



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005).

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Medicines Evaluation Board
Chair Safety Working Party



An agency of the European Union





To be able to give an accurate advice, the physician should be provided with **INFORMATION** on the risk of possible toxicity of a drug to human reproductive function and also on the **MANAGEMENT** of this risk in clinical practice

RECOMMENDATIONS:

1. Non-clinical Assessment process
2. Clinical Assessment Process
3. Integrated Risk Assessment



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Multi-disciplinary expert group of toxicologists and clinicians

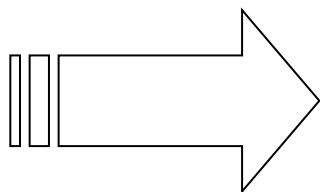
- Purposes of the guideline
 - « Describe the integration process of non-clinical and clinical data ... based on the assessment of reproductive toxicity studies in animals and human clinical data »
 - « Outline how to communicate the potential or identified risk »



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1. Global risk assessment of a drug during pregnancy relies on the combination of relevant experimental and human data
 - **Human data always prevail upon animal data**

2. Integration table for risk assessment and recommendations for use



3. Labelling

Note for Guidance on the Detection of Toxicity to Reproduction or medicinal Products & Toxicity to Male Fertility (*ICH-S5 (R2) March 1994*)

Three types of studies

- Fertility and early embryonic development (FEED)
(Segment 1)
- Embryo-fetal development (EFD)
(Segment 2)
- Pre- and postnatal development (PPND), including maternal function
(Segment 3)

June 2015: Revision will start in ICH.

- Flexibility in study design, use of two species
- More emphasis on in vitro approaches?

Evaluation of the effects

- Recognition of the effect (statistics)
- Cross-species concordance
- Type of effect – morphological effect more weight than general effect (e.g. growth retardation)
- Multiplicity of effects
- Adverse effects/rare effects?
- Dose dependency/ ratio to human exposure

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Data sources for clinical risk assessment

- Case-reports
- Short case series without controls
- Epidemiological studies (gold standard if well-conducted)
 - Population-based national registries
 - Cohorts
 - Pregnancy Registries
 - Retrospective case-control studies
 - Congenital malformations registries
 - Unpublished data...



Clinical data are analyzed and classified according to their relevance

- Drug monitoring systems during pregnancy have all their advantages and inconvenients
- But they ALL contribute to the progress of clinical knowledge and not only the « prospective » double-blind « gold standard » studies
- Pregnancy Registeries, other epidemiological studies (case-control studies), case series, case reports...are of great help
- The accuracy of clinical risk assessment relies on the relevance of the methodological analysis of these studies

Benchmarks have been adopted

Sample sizes calculations extracted from clinical trials tables, with additional safety margins (Strom BL. 2000)

- Baseline incidence of major malformations in humans $\sim 3\%$,
- $\alpha = 5\%$ and $\beta = 20\%$

If no increase in the **global incidence of major malformations** has been observed among at least **300** first trimester prospectively collected pregnancies with known pregnancy outcomes (births or fetopathological examinations), then, the drug is not responsible **for a 10-fold or more increase** of the overall incidence of malformations

If no increase **in the global incidence of major malformations**

has been observed among at least **1000** first trimester exposed prospectively collected pregnancies with known pregnancy outcomes (births or fetopathological examinations),

then, the drug is not responsible **for a 2-fold or more increase** of the overall incidence of malformations

Benchmarks clarify the clinical landscape and allow harmonization and standardization of clinical assessments while clinical experience is increasing



Integration of human and animal data



Integration table for risk assessment and recommendation for use



	Non clinical data	
	Effects detected or inconclusive results	No effect detected
Human data (major malformations)	Conclusion from integration <i>Labelling</i>	Conclusion from integration <i>Labelling</i>
Demonstrated human teratogenicity		
Supposed or suspected human teratogenicity		
≤ 300 prospective 1st trimester exposed pregnancies and no increased risk		
> 300 and ≤ 1000 prospective 1st trimester exposed pregnancies and no increased risk		
> 1000 prospective 1st trimester exposed pregnancies and no increased risk		



Two opposite situations:

- Proven human risk
- Risk in human is unlikely

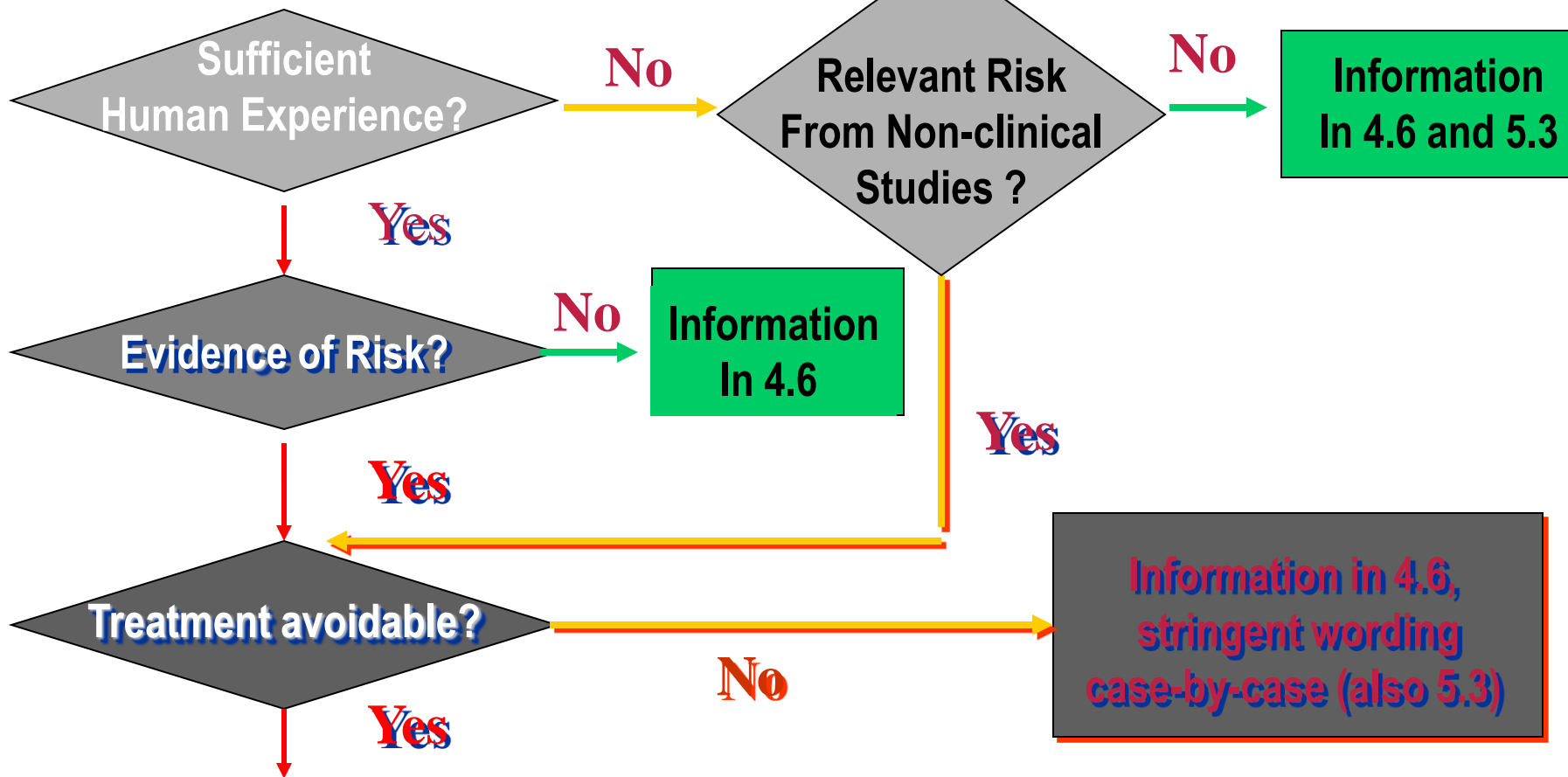
Integration table for risk assessment and recommendation for use



	Non clinical data	
	Effects detected or inconclusive results	No effects detected
Human data (major malformations)	Conclusion from integration <i>Labelling</i>	Conclusion from integration <i>Labelling</i>
Demonstrated human teratogenicity	Proven risk in humans <i>Labelling [1]</i> <i>Contraindication</i>	Proven risk in humans <i>Labelling [1]</i> <i>Contraindication</i>
Supposed or suspected human teratogenicity		
≤ 300 prospective 1st trimester exposed pregnancies and no increased risk		
> 300 and ≤ 1000 prospective 1st trimester exposed pregnancies and no increased risk		
> 1000 prospective 1st trimester exposed pregnancies and no increased risk	Malformative risk unlikely in humans with strong evidence <i>Labelling [8]</i>	Malformative risk unlikely in humans with strong evidence <i>Labelling [8]</i>

Contra-indication Decision Scheme

Documentation of studies by innovator company, as well as literature data



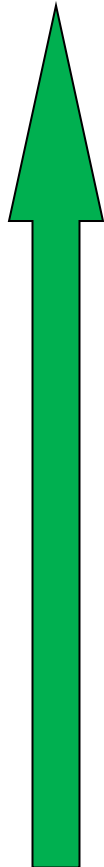
Contraindication in Pregnancy (4.3 and 4.6)

Animal data: no black or white situation.

Gradient:

- **General growth retardation (probably due to maternal toxicity)**
- **Pharmacological effects at high exposure**
- **Malformations**
- **Fetal death**

Integration of human and animal data



Prospective human data of 1 st trimester	Animal data Effects present	Animal data No effects
Demonstrated malformations	High risk	
Suspected malformations		
No or less than 300 outcomes and no increase	Intermediate risk	
Between 300 and 1000 outcomes and no increase		
At least 1000 outcomes and no increase		Low risk



Integration table for risk assessment and recommendation for use



	Non clinical data	
	Effects detected or inconclusive results	No effects detected
Human data (major malformations)	Conclusion from integration <i>Labelling</i>	Conclusion from integration <i>Labelling</i>
Demonstrated human teratogenicity	Proven risk in humans <i>Labelling [1]</i> <i>Contraindication</i>	Proven risk in humans <i>Labelling [1]</i> <i>Contraindication</i>
Supposed or suspected human teratogenicity	Strong suspicion of risk in humans <i>Labelling [2]</i>	Risk is possible in humans <i>Labelling [3]</i>
≤ 300 prospective 1st trimester exposed pregnancies and no increased risk	Risk is possible in humans, not confirmed <i>Labelling [4]</i>	Malformative risk unlikely in humans, but low evidence <i>Labelling [5]</i>
> 300 and ≤ 1000 prospective 1st trimester exposed pregnancies and no increased risk	Malformative risk unlikely in humans but low evidence <i>Labelling [6]</i>	Malformative risk unlikely in humans with moderate to substantial evidence <i>Labelling [7]</i>
> 1000 prospective 1st trimester exposed pregnancies and no increased risk	Malformative risk unlikely in humans with strong evidence <i>Labelling [8]</i>	Malformative risk unlikely in humans with strong evidence <i>Labelling [8]</i>

Human data	Animal data Effects present	Animal data No effects
Demonstrated malformations	X is contraindicated or should not be used	X is contraindicated or should not be used
Suspected malformations	X is contraindicated or should not be used	X is not recommended/ should not be used
No or less than 300 outcomes and no increase	X is not recommended/ should not be used	As a precautionary measure, it is preferable to avoid use of X
Between 300 and 1000 outcomes and no increase	As a precautionary measure, it is preferable to avoid use of X	The use of X may be considered, if clinically needed
At least 1000 outcomes and no increase	X can be used	X can be used



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Narrative texts in a digest format easy to use in daily medical practice

- Summary of risk assessment on fertility, pregnancy and lactation
- Recommendations for use during pregnancy
- If necessary
 - Risk management (prenatal diagnosis...)
 - Specific considerations about disease during pregnancy
- Labellings can be regularly adapted to reflect new clinical data if relevant

No details about studies except main relevant points, no bibliography



Individual statements are looking alike:

- X is not recommended/ should not be used unless needed
- As a precautionary measure, it is preferable to avoid use of X
- The use of X may be considered, if necessary

A Gradient in uncertainty and severity is intended.

In Europe, a standardized policy of risk assessment and labelling in pregnancy is applicable to all existing or future drugs.

This rigorous and flexible tool allows to harmonize and to update drugs in accordance with the evolution of clinical experience in pregnancy and the therapeutical needs of each drug.

This should be performed keeping in mind pragmatic public health needs and constraints towards prescribers and patients.



1. No pregnancy categories: narrative description
2. Similar headings = Fertility, Pregnancy, Lactation
3. Risk assessment approaches scientifically similar, although FDA not explicit about the statistics.



1. FDA: Focus on Pregnancy Registries.
EU: broader on epidemiological data and case reports
(see Guideline)
2. FDA: Include all data summaries, with references
EU: No references. Standard sentences proposed, although
flexible.
Separate animal data in 5.3. More data in EPAR.

Conclusion

Scientifically small differences, but in practice, large differences between EU and FDA, i.e. text in EU concise, and in US extensive.