CBG MEB

MEDICINES EVALUATION BOARD

Regulatory acceptance and context-of-use-qualification: regulatory definitions and needs

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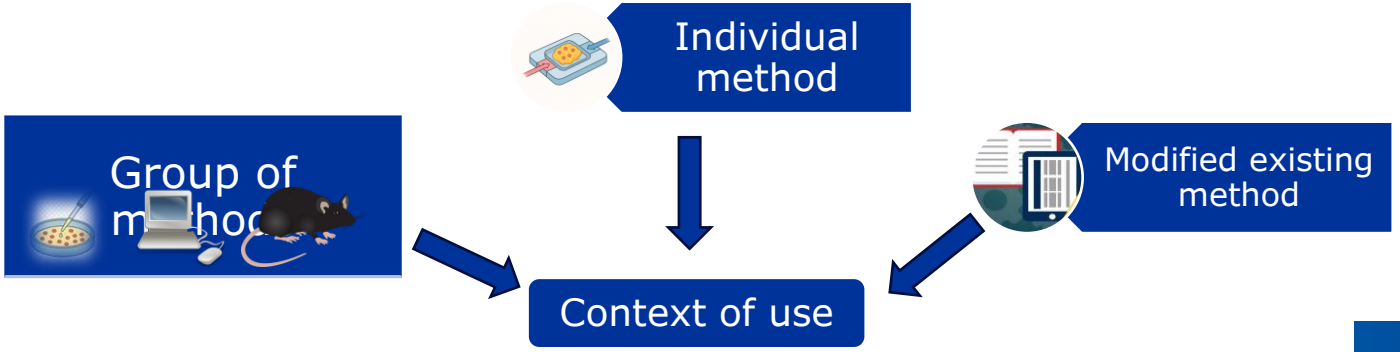
Regulatory acceptance of NAMs: definitions

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*.

NAMs: New Approach Methodologies" (NAMs) are defined as **innovative methods** and **strategies** that aim to **replace, reduce, or refine the use of animals** in the testing of medicinal products, aligning with the 3Rs principles. These methodologies encompass a range of non-animal approaches, including simple and complex human cell-based assays, **microphysiological systems**, in silico modelling and other non-human or human biology-based test methods.



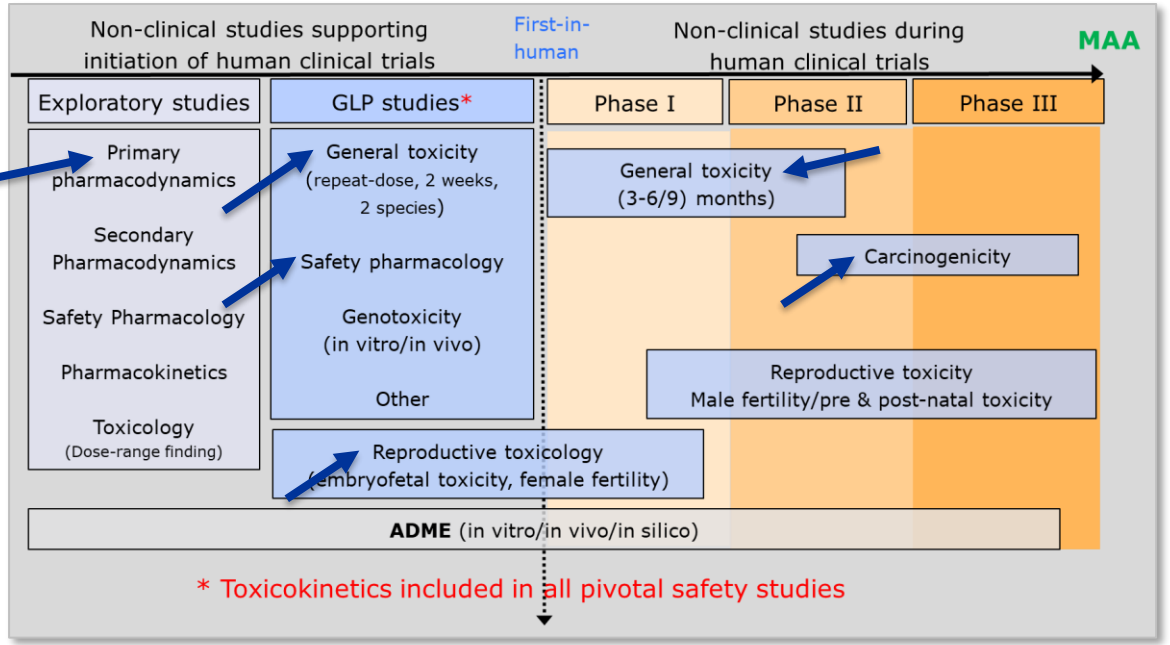
Context of use (CoU)

What specific endpoint is used to predict (human) safety aspects of specific medicines and the conditions under which it can inform regulatory decision making.

Furthermore, a CoU should:

-Define the biological and chemical applicability domain

-Establish boundaries and limitations of the above to ensure the NAM is applied in scope



Regulatory acceptance criteria are driven by the COU

Regulatory use of NAMs is diverse:

- *Integration in Weight-of–Evidence approaches (e.g. ICH S1B(R1))*
- *Part of integrated testing strategies (Q&A ICH S7B/E14)*
- *Very limited 1-to-1 replacement*

Fit for purpose

- Does the method provides data of sufficient quality, reliability, and relevance to support a specific regulatory or scientific decision

To consider:

- Biological plausibility to describe **how** the NAM reflects or predicts biological- processes, mechanisms, or effects that are meaningful for human or animal health outcomes
- Chemical domain to identify **what** molecules can be used in the NAM based on predefined characteristics (e.g. transporter affinity, physicochemical characteristics, MoA, modality, etc.)
    - Use of reference compound lists (identified and broadly accepted positives and negatives)
    - Use of test sets/training sets to demonstrate overall performance
- Performance assessment of the NAM that characterises conditions that cover an appropriate range of biological and chemical domains.

How to achieve Regulatory Acceptance?

1. Integration into Guidelines

- NAMs can be incorporated into official guidance (e.g., ICH, EMA guidelines).
- Example: *ICH M7* allows use of (Q)SAR models for mutagenicity assessment of impurities.

2. 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.

3. 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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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*

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

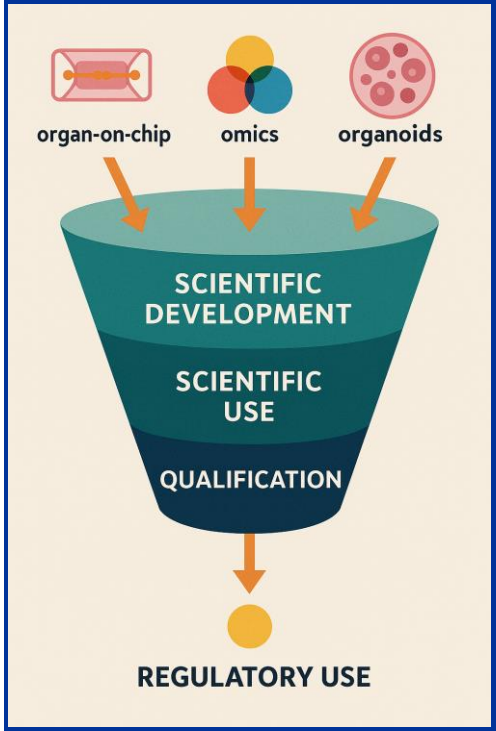
- Scientific approaches to evaluate **Mode of Action** and **Proof of Concept** (efficacy) of a drug are commonly accepted
  - Not captured in guidelines or legislation by design.
  - Early in development or fundamental research, academic and strategic **freedom**
    - Type I error (Suggesting efficacy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

19 December 2022
EMADOC-1700519818-946771
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion for the iBox Scoring System as a secondary efficacy endpoint in clinical trials investigating novel immunosuppressive medicines in kidney transplant patients

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 Fit for Purpose within a well defined Context of Use (**minimising Type 1 and 2 errors**).



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

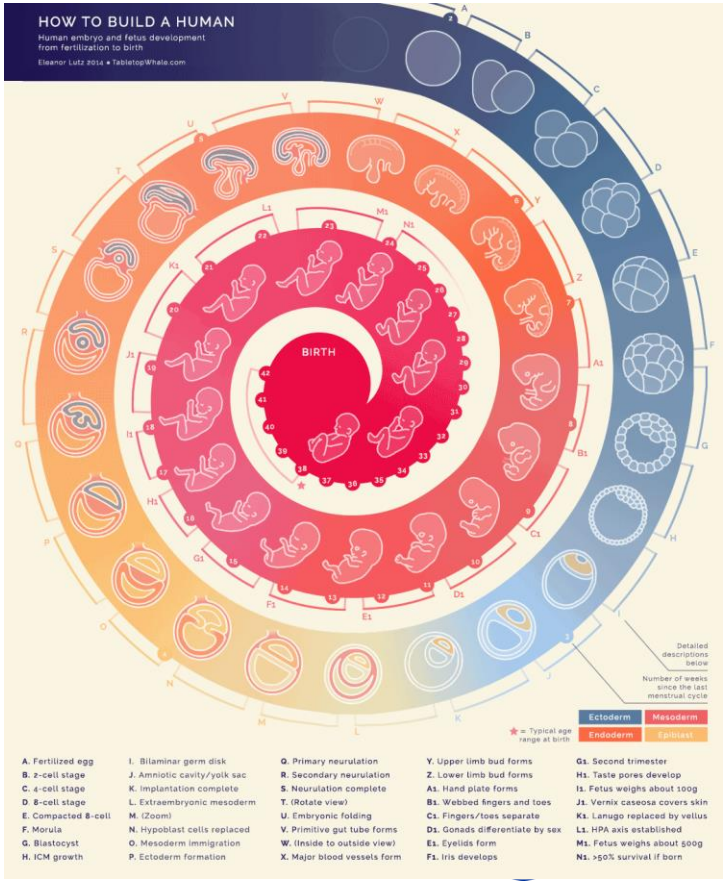
Safe harbour

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

Case study – NAMs for reproductive and developmental toxicity testing

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)
    - Typically in rodent
  - Embryofetal Development (EFD)
    - Rodent and non-rodent studies (rat+rabbit, NHP if justified)
  - Pre- and Postnatal development
    - Typically in rodent
    - NHP if justified (can alter design)



https://eleanorlutz.com/human-development

The promise of ICH S5(R3)

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18 February 2020
EMA/CHMP/ICH/544278/1998
Committee for Medicinal Products for Human Use

ICH S5 (R3) Guideline on detection of reproductive and developmental toxicity for human pharmaceuticals

- A guidance allowed the use of NAMs to evaluate developmental toxicity
  - To support **Phase I + II clinical trials**
  - No additional studies for products that do not reach Phase III !
  - To confirm known teratogenic MoA (WoE)
  - Support SDLT indications
  - Provide data when animal studies are not feasible
- **Provided basic requirements for qualification**

Annex 2 Alternative assays

Data generated from qualified alternative assays (see glossary) conducted alone or in conjunction with one or more *in vivo* studies can be utilized to support hazard identification and risk assessment under limited circumstances.

Potential uses can include:

- circumstances where there is evidence suggesting an adverse effect on EFD (e.g., a mechanism of action affecting fundamental pathways in developmental biology, phenotypic data from genetically modified animals, class effects) (see Section 1.2.2 and Figure 1 of this Annex)
- toxicity in animal species precludes attaining systemic exposures relevant to the human exposures under conditions of use
- as support for a weight of evidence assessment when there are equivocal findings in animal studies
- as partial support for clinical trials including up to 150 WOCBP for up to 3 months duration (see Section 4.2.3 of Guidance)
- pharmaceuticals being developed for certain severely debilitating or life-threatening diseases or late-life onset diseases (see Sections 1.2.3, 1.2.4 and Figure 2 of this Annex).

When alternative assays are used to support risk assessment, incorporation of these assays into an integrated testing strategy should be justified. Assay(s) used for risk assessment should be conducted in accordance with GLP and qualified for context of use (i.e. applicability domain and regulatory conditions under which assay results are reliable). Strategies incorporating alternative assays should also assess the effects of drug metabolites when warranted (ICH M3). This annex does not recommend specific assays; instead, basic scientific principles are included to assist in assay qualification for regulatory use. Alternative assays used to explore mechanism of action, or otherwise not intended to substitute for *in vivo*-derived EFD endpoints, are not expected to be qualified in this rigorous manner.

1.1 Qualification of alternative assays for prediction of MEFL

Test methods must be appropriate in order for test results to be of value. Accordingly, the endpoints measured should be scientifically justified with respect to assay objectives and predictions. The relationships among the assay's predictions, endpoint(s) assessed, and the applicability domain, should be supported empirically. To qualify[1] an alternative assay or a combination of assays for use in risk assessment for regulatory purposes, a comprehensive description of the methodology and findings should be provided, including the following:

- A thorough description and justification of the predictive model, including which species (e.g., rat, rabbit and/or human) and endpoint(s) it is predicting. The currently available *in vitro* alternative assays used for evaluating potential hazards to development are designed to detect MEFL.
- An evaluation of the biological plausibility of the model including a description of the mechanisms of embryo-fetal development (e.g., cell migration, differentiation, vasculogenesis, neurulation, gastrulation) and subsequent developmental adverse effects studied with the model. In addition, any limitations of each of the individual assays should be discussed. The description should include

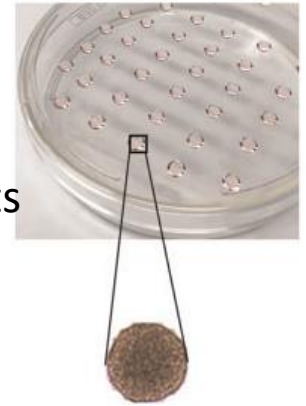
Qualification Criteria using an EST as an example

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

Toxicity of mouse embryoid bodies by small molecules is a predictor of teratogenicity to support phase I/II clinical development, SDLT development or when animal studies are not feasible

Biological applicability domain

Demonstration that mouse Embryonal Stem cells can be **inhibited from differentiation to cardiomyocytes**, which is a **surrogate for MEFL in rodent**



Chemical applicability domain

Small molecule pharmaceuticals (not biologics, *limitation*!) basedon a **RCL** of known or suspected human teratogens, expanded by training sets / test sets based on exposure data

Fit-for-purpose

An assessment of the accuracy and ability to detect MEFL:

- Standardised, well defined defined protocol to provide:
- Statistical evidence (robustness, accuracy, prediction, sensitivity, specificity,…)

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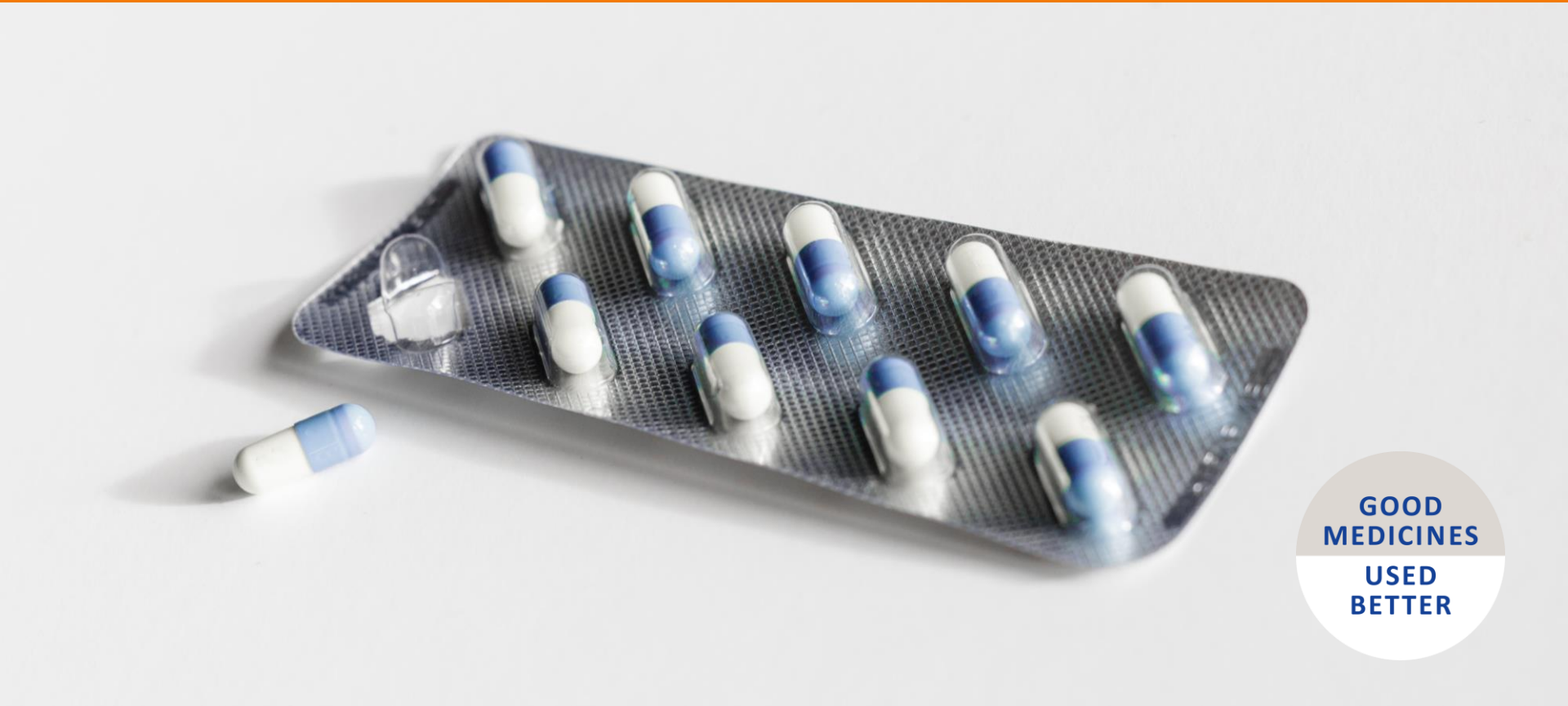

GOOD MEDICINES USED BETTER