CBG MEB | MEDICINES EVALUATION BOARD

Alternative approaches to non-human primate use for reproductive toxicity testing

Peter van Meer, Antwerp Feb 2024

GOOD MEDICINES USED BETTER

Disclaimer

These opinions are my own and not necessarily those of the MEB, EMA or any of its committees or working parties.

Mandatory slide: Thalidomide

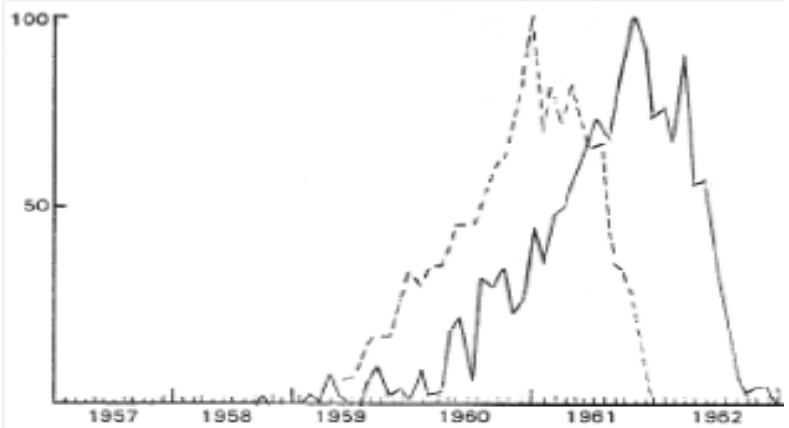
THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (' Distaval ') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

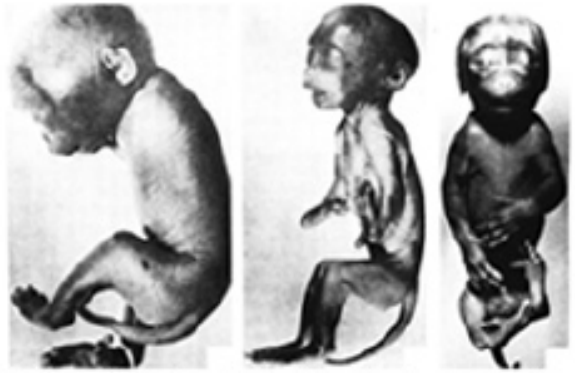
Hurstville, New South Wales. W. G. McBRIDE.



Graph showing the relation between the malformations of the thalidomide type and the sales of thalidomide (figures for Germany excluding Hamburg).

– – – Thalidomide sales (January 1961 = 100)
——— 845 abnormalities of the thalidomide type (October 1961 = 100)

(After Leck 1979)



Thalidomide induced limb defects in rhesus monkey; micrognathia is also present (Schardein 1993).

Fast forward 50+ years

Carcinogenicity Studies S1A - S1C

Genotoxicity Studies S2

Toxicokinetics and Pharmacokinetics S3A/B

Toxicity Testing S4

Reproductive Toxicology S5

Biotechnological Products S6

Pharmacology Studies S7A/B

Immunotoxicology Studies S8

Nonclinical Evaluation for Anticancer Pharmaceuticals S9

Photosafety Evaluation S10

Juvenile Toxicity S11

Nonclinical Safety Studies M3

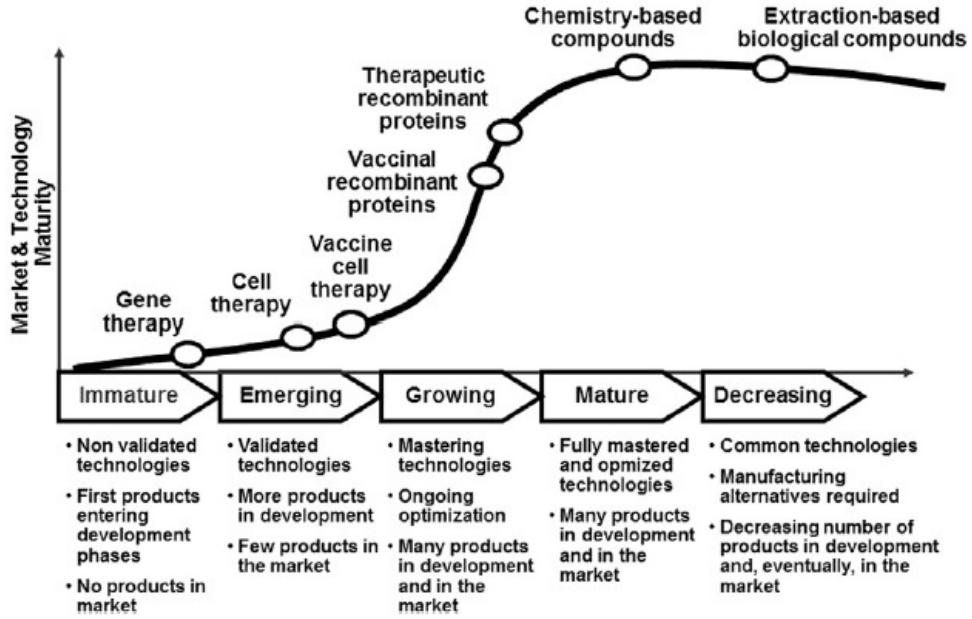
Genotoxic Impurities M7

…

ICH
harmonisation for better health

Most guidance for the oldest products

- The older the product
  - The more guidance exists
  - The less guidance is needed
- The more novel the product
  - The less guidance exists
  - The more guidance is needed



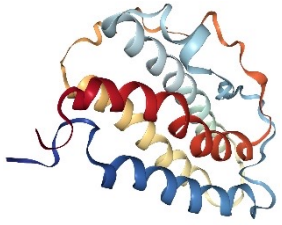
- With novel product classes, complexity increases
  - With increasing complexity
    - Specificity increases to a point that animal models become less or irrelevant
    - Off target effects become less common
    - PK-PD relationships become predictable (or irrelevant)
    - Return on investment from a data perspective decreases rapidly

A look at ICH S6: Intrinsic properties of mAbs drive high translation

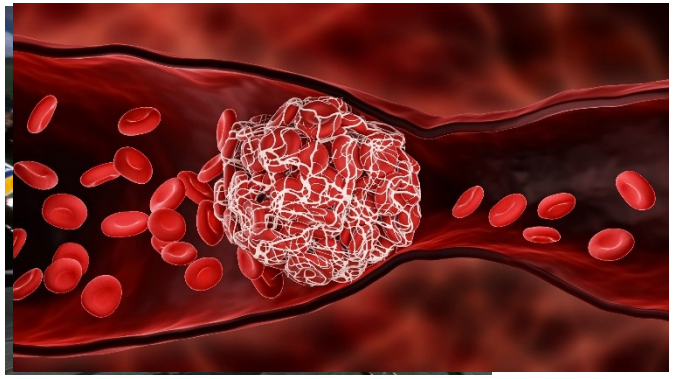
- High specificity limits pharmacologically responsive species to NHP
- NHP predominantly used for safety evaluation of proteins, particularly so for DART evaluation
- There are, generally, 3 types of findings in chronic safety studies with mAbs in NHP (Bugelski and Martin 2012 ,van Meer 2013, Chien 2023)
    1. Effects driven by the pharmacology of the product, **can be adverse** (exagerrated pharmacology)
    2. Effects driven by immune responses
        a. Anti-drug-antibody formation (ADA, immunogenicity) or ADA mediated toxicity
    3. No notable effects (historically roughly 50% of marketed products, van Meer et al 2013, **Chien et al 2023**)

1 we can predict and anticipate, **2** we can not predict nor translate but expect, **3** happens if there is no or almost no target in the test system (anticipated lack of RoI!)

Would this be any different for reproductive toxicity studies in NHP?



Epoetin (not a mAb) is indicated for the treatment of anemia secondary to chronic kidney disease and chemotherapy-induced anemia in patients with cancer



ePPND studies in line with ICH S6(R1)

ePPND design (See ICH S6(R1) notes and publication of Jarvis et al for jusitification of sample size and design considerations)

16 pregnant females per group, generally control + 3 dose groups

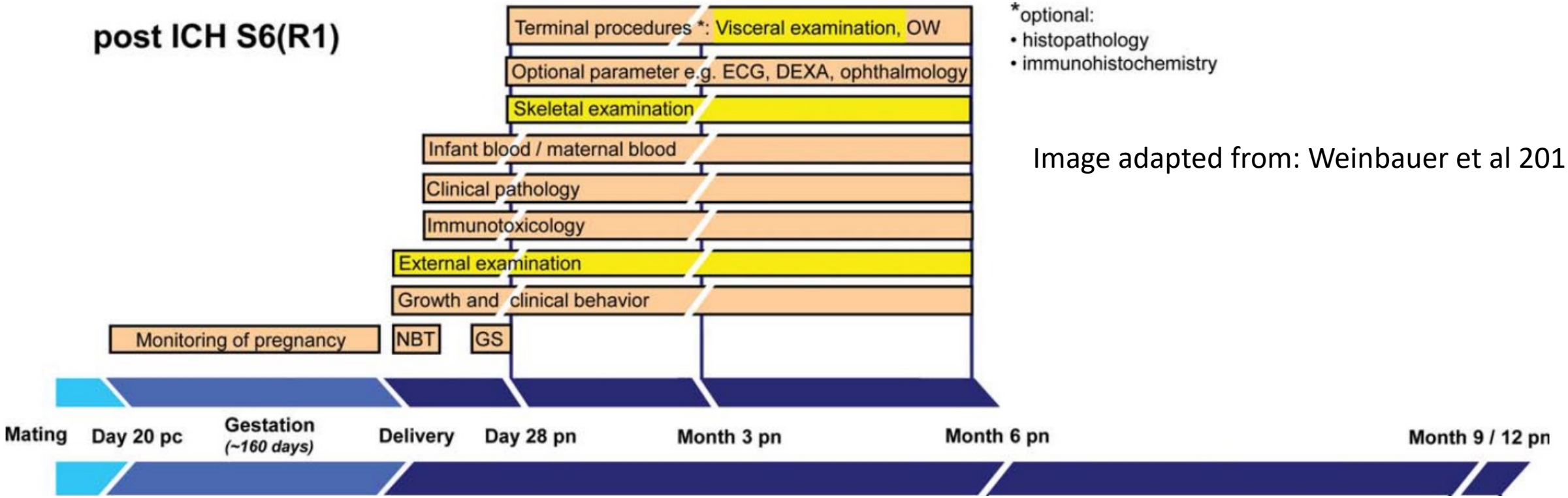


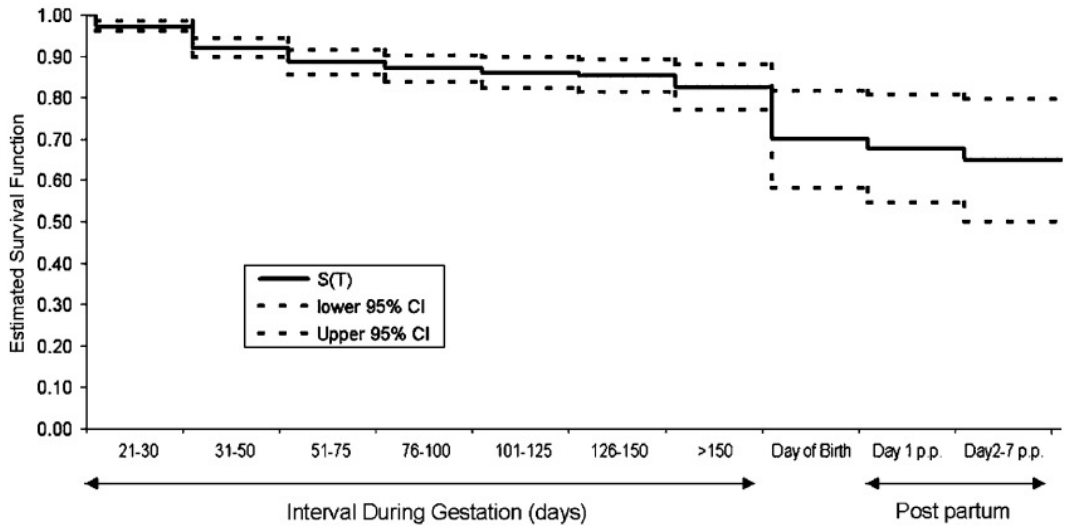
Image adapted from: Weinbauer et al 2011

ePPND studies in line with ICH S6(R1) and the problem with animal studies for DART with mAbs

1. Limited supply of sexually mature monkeys and long lead time to maturity (3-6 years)
2. Relatively long gestation compared to rodents, increasing the study duration
3. Low fertility rate (35-45% per cycle and ~60% per female) and high spontaneous abortion rate ~30%
4. Single births, resulting in limited offspring for evaluation
5. Shortages possible (e.g. global pandemic)

This further stresses the need to only do the study when there is a scientific justification to initiate a study

So how to determine need?



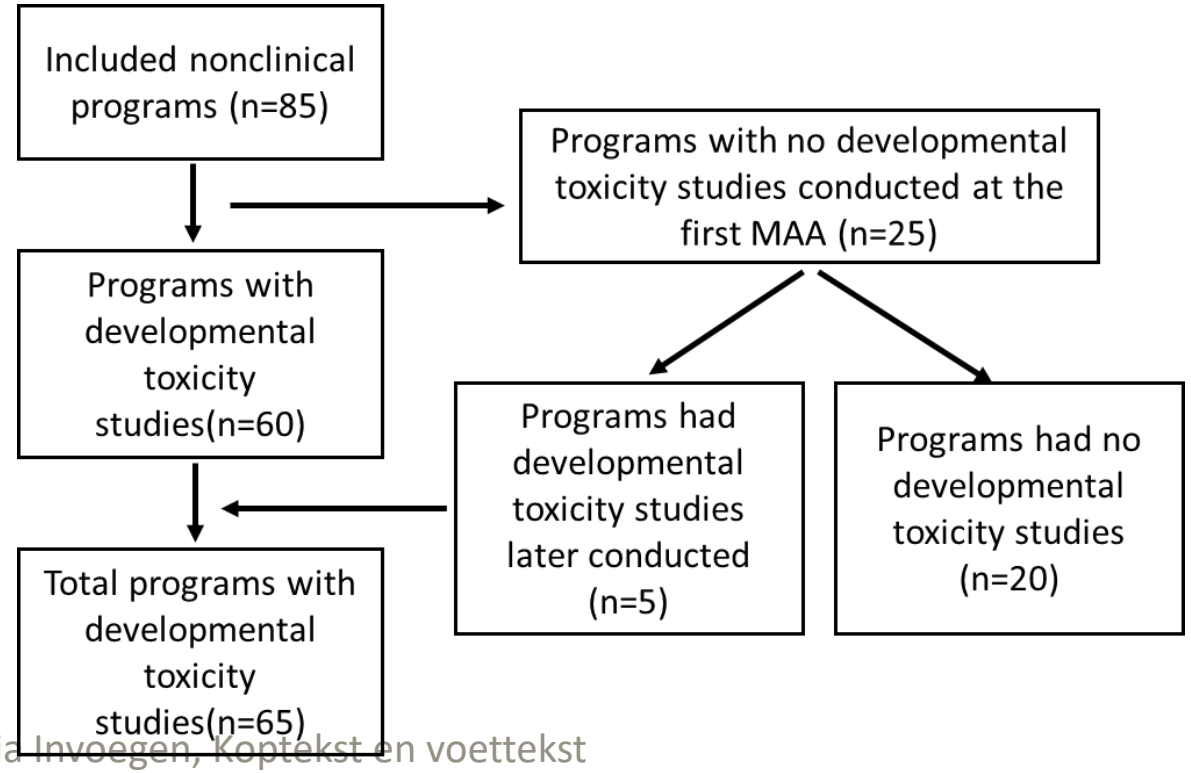
ig. 2. Kaplan-Meier estimate of the survival function and 95% confidence intervals for 722 cynomolgus monkey pregnancies.

irth Defects Research (Part B) 89:175–187, 2010

Further reading: Chellman 2009

What has been the experience with DART studies (pre and post ICH S6(R1) in the EU?

- Data from 85 therapeutic mAbs marketed in the EU between 01-01-1998 and 01-08-2021 were collected
  - We excluded duplicate applications, biosimilars, diagnostics and ADC
  - DART studies were performed as part as the first MAA or as a line extension
- 65 non-clinical programs included DART studies



High variability, likely due to time

Of 65 DART programs

- 40 used NHP as primary test species, 2 used rabbit only
- 12 used non-rodent (NHP and/or rabbit) and rodent as test species
- 13 used rodent (tg) mouse (using surrogate), also guinea pig or rat)

High variability in DART program, with 1, 2, 3 or more studies.

Studies were combinations of EFD, FEED-EFD, FEED-PPND, PPND or ePPND

# Studies per program	# Study type(s) per program					Species used	# mAbs
	EFD	FEED-EFD	PPND	FEED-PPND	ePPND		
Non-rodent only (n=43 mAbs)							
1	1					C	10
	1					Rb	2
					1	C	19
2					2	C	1
	1		1			C	5
	1				1	C	4
	1 (Rb)				1 (C)	Rb + C	1
3	2		1			C	1
Rodent + non-rodent (n=10 mAbs)							
2	1 (C)		1 (M*)			M* + C	1
	1 (R)				1 (C)	R + C	1
		1 (M*)			1 (C)	M* + C	1
3	2 (M, Rb)		1 (M)			M + Rb	1
	2 (Mt)		1 (M)			M + Mt	1
	2 (Rb, R)			1 (R)		R + Rb	1
	1 (Rb)	1 (R)	1 (R)			R + Rb	1
4	1 (Rb)	2 (R)	1 (R)			R + Rb	1
	2 (C, M*)		2 (C, M*)			M* + C	1
	3 (C, G)				1 (C)	G + C	1
Rodent only (n=12 mAbs)							
1	1					M*	4
	1					M	1
	1					TG	1
	1					G	1
2	1		1			R*	1
	1		1			M*	3
3	1	1	1			R	1

What has been the experience with DART studies (pre and post ICH S6(R1) in the EU?

mAbs which evaluated reproductive toxicity through DART studies

- No or no adverse findings of human conern were identified in **80% of the cases** (52/65)
- Equivocal findings were identified in 5% (3/65)
  - 2 cases of MEFL, 1 other toxicity
- Findings of fuman concern were identified in 15% of the cases (10/65)
  - **In 90% of these (9/10), findings were related to PD**
  - One other case of MEFL that could not be directly attributed to PD

Equivocal findings with MEFL, the case of Yervoy (ipilimumab, anti CTLA-4, TA: oncology)

- 2 rare cases of urogenital malformation in presence of increased abortion exceeding historical control

Equivocal finding other toxicity, the case of Ocrevus (Ocrelizumab, anti CD-20, TA: immune suppressor

- Dose-dependent minimal to mild glomerulopathy was noted in treatment group neonates only

What has been the experience with DART studies (pre and post ICH S6(R1) in the EU?

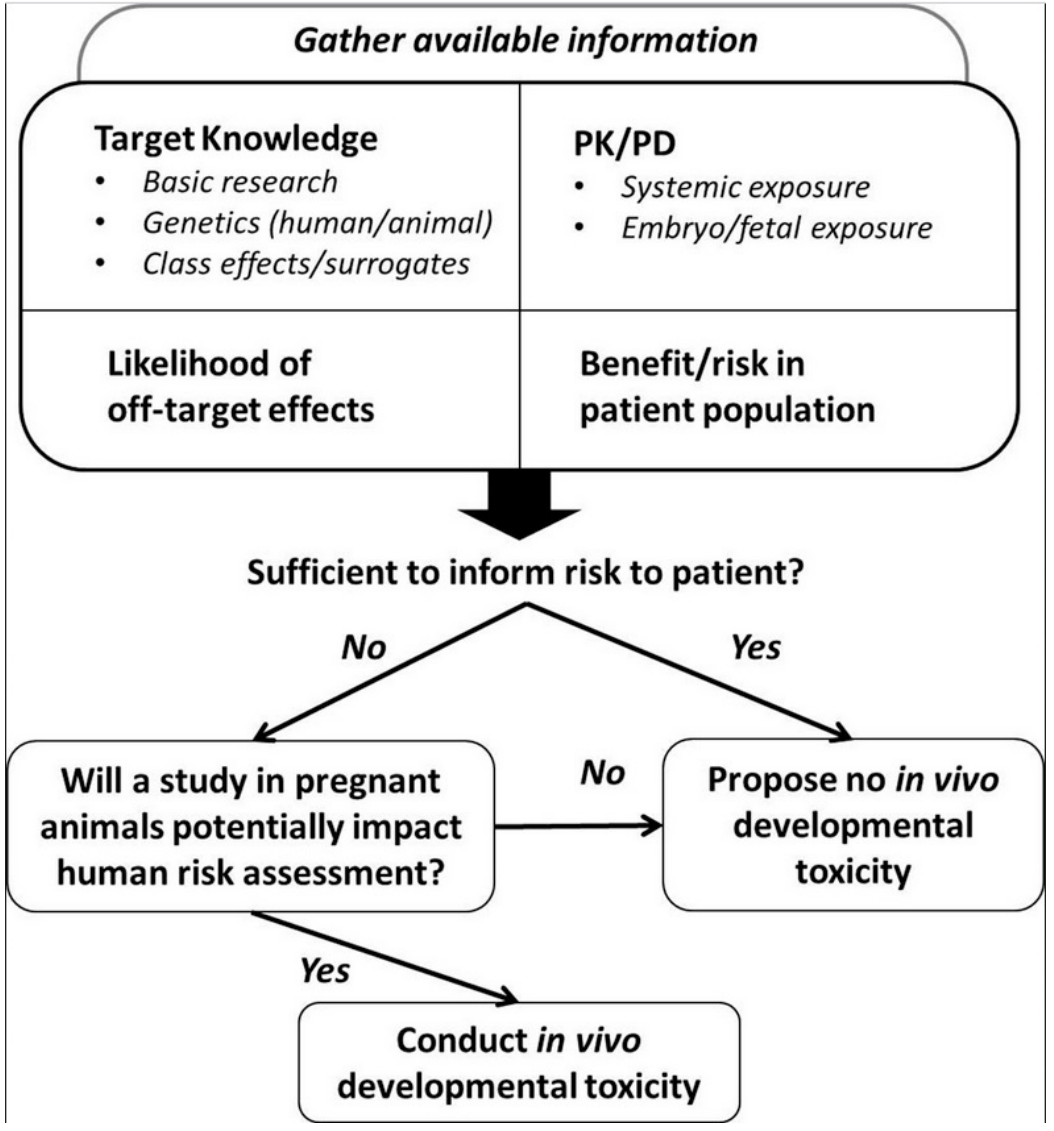
mAbs without DART studies (n=25)

- Eighteen products were developed for advanced cancer indications, generally not requiring DART assessment in line with ICH S9
- Three mAbs targeted an exogenous epitope not requiring DART evaluation in line with ICH S6(R1)
- Two mAbs were developed for indications in post menopauzal women (not WoCBP)
- One mAb was intended for short term use allowing a waiver of DART studies
- One mAb had no pharmacologically relevant animal model to conduct the study in

Could we predict this using a Weight of Evidence model?

A WoE approach is a radically novel concept and has only been accepted to waive studies in: carcinogenicity (ICH S1B), juvenile toxicity (ICH S11) and reproductive toxicity (ICH S5(R3))

Can we use a standardised Weight of Evidence with specific risk factors developed by Roca et al?



Before we start with the WoE…

Very briefly,:

Either no finding, or reproductive toicity can be attributed to the PD. Comparable to chronic toxicity

In a few cases, it is not clear although a target related effect cannot be ruled out.

Applicants indeed successfully used WoE (factors) already to waive ePPND

Weight of evidence approaches* were submitted in 20/25 cases (also in line with ICH S6(R1)/S5(R3)

- 10 products provided **evidence of risk**, which was reflected in the SPC in 9/10 cases (very limited literature)
- 6 products provided evidence of **absence of risk** based on exogenous target, low systemic exposure, absence of systemic toxity, advanced cancer or short term use

Using a WoE to retrospectively predict DART in animal studies

Going through all the data, the model by Roca was able to:

1. Identify 9/10 mAbs with DART and identified 1 as a potential toxicant
2. Overestimated risk for 9 mAbs
3. Identified 29/52 mAbs without risk and overpredicted risk for 23 mAbs

WOE assessment

In vivo DART data	Predicted Yes	Predicted No	Predicted equivocal
Total mAbs (n=65)			
Actual Yes (n=10)	9	0	1
Actual No (n=52)	9	29	14
Deemed equivocal (n=3)	0	2	1

- The current model is very effective in stratifying high risk and low risk products
- It is conservative (thus suggesting studies are need too ofen)
- A more stratified WoE model would potentially yield better stratification.

Case study of positive risk: Avastin (bevacizumab)

mAb	Literature data on target biology/modulation			Experience with molecule		Class effect		WOE assessment result			Dev tox studies				
	Role in EF development		Role in maintaing pregnancy	In vivo		Adverse pregnancy outcome		Need for dev tox studies			Study outcome				
	Evidence of malfo, growth retardation	Impaired organ system function	Impaired FM tolerance, uterine physiology, placenta toxicity	Adverse effects of concern	Reversibility/ Severity	Nonclinical	Clinical	Malformation / growth retardation	Abortion	Irreversible fetal harm	Malformation	Abortion	Irreversible fetal harm	Target	
Avastin														VEGF	bevacizum
Lucentis														VEGF-A	ranibizum
Beovu														VEGF-A	brolucizun

Mode of action: inhibition of VEGF leading to disruption of angiogenesis (cutting off bloodflow to tumor), TA: oncology (+wet AMD off-label)

Role in development: Cardiovascular failure in VEGF3R KO mice (leading to mortality)

Maintenance of pregnancy:VEGF expression on placental syncytiotrophoblast cells and invasive chorionic trophoblast cells during pregnancy.

Anticipated DART based on the critical role of angiogenesis in ovarian function and normal fetal development described in literature

In vivo with molecule: Reduced ovarian and uterine weights, less or no corpora lutea, reduced cartilage growth plate and physial dysplasia, decreased #cycles

WoE conclusion: High risk as developmental toxicant. Positively correlated with nonclinical outcome:

DART studies with Avastin: mAb is embryotoxic and teratogenic in rabbits.

In vivo in class: Other mAbs/fabs used an intravitreal RoA (TA:ophthalmology) so no systemic exposure. No dev tox with Beovu in NHP, potential ADA mediated placental transfer for lucentis leading to DART.

Clinical experience: case report of successful birth after accidental ivt admin, 2 case reports of abortion for ivt admin (note: offlabel use)

Case study of negative risk: Ultomiris (ravulizumab)

mAb	Literature data on target biology/modulation			Experience with molecule		Class effect		WOE assessment result			Dev tox studies				
	Role in EF development		Role in maintaing pregnancy	In vivo		Adverse pregnancy outcome		Need for dev tox studies			Study outcome				
	Evidence of malfo, growth retardation	Impaired organ system function	Impaired FM tolerance, uterine physiology, placenta toxicity	Adverse effects of concern	Reversibility/ Severity	Nonclinical	Clinical	Malformation / growth retardation	Abortion	Irreversible fetal harm	Malformation	Abortion	Irreversible fetal harm	Target	
Ultomiris														C5	ravulizum
Soliris														C5	eculizuma

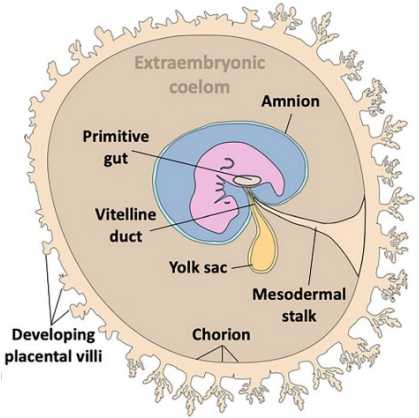
Mode of action: inhibition of complement C5, limiting complement activation cascade and hemolysis (TA:blood, paroxysomal nocturnal haemonuria)
Role in development: None (complement activation is a risk factor)
Maintenance of pregnancy: None
In vivo with molecule: No remarkable findings
WoE conclusion: No risk
DART studies with Ultomiris: No test article related findings
In vivo in class: None
Clinical experience: No or limited data

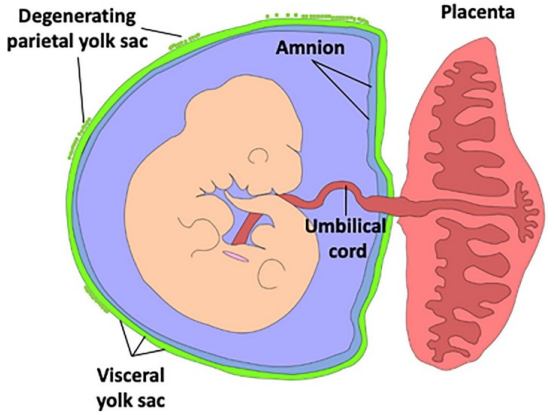
Alternatives to ePPND studies with NHP: the way forward

A step-wise approach to the use of NHP in developmental and reproductive toxicity studies

1. Weight of evidence models
    1. A refined WoE model is likely to better predict risk-on and risk-off products.
    2. Accepted already in presence of risk, also by FDA in absence of risk (Hoberman et al.)
    3. If uncertainty remains based on the evidence, go to step 2

2. Select lower species if these are pharmacologically responsive
    - Many (and recent) cases of rodent or rabbit studies to evaluate reproductive toxicity
    - Earlier placental transfer due to differences in anatomy: careful translation of effects





Alternatives to ePPND studies with NHP: the way forward

3. If lower pharmacologically relevant species are not available, use of surrotage antibodies may be considered and must be justified

- Unsurprisingly, this is already accepted in ICH S6(R1): '…when no relevant species can be identified …use of homologous molecules or transgenic models can be considered (to identify hazard).

4. If lower pharmacologically relevant species are not available, use of transgenic animals may be considered and must be justified

- Unsurprisingly, this is already accepted in ICH S6(R1): 'When no relevant animal species exists... the use of transgenic mice expressing the human target can be considered, [providing that] sufficient background knowledge exists

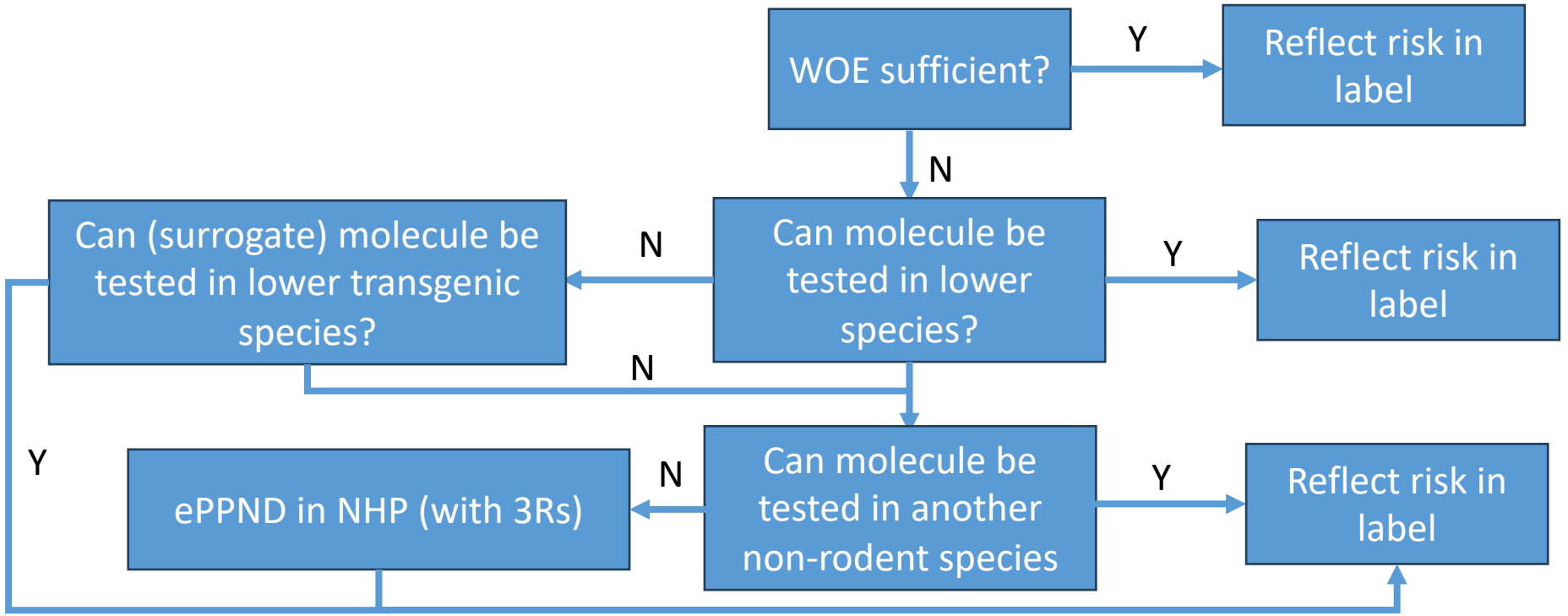
5. If lower species are not feasible, the use of mini-pig may be acceptable as a replacement for NHP and can be a better model.

- ~~Unsurprisingly, this is already noted in ICH S6(R1):~~

Alternatives to ePPND studies with NHP: the way forward

6. If NHP studies are still needed, consider 3Rs options

- Unsurprisingly, this is already accepted in ICH S6(R1): The developmental toxicity studies in NHP .. are **just** hazard identification studies; … it might be possible to conduct these studies using a control group and one dose group, provided there is a scientific justification for the dose level selected



Reflecting risk in the label for the prescriber

While I am mentioning reflecting risk in the label….

There are 9 categories of risk to use in section 4.6 of the SPC on animal and/or human data

- 1 category forbids use based on animal and human data (contra-indication)
- 6 categories recommend that pregnant women do not use the drug based on (positive or negative) animal and (varying degrees of human data)
- 1 category recommends the use of the drug in pregnant woman based on sufficient prospective pregnancies and animal data (which is less relevant)
- 1 category recommends the use of the drug in pregnant woman because systemic exposure to the drug is negligible

- Option 7…. What about NAMs?

Evaluation of DART outcomes and

Thanks to:

Hsiaotzu Chien, MEB/RUN
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Peter Theunissen, MEB

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List of references