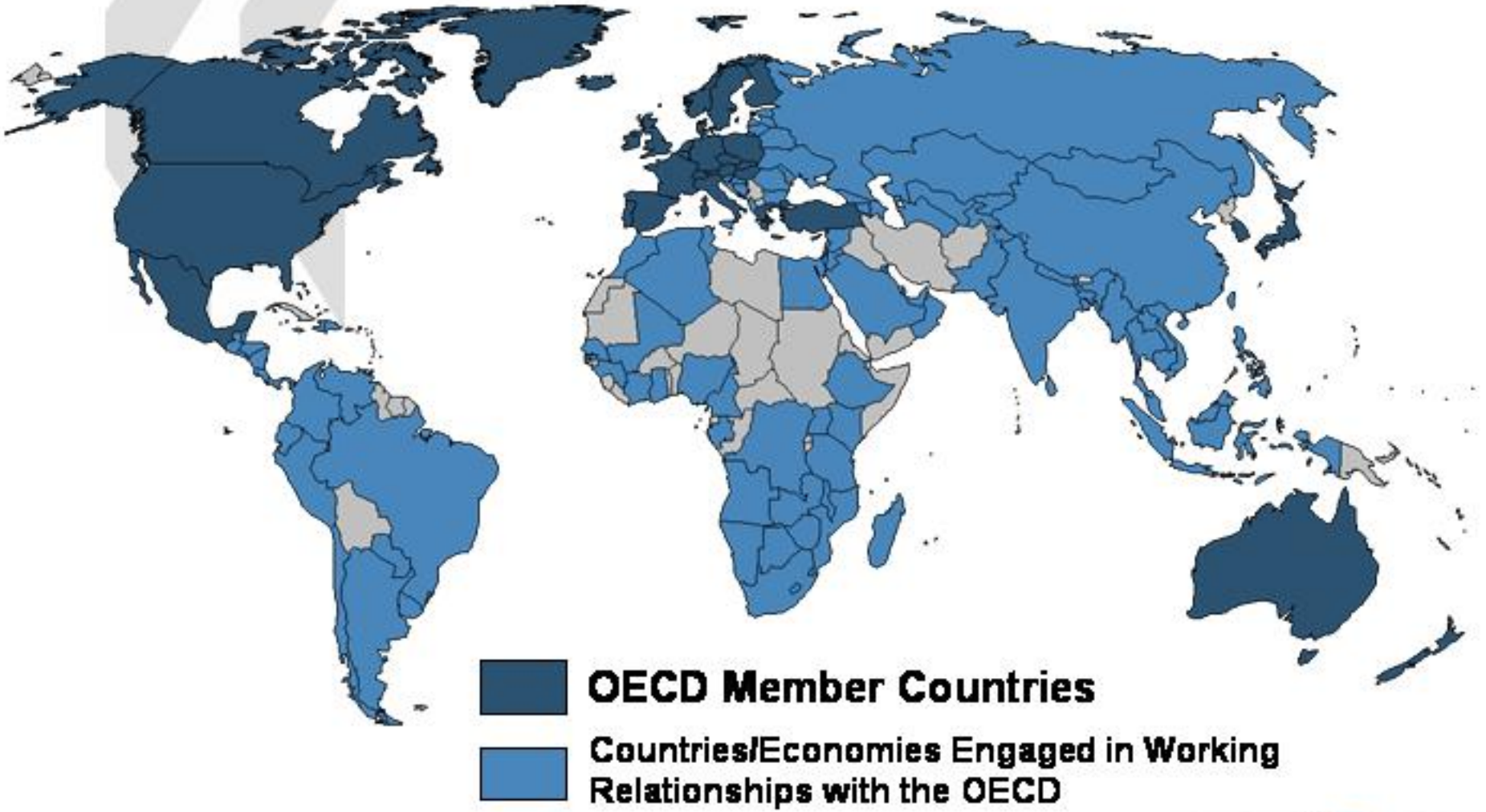
A global outreach



OECD Council Decision (1981)
Mutual Acceptance of Data (MAD)

"Data generated in the testing of chemicals in an OECD Member Country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice (GLP) shall be accepted in other Member Countries for purposes of assessment and other uses relating to the protection of man and the environment."

- → Avoids duplication of testing by industry
- → Avoids non-tariff trade barriers
- → Reduces the number of laboratory animals used

The Test Guidelines Programme (TGP)

- Established 1981 (ENV DIR/EHS DIV)
- MAIN TASK: Develop and revise Test Guidelines for the testing of chemicals for human health and the environment
- Original publication in 1981: 51 TG's
- Today: 100+ new or updated Guidelines
- At presently 80+ projects in the work-plan
  - Special activities: EDTA (VMG mammalian, eco and non-animal

Publication of OECD Test Guidelines

- **Test Guidelines are legal instruments in OECD Member countries. There are 4 series:**

  100 - Physical-Chemical Properties *(blue)*

  200 - Effects on Biotic Systems *(green)*

  300 - Degradation and Accumulation *(yellow)*

  400 - Health Effects *(pink)*

- **Guidance Documents**
- **Detailed Review Papers**
- **Background Review Papers**

THE OECD SUBMISSION AND ADOPTION PROCESS

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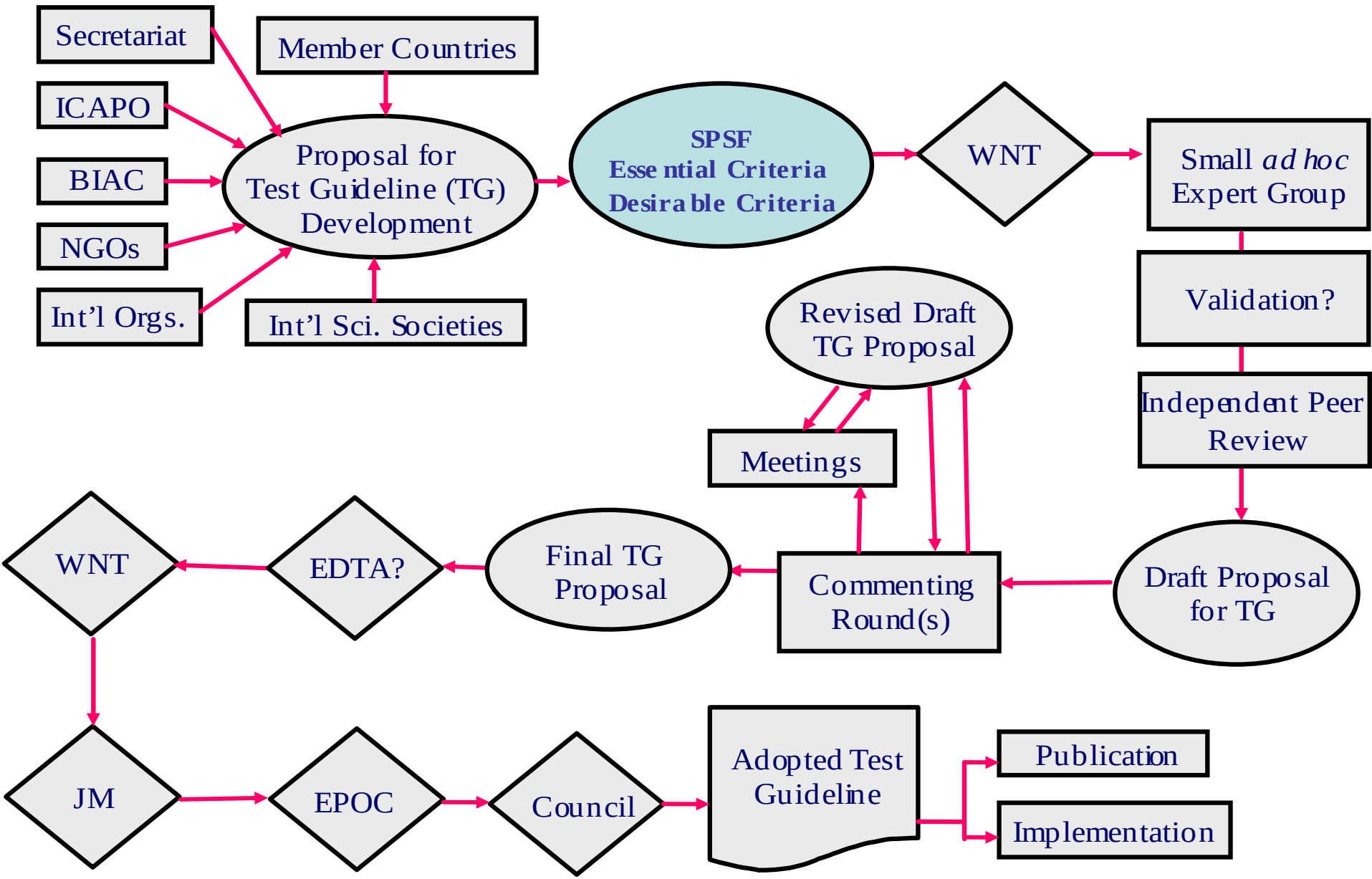


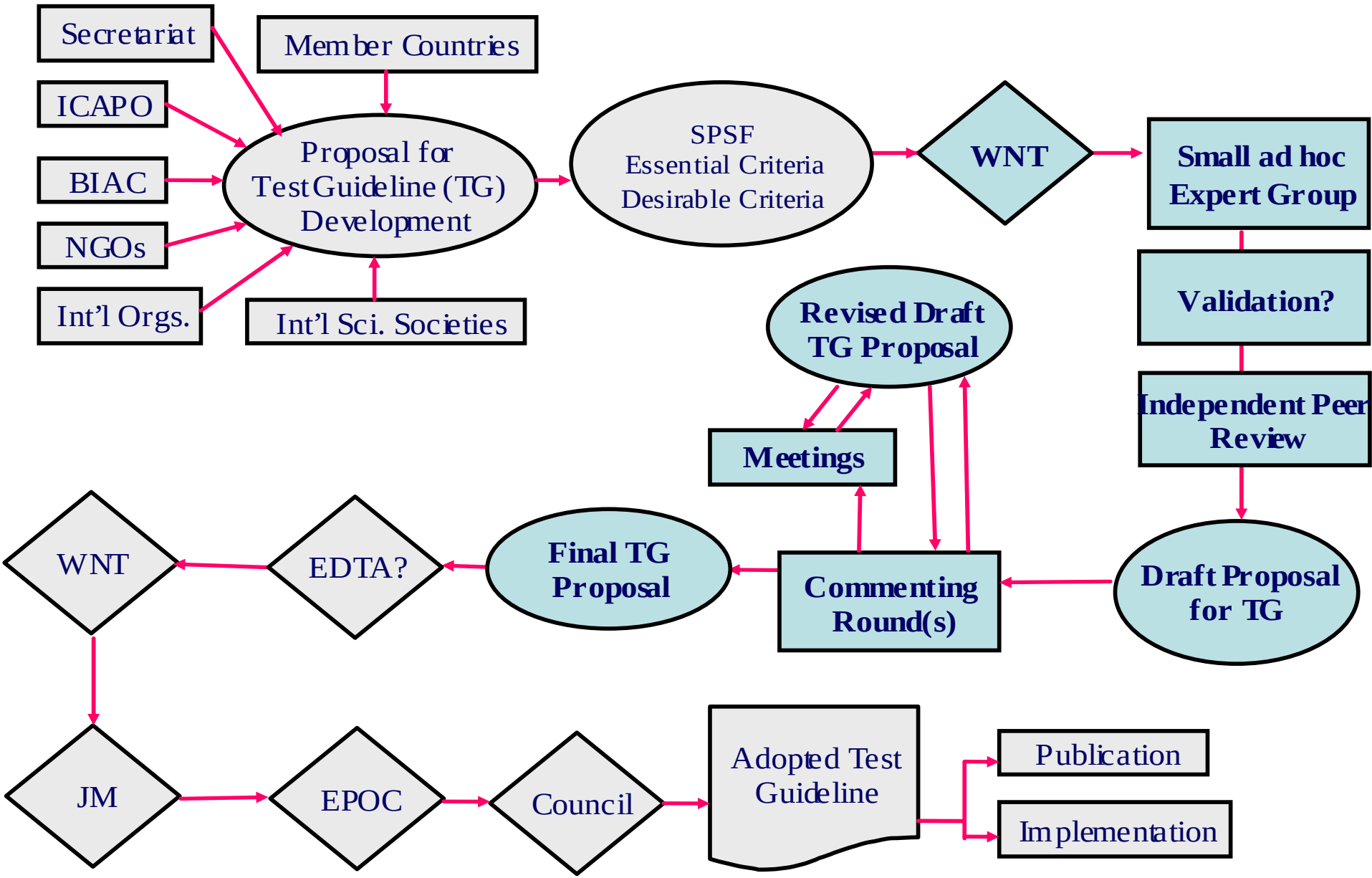
Standard Project Submission Form (SPSF) - Essential criteria

- Defined regulatory need/Data requirement
- Contributes to the International Harmonisation of Hazard and Risk Assessment
- Addresses a health or environmental concern
- Considerable support from Member countries
- Lead country or Stakeholder identified

Standard Project Submission Form (SPSF) - Desirable criteria

- Test Guideline intended for general/broad use
- Scientifically valid, reliable, relevant
- Addresses endpoints not yet covered
- Existing national/regional protocols as a basis
- Animal welfare concerns are addressed
- Contributes to saving resources
- For guidance documents:
  - essential or helpful
  - linked to (a) specific TG's or for general guidance

THE OECD SUBMISSION AND ADOPTION PROCESS



Common Stumbling-blocks in the Development Process

- Material supporting the performance/validity of the test is not attached or of poor quality
  - Statistical evaluations, scientific references, validation reports, peer review reports, etc.
  - Validation criteria outlined in GD No.34 →
- A poorly written draft Test Guideline
- A poorly defined/or changed regulatory purpose of the TG
- Low level of commitment by the lead country
- Need for Expert Consultation or DRP

OECD Validation Criteria

- Available in the **OECD GUIDANCE DOCUMENT NO. 34 ON THE VALIDATION AND INTERNATIONAL ACCEPTANCE OF NEW OR UPDATED TEST METHODS FOR HAZARD ASSESSMENT** as agreed by the JM
- Applicable to all sorts of tests
- Based on the Solna principles from WS 1996
  - Criteria for principles of validation
  - Criteria for principles of regulatory acceptance
- International Validation Institutes: ECVAM, ICCVAM and JACVAM

Common Stumbling-blocks in the Development Process

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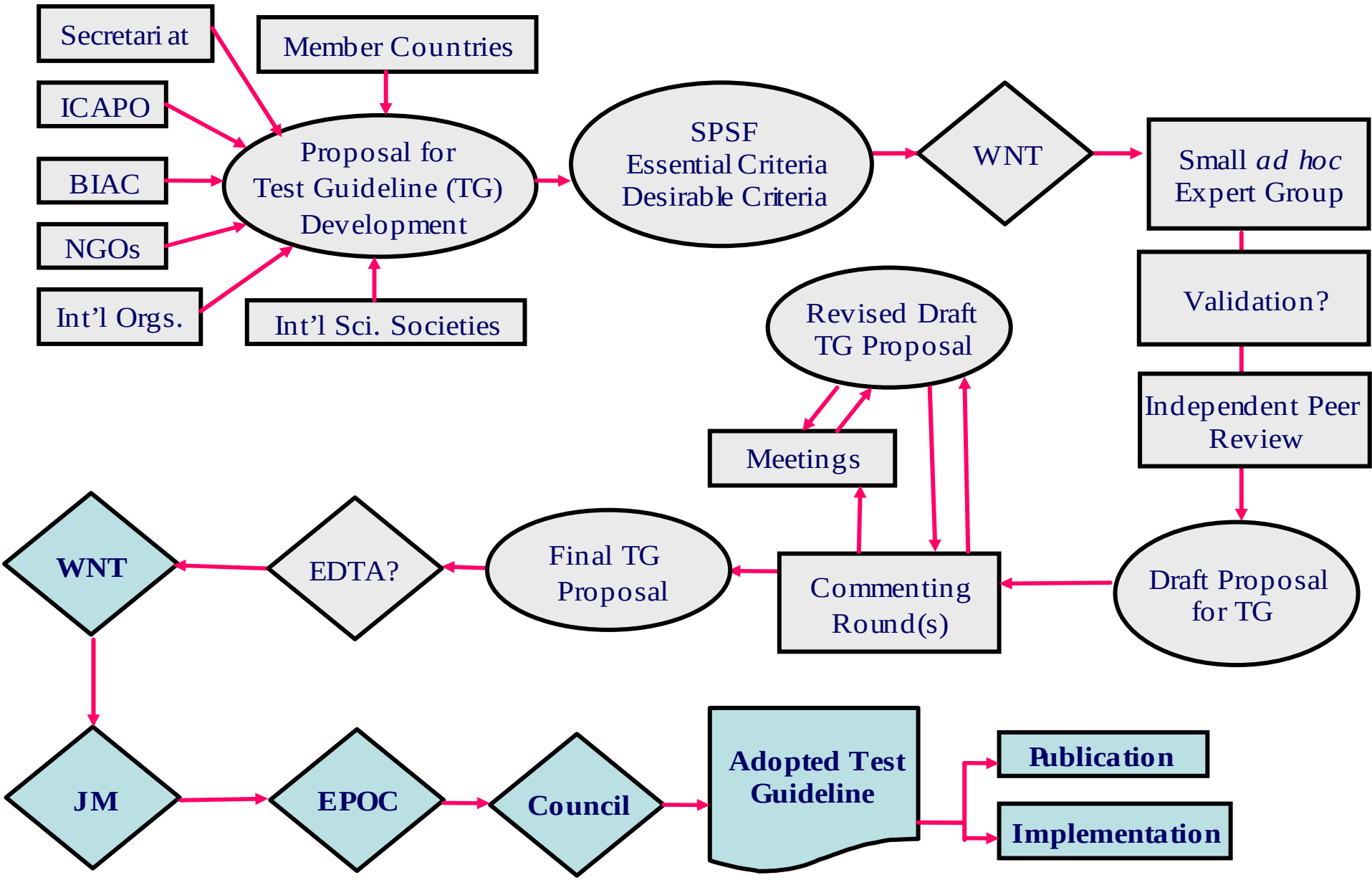
THE OECD SUBMISSION AND ADOPTION PROCESS



Example of regulatory acceptability at OECD level for a test method developed in the EU

R&D	5-10 years !?
Prevalidation	2 years
Validation	3 years
Peer review	2 years
EU regulatory acceptance	2 years
OECD regulatory acceptance	2 years+

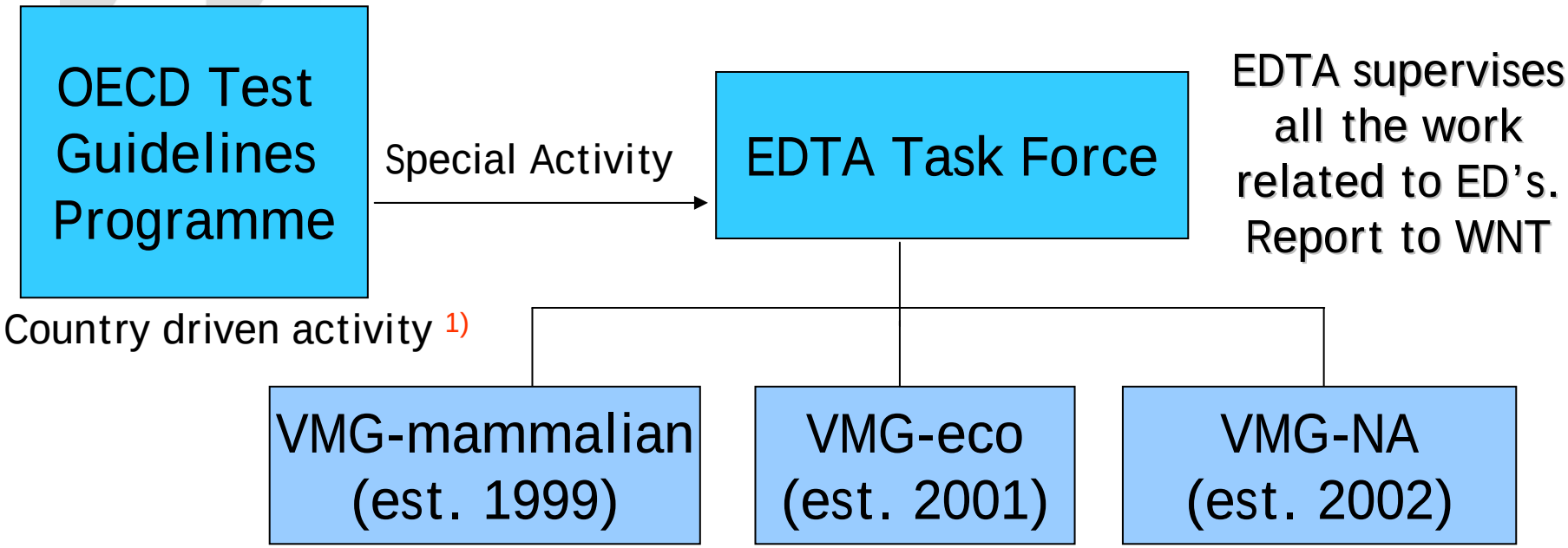
Refocusing of the Test Guidelines Programme

- **<u>Main aim:</u> To more efficiently develop new or revised validated Test Guidelines that meet the regulatory need of Member countries**
- An earlier control of new proposals
- Lead countries need to clearly state their degree of commitment: timelines for deliveries, number of researchers involved, estimated costs, etc.
- Revision of the SPSF and Guidance Document No.1 on “Test Guidelines Development”

EDTA

The Endocrine Disruption Testing and Assessment Taskforce of the Test Guidelines Programme

The OECD Work on ED: A Special Activity of the Test Guidelines Programme *)



*) Basic goal and scope of TGP: MUTUAL ACCEPTANCE OF DATA.

1) OECD Member countries make proposals to develop new or update existing TG; proposals are prioritised by countries (WNT) and a lead is designated for the work.

EDTA6

Tokyo 24th-25th June 2002

- The EDTA6 considered it timely to establish a third VMG, the VMG-NA.
- Urgent need for relatively cheap and quick screens and test methods not requiring animals
- The objective of VMG-NA is to provide tools necessary for Level 1 (Sorting and prioritizing based on existing information) and Level 2 (in vitro assays providing mechanistic data)

The OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters as agreed by the EDTA6 (2002)

Level 1
Sorting & prioritization based upon existing information

- physical & chemical properties, e.g., MW, reactivity, volatility, biodegradability,
-human & environmental exposure, e.g., production volume, release, use patterns
- hazard, e.g., available toxicological data

Level 2
In vitro assays providing mechanistic data

- ER, AR, TR receptor binding affinity
- Transcriptional activation
- Aromatase and steroidogenesis *in vitro assays*
- Aryl hydrocarbon receptor recognition/binding
- QSARs
- High Through Put Prescreens (HTPS)
-Thyroid function
- Fish hepatocyte VTG assay
- Others (as appropriate)

Level 3
In vivo assays providing data about single endocrine mechanisms and effects

- Uterotrophic assay (estrogenic related)
- Hershberger assay (androgenic related)
- Non -receptor mediated hormone function
- Others (e.g. thyroid)

- Fish VTG (vitellogenin) assay (estrogenic related)

Level 4
In vivo assays providing data about multiple endocrine mechanisms and effects

- enhanced OECD 407 (endpoints based on endocrine mechanisms)
- male and female pubertal assays
- adult intact male assay

- Fish gonadal histopathology assay
- Frog metamorphosis assay

Level 5
In vivo assays providing adverse effects data from endocrine & other mechanisms

- 1-generation assay (TG415 enhanced)[1]
- 2-generation assay (TG416 enhanced)[1]
- reproductive screening test (TG421 enhanced)[1]
- combined 28 day/reproduction screening test (TG 422 enhanced)[1]

- Partial and full life cycle assays in fish, birds, amphibians & invertebrates (developmental and reproduction)

The OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters as agreed by the EDTA6 (2002)

Level 1

Sorting & prioritization based upon existing information

- Physical & chemical properties, e.g., MW, reactivity, volatility, biodegradability,
- Human & environmental exposure, e.g., production volume, release, use patterns
- Hazard, e.g., available toxicological data

The OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters as agreed by the EDTA6 (2002)

Level 2

In vitro assays providing mechanistic data

- **ER, AR, TR receptor binding affinity**
- **High Through Put Prescreens**
- **Transcriptional activation**
- **Thyroid function**
- **Aromatase and steroidogenesis *in vitro***
- **Fish hepatocyte VTG assay**
- **Aryl hydrocarbon receptor recognition/binding**
- **Others (as appropriate)**
- **QSARs**

Main Aim of the VMG-NA is to;

- Identify and propose assays or review documents with a view to the adoption of available, valid tests as OECD Test Guidelines or Guidance documents

- Propose activities on promising tests that need experimental pre-validation/validation work

Initial questions asked by the 1st VMG-NA

- Are there validated assays that should be given highest priority?
- Are there pre-validated assays that require validation work?
- Are there promising assays that need optimisation, pre-validation before being further considered ?
- Is there a need to develop DRP's?

VMG-NA's Five Main Areas

- I. HTPS-Receptor Binding Assays (ER, AR, TR)
- II. HTPS-Aromatase and Steroidogenesis assays
- III. HTPS-Reporter Genes and Transcriptional Activation Assays
- *IV. In Vitro* Cell/Tissue Assays
- V. QSARS and other *In Silico* Methods

I. HTPS-Receptor Binding Assays (ER, AR, TR)

- **Human recER receptor binding assay (Japan, US, EC)**
  - Several protocols are being tested. Will be merged to one ("GST-fused human estrogen receptor ligand binding domain expressed in *E. coli*" (CERI protocol), Pan Vera flourescent protocol)
  - Pre-validation underway
- **ER (rat uterine cytosol) and AR (rat prostate cytosol) receptor binding asays (US)**
  - Prevalidation and validation underway
- **Rat recAR (PanVera) binding assay (US)**
  - Looking for collaborators for the validation study
- **Thyroid Disrupting Assays**: Development of a DRP (US)
  - Joint activity between VMG NA, Eco and Mammalian

II. HTPS-Aromatase and Steroidogenesis assays

- **DRP's Aromatase and Steroidogenesis (US)**
  - Projects finished, recommendations followed
- **H295R Human Female Adrenocortical Carcinoma assay for steroidogenesis testing (US: collaboration with Japan and Denmark**
  - **Pre-validation underway, validation in 2007**
- **Sectioned Testis Steroidogenesis (US)**
  - Large variability in validation study, optimisation needed?
- **Human Recombinent Aromatase Assay and Placental Aromatase Assay (US)**
  - Validation done, peer review in 2006
- **Aromatase Inhibition/Induction (KGN-Cells) (Japan)**
  - Pre-validated, invitation to collaborators for validation study

III. HTPS-Reporter Genes and Transcriptional Activation Assays

- **Transient and stable ER/AR-Mediated Reporter Gene Assays (Japan)**
  - The transient assays are already validated
  - The stable assays will be validated in 2006/07
- **ER-TA Assay and Lumi-Cell Assay (US, Japan)**
  - Validation expected to be done in 2006/07, collaborations are sought
- **Other ER and AR TA Assayss that are under consideration for initial testing and prevalidation include ER-Calux and MELN(human breast cancer cell lines), AR-CALUX (bone cell line) and PALM (prostate adenocarcinoma cell line)**

IV. In Vitro Cell/Tissue Assays

- **Metabolism DRP (Belgium)**
  - Investigates metabolism in cell lines and gives recommendations, including a testing strategy
  - Final version will be presented at the VMG-NA3-meeting
- **In Vitro Vitellogenin DRP (Japan, UK and Sweden)**
  - A first draft will be presented at the VMG-NA3-Meeting
  - Describes factors needing optimisation before final test methods can be developed
  - SPSF not yet adopted by Member countries

V. QSARS and other *In Silico* Methods

- **An ED QSAR Task Group was established in 2005 and will be lead by EC-JRC; comprising experts from the US-EPA, ICCVAM, CERI and NIHS**
  - First task to develop QSARs for ER and AR binding
- **QSAR for ER-Binding (NIHS, CERI) and a Surface Plasmon Resonance System (NIHS) will be reported at the next VMG-NA**
- **Computox Programme (US)**
  - Goal to optimize *in vivo* and *in vitro* assays by using in silico methods for initial screening and prioritization

Synopsis

- The OECD is heavily engaged in validation of assays for ED assessments through the EDTA and the 3 VMG's
- At presently several assays are undergoing different stages of validation at the VMG NA
- A number of new *in vitro* Test Guidelines are expected to be proposed in the coming years for the level 2 of the EDTA Conceptual Framework.
- Challenges for the future:
  - How will the Conceptual framework be used?
  - Is there a need for a new testing strategy for ED chemicals?
  - Implications for MAD!

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