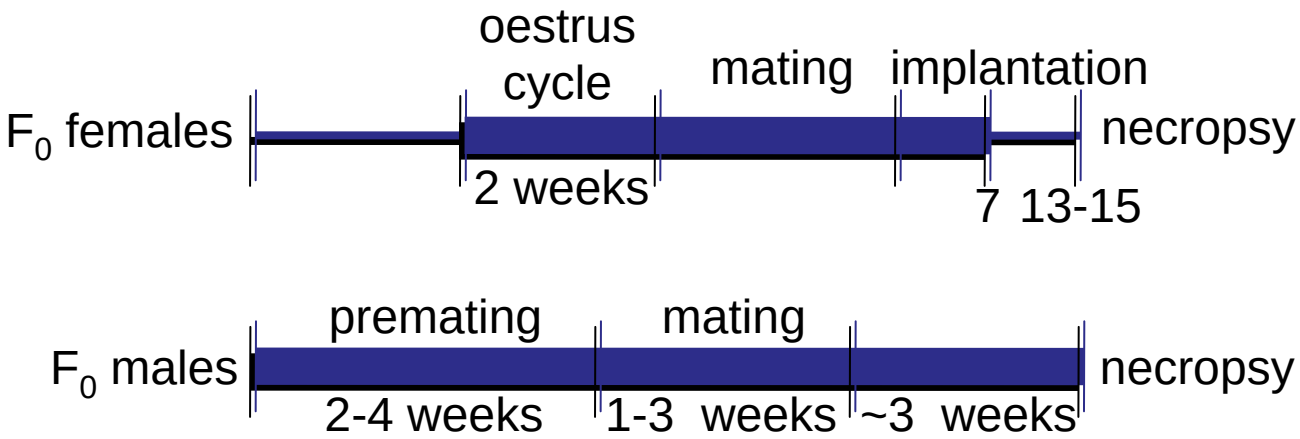
Fertility and early embryonic development



- From **before mating** through **mating and implantation**
- Usually in one species (rat)

Males: Also histopathological evaluation from at least 4 week repeat toxicity studies to discover effects on spermatogenesis!

Fertility and early embryonic development

Parameters to evaluate include:

- Body weight, clinical signs etc
- Maturation of gametes
- Mating behaviour
- Fertility
- Pre-implantation stages of the embryo
- Implantation

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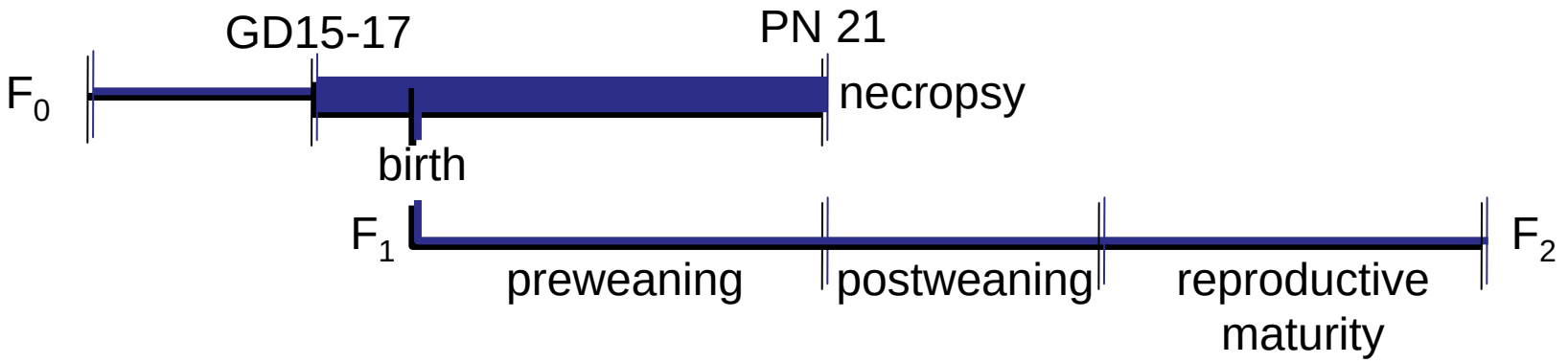
Pre- and postnatal development, maternal function



- From end of **major organogenesis** until the end of **lactation**
- Observations of offspring through sexual maturity
- At least in one species (rat)

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Pre- and postnatal development, maternal function

Parameters evaluated include:

–Maternal (F_0)
- Body weight, clinical signs etc
- Duration of pregnancy
- Parturition
- Behaviour

–Offspring (F_1)
- Survival
- Abnormalities
- Physical development (incl. body weight), sensory functions and reflexes, behaviour
- Attainment of full sexual function

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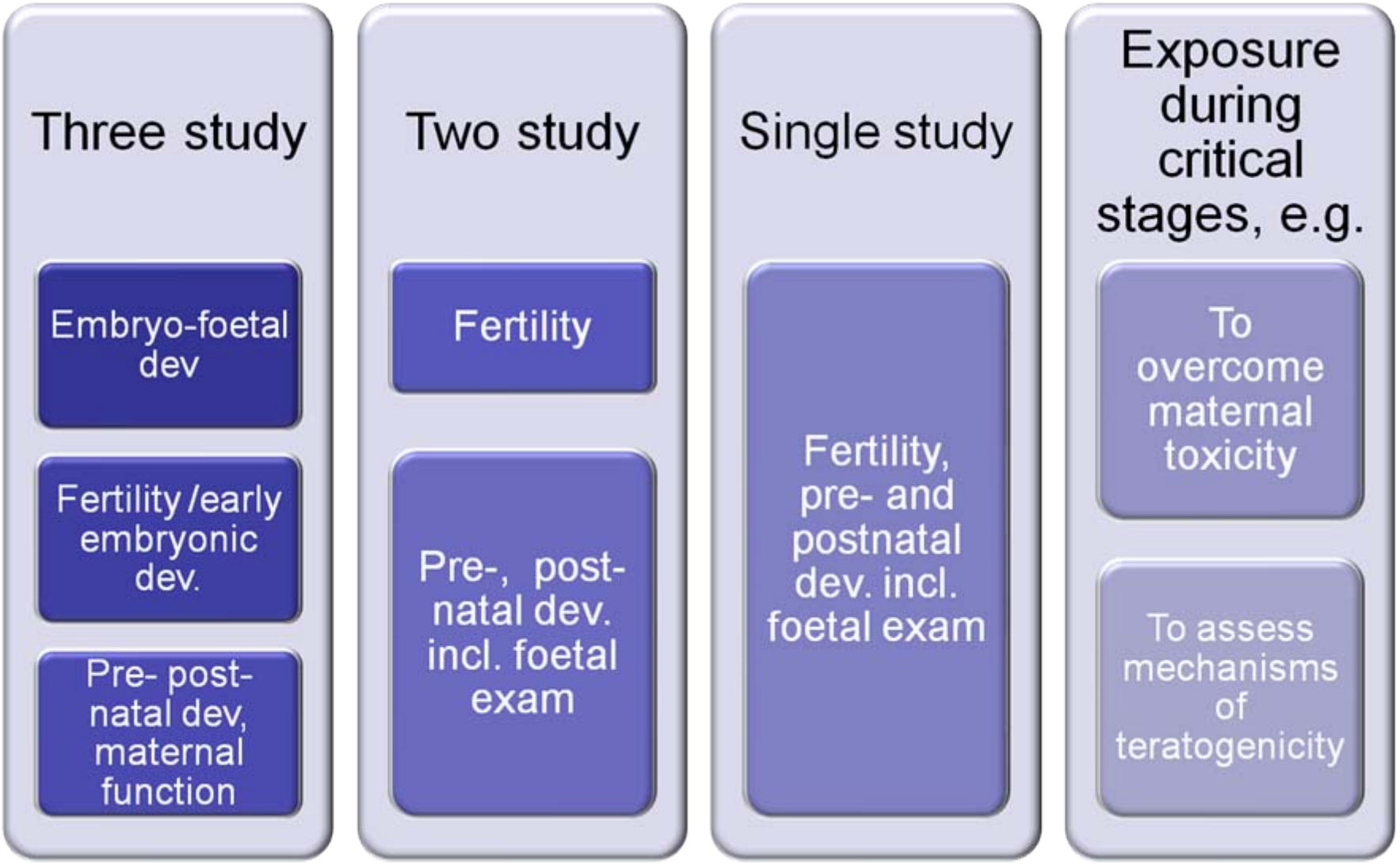
Flexibility in study designs



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Measure systemic exposure!

To verify exposure!

To relate to human exposure!

– Consider that kinetics may differ in pregnant animals

ICH S3A (Toxicokinetics)

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Timing of studies – ICH M3

- To support first dose in human
  - Men, non-fertile women
    - histopathology of reproductive organs in general toxicity studies
  - Women of childbearing potential
    - developmental (teratology) toxicity studies before inclusion
- Extended clinical trials
  - effect on fertility before phase III
- Marketing approval
  - peri-post natal effects

Under discussion!

Data to inform trial subjects/patients about risks and to minimise these risks!

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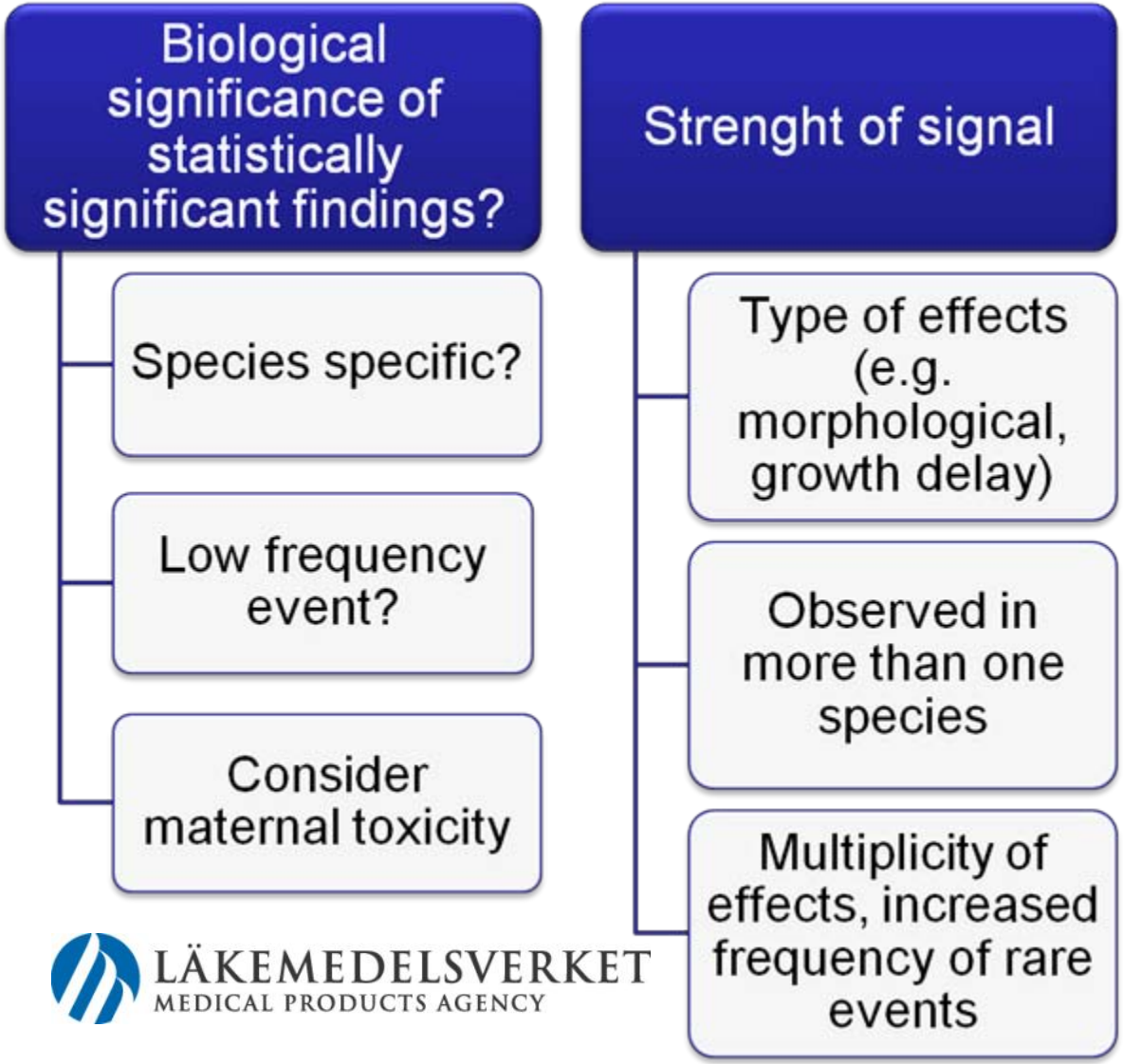
Non-clinical findings - Identify potential risks Consider relevance - Weigh the risks



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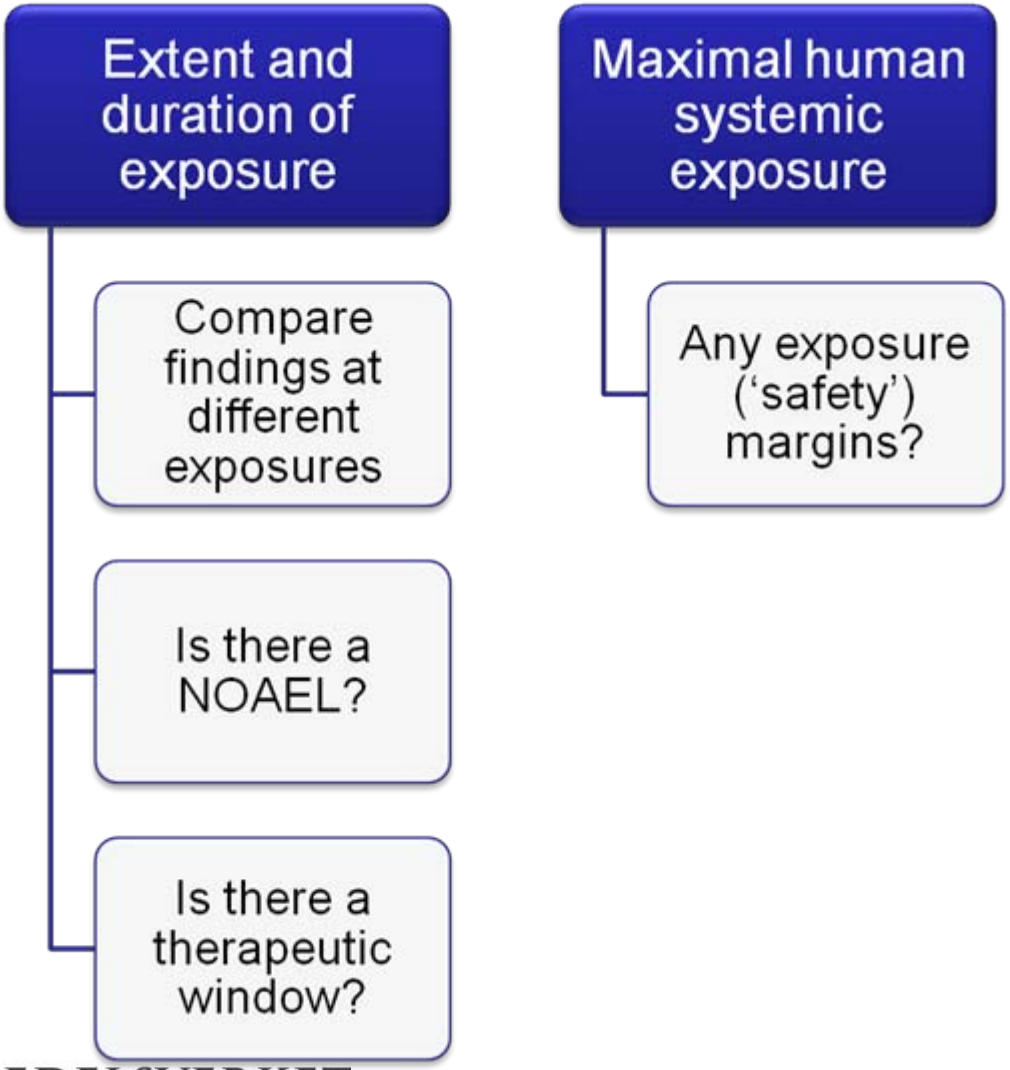
Relate non-clinical findings to



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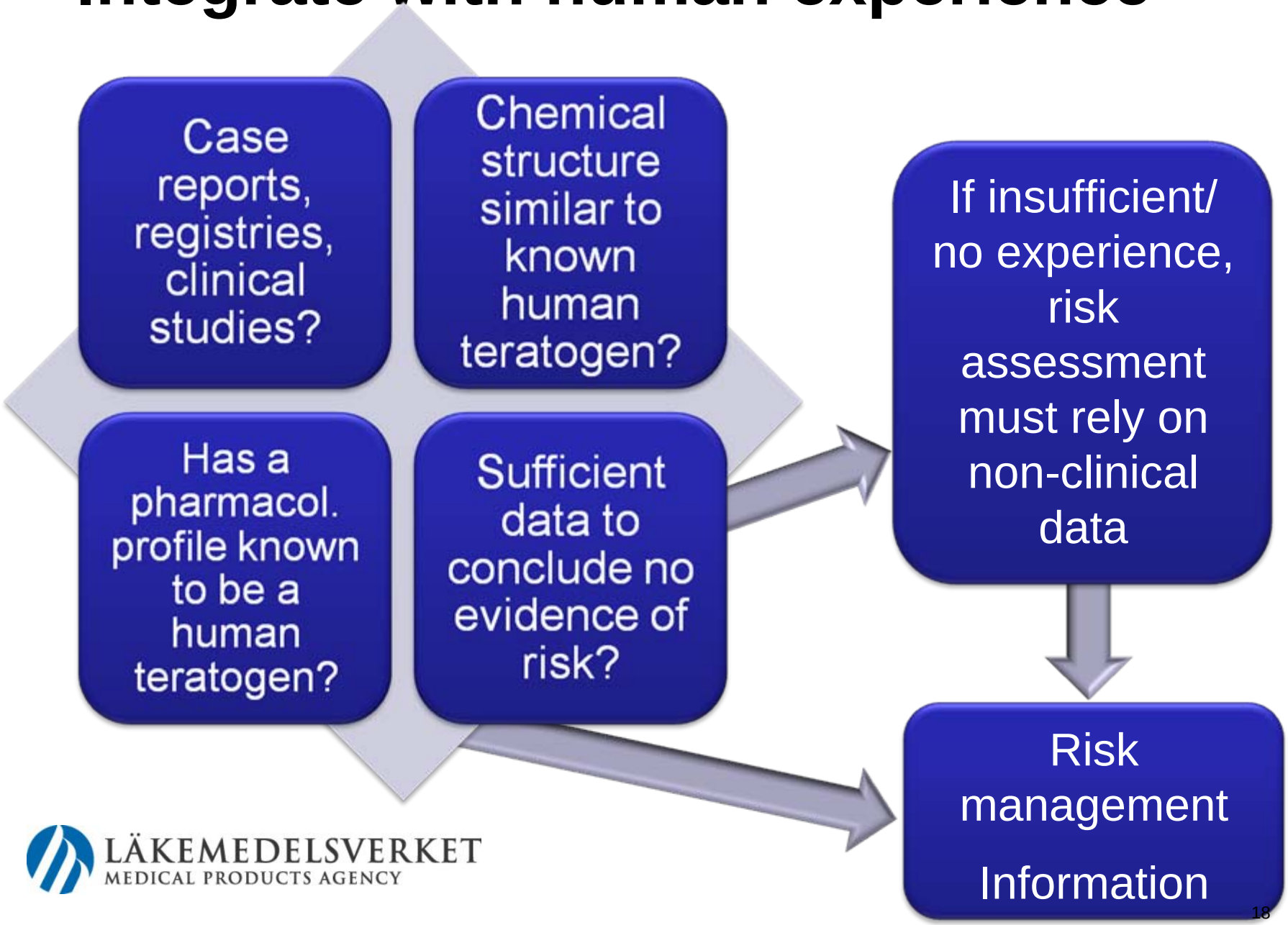
Integrate with human experience



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Summary of Products Characteristics

- 4.6 Use during pregnancy and lactation
  - Human experience
    - information on adverse events and extent of human exposure
  - Non-clinical data
    - relevant conclusions from animal reprotoxicity studies and milk transfer data. Further details in section 5.3
  - Recommendations
    - use and management during pregnancy, breast feeding and when pregnancy is planned but fertility might be affected

- 5.3 Preclinical safety data
  - Reprotoxicity findings of relevance for the prescriber, not addressed elsewhere in the SPC

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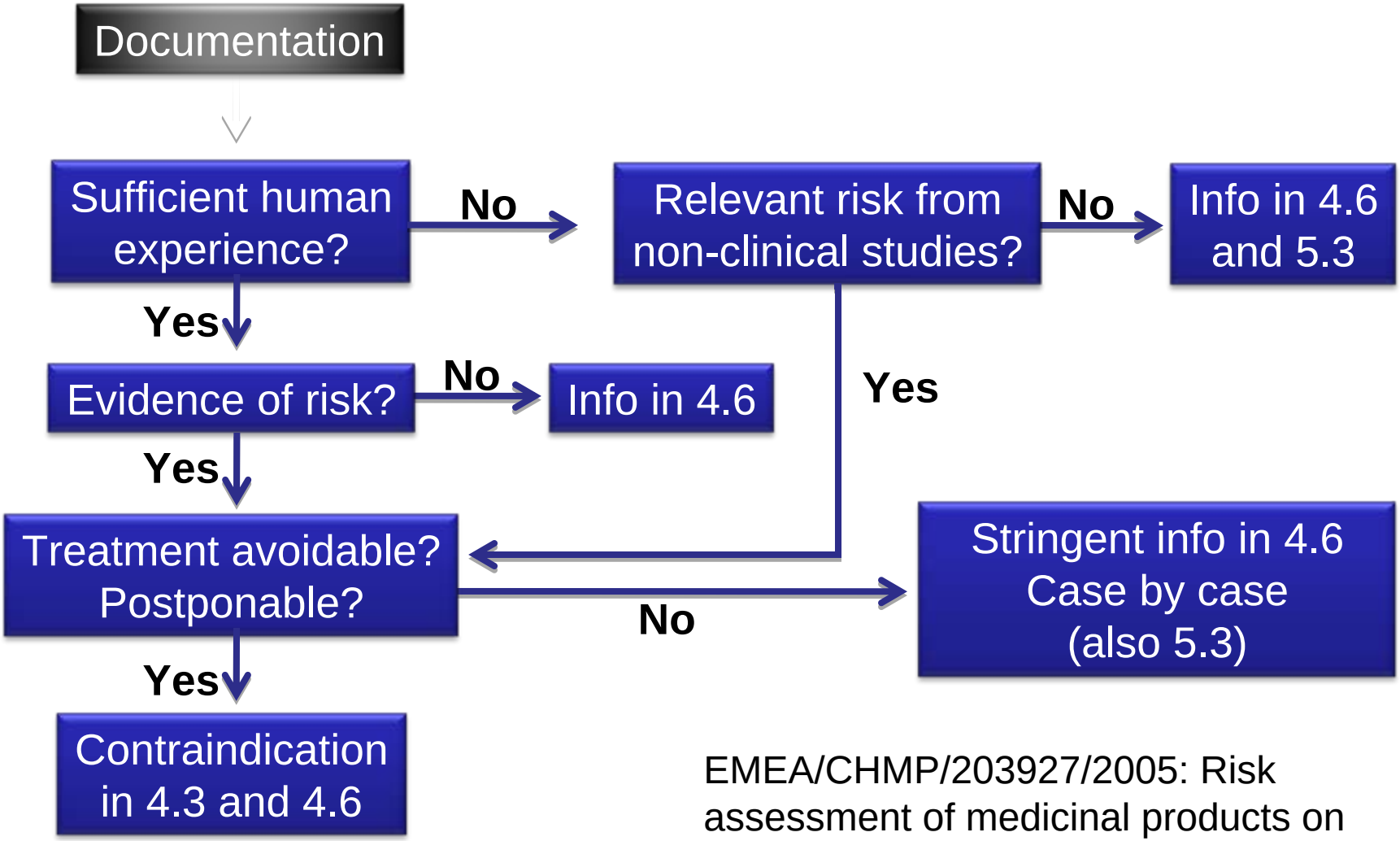
Contraindication in pregnancy



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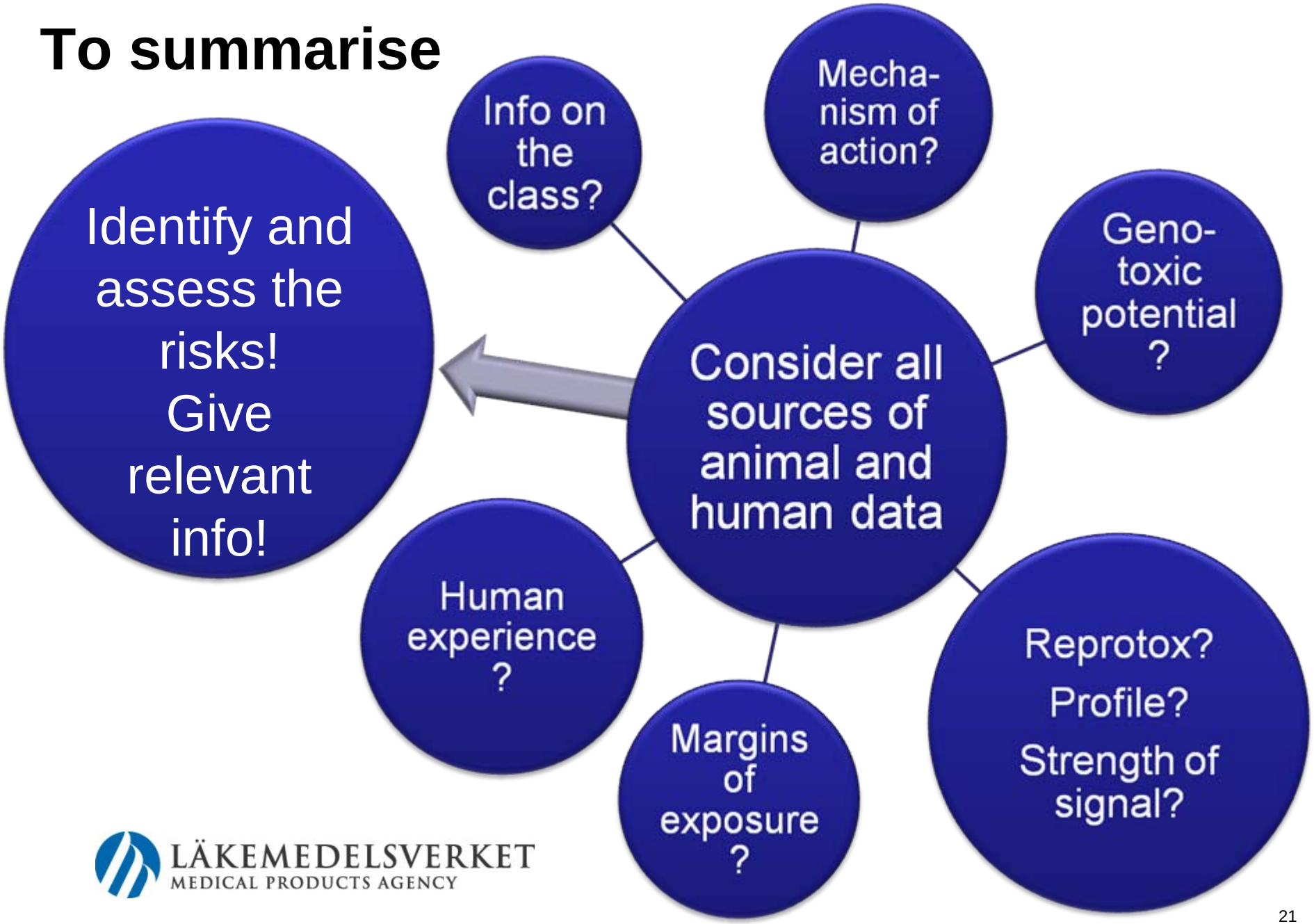
EMEA/CHMP/203927/2005: Risk assessment of medicinal products on human reproduction and lactation: From data to labelling.

To summarise



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Thanks for your attention!!

Uppsala Castle and Cathedral

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Relevant guidelines

- **ICH S5A** (CPMP/ICH/386/95): Reproductive toxicology: Detection of toxicity to reproduction for medicinal products including toxicity to male fertility
- **ICH M3** (CPMP/ICH/286/95): Non-clinical studies for conduct of human clinical trials for pharmaceuticals
- **EMEA/CHMP/203927/05** Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling
- **ICH S3A** (CPMP/ICH/384/95) Toxicokinetics: the assessment of systemic exposure in toxicity studies

- CPMP/SWP/2600/01 PtC on the Need for assessment of reproduction toxicity of human insulin analogues
- CPMP/SWP/465/95 Pre-clinical pharmacological and toxicological testing of vaccines
- ICH S6 Preclinical safety evaluation of biotechnology-derived pharmaceuticals
- EMEA/CHMP/313666/2005 Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data

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