



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Cell-based therapies for cardiac repair

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NON-CLINICAL ASPECTS

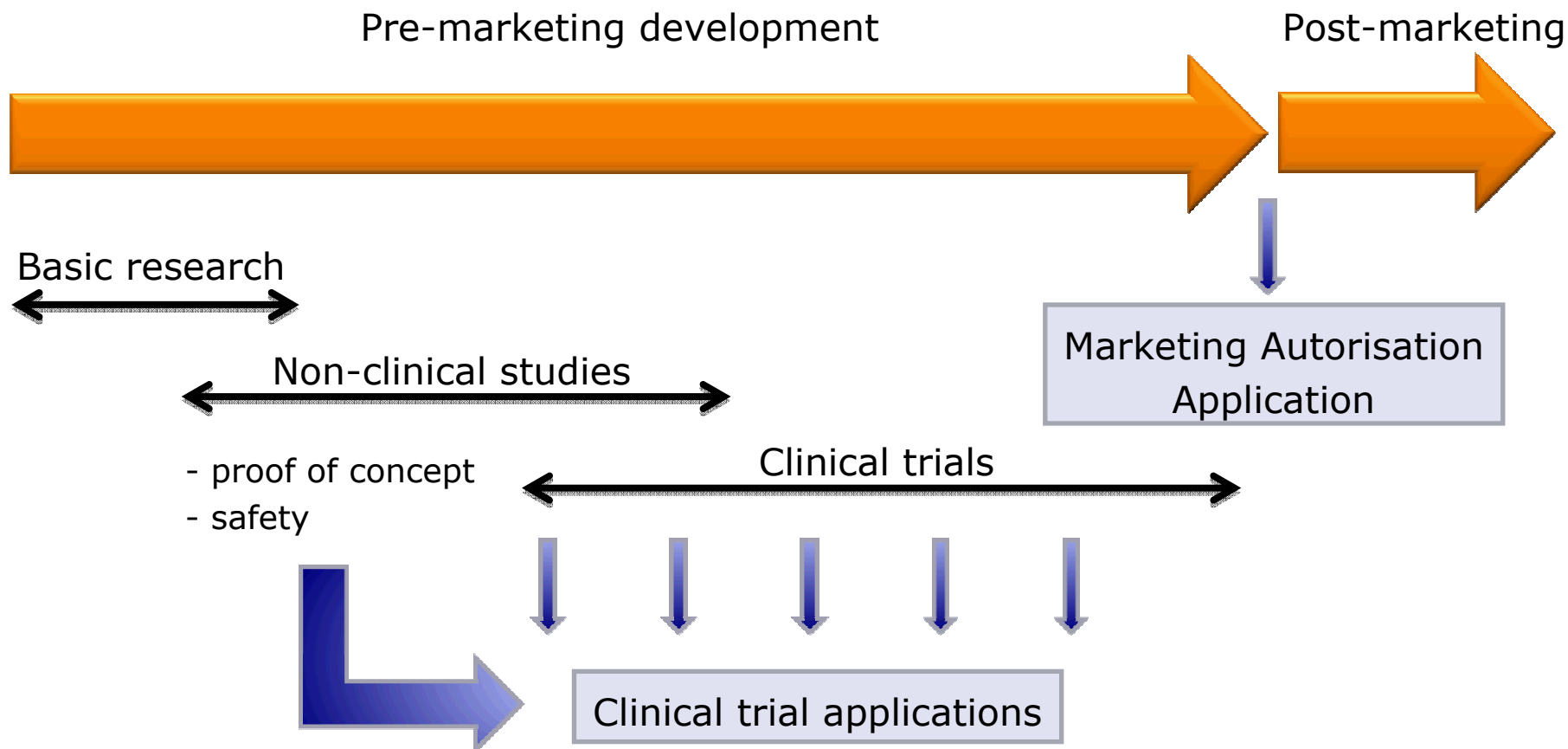
Presented by: Beuneu Claire  
CAT-DGTI-GSCN Workshop, 11 September 2014, Dresden

An agency of the European Union





# Drug development





# EMA guidance – cell based products

Topic	Documents	Reference number	Publication date	Effective date	Remarks
Clinical aspects related to tissue engineered products	Draft reflection paper	CAT/CPWP/573420/2009	Released for consultation Apr 2012		Deadline for comments 31 July 2012
Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products	Adopted guideline Draft guideline Concept paper	CAT/CPWP/686637/2011	March 2013	February 2013	
CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products	Adopted guideline Overview of comments Draft guideline	CHMP/CAT/BWP/353632/2010	June 2011	June 2011	
Reflection paper on stem cell-based medicinal products	Overview of comments Adopted reflection paper Draft reflection paper	CAT/571134/09	February 2011	January 2011	
Reflection paper on <i>in-vitro</i> cultured chondrocyte containing products for cartilage repair of the knee	Overview of comments Draft reflection paper Adopted reflection paper	CAT/CPWP/568181/2009	May 2010	April 2010	
Potency testing of cell based immunotherapy medicinal products for the treatment of cancer	Overview of comments Adopted guideline Draft guideline	CHMP/BWP/271475/06	December 2007	May 2008	
Guideline on xenogeneic cell-based medicinal products	Adopted guideline Draft guideline Concept paper	CHMP/CPWP/83508/09	December 2009	January 2010	
Human cell-based medicinal products	Overview of comments Adopted guideline Draft guideline	CHMP/410869/06	June 2008	September 2008	



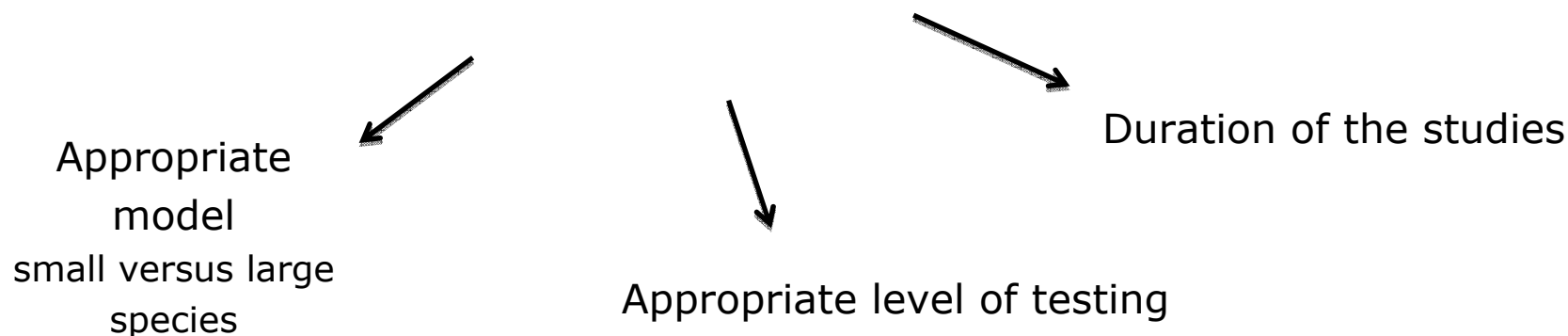
# Cell based products: main risks

- infections
- loss of function
- immunogenicity
- tumourigenicity
- ectopic engraftment



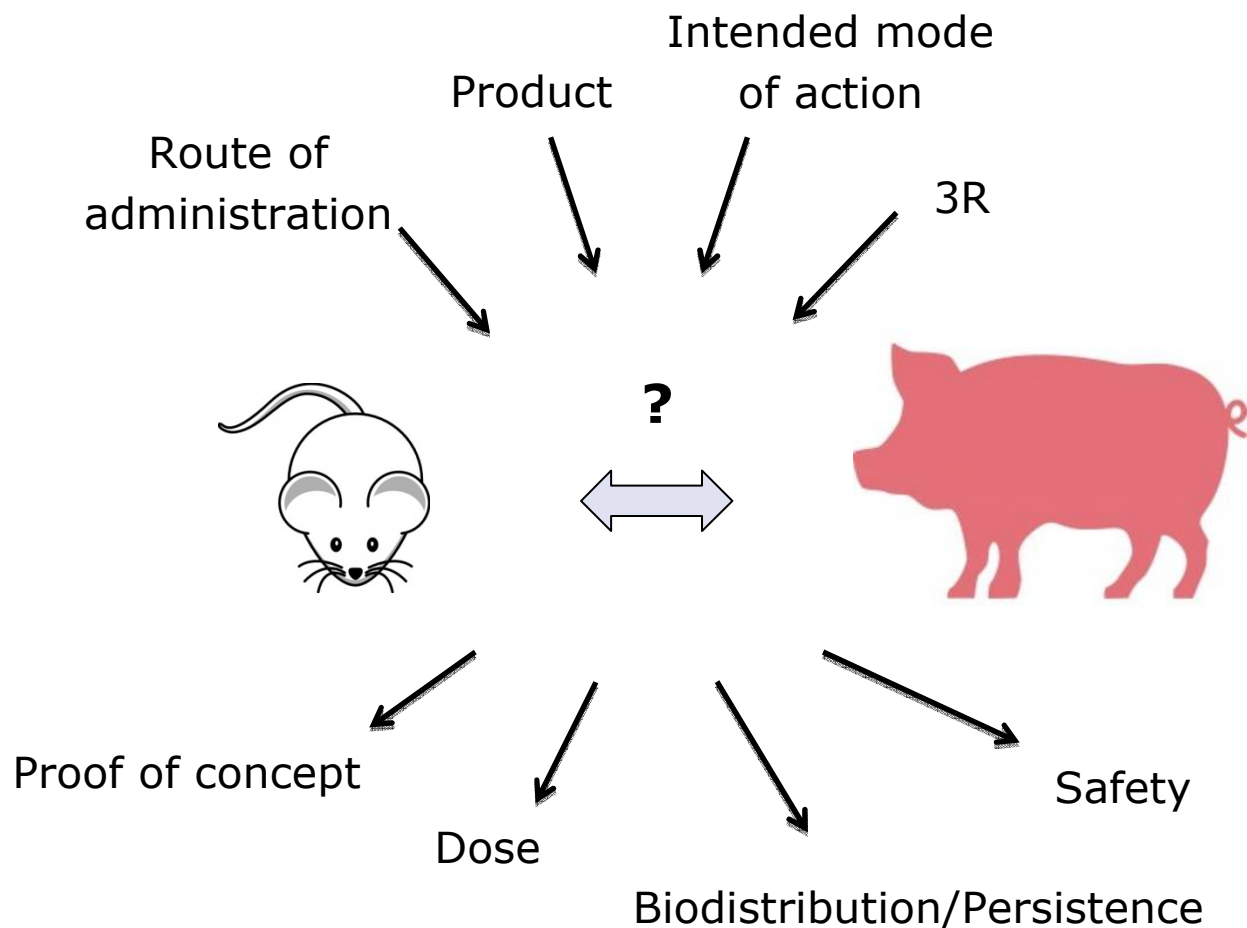
# Non-clinical questions

- 1- **Proof of concept** and **dose-finding** studies
- 2- **Biodistribution/migration and persistence** of the cells in the body
- 3- **Safety studies**: general organ toxicity, tumourigenicity...





# Non-clinical issues





# Non-clinical questions



UMC Utrecht



## Animal models of ischemic heart disease for biologics evaluation

Steven A.J. Chamuleau, MD, PhD

*Cardiologist*



# Large animal models : pros and cons

## Pro

- Proof of concept
- Safety, feasibility
- Training



Route of administration  
Allogeneic versus autologous  
Use of specific medical devices ...

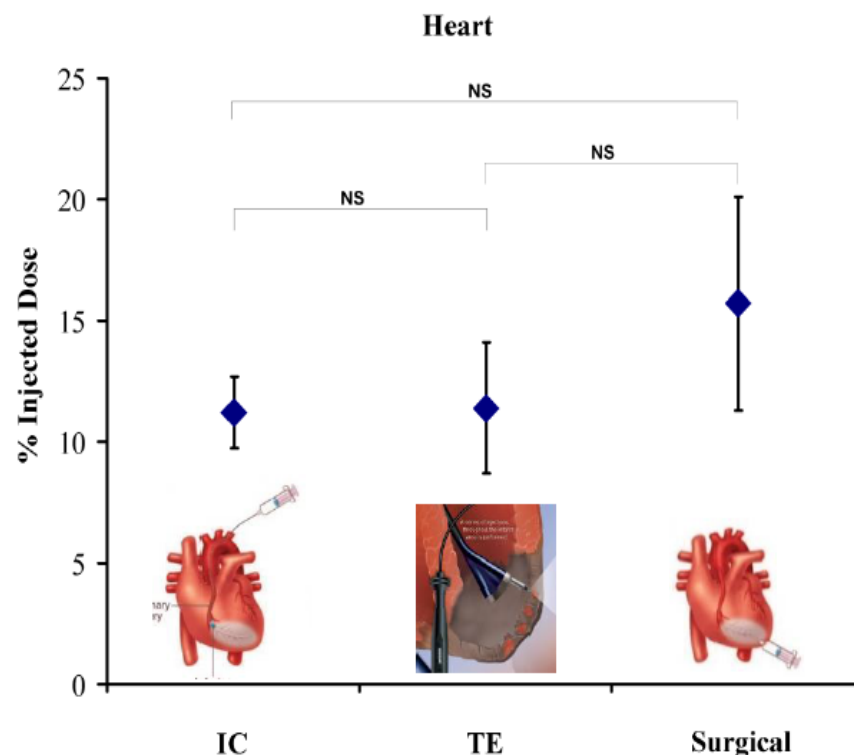
## Con

- Healthy young animals
- Laborious and expensive



# Method of cell delivery

## Porcine model of ischaemic cardiomyopathy



*van der Spoel, et al, JCM 2012; 91(4): 649-658.*



# Non-clinical models: meta-analysis



Cardiovascular Research (2011) **91**, 649–658  
doi:10.1093/cvr/cvr113

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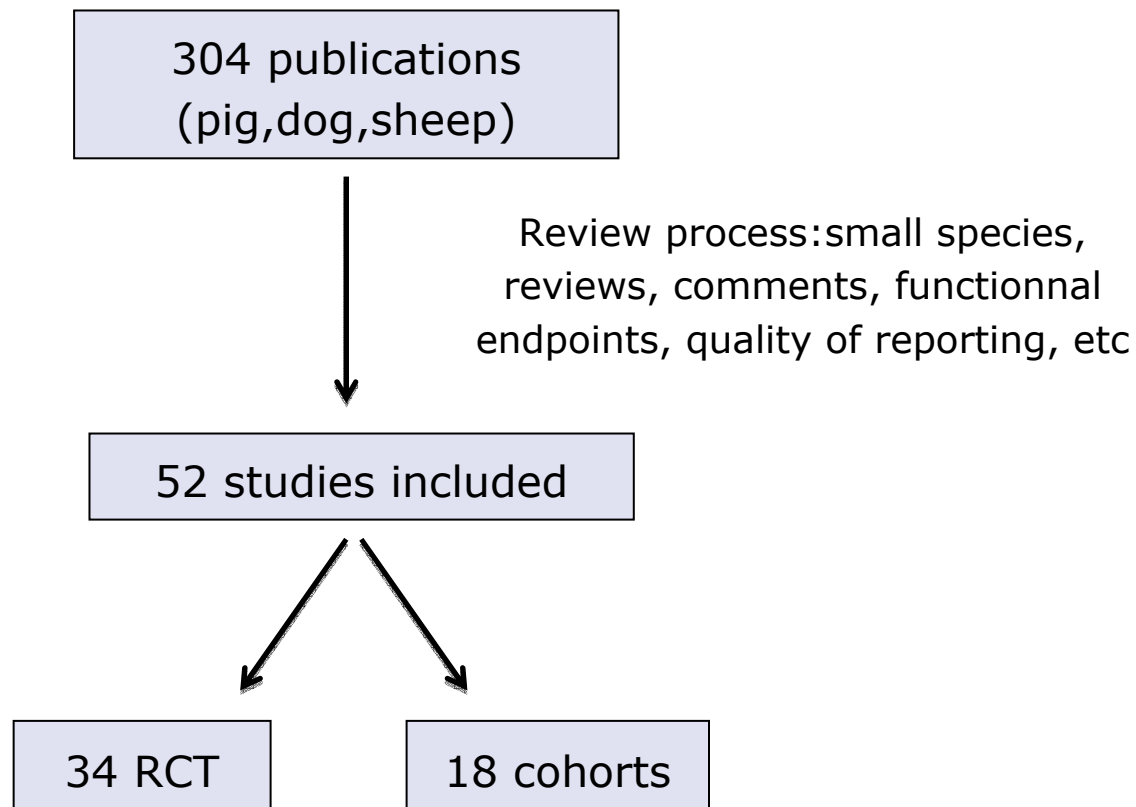
## **Human relevance of pre-clinical studies in stem cell therapy: systematic review and meta-analysis of large animal models of ischaemic heart disease**

**Tycho I.G. van der Spoel<sup>1\*</sup>, Sanne J. Jansen of Lorkeers<sup>1</sup>, Pierfrancesco Agostoni<sup>1</sup>, Eric van Belle<sup>1</sup>, Mariann Gyöngyösi<sup>2</sup>, Joost P.G. Sluijter<sup>1,3</sup>, Maarten J. Cramer<sup>1</sup>, Pieter A. Doevendans<sup>1,3</sup>, and Steven A.J. Chamuleau<sup>1</sup>**

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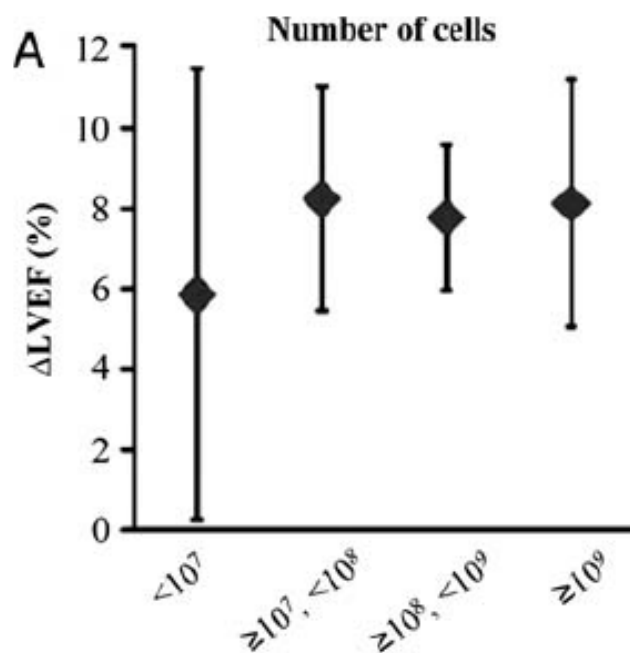


# Non-clinical models: meta-analysis





# Results



- Results RCT = comparable to clinical meta-analysis
- No increased mortality
- Effect fading away after 8 weeks
- Type of cell
- Timing of treatment



# Cell type

- 82 controlled preclinical trials (1415 animals)
- unmanipulated stem cells
- large animal models

[Circ Res.](#) 2014 Sep 3. [Epub ahead of print]

**Similar Effect of Autologous and Allogeneic Cell Therapy for Ischemic Heart Disease: Systematic Review and Meta-Analysis of Large Animal Studies.**

[Jansen Of Lorkeers SJ](#)<sup>1</sup>, [Eding JE](#)<sup>1</sup>, [Vesterinen HM](#)<sup>2</sup>, [van der Spoel TI](#)<sup>1</sup>, [Sena ES](#)<sup>2</sup>, [Duckers HJ](#)<sup>1</sup>, [Doevendans PA](#)<sup>1</sup>, [Macleod MR](#)<sup>2</sup>, [Chamuleau SA](#)<sup>3</sup>.



# Conclusions

- Large species are relevant for translational research
- Interests and limitations of metanalysis:
  - Publication bias
  - Incomplete data set
  - Variety of protocols

⇒ CAMARADES [www.camarades.info](http://www.camarades.info)

⇒ [www.preclinicaltrials.eu](http://www.preclinicaltrials.eu)

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