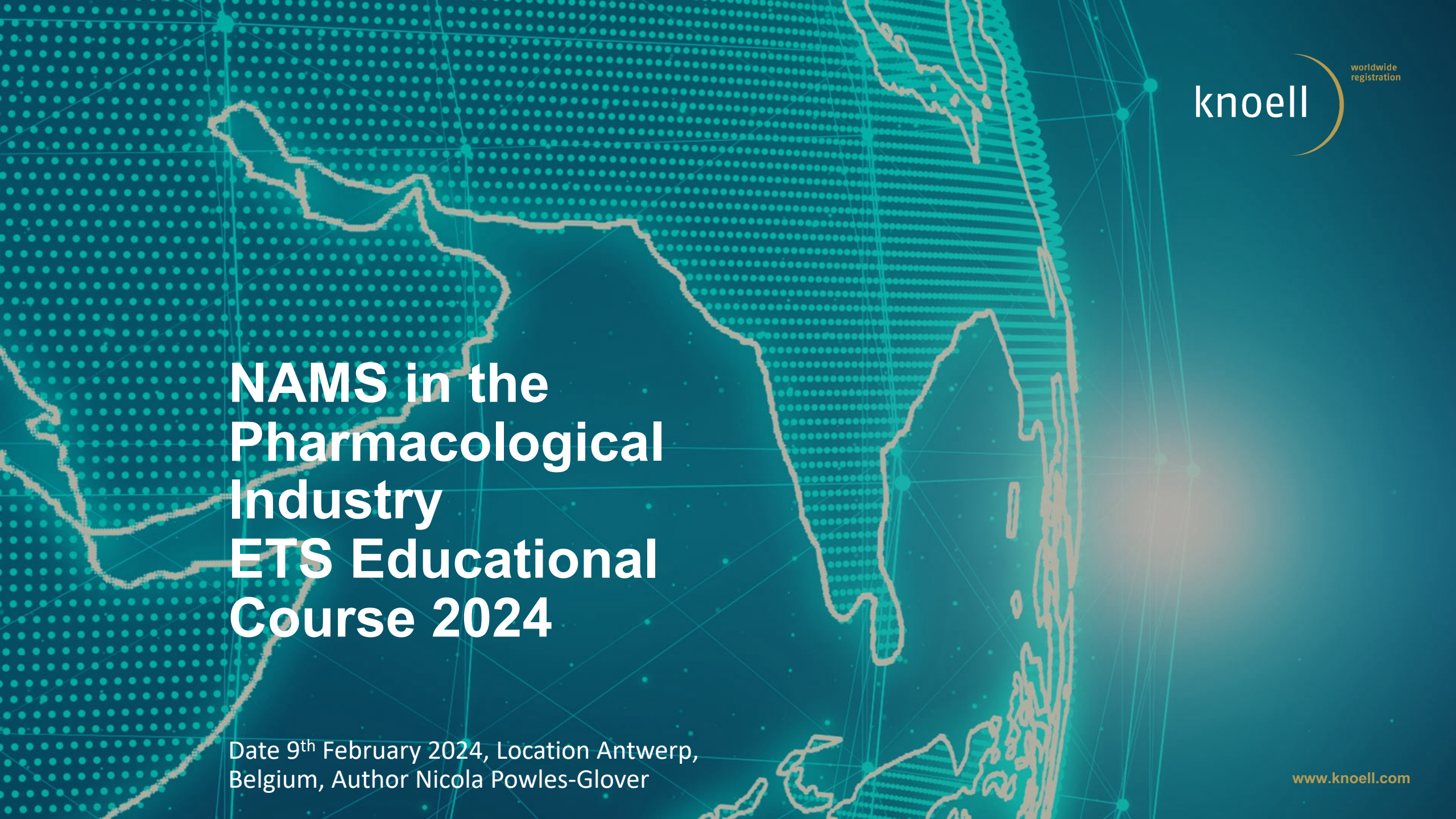

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NAMS in the Pharmacological Industry ETS Educational Course 2024

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NAMS: What are they?

- New Approach methodologies (NAMS) are alternatives to ‘’standard’’ animal models:

- With a potential to replace and/or reduce in vivo animal studies
  - By enabling toxicity assessments in human cells or cell based models
  - By shifting in vivo studies to phylogenetically more primitive species

- NAMS can often provide additional insight into toxicological mechanisms/pathways
  - Can inform on relevance of adverse non clinical findings for human risk assessment

- ICH S5 (R3) guideline introduced the use of NAMS as an alternative to using a second species, or alongside in vivo studies as a weight of evidence and/or to support in vivo studies when investigating mechanism of action

NAMS: Regulatory Acceptance?

- The ICH S5 (R3) Guidelines are recognised globally as the Guideline to use in preparation for acceptance of a DART regulatory package for drug development, submission and registration.

- Regulatory adoption of NAMS based approaches for assessing embryofetal development (EFD), fertility or reproductive endpoints for pharmaceuticals has been challenging due to:
  - Dynamic changes in the conceptus and placenta during development
  - Impact of the agent on the mothers' physiology (e.g. mechanical changes and e.g. blood volume and pressure)

NAMS: What is available?

- Several EFD NAMS have been available since the 1980's
- Have been used by some pharmaceutical companies for more than 20 years
- To name a few, which have been well studied:
  - mEST (mouse Embryonic Stem Cell Test
  - rWEC (rat Whole Embryo Culture)
  - ZEDTA (Zebrafish Embryo Developmental Toxicity Assay)
  - MM (micromass)
  - FETAX (Frog embryo teratogenesis assay-Xenopus)

  - Other in vitro e.g. C. elegans and gastruloid or in silico

  - Human cell based assays available from companies (e.g. Toxys and Stemina)

NAMS: ECVAM and other information

- mEST, rWEC and MM have previously been validated for reproductive and embryo toxicity by the European Centre for the Validation of Alternative Methods (ECVAM)
- Current users of these assays may have modified the (ECVAM) assays to improve predictivity for the individual application
- Further studies using the predictive model for the mEST showed that in a pharmaceutical context of use, the predictivity of the statistical model was greatly reduced
- In the US, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) evaluated the FETAX for developmental toxicity, but concluded the assay showed sensitivity issues and practical constraints and was therefore not adopted
- Many groups have assessed the sensitivity and specificity of the assay, it has not been validated through ICCVAM/ECVAM

Cross Pharma Validation vs in House Qualification

- Cross pharma validation of assays is very time consuming and have an uncertain outcome
- Some groups/companies advocate to move away from a cross-pharma validation paradigm and put more focus in in-house qualification of an assay
- This qualification consists of an internal validation in which the context of use of the assay/assays is clearly defined
- Qualification of assays is also in line with the updated guidance in ICH S5 (R3)

Current Status in the Pharma World: Take Home

- Use of NAMS is advocated in the ICH S5 (R3) Guidance document
- Currently NAMS are used by some companies, their primary use is for screening candidate drugs early in drug development, primarily if the target population are of reproductive age or pregnant
- Regulators/regulatory authorities would appreciate the submission of this data alongside in vivo regulatory studies for a WoE approach to data interpretation (currently very few companies submit this data at all, despite attaining it)
- There is relative reluctance for pharmaceutical companies to use EFD NAMS in a regulatory context despite the fact that the revised ICH S5 (R3) guideline openly provides opportunities to do so.