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What I think about when I talk about NAMs

Considerations on evidence generation for achieving regulatory acceptance of NAMs

Peter van Meer (EMA NcWP, MEB)

Disclaimer

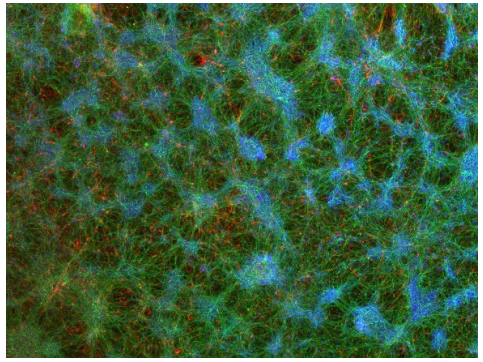
The content in this presentation is the opinion of the speakers and should not be understood as the opinion or position of the EMA, MEB or any of its committees or working parties.

Table of contents

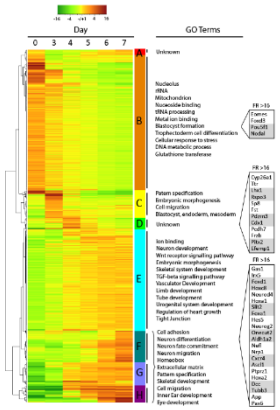
- Why NAMs and what are they?
  - Definitions
  - How to achieve regulatory acceptance?
- Regulatory acceptance, what is it, when is it needed and how should this be achieved?
- Requirements and building blocks towards regulatory acceptance of NAMs
- EMA procedures supporting regulatory acceptance
  - Qualification procedure
  - Other mechanisms
- Demonstrating scientific validity of a NAM: case example

New Approach Methods in regulatory drug development and safety testing

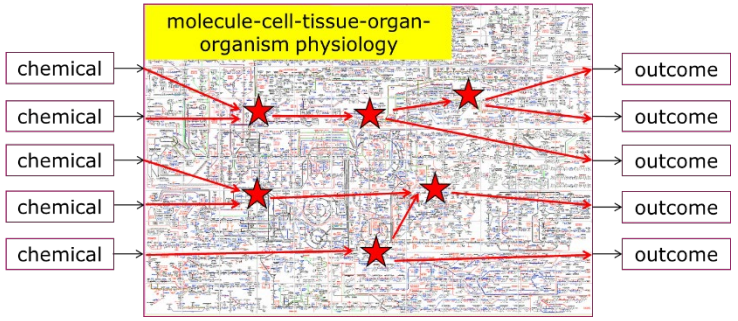
Whole slide Imaging



X-OMICS



AOPs

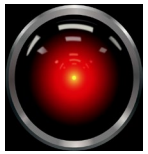


AI/ML

Machine Learning for Toxicity Prediction Using Chemical Structures: Pillars for Success in the Real World

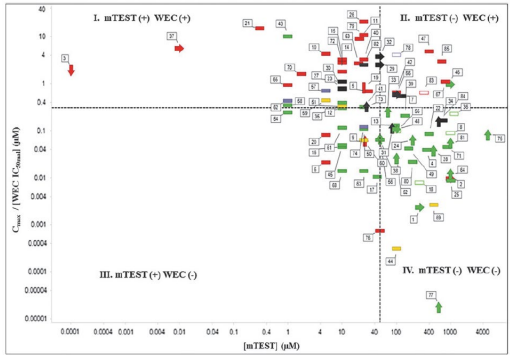
Srijit Seal,* Manas Mahale, Miguel García-Ortegón, Chaitanya K. Joshi, Layla Hosseini-Gerami, Alex Beatson, Matthew Greenig, Mrinal Shekhar, Arijit Patra, Caroline Weis, Arash Mehrjou, Adrien Badré, Brianna Paisley, Rhiannon Lowe, Shantanu Singh, Falgun Shah, Bjarki Johannesson, Dominic Williams, David Rouquie, Djork-Arné Clevert, Patrick Schwab, Nicola Richmond, Christos A. Nicolaou, Raymond J. Gonzalez, Russell Naven, Carolin Schramm, Lewis R Vidler, Kamel Mansouri, W. Patrick Walters, Deidre Dalmas Wilk, Ola Spjuth,* Anne E. Carpenter,* and Andreas Bender*

Cite This: *Chem. Res. Toxicol.* 2025, 38, 759–807 Read Online

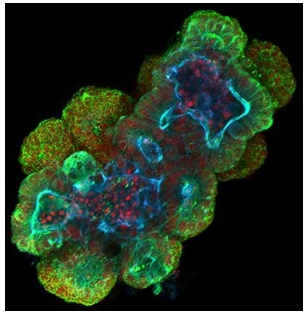


Alt vivo models

Tiered approach
Testing Batteries

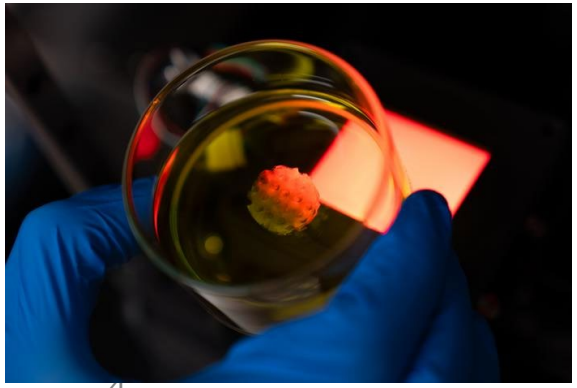


Organoids

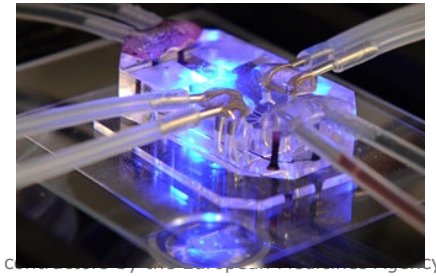


Ex vivo models

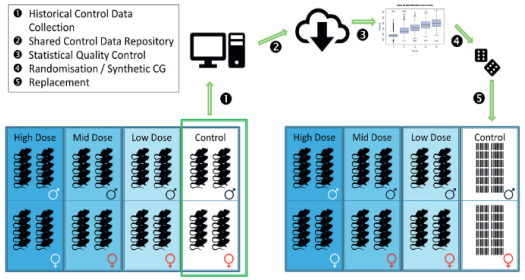
Printed/complex 3D tissue models



Organ on Chip

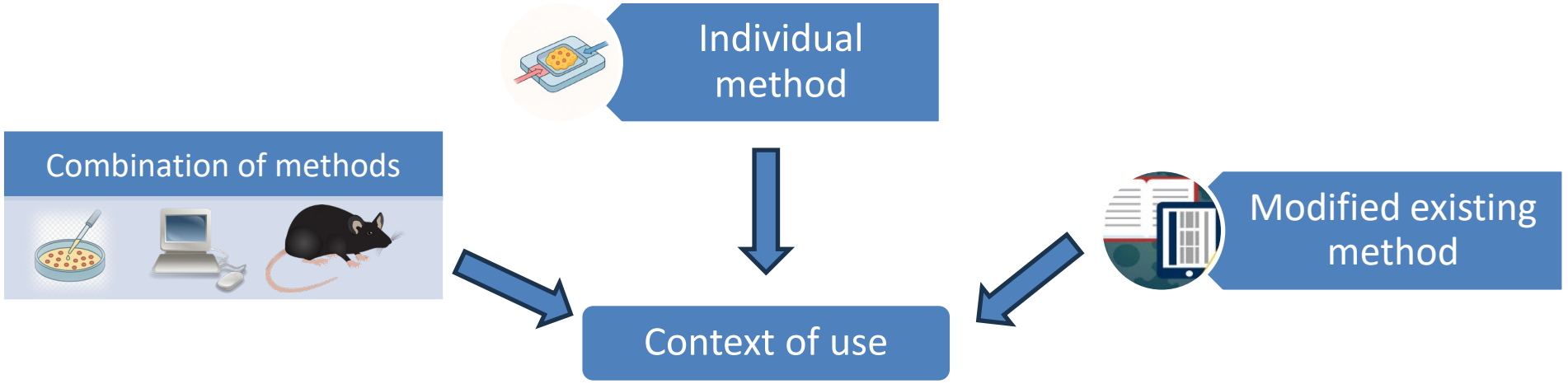


Virtual control animals

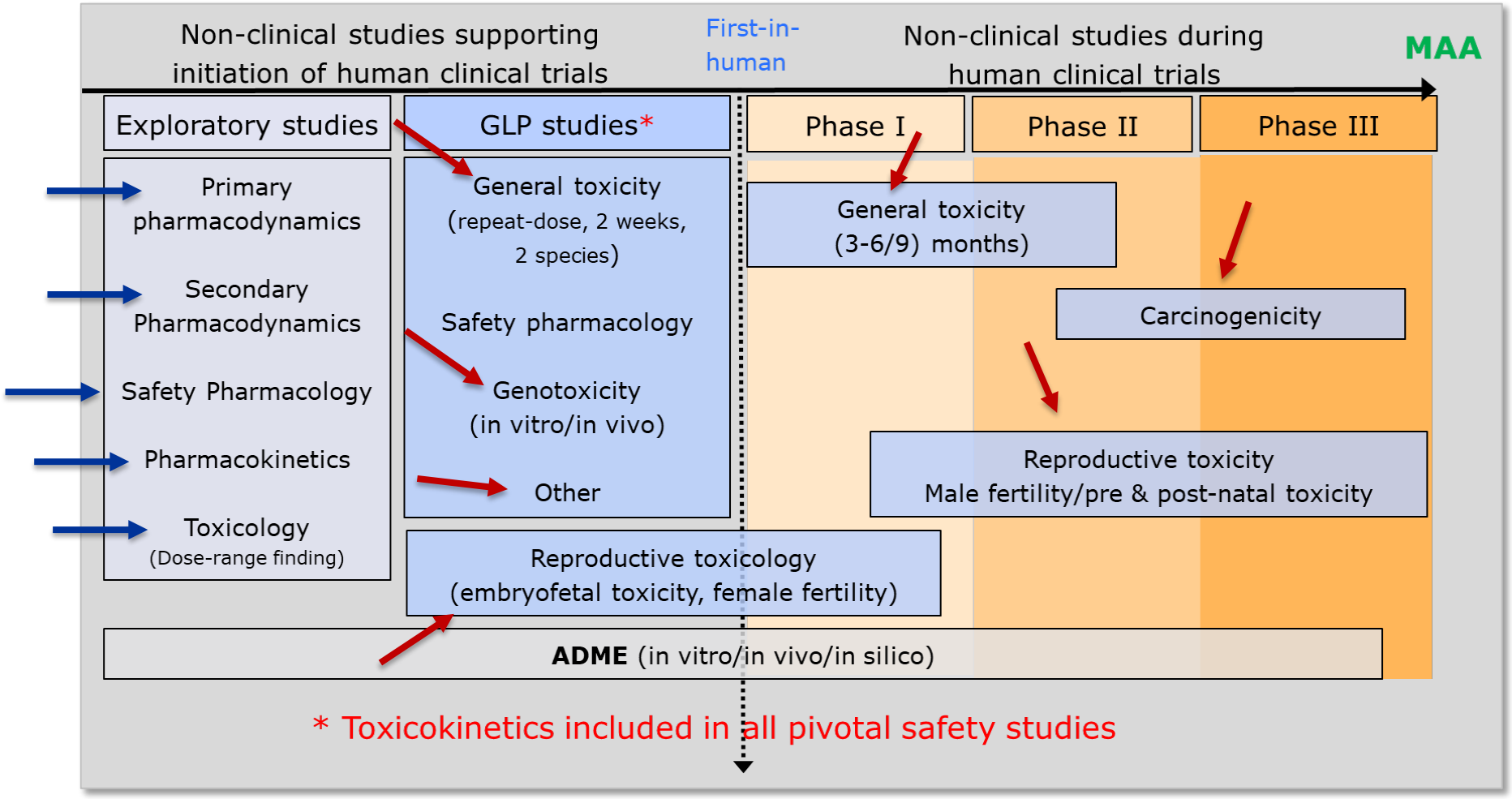


What is a NAM?

- **New Approach Methodologies (NAMs) are innovative test methods or testing approaches aimed to progressively replace, reduce, and refine (3Rs) traditional animal studies.** *These include in vitro, in silico, in chemico, ex vivo, refined in vivo and other advanced biology-based approaches and* ***structured combinations of these in a Weight of Evidence approach***
- NAMs are designed to generate data that provide an equivalent or improved translation (as compared to current test methods) to **support** human or target species-relevant **regulatory decision making**.



Where are NAMs accepted by Health Authorities?



What is Regulatory Acceptance?

Regulatory acceptance refers to the official recognition by a regulatory authority (such as the EMA) that a method, tool, or dataset is scientifically valid and suitable for use in regulatory decision-making

Context-of-Use

A CoU defines the specific intended application of a NAM in the development or regulatory assessment of medicinal products, and the conditions under which it can inform regulatory decision making.

NAM data as part of a Weight-of-Evidence approach

- Evaluation of information from several sources supports decision making
- Weight given to available evidence depends on:
  - robustness/reliability of data sources
  - data quality, consistency of results, nature & severity of effects, relevance of info
- Use of scientific judgment
- Integration of NAM data!


ICH Member

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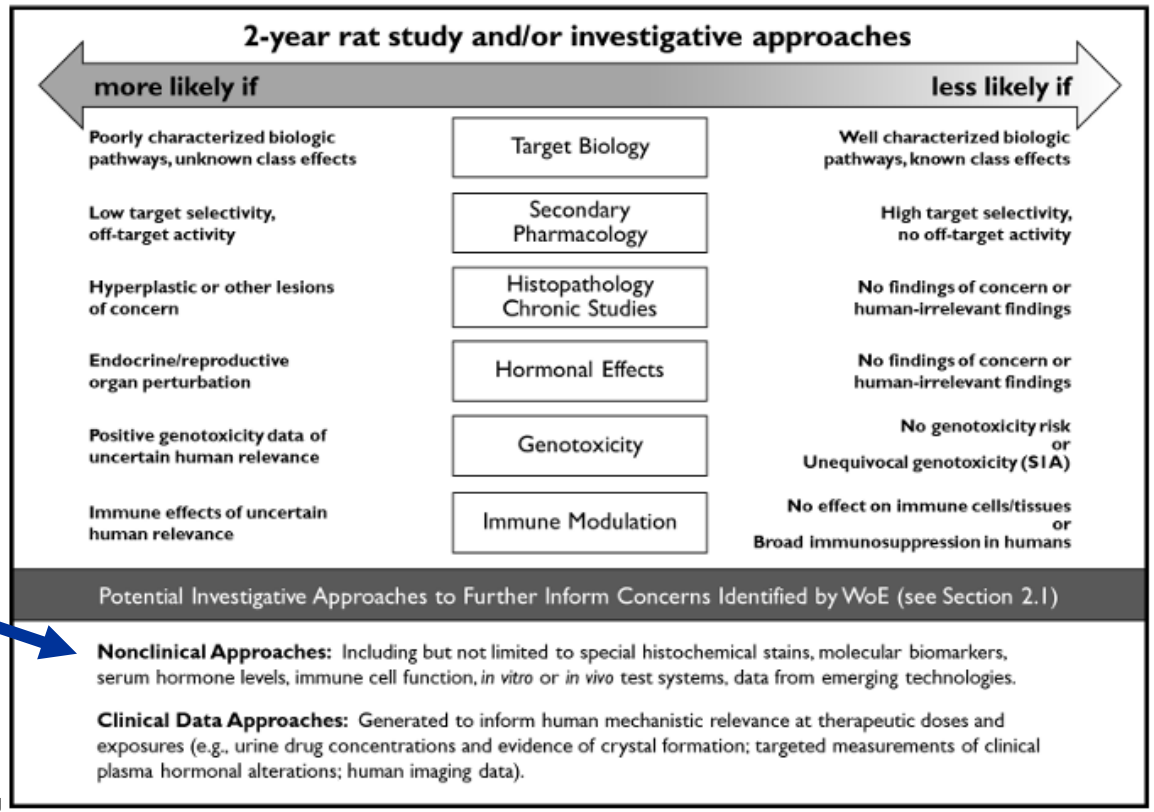
16 September 2022
EMA/774371/2022
Committee for Medicinal Products for Human Use

ICH guideline S1B(R1) on testing for carcinogenicity of pharmaceuticals

Step5



Context of Use: trickiest to get right

Biological Plausibility

Relationship of test method to endpoints and how these translate to a biological outcome

Context of Use

Regulatory use or decision context in which the NAM is intended to be applied

Limitations

Explicitly state what is out of scope for the test method/CoU

Stage of development

Discovery, FIH, late clinical development, MAA

Test method

SOP with basic biological and technological characterisation as well as primary endpoints measured

Applicability domain

Justification of what type of products fall in scope for use in the test method

Determining Scientific Validity within the CoU

Description of Test Method

- Overview of primary endpoints
- Proposed use of the method
- Mechanistic basis and relationship to Eps (e.g. functional, empirical)
- History of the use of the test method

Test method reliability

Extent that a test method can be performed reproducibly over time using the same SOP

Test method Validity

Reference compounds

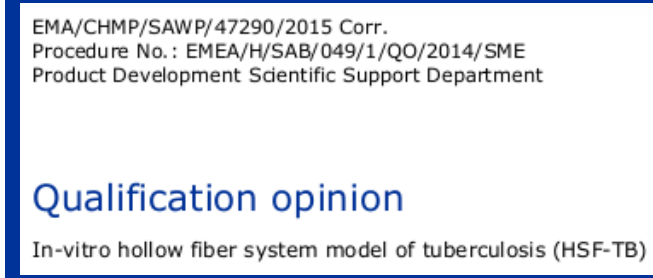
Curated, well-characterised set of molecules with known and reproducible biological, toxicological, or pharmacological effects that are used to benchmark and qualify a test method or model

Test Method relevance

- Performance assessment over range of biological/chemical applicability domains
- Extent to which method predicts EPs based on **reference compounds**
- Demonstration of accuracy, sensitivity, specificity

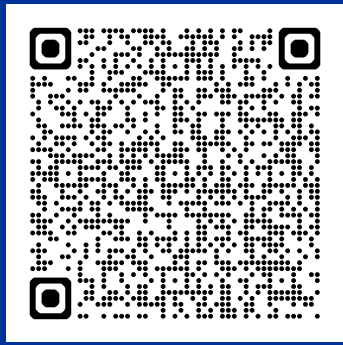
Non-clinical **efficacy** versus safety: Regulatory expectations differ

- Scientific approaches to evaluate **Mode of Action** and **Proof of Concept** (efficacy) of a drug are commonly accepted
  - Not captured in guidelines or legislation by design.
  - Early in development or fundamental research, academic and strategic **freedom**
    - Type I error (Suggesting efficacy when there isn't)
- **No barriers to regulatory acceptance** for MoA and PoC beyond **scientific validity**
- But for regulatory acceptance of **clinical efficacy** markers, **qualification is needed**


EMA/CHMP/SAWP/47290/2015 Corr.
Procedure No.: EMEA/H/SAB/049/1/QO/2014/SME
Product Development Scientific Support Department

Qualification opinion

In-vitro hollow fiber system model of tuberculosis (HSF-TB)

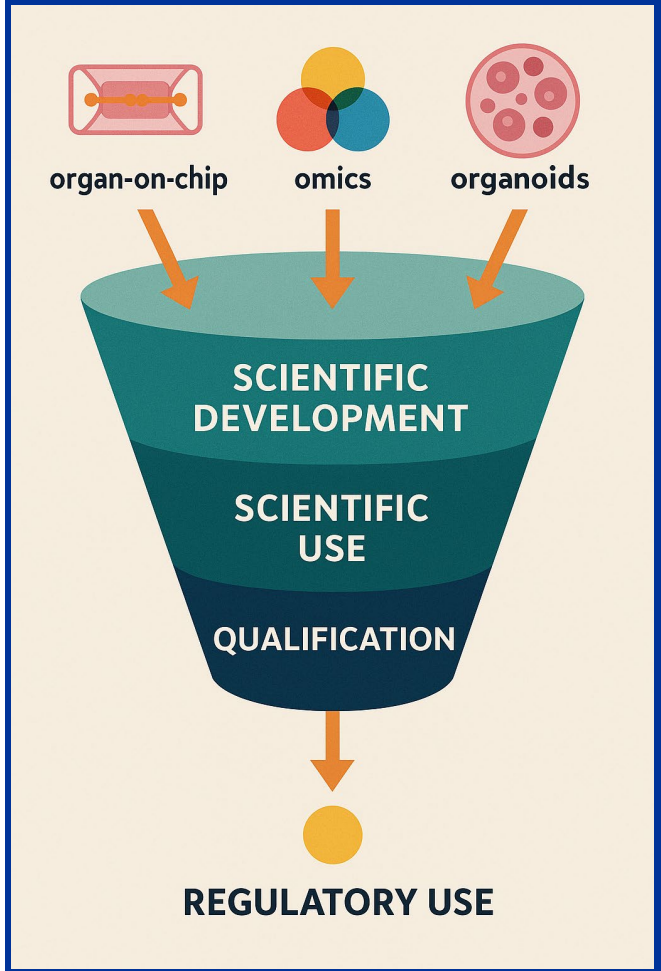


PKPD antibiotics in TB patients

Dose selection clinical trials

Non-clinical efficacy versus **safety**: Regulatory expectations differ

- Safety evaluation is captured in detailed global guidance
  - Type II error: NAM suggests safety when it is not
- **No need for regulatory acceptance if**
  - Used for in-house screening and lead selection
  - Used to supplement safety studies (e.g. mechanistic investigation)
- NAMs as a primary source of safety evaluation requires **regulatory acceptance**, demonstrating **scientific validity** within a well defined **Context of Use** (minimising Type 1 and 2 errors).



Regulatory Acceptance

- Not all NAMs have to be qualified for use!
- Dependent on application and context of use
- Likely needed for broad NAMs applications

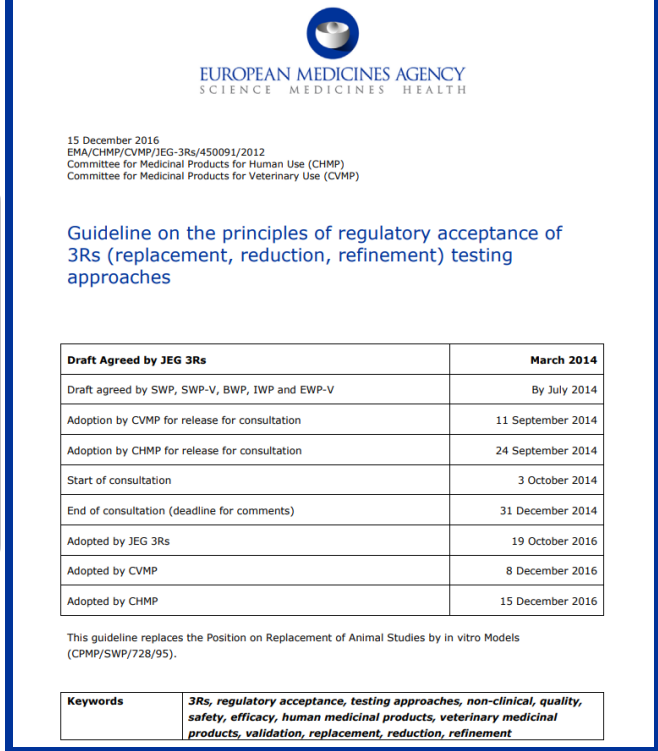
- Evaluated ba… …ent and relevance to the medicinal product and target indication.

2. Qualification procedure at EMA

- A formal EMA process to assess and endorse a novel method for a specific use in the development of a medicinal product.
- Provides early scientific advice and regulatory endorsement for broader application

3. Integration into Guidelines

- NAMs can be incorporated into official guidance (e.g., ICH, EMA guidelines).



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15 December 2016
EMA/CHMP/CVMP/JEG-3Rs/450091/2012
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches

Draft Agreed by JEG 3Rs	March 2014
Draft agreed by SWP, SWP-V, BWP, IWP and EWP-V	By July 2014
Adoption by CVMP for release for consultation	11 September 2014
Adoption by CHMP for release for consultation	24 September 2014
Start of consultation	3 October 2014
End of consultation (deadline for comments)	31 December 2014
Adopted by JEG 3Rs	19 October 2016
Adopted by CVMP	8 December 2016
Adopted by CHMP	15 December 2016

This guideline replaces the Position on Replacement of Animal Studies by in vitro Models (CPMP/SWP/728/95).

Keywords	*3Rs, regulatory acceptance, testing approaches, non-clinical, quality, safety, efficacy, human medicinal products, veterinary medicinal products, validation, replacement, reduction, refinement*

Regulatory Acceptance

Recognition by a regulatory authority that a method, tool, or dataset is scientifically valid and suitable for use in regulatory decision-making.

1. Case-by-Case Acceptance

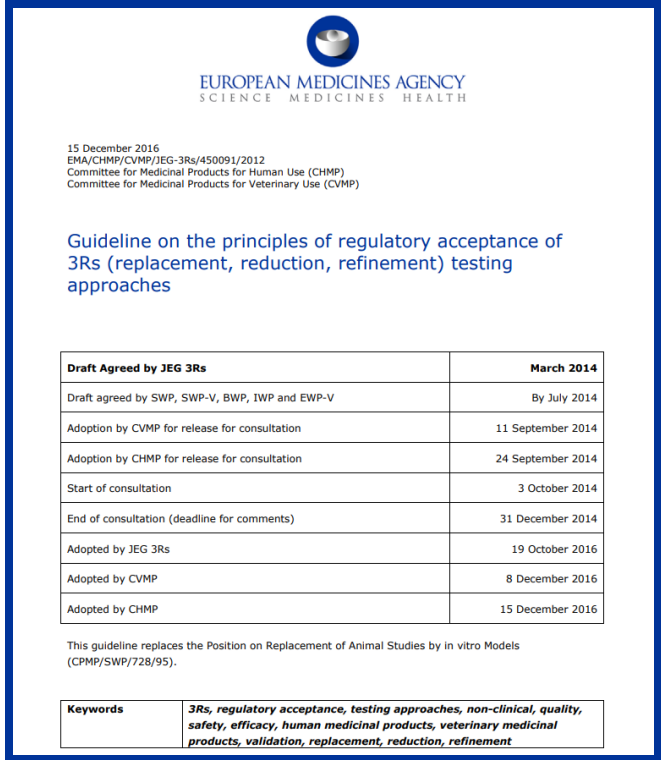
- Used in products submissions (e.g., marketing authorization) for regulatory decision making.
- Evaluated based on scientific merit and relevance to the medicinal product and target indication.

2. Qualification procedure at EMA

- A formal EMA process to assess and endorse a novel method for a specific use in the development of a medicinal product.
- Provides early scientific advice and regulatory endorsement for broader application

3. Integration into Guidelines

- NAMs can be incorporated into official guidance (e.g., ICH, EMA guidelines).



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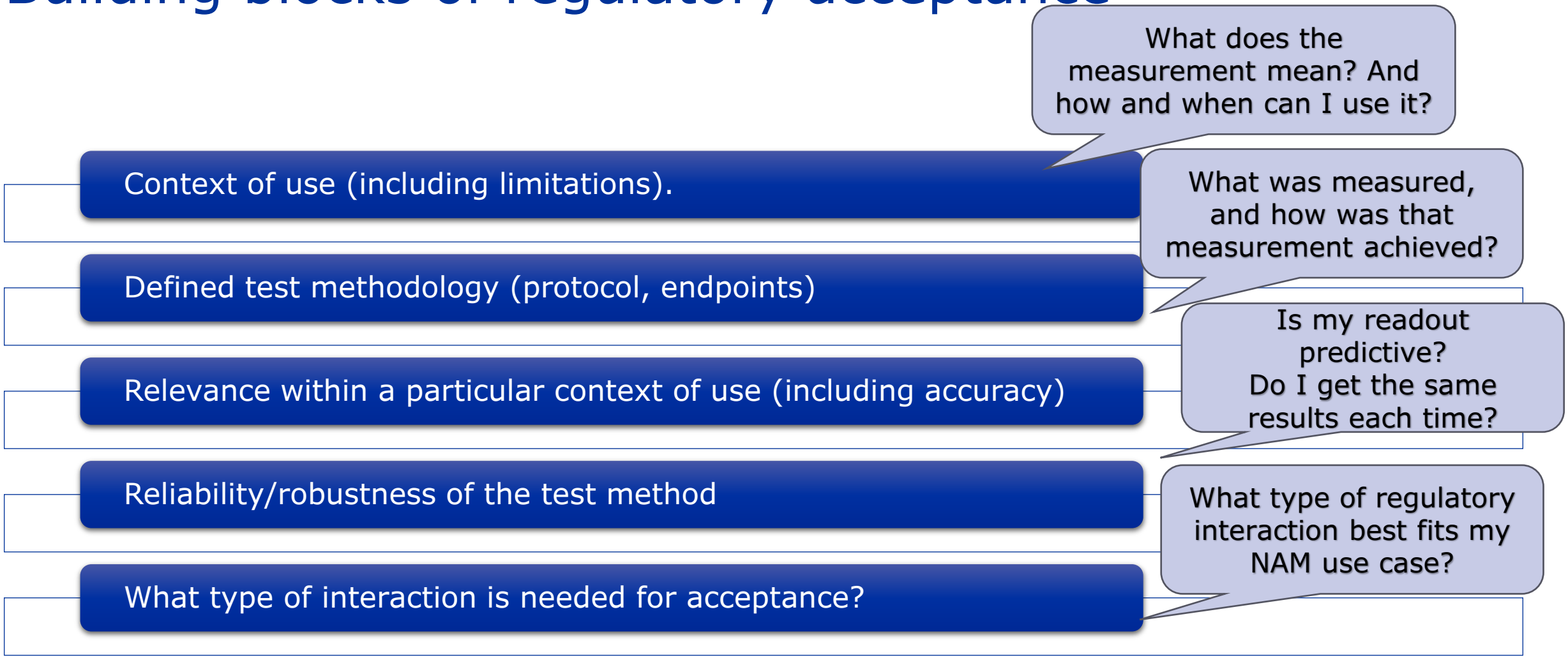
Building blocks of regulatory acceptance



EMA interaction to foster regulatory acceptance of NAMs

Innovation Task Force

- Early Dialogue
- Informal exchange
- Regulatory, technical & scientific topics
- Free of charge

Portfolio and technology meetings

- Pharma companies with large medicinal product portfolios
- Issues impacting portfolio progression
- Anticipate scientific & regulatory needs
- Identify innovative technologies

Scientific Advice

- Product Specific
- Formal scientific guidance

Qualification of a Novel Methodology

- Innovative methods, medicines R&D
- Acceptability of a methodology in a specific context of use

Safe harbour

- Voluntary data submission
- Independent evaluation outside of a formal procedure
- Builds regulatory confidence & experience

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Thank you

Special thanks to:

Stefano Ponzano (EMA)

Regulatory acceptance of 3Rs testing approaches drafting group

Follow us

Open discussion

- Context of Use, WoE approach, scientific validity, regulatory acceptance vs qualification

- Efficacy vs Safety regulatory requirements for NAMs

Any clarification needed? How do you integrate these aspects when developing NAMs?

What are the challenges you face when developing a NAM for regulatory decision making?

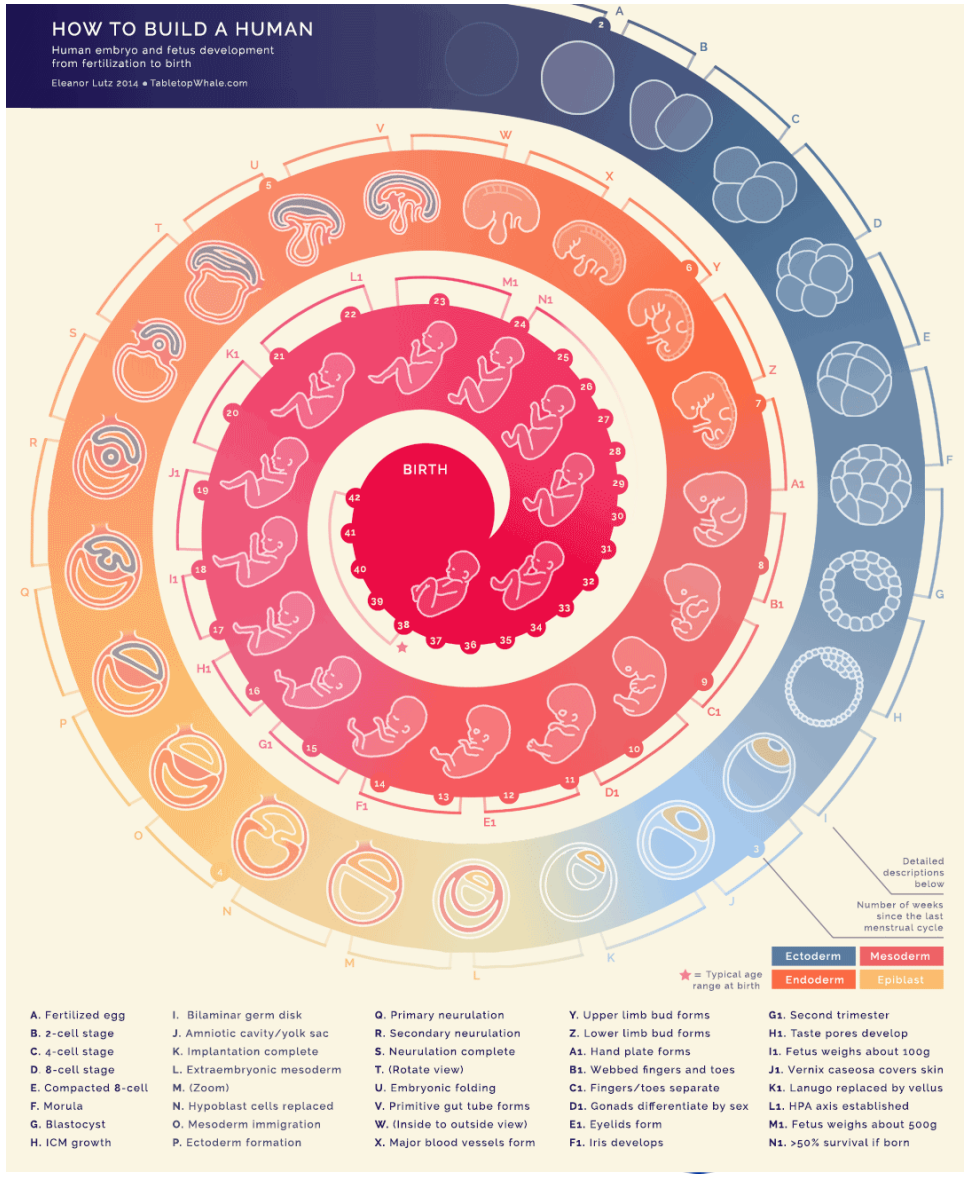
What has been your experience interacting with regulators, including EMA, during the development or qualification of a NAM?

How can regulators and the academic community better engage with each other to support the uptake of NAMs?

Case study

Reproductive and developmental safety (ICH S5)

- Evaluation of the effects of a drug on one complete life cycle from conception in one generation through conception in the following generation
- GLP compliant studies
  - Fertility and Embryofetal Development (FEED)
  - Embryofetal Development (EFD)
  - Pre- and Postnatal development
- ICH S5 allows NAMs under a specific CoU and includes basic requirements for qualification



https://eleanorlutz.com/human-development

Qualification Criteria using an EST as an example

*Description and justification of predictive model (**Context of Use**)*

- Demonstration that mouse Embryonal Stem cells can be **inhibited from differentiation to cardiomyocytes**, which is a **surrogate for MEFL in rodent**
- Evaluates toxicity during **embryofetal development**
- Use of **small molecule pharmaceuticals** as potential inhibitors may **predict human teratogens**
  - **Not** for biologics (limitation)
- **Outcome supports Phase I/II, Confirms known MoA, supports SDLT indications or when animal studies are not feasible**

EMA

Qualification Criteria using an EST as an example

An assessment of the accuracy and ability for the alternative assay to detect MEFL (Fit-for-purpose)

- Using a defined protocol to provide:
- Statistical evidence to predict MEFL in a species (accuracy, prediction, sensitivity, specificity etc.)
- Using a **reference compound list** of known or suspected human teratogens, expanded by training sets / test sets based on exposure data


Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Analysis of exposure margins in developmental toxicity studies for detection of human teratogens

Paul A. Andrews[a,*], Diann Blanset[b], Priscila Lemos Costa[c], Martin Green[d], Maia L. Green[e,1], Abigail Jacobs[d], Rajkumar Kadaba[f], Jose A. Lebron[e], Britta Mattson[e], Mary Ellen McNerney[g], Daniel Minck[d], Luana de Castro Oliveira[c], Peter T. Theunissen[h], Joseph J. DeGeorge[e,2]

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