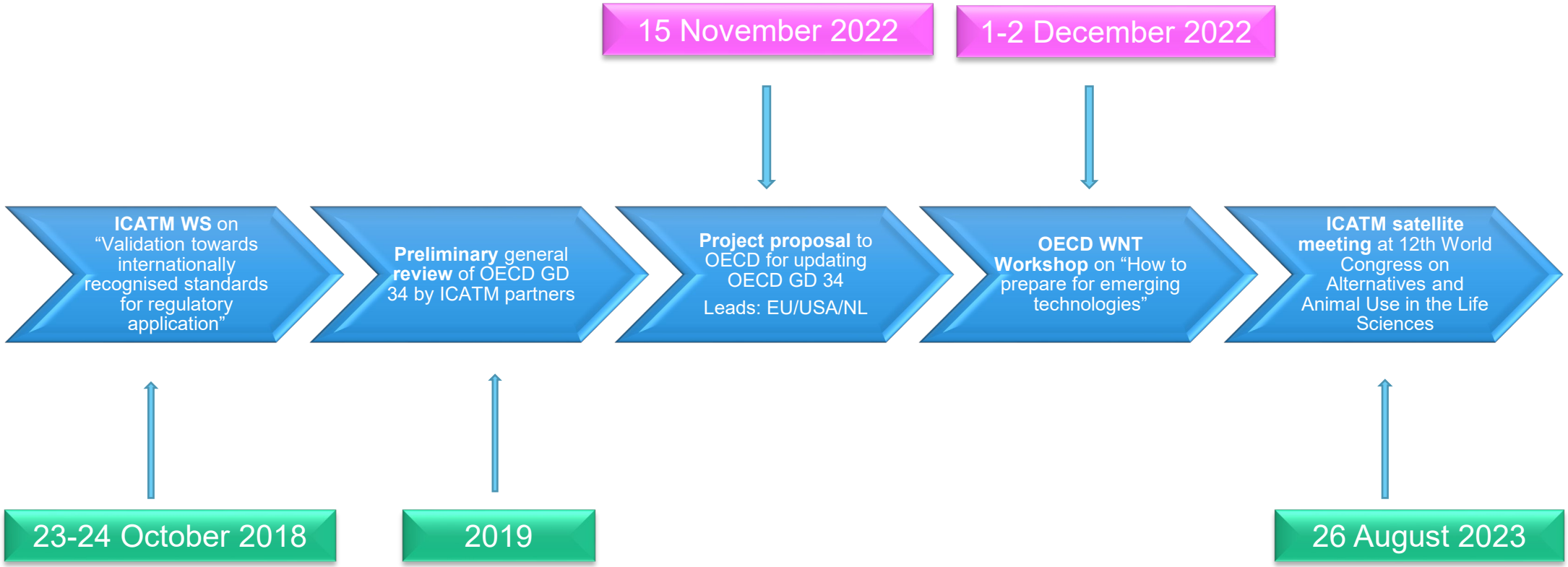
Update on OECD GD 34 and ICATM views

SACATM meeting, Research Triangle Park, NC 27709
21-22 September 2023

Valérie Zuang

European Commission, Joint Research Centre, Ispra, Italy

Background



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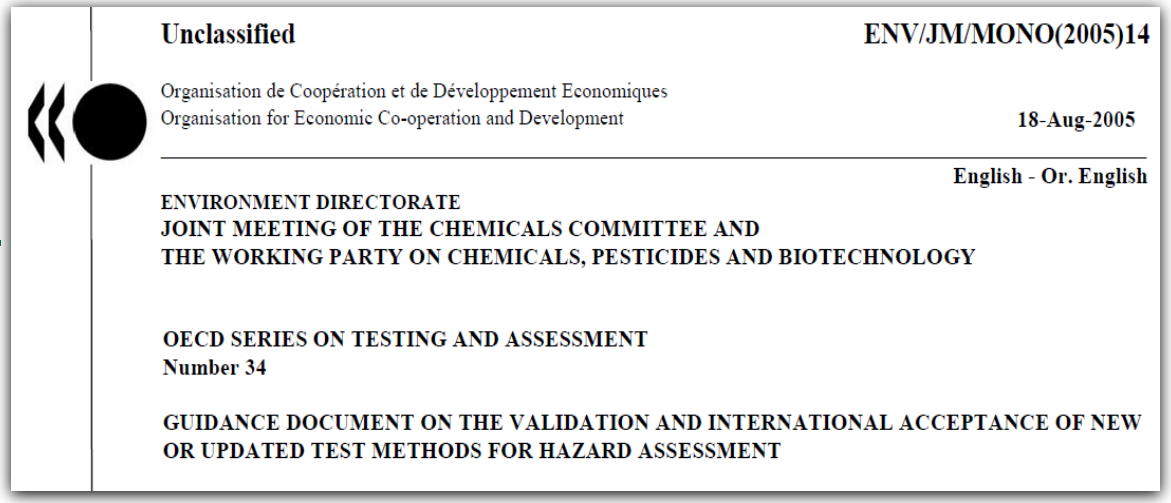
The principles and process of validation

- PRINCIPLES are universal and valid
- PROCESS for validation and international acceptance described in GD34 no longer reflects current state-of-the art
- Revision needed to keep pace with rapid scientific progress (e.g. emergence of defined approaches (data integration), computational models, new technologies such as Organ-on-Chip)



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Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

18-Aug-2005

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

OECD SERIES ON TESTING AND ASSESSMENT
Number 34

GUIDANCE DOCUMENT ON THE VALIDATION AND INTERNATIONAL ACCEPTANCE OF NEW OR UPDATED TEST METHODS FOR HAZARD ASSESSMENT

Leads: EU, USA, NL

OECD WNT project group established

European Commission

Organisation for Economic Co-operation and Development

ENV/CBC/TG/A(2022)2

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30 November 2022

ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

Working Party of National Coordinators of the Test Guidelines Programme

AGENDA

Workshop of the Working Party of the National Coordinators of the Test Guidelines Programme: "How to prepare for emerging technologies?"

1-2 December 2022
Paris, France

Main issues discussed:

- Test method readiness criteria
- Evolving the concept of Performance Standards
- Acceptance of mechanistic methods
- Validation of batteries of assays

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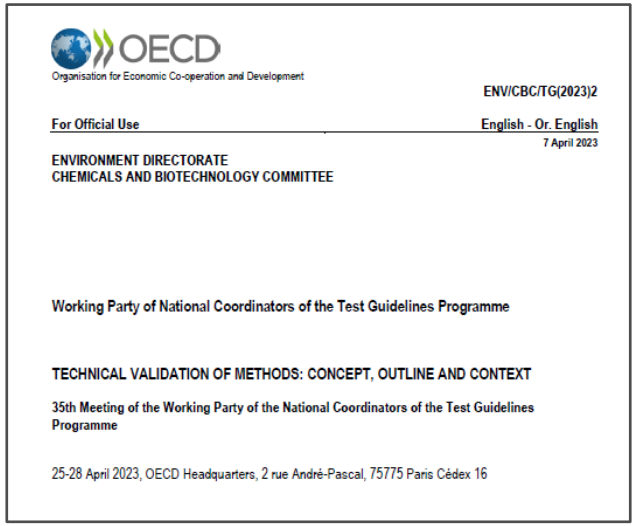
Technical validation



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7 April 2023

ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

Working Party of National Coordinators of the Test Guidelines Programme

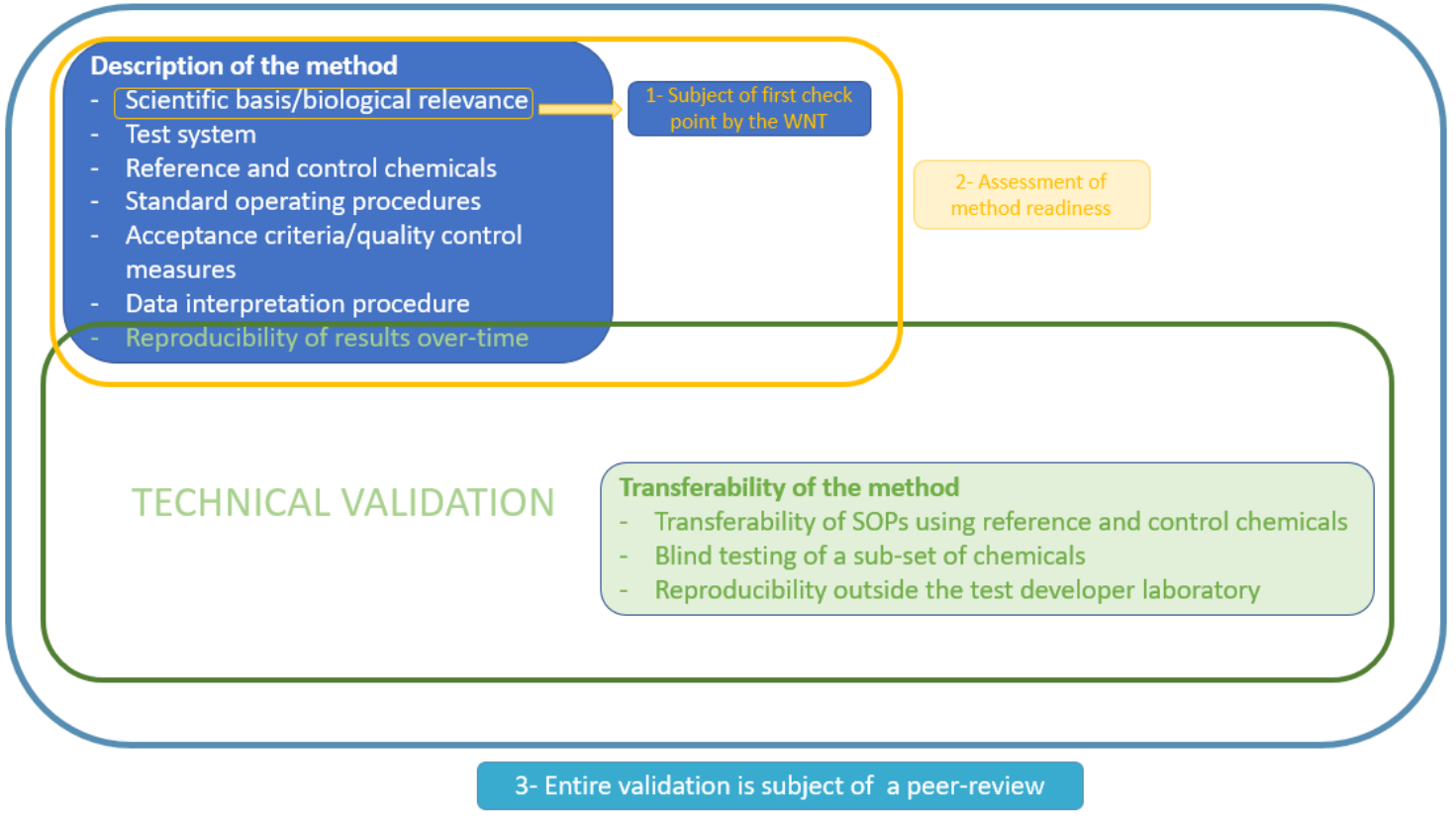
TECHNICAL VALIDATION OF METHODS: CONCEPT, OUTLINE AND CONTEXT

35th Meeting of the Working Party of the National Coordinators of the Test Guidelines Programme

25-28 April 2023, OECD Headquarters, 2 rue André-Pascal, 75775 Paris Cédex 16

Key features:

- More emphasis on scientific basis/biological relevance of non-stand-alone mechanistic methods which need to be combined in DAs/IATAs for regulatory application
- Assessment of method readiness to undergo technical validation on the basis of method description + WLR data
- More emphasis on WLR and transferability to a second lab and less on multi-lab ring trials



ICATM Satellite Meeting WC12
Niagara Convention and Civic Centre
Meeting Room 201/202 (Level Two)
Saturday, August 26, 2023
10:00 AM – 4:00 PM

Time	Agenda Item	Leads
10:00 AM	**1. Overview of SPSF for Updating GD34**	João Barroso, EURL-ECVAM
10:20 AM	**2. ICATM Comments Received In 2019**	Alison Harrill, US EPA
10:30 AM	**3. ICCVAM Validation Work Group Report**	Suzy Fitzpatrick, US FDA Elijah Petersen, NIST
10:50 AM	**4. Validation Study Perspectives** – Roundtable discussion of experiences: all ICATM members and OECD colleagues – Challenges: logistical, financial, technical, scientific regulatory, others	All participants
11:20 AM	**5. ICATM Discussion on GD34 Updates**	Nicole Kleinstreuer, NICEATM Dave Allen, NICEATM (Rapporteur)
	Technical Validation – Quality system – GLP, GIVIMP, and/or other? – Method description, statistical analyses, variability – Need for ring trials? – Applicability domain (for reference methods as well) – Repository/DB of technically validated methods – Need for stand-alone guidance document?	
12:00 PM	**LUNCH (off-site)**	
2:00 PM	**6. ICATM Discussion on GD34 Updates (Continued)**	Alison Harrill Dave Allen (Rapporteur)
	How to validate DA – As combined approach rather than validating each individual method – Need for individual TGs? – Assessment of predictive performance of each method/info source?	
3:30 PM	**7. Follow-up Activities** – Additional Topics for GD34 Update? – ICATM Recommendations to OECD EG/WNT?	Valérie Zuang, EURL-ECVAM
4:00 PM	**ADJOURN**	

Validation study perspectives

Cost/Time	Need to integrate non-stand-alone test methods in DAs/IATAs to address complex endpoints; Cost and time required for validation like stand-alone methods are not sustainable
Transferability/Ring Trials	Protocols not fully developed; critical procedural elements not described; language barrier and time differences in international ring trials; inconsistency in quality system used
Reference Chemicals	Unclear selection criteria; lack of reference data; poor/unknown quality of reference data; no consensus on adequate representation
Acceptance Criteria	Lack of sufficient data to establish criteria; setting of a priori, often arbitrary, criteria for performance resulting in increased cost and time without real benefit; little/no consideration of *in vivo* reference test method variability in the assessment of performance
Peer Review Process	Too many different reviews of the validation study data; need to minimize “moving the goal posts” and need for iterative revisions between developer and validation manager

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Technical validation- Quality system – GLP, GIVIMP, and/or other for data integrity and transparency

- According to OECD GD 34, validation studies should follow the principles of GLP
- Mostly not done in the past but not a problem because studies were coordinated by independent parties
- Now managed by commercial parties
- Important to demonstrate the integrity and credibility of the results, from the raw data through to the final report

Standards to ensure **Reliability** and **Data Integrity**

Available in the
OECD Series on Testing and Assessment No. 286

- Need for some level of quality management (e.g., GIVIMP) in validation studies for non-GLP labs
- Need to be more explicit in GD34 about what specifically is meant by quality assurance
- In some countries, many labs are ISO-certified

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Technical validation - Method description

A revision of GD 34 should definitely include the requirements for an adequate method description

- Information on a method provided in published literature is not sufficiently detailed

The selection of reference chemicals is also essential

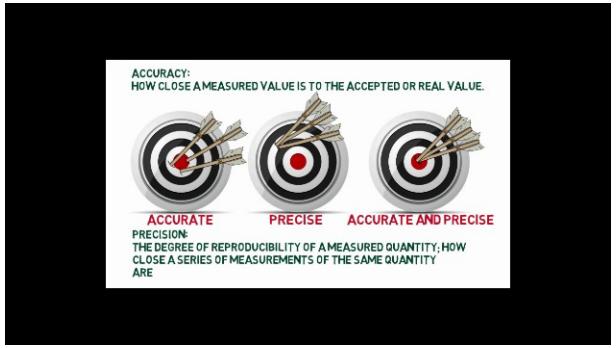
- Need to define criteria for selection (types and numbers)
- Appropriate selection of chemicals for the different phases of a validation study (training, transferability, reproducibility assessment, performance standards)
- Use multiple data and WoE when defining hazard profile of reference chemicals if these are used to measure “accuracy”
- Describing chemical space rather than fixed lists of chemicals?

Could it be considered to add another category below test guidelines within OECD – Test Method description + WLR (lower criteria for adoption than TG)?

- Could provide flexibility – include methods which are adequately described and for which WLR has been demonstrated (prior to transferability and incorporation into a DA)

Technical Validation – Need for Ring Trials?

- Demonstrating reproducibility is essential
- Ring trials are the most time-consuming and expensive part of a validation study and are often more a reflection of laboratory quality or expertise than of a NAM's reproducibility
- Properly designed training and transferability studies are essential and informative
- Proficiency testing adds confidence on capacity of a laboratory to perform test



WLR and BLR of validated *in vitro* methods

Method (eye irritation)	WLR	BLR
EpiOcular EIT	95%	93%
SkinEthic HCE	92%	95%
LabCyte EIT	96%	87%
MCTT HCE EIT	93%	90%
SkinEthic HCE TTT	85-100%	90-100%
Vitrigel	80-100%	92%
Ocular Irritection	80-90%	84-86%

Method (skin sensitisation)	WLR	BLR
DPRA	85%	80%
ADRA	100%	100%
kDPRA	96%	88%
h-CLAT	80%	80%
U-SENS	90%	84%
IL-8 Luc	88%	88%
GARDskin	82-89%	92%

Technical Validation – Applicability Domain

- The applicability domain of a test method does not have to be defined *a priori* and as experience is gained on the method through testing, the applicability domain evolves

- Updated GD34 is an opportunity to clarify what we mean by applicability domain – the distinction used for *in vitro* and *in silico* should also be clarified

Technical Validation – Repository/Database of technically validated methods

- Is a repository of technically validated methods needed?
  - Yes for the majority, however, some concern expressed over the extent to which it would actually be used and other practical reasons to not create one
  - Need to have a **central** repository to avoid confusion
- However, repositories are already available (e.g., DB-ALM, TSAR) – need protocols deposited for standardization (perhaps have grant requirements that the protocol is deposited)

Need for stand alone guidance on technical validation?

- No not needed, can be described in the update of GD34
- However, need to clearly define the scope of the updated GD (i.e. does it serve the OECD TGP only or more broadly also other programmes (e.g. WPHA) and purposes (e.g. IATA, physiological validation, permutations of testing strategies that are chemical or biology-specific etc)
- Need to remove redundant terms and concepts
- Need to be high level, simple, easily digestible so that the guidance is fully implemented
- Importance to view validation as a flexible/modular approach adaptable to the needs/context (e.g. in certain instances/contexts of use, the extent of validation can be less or more)
- For *in silico* methods/non-testing methods, the QSAR assessment framework was considered a good reference/adaptable framework
- Focus on validation only and remove international acceptance (which could eventually be the scope of another document) but clarify what is meant by “for a defined purpose” in the definition of validation

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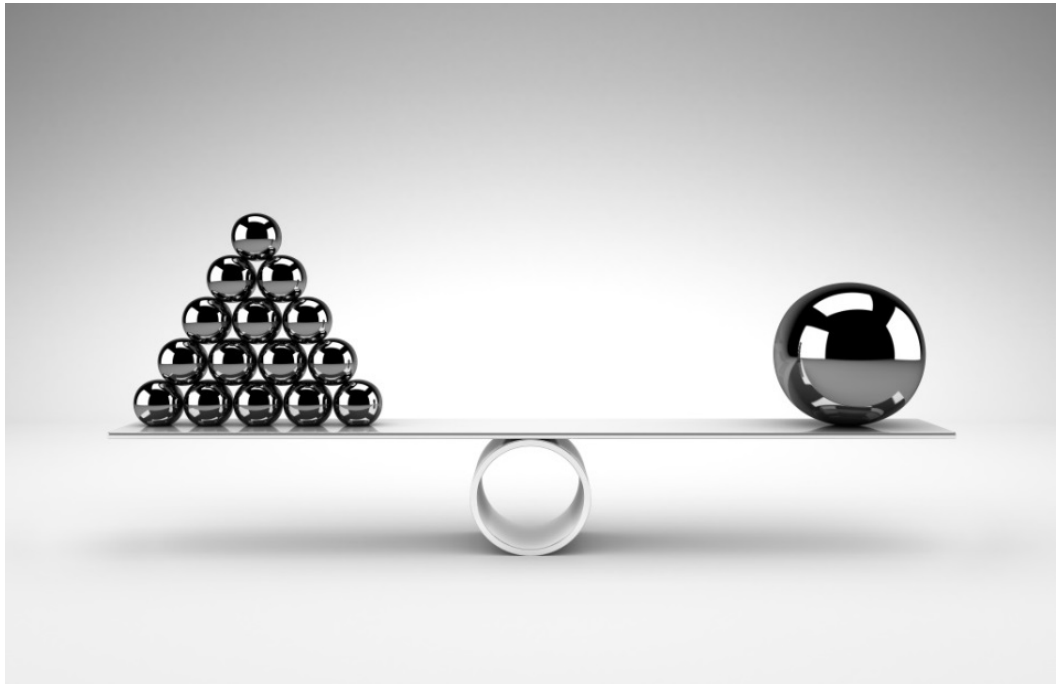
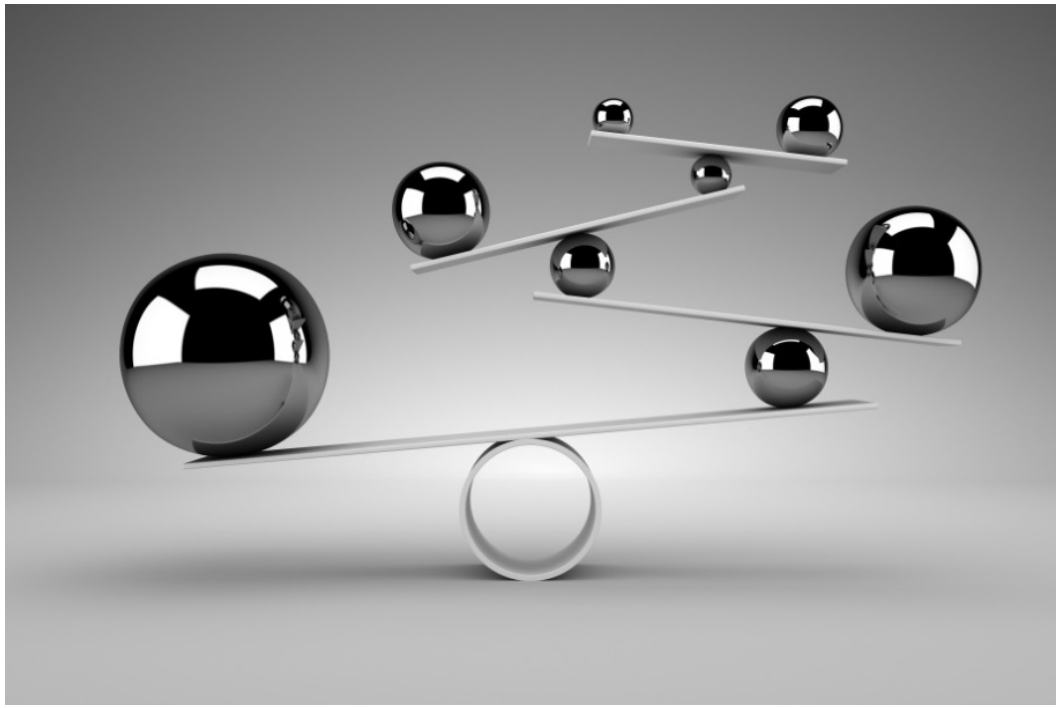
Concept and validation of Defined Approaches and IATA

Defined Approach

- Fixed information sources
- Fixed Data Interpretation Procedure

➥ **Can be validated and falls under MAD**





Integrated Approach to Testing and Assessment

- Flexible approach
- Weight of evidence/expert judgement

➢ Need for a confidence building framework

➢ Characterise uncertainties

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How to validate and accept mechanistic methods that are part of a Defined Approach?

- What level of validation and approval for individual methods is required prior to DA consideration and adoption?
- Expedite TG development and approval for individual methods after DA approval

Thank you

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