Non-rodent species selection from a pharmaceutical company point of view

Ellegaard Göttingen Minipigs "live-webinar-event"

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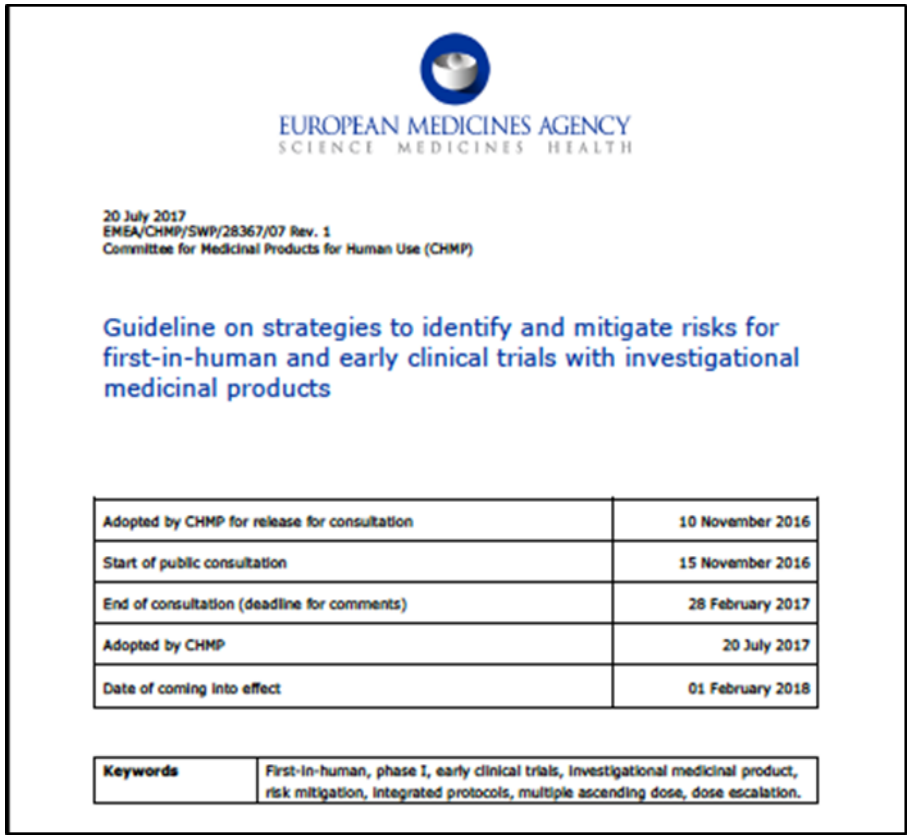
25 Januar 2022 | public use

EMA First-In-Human Guideline 2017 – Non-clinical aspects

Relevance of the animal model used in non-clinical studies has to be explored prior to first-in-human trials

- **Need to justify or dis-qualify animal species for toxicity testing**
  - Pharmacological activity
  - Metabolite pattern in animals compared to man
  - Limitations for PD readout of certain targets in healthy animals

- **Is a species relevant?**
  - 👍 Go with a rodent and a non-rodent, or go with single relevant species
  - 👎 Go with a surrogate/homologue or in vitro data only



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
EMEA/CHMP/SWP/28367/07 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

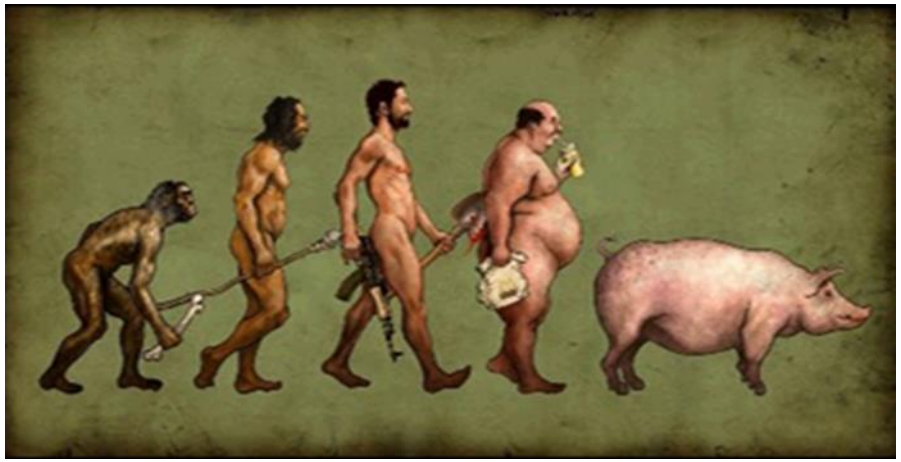
Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016
End of consultation (deadline for comments)	28 February 2017
Adopted by CHMP	20 July 2017
Date of coming into effect	01 February 2018

Keywords	First-in-human, phase I, early clinical trials, investigational medicinal product, risk mitigation, integrated protocols, multiple ascending dose, dose escalation.

Human Relevant Safety Assessment

Maximize the likelihood of identifying responses that are similar to those expected in human

- **What defines a responder species?**
  - Is target expression / tissue distribution in animals comparable to human?
  - Degree of target / pathway homology between species?
  - Do we expect same / similar target mediated effects as in human (pathway/regulatory mechanisms)?

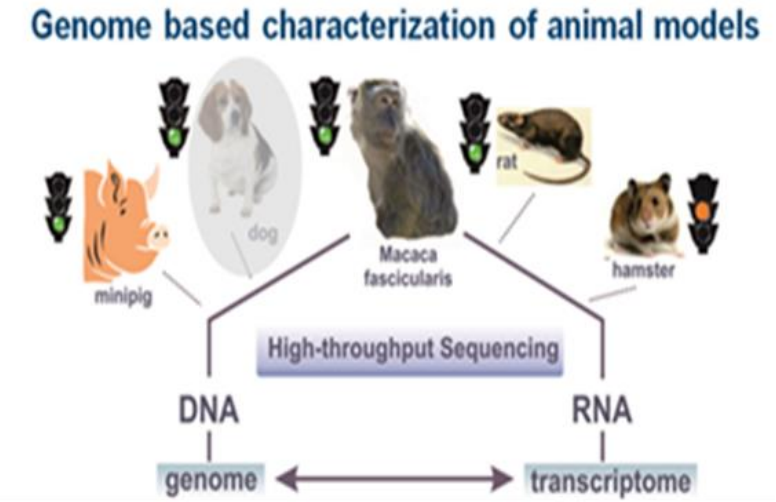


- **Why is it important to use relevant species?**
  - 3Rs principle (Replace, Reduce, Refine), i.e. trying to minimize animal use and maximize the likelihood of identifying responses that are similar to those expected in humans
  - Avoiding potentially irrelevant findings for human risk assessment
  - Judging potency for safety margin calculation for human starting dose

Non-rodent species selection at Roche

Use of any of the non-rodent species requires appropriate scientific justification

- **Species selection is an important part of an overall project strategy discussion** and is initiated at target selection phase
  - based on evidence from literature and in-house databases allowing genome-based characterization of animal species
  - binding / functional data in human and animal species to compare activity, whenever feasible
- For many years **Göttingen minipig or cynomolgus monkey were the non-rodent species of choice**
- With increasing ethical concerns relating to the use of primates and increasing problems with regard to supply **use of minipigs is rising and dog is considered again**
- For biotechnology-derived products with increasing complexity of the modalities and targets, in vitro only approaches are increasingly applied at Roche, i.e. using relevant human in vitro models rather than surrogate molecules or transgenic animal models



[green light indicates complete genome and protein annotation]

Göttingen minipigs @Roche – some case examples

The Göttingen Minipig is a well recognized and valuable species in safety pharmacology

- The minipig is suitable to detect QT prolongation as published and also proven in internal studies with reference compounds (invasive telemetry as well as jacketed ECGs)
- Sensitive to body temperature changes which influences the QT interval (decrease in body temperature leads to QT prolongation and vice versa)
- Less prone to CNS driven heart rate changes and vomiting compared to dog
- Important aspects for safety assessment of CNS active drugs
- The minipig is suitable for Functional Observational Battery (FOB) and respiratory assessment if needed for toxicity studies (based on literature)

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Appraisal of state-of-the-art

Preclinical QT safety assessment: Cross-species comparisons and human translation from an industry consortium

Henry Holzgrefe [c,*], Georg Ferber [h], Pascal Champeroux [b], Michael Gill [a], Masaki Honda [d], Andrea Greiter-Wilke [e], Theodore Baird [f], Olivier Meyer [e], Muriel Saulnier [g]

Characterization of Göttingen Minipig for Single Stranded Oligonucleotide safety testing

Characterization of 4 Single stranded Oligonucleotides (SSO) in minipig for assessing SSO safety relative to cynomolgus monkey & human duration & dose regimen:

- So far the Cynomolgus monkey has been broadly used as non-rodent model for assessing SSO safety
- Assessing SSO safety with focus on tissue exposure, target organs of toxicity, pharmacokinetics and pharmacodynamic effects
- Target organs of toxicity same (kidney & liver) as in cynomolgus monkey & human
- Pharmacokinetics and pharmacodynamics similar to cynomolgus monkey & human

- **No unexpected additional findings in minipig**

Toxicol Sci. 2017 May; 157(1): 112–128. PMCID: PMC5414856
Published online 2017 Jan 25. doi: 10.1093/toxsci/kfx025 PMID: 28123102

From the Cover: The Minipig is a Suitable Non-Rodent Model in the Safety Assessment of Single Stranded Oligonucleotides

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Example 1: Anti-Atherosclerosis Drug (Small Molecule)

Göttingen minipig chosen as non-rodent species as 3rd choice (in 2009)

- **Cortical atrophy seen in dog adrenal gland** lead to termination of frontrunner molecule
  - maybe related to lack of LDL as a source of cholesterol
- **Cynomolgus monkey showed very low plasma exposure**, i.e. no exposure margin to anticipated human efficacious plasma exposure
- **Göttingen Minipig showed acceptable plasma expoure** after high fat diet
- **Challenges** could be managed (limited compound availablitiy)

High fat diet has 25% more energy per unit	**Pharmacology unknown in Minipig**
To avoid the excess body weight gain, amount of food (total 250 g) was adjusted to normal regime: 175 g in the morning (effects exposure) + 75 g in the afternoon	HDL as functional biomarker Cloning of target in minipig (was planned, but target discontinued)

Example 2: Neurodevelopment indication drug (Small Molecule)

Göttingen minipig prioritized over cynomolgus monkey despite faster clearance

- Target well conserved across all species
- Target distribution aligned across species
  - BUT target is highly expressed in testis and thyroid gland in minipig only
- Pharmacokinetics in minipig suboptimal compared to cynomolgus monkey, i.e. faster clearance
- Due increasing ethical concerns relating to the use of primate, minipig was prioritized over cynomolgus monkey

Fast Clearance in Minipig	**Lack of Minipig binding assay**
Exposure margin could be achieved by BID dosing No limitations on compound availability	Receptor isolated from the minipig brain and in vitro pharmacology studies showed similar affinity compared to the human and rat receptor

Example 3: Oncology drug (Small Molecule)

Göttingen minipig prioritized over cynomolgus monkey due to better pharmacokinetics

- Target very well conserved across all species and with highly similar tissue distribution
- Unacceptable pharmacokinetics in cynomolgus monkey [fast clearance and low bioavailability (9%)]
  - impossible to achieve meaningful multiples in toxicity studies
- Very good pharmacokinetics in Göttingen minipig
- Considered a good model for potential off-target skin findings

Compound availability was an issue
High pressure on our colleagues in chemistry (high priority program) – they managed with minimal delay

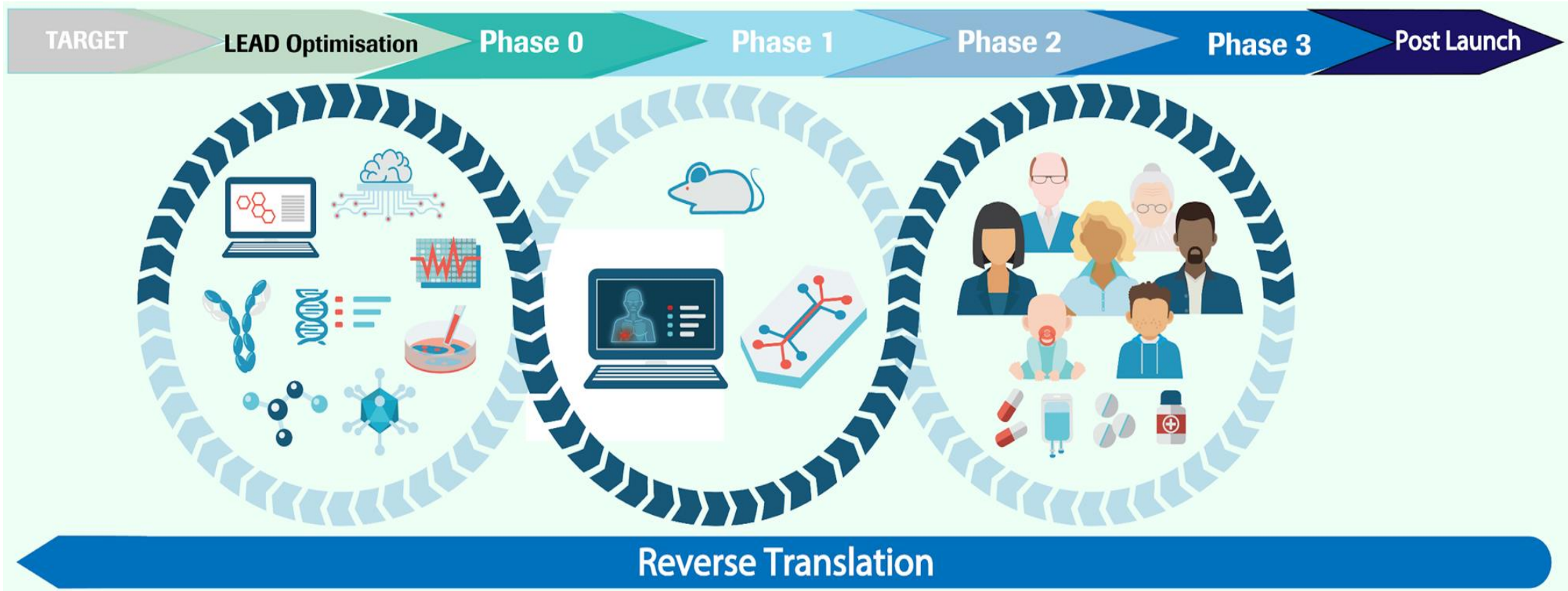
Example 4: Anti-Inflammatory drug (Small Molecule)

Different non-rodent species for same target in different indications

- Target Homology and Tissue Distribution suggests translatability across species
  - Ubiquitous expression of target in all tissues and species (human, cyno, dog, minipig)
  - Similar gene expression across species, high protein similarity to humans
  - Binding pocket of target enzyme fully conserved in human and non-clinical species

Cyno for CNS indication	**Minipig or dog for gut indication**

• Brain specific off-target pathway better characterized in cynomolgus monkey
• Highest sequence homology of target and off-targets to be avoided
 
	• Peripheral restricted molecules, i.e. no brain penetration
	• Gut anatomy of pig most similar to human
	• Potential on-target effects on lipid metabolism
	  • Lack of LDL in dog might lead to adrenal tox
	  • In minipig high LDL, low HDL as in human
	  > **(PK and MetID pending)** 



- ***The perfect animal model does not exist***
- ***Göttingen minipigs as non-rodent species are as suitable for safety assessment as dogs and non-human primates***

Doing now what patients need next