

Exclusion by default....

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Disclaimer

- The views in this presentation are mine only and do not represent the views of any organisation I work or have worked for.

Protection by exclusion ?

Not really.....

- Thalidomide (1953, teratogenicity, withdrawn 1961)
- Di-ethyl stilbestrol (1938, 1970 reproductive system toxicity in children exposed, withdrawn 1971-83)
- Valproate (1967, teratogenicity and neurodevelopmental toxicity, still used with restrictions 2010...2023)
- Retinoids (1980, 1985 teratogenicity, now used with pregnancy prevention programme)

• And more...

Somewhat late

- Covid-19 vaccines, later shown to be safer than COVID...

Stating the obvious...

- Pregnant women can become ill (pregnancy related or not)
- Ill women may want to become pregnant
- Ill women may become pregnant
- Some diseases are more serious in pregnant women
- Lactating/BF women, yes there are alternatives to using breast milk but...

- 1 in 2000 pregnant women is affected by cancer
- Odds of cancer at delivery is increasing... to 4.43 per 10,000 in 2013¹ independently of maternal age

3.6 million births per year in EU².....680,000-720,000 births in France

Not a small problem

It cannot wait 9 months to be addressed

Ethical duty to generate evidence

¹Ma KK et al Am J Perinatol 2022

²Eurostat 2023

Maternal Investigation Plan ?

- 50 years of inaction in paediatrics... until legal and regulatory obligations generated data, research and approved products
- Nothing will happen for pregnant women by just 'recommending'
- **New product development that is planned, managed, transparent and shared**
- Based on needs and priorities, with timelines/milestones to stop and review
- Need for more research (teratogenicity mechanism, embryo vs fetus, PK and PD...)

Generating data with precaution

Pregnant women are not men! and, not even, non-pregnant women

- Physiological differences lead to PK PD differences that must be defined (using PD modelling, simulation)
- Non-clinical data: Genotoxicity, Reproductive toxicity/DART (ICH S5, M3), Toxicokinetics
- Pharmaceutical or biological product structure, similarity
- Clinical data from prospective trials, phase II and III (**ICH E21**)
- **THEN**.... post approval data, Real World Evidence
- **AND** Follow up of all (incl. unintended) pregnancies during clinical trials
- **AND** Follow up of infants' development beyond pregnancies (cf valproate)

So few clinical trials with pregnant women¹

Refusing Exclusion by default in protocols

- High priorities and needs : Protocol inclusion of pregnant women as of phase II and III, with informed consent
 - DSMB required, active monitoring of women, collection of specific safety data
- Low priorities or needs : firstly, data in women with contraception
- Systematic data and protocol discussion at regulatory review time (development advice and approval review)
- Sharing results to avoid repetition and increase learning

¹ In 2025 142 publications in PubMed with key words: Pregnancy, cancer and trials. Only one corresponds to a clinical trial in pregnant

Breast-feeding

- Human milk is better for children, especially where there is no clean water, or no resources to buy formula
- Provide evidence to guide recommendations by Health Professionals to women
- Develop better methods for measuring milk transfer and understanding of effects on infants

ICH E 21 guideline

- Draft guideline 2025 (Topic agreed 2022, Concept Paper May 23)
- Strong points: pregnant and lactating women should be included in drug development, ICH is the reference
- Weak points:
 - Too much focus on safety instead of benefit/risk, women benefit only, cancer missing,
 - Vague language on timing, obligations, needs, missing DSMB, weak approach to PK/PD, etc. Gives too much power to sponsors.
- Comments were expected until Sept 2025. Very slow process.

Fear or Science ? Time to Act !

- We cannot continue with exclusion or maleficence due to ignorance
- Evidence-based prescriptions for (pregnant) women require data
- Only counting accidents post-marketing is not acceptable
- NB : pregnant women are NOT vulnerable but autonomous (except those who are still children)
- They may, and some do agree to participate in research concerning their own health and/or that of their future children is at stake¹, especially when research is explained



¹Palmer et al 2016