Workshop on Particle Risk Assessment – June 2025

Toward Scientifically Grounded Criteria for Accepting Historical Toxicology Data

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The Need to Substantiate Historical Data
A view from Industry

- Historical safety studies represent a significant investment for a company, typical data package for a new ingredient averages between 400,000 – 600,000 €
- Requiring companies to completely repeat particular studies to meet evolving guidance creates prohibitive additional costs, inhibits innovation and job creation in the EU
- From the point of the 3Rs for Animal Research, (Replacement, Reduction, and Refinement) it is critical to avoid unnecessary use of additional animal studies
- Finally, repeating studies adds additional time towards approval, resulting in a significant economic loss for an applicant company, in terms of missed sales and loss on patent protection

Validating Historical Toxicology Data

Currently historical toxicology data is assessed primarily on two points

Dispersion

- For ingredients that have a fraction of small/nano particles, did the dispersion technique used at the time:
  - Disperse the product sufficiently so that a fraction of small/nano particles were present in the material used in the evaluation
  - Was the dispersion adequate for all the doses evaluated?

Study selection and Study design

- Appropriate studies for nano material (Ex. Exclusion of AMES study)
- Appropriate sample preparation and/or testing under realistic exposure scenario(s).
- Information on the systemic presence of small/nano particles can be useful for interpreting the study for risk assessment.

A Case for Relevance Over Formalism

Not done according to nano-specific requirements" — this single phrase can invalidate years of safety research.

But what if the data still answers the safety question?

Historical studies are disqualified not for poor science, but for procedural misalignment.

Guidance is evolving — yet applications are judged retroactively.

Historic studies may not follow 2021 Nano Guidance strictly

When is there sufficient information for an adequate risk assessment?

Developing a more nuanced approach to validating historical data

It is critical to come to a system that allows for a more nuanced evaluation of historical data

- Scoring system: weighing different aspects of a historical study
- Guidance on how to integrate additional studies to address gaps, that do not include repeating the study
- Setting minimum criteria for establishing similarity between current and historical batches
  - *Note: Material is the same, dispersion is different*

Can a general scoring system for appraising nano-specific aspects of study internal validity be developed?

A general scoring system can be developed, and it's needed to avoid all-or-nothing judgments:

Parameters: An appropriate weight should be assigned to each parameter

1. Material Characterization
2. Method of dispersion
3. Agglomeration state
4. Exposure Route
5. Dose
6. Target site bioavailability
7. Functional endpoints
8. Evidence from other studies

Scoring application concept:

High validity	– Fully meets criteria and can support nano-relevant
Partial Validity	– Some limitations, however, can be bridged with additional supporting studies
Low validity	– Major gaps - requires repeat or complementary nano-specific studies

Rejecting a study based solely on procedural details — without weighing biological evidence — weakens science.

How to integrate historical toxicological studies in the Weight of Evidence (WoE) risk assessment

Conventional toxicology studies may still provide robust and relevant insight into:

- Systemic toxicity and target organs, which remain valid whether particles are nano or micro
- Genotoxicity, oxidative stress, and inflammation endpoints — shared across size scales
- In vivo barrier interaction (e.g., GI tract..) that can be indicative of nano-behavior when systemic absorption is low
- Realistic exposure

Practical Example of Inclusion

Historic 90-day oral toxicity study

- No formal nano dispersion used
- No systemic absorption, no toxicity or genotoxicity

→Additional studies: we re-made the diet to show a fraction of small particle and good dispersion

Weight of Evidence is not a compliance checklist; it is a structured judgment on whether the totality of available data addresses the biological risk. Historic studies remain valuable when framed with particle characterization and exposure relevance

Minimum criteria for establishing similarity between a present and a historically produced and tested small/nano particulate material

Indeed – Especially if particle morphology hasn't changed!

Some minimum criteria to establish similarity:

1. Same synthetic process
2. Same chemical identity
3. Matching particle size distributions
4. Confirm nano-fraction
5. Post hoc dispersion analysis possible

Not all criteria may be needed equally: apply WoE and fit-for-purpose logic.

In our case, archived samples were re-evaluated:

→ Morphology, surface, and nano-fraction all aligned

→ Only dispersion conditions differed, not the material

Developing a Scientific Approach to Historical Study Assessment

Key points

Validating historical data is important from both an ethical and economical point of view

- High-quality historic data, if contextualized correctly, reduces animal use and cost.

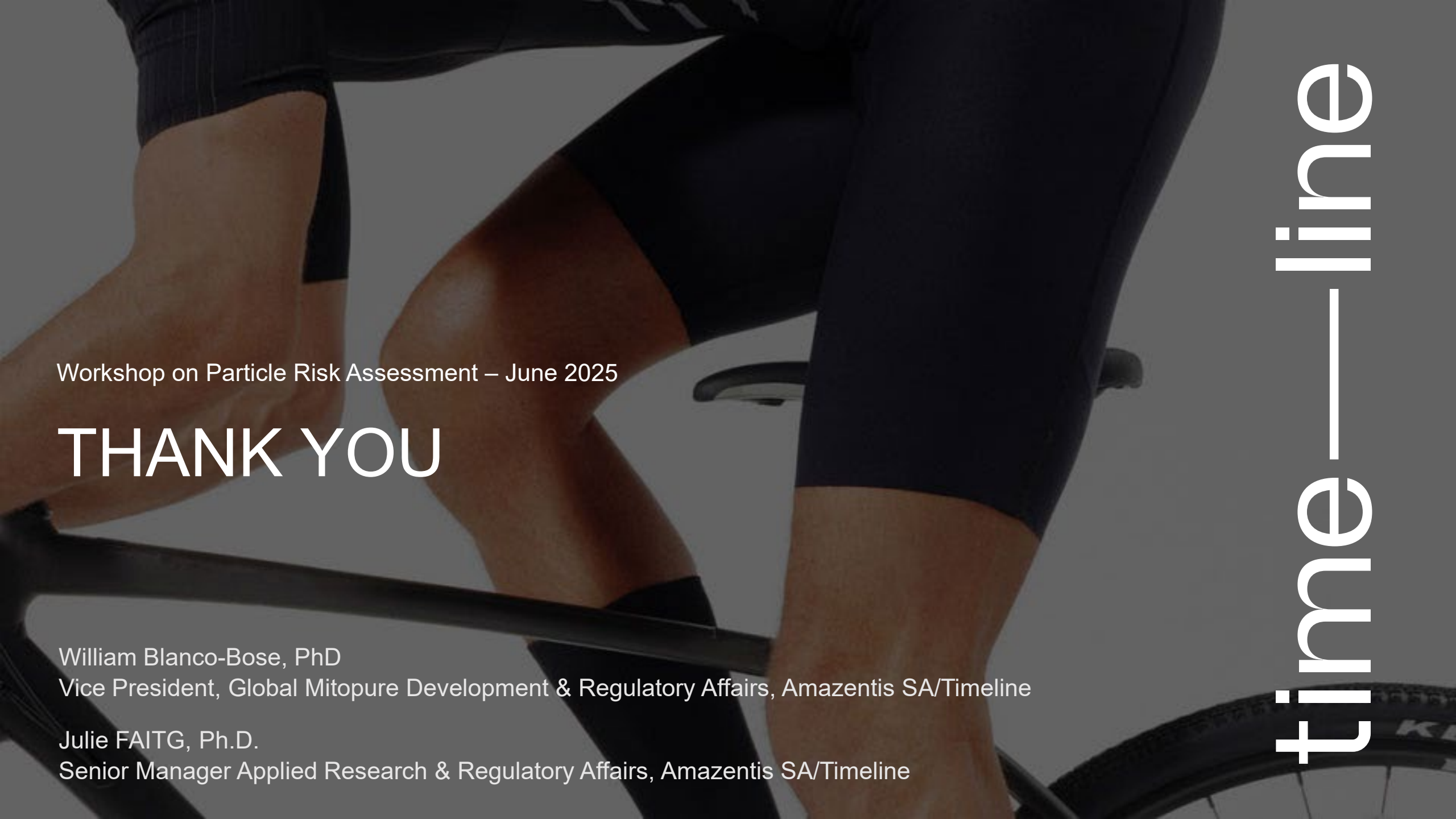
The current system needs the development of a more nuanced approach that allows the maximum valorization of existing safety data for the risk assessment

- Moving from“tick-box rejection” toward scientific bridging and contextual validation.
- Defining acceptance thresholds for older studies
- Complementarity: Combine historic in vivo with modern in vitro mechanistic data

More emphasis is needed on the WoE, when considering applications that were filed prior to the introduction of new guidance

- Conventional studies can be part of the nano risk WoE
- Negative results across endpoints: If no toxicity or genotoxicity is seen, how much more does a perfect dispersion add?

Applicants should be encouraged to archive testing material for future consideration



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THANK YOU

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