OECD PERSPECTIVES ON TEST METHODS VALIDATION

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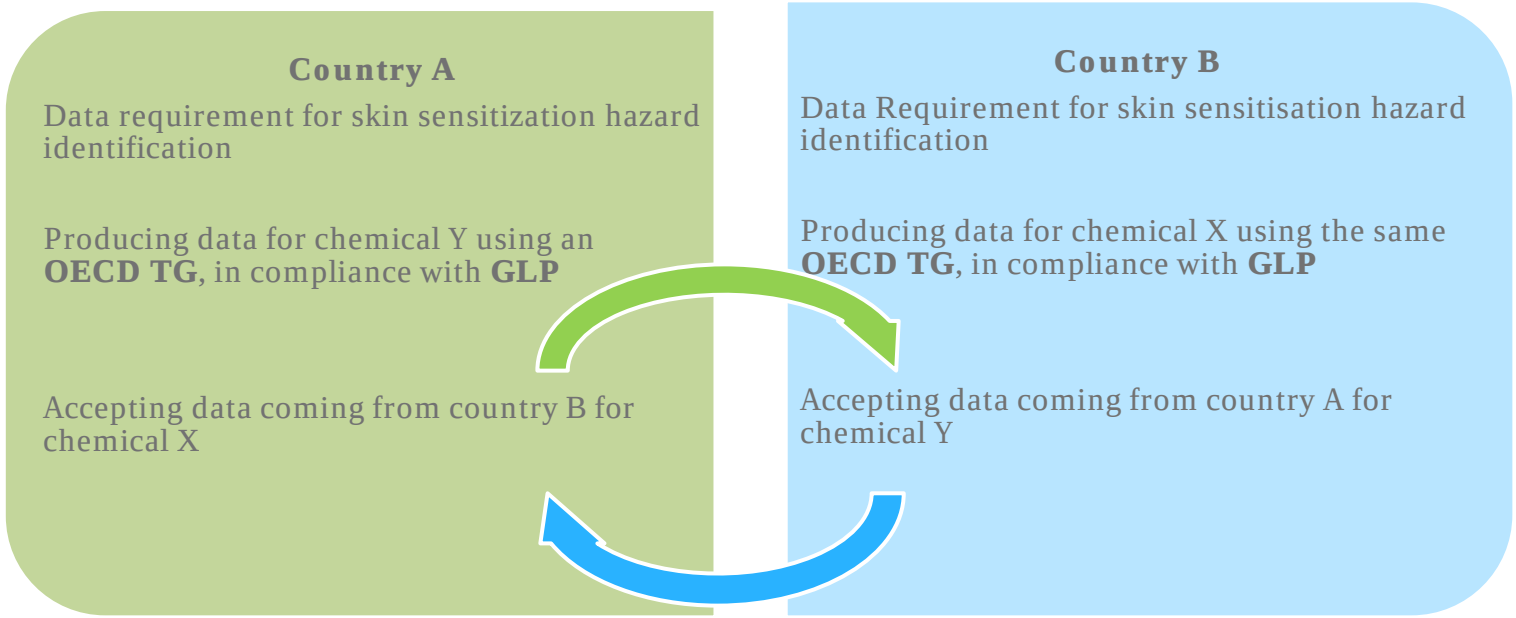
BETTER POLICIES FOR BETTER LIVES

What is the Mutual Acceptance of Data system about?

- Recognition by adhering countries that data produced using adopted OECD TG and GLP is accepted across countries having the same data requirement



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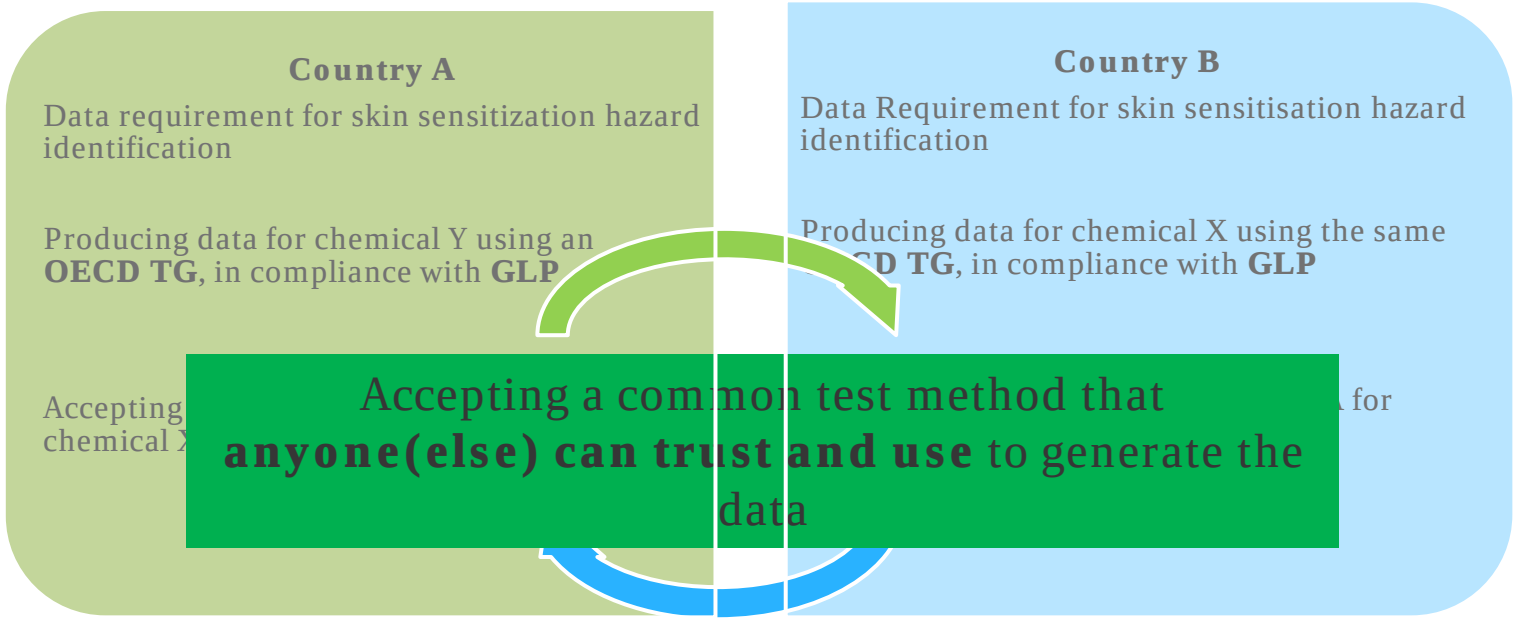


Is validation important?

- What happened before the era of validation?
  - Animal methods, mostly adverse or apical effects measured, (human) biological relevance was assumed
  - Assumed quality and reproducibility, but not often verified, not very precise
  - More subtle measurements introduced (e.g. histopathology)
    - Room for subjectivity
    - Trust is essential for acceptance
    - Verification and peer-review introduced
  - If regulatory decisions are going to be taken, better be sure basis is sound and immune to controversy (a liver is a liver!)

- Validation as a means to build confidence and reach acceptance
  - Not an impediment or a constraint
  - Acceptance cannot be imposed

All about **relevance** and **reproducibility**

- Validation is modular and flexible
  - Demonstration evidenced by facts/data ("I need to test by myself before accepting")
  - Removes or minimise bias/judgement/belief
  - Not a dogma, not a set of rigid rules

Feedback on experience with validation for standardised guidelines at OECD

- Modularity/flexibility has been important to focus on important questions/aspects of a protocol and keep exercise manageable

- Reporting, transparency, open reviews have been key to receive feedback and improve clarity of experimental procedures and data interpretation

- The MAD system functions because adhering countries have the possibility of implementing methods they have not developed but for which they can develop skills and experien
  - Transferability is a key topic

- Everyone agrees that:
  - the experimental demonstration or inclusive retrieval/analysis of existing data was important for adoption of test methods
  - the diversity of methods validated shows *if there is a will there is a way*, despite perceived obstacles

Regulatory context is instrumental

- 2013: Europe bans use of animal testing for cosmetics
- 2013-: several in vitro OECD TGs adopted for skin and eye irritation/corrosion
- 2014-: two *in vitro* OECD *TGs* adopted for skin sensitisation
    - Application not fully defined at time of adoption
- 2016: IATA case studies and 12 Defined Approaches proposed
    - Users and industry had ideas on possible solutions (and data to support claims!)
- 2016-2017: ICATM partners join forces to propose the development of a Guideline on DAs for skin sensitisation to be covered by MAD
- 2017-2018: US EPA announces replacement of the 6 acute toxicity tests and adopts a policy for non-animal skin sensitisation testing

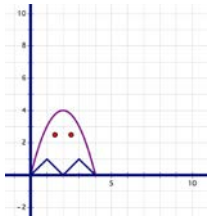
What about failures?

- Causes of failures during validation include:
  - Contamination of the biological material
  - Difficult to test substances (volatile, adsorbing, degrading)
  - ➡ Only became obvious after quality checks/verifications

- Causes of failure after validation include:
  - Unclear data interpretation and implications for regulators
  - Mechanistic rationale of the assay was unclear
  - Availability of the test system/material not easy or not at reasonable conditions

Lessons learned and expectations today

- ‘Easy’ validation of stand-alone methods is over
- Need to be more efficient in validation (®evolution ?)
- New issues have emerged that cannot be ignored:
  - IP rights on assays,
  - Identifying REFERENCE data and REFERENCE chemicals
  - How to gain acceptance of negative outcomes?
- Important to distinguish between perceived problems and true issues:
  - hear and understand where the former comes from, address the latter



Time taken to validate an assay and approve the test guideline

- Varies depending on:
  - Preparatory work on the standardisation of the assay and testing procedures
  - Identification of reference chemicals
  - Availability and distribution of test chemicals/test system components
  - Recruitment of participating laboratories
  - Sense of urgency on the regulatory need

Factors that can really slow down the process

Collaborations are essential

Factor that can speed up the process

Is validation truly the problem?

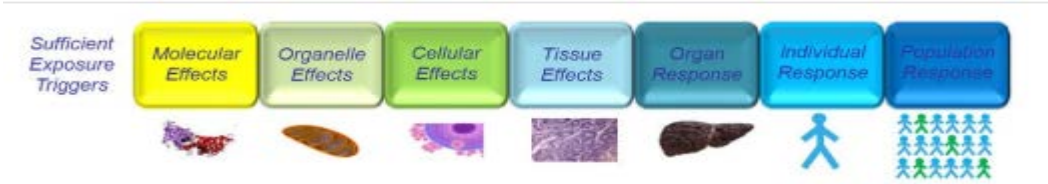
Not having an overview or ability to reach alternative solutions for complex endpoints makes us blame what can be improved and complain that there is a long and onerous way to go.

How to ‘modernise’ validation for more complex hazard endpoints?

- Find new sources of reference data and reference chemicals
  - Get access to proprietary data (ECHA Chem? EPA Pesticides registry?)
  - Make better use of existing data (e.g. systematic reviews)

  So far, we have not often made the best use of available information

- Increasing human relevance
  - Expand databases beyond animal tests because too few chemicals
  - Can scientists get access to clinical studies to get human data (data ownership issues?)
  - Define perturbations (beyond adaptation) that lead to adversity
    ...use that in AOP descriptions



- Identify testable key events /assays and start standardisation
  - Apply good in vitro methods practices early on
  - Work on combinations or sequences of assays that are meaningful together

Building a Cycle for IATA /Defined Approaches Development

IATA for Developmental Neurotoxicity Project

Non-Genotoxic Carcinogenicity IATA Project

- **IDEAL STARTING POINT:** AOP Development Programme
- Multi-disciplinary participation
- Human relevance

AOP providing the mechanistic basis for new approaches

Test methods to probe the key events

Outline of strategy to combine methods/data

- Input from the TGP
- Expert Groups by hazard area
- Identification of promising assays and testing
- Reproducibility of results

Data interpretation procedure

IATA for Serious Eye Damage and Eye Irritation

IATA for Skin Corrosion /Irritation

Opportunities for review and adjustments

Where validation issues arise

T&A strategy harmonized for specific regulatory question = **DEFINED APPROACH**

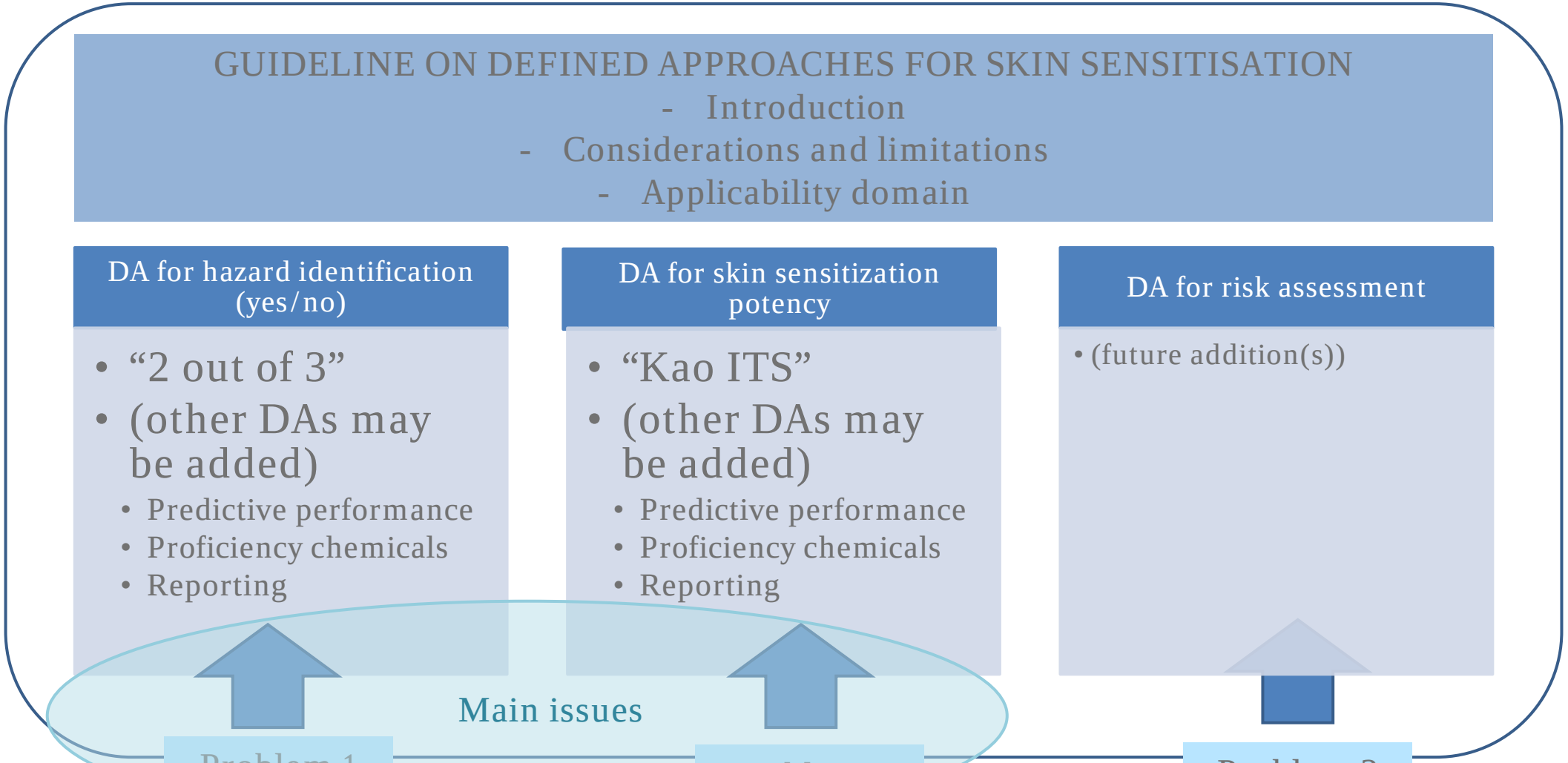
Consolidate with case studies

- Input from the Case Studies Project
- Generation/collection of existing data to expand applicability domain

Defined Approach for Skin Sensitisation

- Input from WNT and WPHA
- Input from the WG GLP for aspects related to non testing elements of the DA
- Gaining regulatory acceptance
- Characterising uncertainty

Building solutions around a clear problem formulation



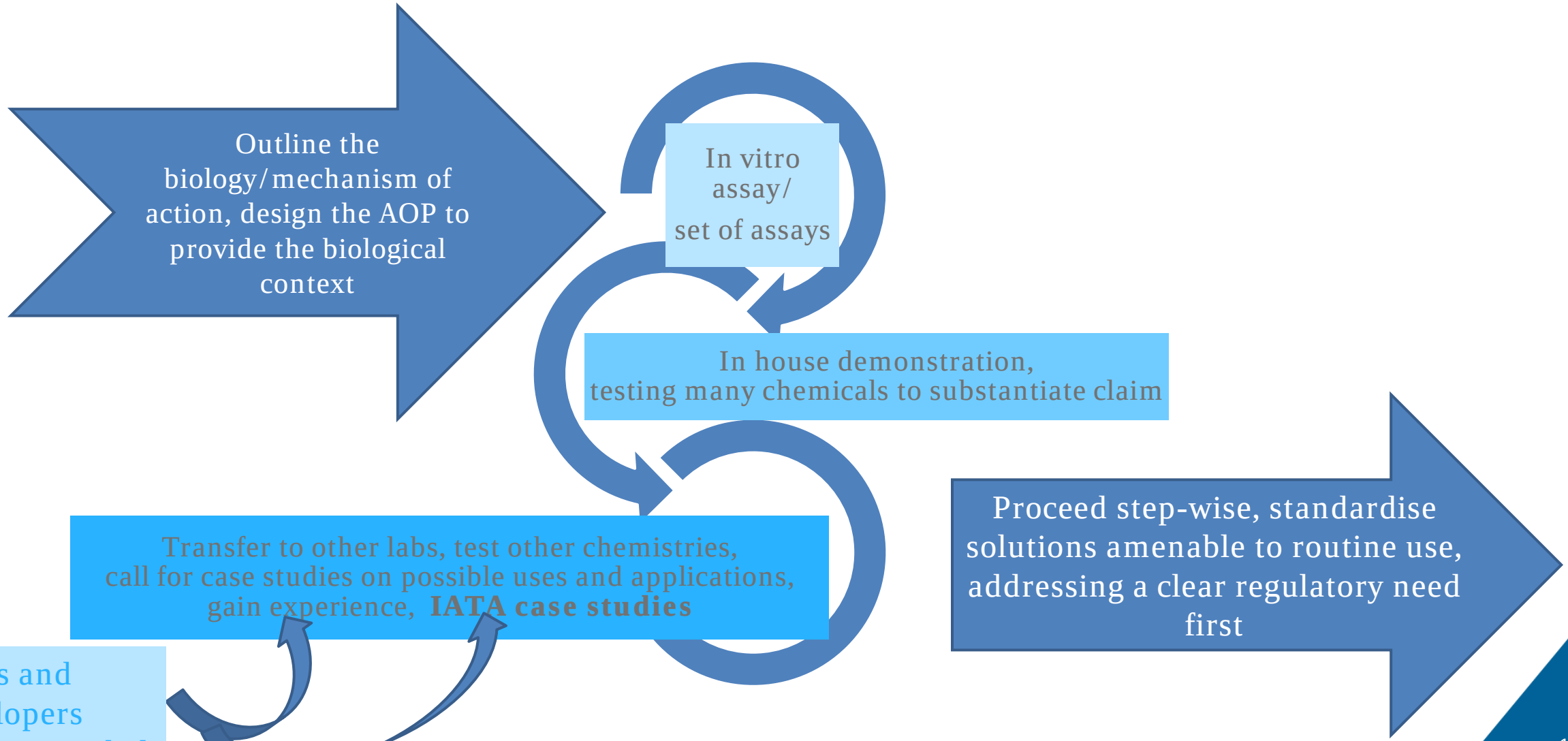
New and emerging issues: intellectual property rights

- Philosophy of Test Guidelines= methods should be transferable = part of the trust deal

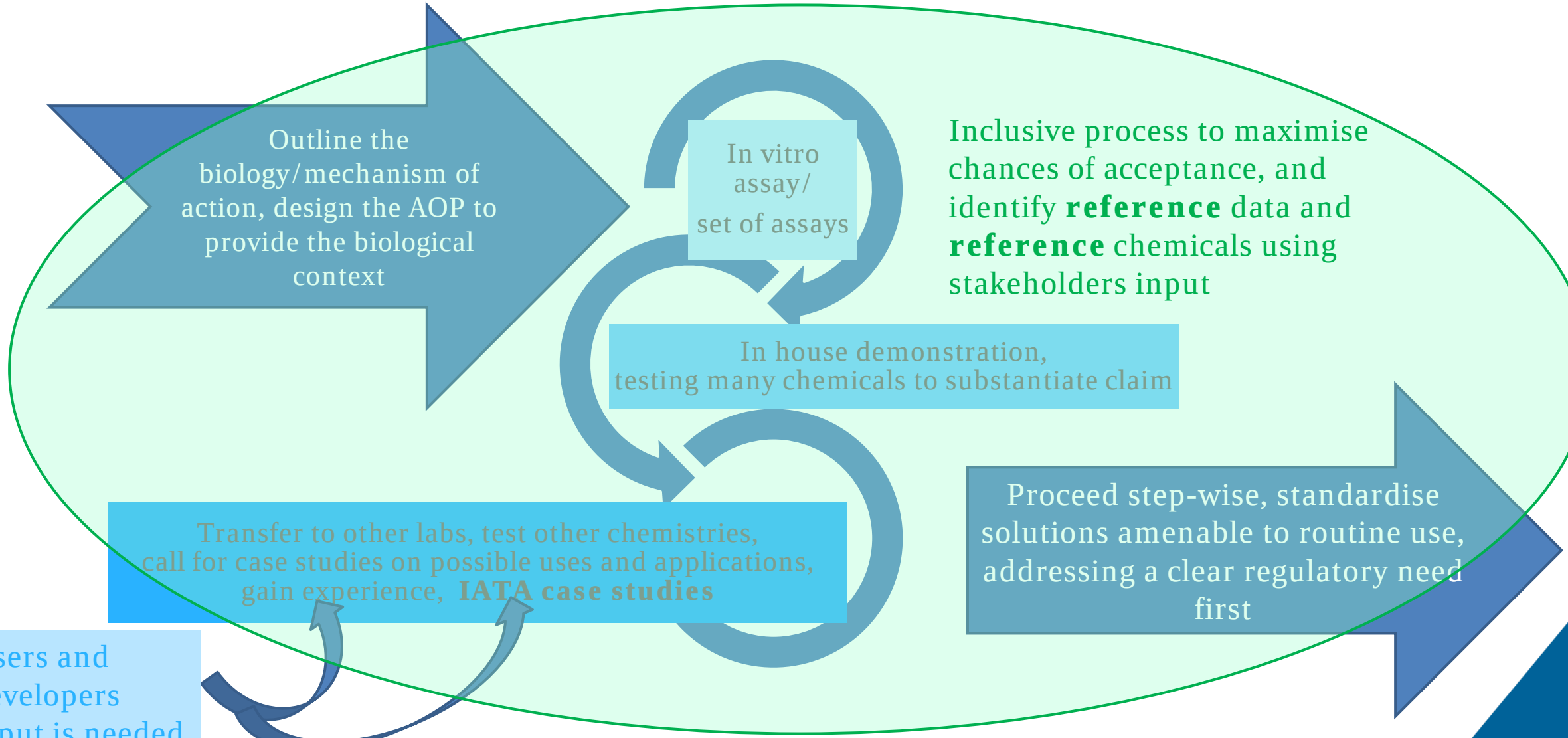
  - No monopoly on the use of test methods, technology should be accessible, at least to the proficient/competent labs in countries
  - Not 'healthy' to rely on single data source
- Find work around solutions
  - Performance standards
  - Reference chemicals
  - Predictive capacity

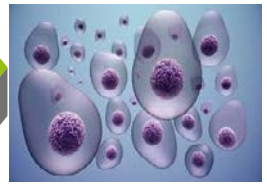
Reduces abuses of monopoly by allowing multiple solutions,
but does not necessarily help acceptance in the first place (issues of transparency, transferability, reliability)

How data can contribute to building confidence in relevance and reliability?

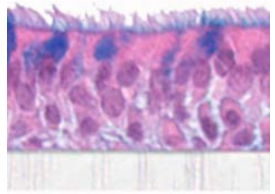


How data can contribute to building confidence in relevance and reliability





Other solutions than DA in the pipelines?



- Organoids/organ-on-a-chip
  - Can modern chemical safety testing do without these in future?
  - Will IP issues be an obstacle?
  - Is the technology affordable and transferable?
  - Is it amenable to routine use for chemical safety testing?
  - How much capacity required for a lab to use proficiently?
  - Do we need to engage early on with developers?
  - What incentives for them to engage?
  - Probably not stand-alone, but used in combination?
- Other solutions?....

Preparing the ground for a favourable context

- OECD working with member countries/EU (incl. private sector/IP lawyers) on developing Guidance for good licensing practices for methods/solutions containing IP elements
- Propose a series of webinars on possible future solutions for targeted hazard endpoints
  - Exploratory nature, light and attractive format of 2 hours
  - Get the developers engaged early on in dialogue with regulators/potential users
  - Identify issues to be addressed by various stakeholders for possible validation/standardisation of solutions

Resources and possible partnerships ?

- Understand what's going on in other areas and places and find out synergies and complementary activities
  - E.g. TEX-VAL in US

TEX-VAL: Texas A&M Tissue Chip Validation Center This proposal is to establish a Tissue Chip Validation Center at Texas A&M University (TEX-VAL) which will conduct testing of the microphysiological systems developed by NIH grantees. Our goal is to provide resources, personnel and infrastructure for establishing functionality, reproducibility, robustness and reliability of 8-12 tissue chip models that will represent a wide array of human organ and tissue systems. To achieve this goal we have assembled a team of 7 outstanding investigators who specialize in toxicology, in vitro and in vivo testing, microscopy, genomics, pharmacokinetic modeling, bioengineering, analytical chemistry and risk assessment. These investigators will closely oversee a team of highly qualified staff membe developers, will conduct validation experiments, analy ensure that the data are available to the NIH Tissue C database. Quality management plan and quality assur overseen by a staff member with experience in these p experimental protocols and data records will adhere t existing Organization for Economic Cooperation and D describing non-guideline in vitro test methods, as well alternatives to animal methods from the Food and Dru Toxicology Program. The TEX-VAL Center will utilize T infrastructure for medium- and high-throughput in vitro screening and high-content imaging at

Role of chemicals regulations and capacity to evolve?

- Many methods have been validated and standardised, but what do we know about regulatory use in practice?
- What are the impediments?
  - Concern about impact of test outcome if regulatory decision follow (i.e. beyond just priority setting)
  - Regulators are concerned about reliability because method is not 100% predictive
  - Accepting negative test outcome
- If methods are not transferable, what role can they play in chemical safety testing and decision making?
- Some suggest changing target by basing regulatory decisions on mechanistic information
  - What does that mean exactly? No NOAEL? What about uncertainty considerations?
  - Will the regulated community use such information?

Thoughts and conclusions

- Validation can evolve in the international context, some principles will stay valid nevertheless (transparency, transferability, reproducibility)

- Main issues are:
  - To reach out to solutions for complex hazard endpoints
  - To access relevant data and identify reference chemicals

- Lots of issues to be addressed should not be seen as a stopping lights

- Make good use of strong networks at the right time (ICATM, industry consortia, scientific societies, reg. agencies having access to data, OECD)

Thank you for your attention!

OECD Secretariat staff involved with validation/chemicals testing and assessment projects:

- Patience Browne (ED, *in vitro* tox, DA)
- Nathalie Delrue (genotox, skin sensitisation)
- Leon Van der Wal (ecotoxoicity)
- Eeva Leinala (hazard assessment, IATA, DA)
- Anne Gourmelon (TGP in general)
- Bob Diderich (Head of Division)

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