# The ECVAM's Business Plan: Realistic approach to deal with the upcoming dead-line challenge

*Elke Anklam*

**European Commission**

**Joint Research Centre**

**Institute for Health and Consumer Protection**

# The Mission of the EC-Joint Research Centre

**… is to provide customer-driven scientific and technical support for the conception, development, implementation and monitoring of EU policies.**

**As a service of the European Commission, the JRC functions as a reference centre of science and technology for the Union.**

**Close to the policy-making process, it serves the common interest of the Member States, while being independent of special interests, whether private or national.**

# 7 Institutes in 5 Member States

**IE - Petten The Netherlands**
**- Institute for Energy**

**IRMM - Geel Belgium**
**- Institute for Reference Materials and Measurements**

**ITU - Karlsruhe Germany**
**- Institute for Transuranium Elements**

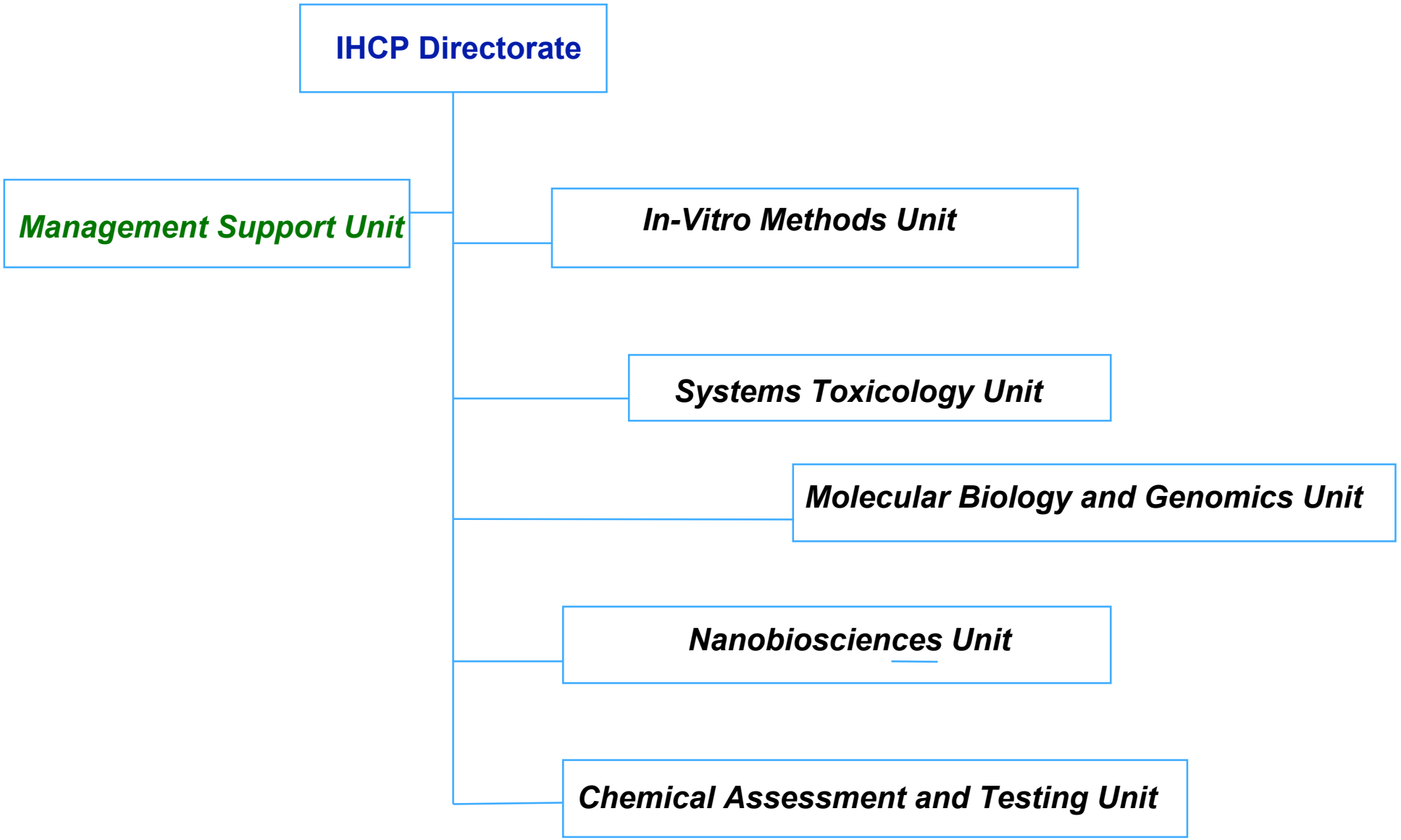
**IPTS - Seville Spain**
**-Institute for Prospective Technological Studies**

**IPSC - IHCP - IES - Ispra Italy**
**- Institute for the Protection and Security of the Citizen**
**- Institute for Health and Consumer Protection**
**- Institute for Environment and Sustainability**

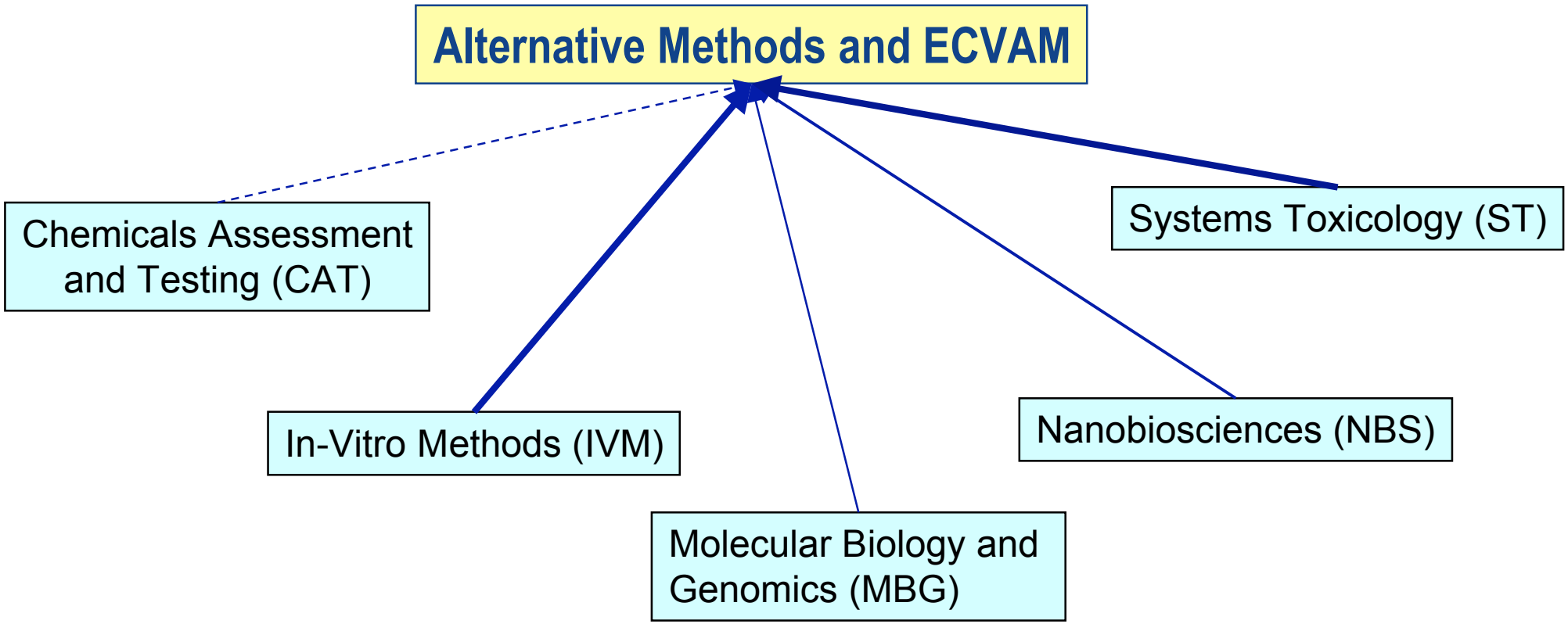
# The Mission of the IHCP

- *Is*
- to protect the interests and health of the consumer in the framework
- of EU legislation on chemicals, food, and consumer products by
- providing scientific and technical support including risk- benefit
- assessment and analysis of traceability.

***Science for a healthier life***


IHCP Directorate
Management Support Unit
In-Vitro Methods Unit
Systems Toxicology Unit
Molecular Biology and Genomics Unit
Nanobiosciences Unit
Chemical Assessment and Testing Unit

# JRC-IHCP Units Supporting ECVAM



# The ECVAM Action Plan 2008-2013: Rationale

**A previous business plan existed, however needed to be aligned as situation on available methods for validation was too optimistic**

**New business plan was requested by Commissioner J. Potocnik and JRC Director General R. Schenkel**

**Reasons:**

- **Deadlines of Cosmetics Directive**
- **Political Pressure**
- **Budget Complaints**

**ECVAM is an action within the JRC and has a multi annual and annual workplan**

# The ECVAM Action Plan 2008-2013: Contents

- Overview on toxicological endpoints and prospect of validation
- Overview on ECVAM's activities and methods validated so far
- Status of methods for deadlines as stated in Cosmetics Directive
- Barriers (bottlenecks) to validation
- The ECVAM action plan

# The ECVAM Action Plan 2008-2013: Bottlenecks to Validation

- Lack of availability of scientifically sound methods or testing strategies
- Lack of information on reference methods (from animal tests) or reference data on human effects
- Lack of test system materials (i.e. human tissue or cells)
- Difficulties in using human stem cells
- Lack of processes to validate test batteries ans strategies
- Duration of validation is long and costs are high

# The ECVAM Action Plan 2008-2013: Bottlenecks to Acceptance

- **Lack of information on reference methods (from animal tests) or reference data on human effects**
- **Regulatory acceptance process is too slow**
- **Too many players with different approaches in the regulatory acceptance field?**

# Main Provisions of Cosmetics Directive 2003/15/EC in Relation to Alternative Methods

- **An immediate marketing ban on new cosmetics** (finished products and ingredients) **tested on animals where alternative test methods have been validated** by ECVAM and accepted by the Community.

- **A complete marketing ban on cosmetics tested on animals 6 years after entry into force of the Directive, i.e. from 2009.**

(This date applies to all human health effects, apart from the toxicological areas which are exempted, and cannot be extended).

# Main Provisions of Directive 2003/15/EC in Relation to Alternative Methods

- **A marketing ban on cosmetics tested on animals for repeated-dose toxicity, reproductive toxicity and toxicokinetics 10 years after entry into force of the Directive, i.e. from 2013.**

(This date can be postponed by co-decision procedure, if for technical reasons one or several of these tests will not be validated and accepted by that date).

- **An immediate ban on animal testing for cosmetic finished products**.

- **A complete ban on animal testing for cosmetic ingredients 6 years after entry into force of the Directive, i.e. from 2009**.

(including the areas of repeated-dose toxicity, reproductive toxicity and toxicokinetics).

# 2009 deadline (test and marketing ban)



| Key area | Sub area | Status of alternative methods | Prospect of validation |
|---|---|---|---|
| *Systemic toxicity* | Acute oral toxicity: Neuro-, Nephro-, Hepato-, Hemato - toxicity, etc. | Methods under pre-validation*<br><br>Partial replacement method (for non-toxic substances) under validation | Some endpoints 2009-2011/2013<br><br>2009 |
| *Topical toxicity* | Skin corrosion | Replacement methods available EST-1000 assay (CellSystems; similar assay) under ESAC peer review | Done<br><br>2008 |
| | Skin irritation | Replacement method available; More methods (SkinEthic™ and updated EpiDerm™ assays) under ESAC peer review | Done<br><br>2008 |
| | Eye irritation | Methods for severe irritation available<br>Methods based on human reconstituted tissue models<br>Cell function-based/cytotoxicity assays retrospective validation (all methods need to be used in test strategies) | Done<br><br>2008-2010<br><br>2008-2009 (ESAC statement) |
| | Phototoxicity | Replacement method available | Done |
| | Skin penetration | Replacement method available | Done |

# 2009 deadline (test and marketing ban) - continued

| Key area | Sub area | Status of alternative methods | Prospect of validation |
|---|---|---|---|
| *Genotoxicity* | Genotoxicity | Methods validated (need to be used in test strategies. (In case of positive results, they require add. in-vivo tests)<br>Methods under pre-validation<br>Optimisation of existing testing strategy | Done<br><br><br><br>> 2010<br>2010-2015 |
| *Photogenotoxicity* | *Data on* photogenotoxic potential of a substance is not requested by SCCP | External validation study? | |

*within A-cute-tox

# 2013 deadline (marketing ban)



| Key area | Sub Area | Status of alternative methods | Prospect of validation |
|---|---|---|---|
| *Systemic toxicity* | Repeated dose toxicity | Some methods under R&D** | > 2013 |
| *Sensitisation* | Skin sensitisation | Refinement method available<br>Partial replacement methods under validation (need to be used in test strategies – no stand alone)<br>Methods under R&D*** (need to be used in test strategies – no stand alone) | Done<br>2010-2011<br>> 2012 |
| | Respiratory sensitisation | No methods | Unpredictable |
| *Carcinogenicity* | Carcinogenicity | Cell transformation assays under validation (partial replacement)<br>More methods under R&D**** | 2010-2012<br>> 2013 |
| *Reproductive Toxicology#* | Embryotoxicity | Embryotoxicity methods validated for a specific applicability domain | Done |
| | Testicular toxicity | Testicular toxicity methods optimised | > 2012 |
| | Female germ toxicity | Female germ toxicity methods optimised | > 2012 |
| | Endocrine disruptors, etc. | Endocrine disruptor methods in pre-validation and optimisation | 2009-2010 |
| | | Methods under R&D***** | > 2013 |
| | | Teratogenicity | > 2013 |
| | | Test batteries and strategies in development | > 2013 |
| | | Developmental neurotoxicity | |

# 2013 deadline (marketing ban) - continued

| Key area | Sub Area | Status of alternative methods | Prospect of validation |
|---|---|---|---|
| *Toxicokinetics#* | Blood brain barrier | Methods under pre-validation | 2013 |
| | Intestinal permeability | Methods under pre-validation | 2013 |
| | Biokinetics/Physiologically based kinetic modelling | Methods under R&D** | > 2013 |
| | Metabolism | Method under pre-validation | 2013 |
| | Metabolic induction | Method under pre-validation | 2013 |
| | Metabolism-mediated cytotoxicity | Method proposed for pre-validation | 2013 |

# Progress ECVAM activities in 2008

| | Development | Prevalidation | Validation | Regulatory acceptance |
|---|---|---|---|---|
| Skin Corrosion | ✓ | ✓ | ✓ | ✓ |
| Acute Phototoxicity | ✓ | ✓ | ✓ | ✓ |
| Skin Absorption / Penetration | ✓ | ✓ | ✓ | ✓ |
| Skin Irritation | ✓ | ✓ | ✓ | ongoing |
| Eye Irritation | ✓ | ✓ | ✓* | ongoing* |
| Acute Toxicity | ✓ | ✓ | ongoing* | |
| Genotoxicity / Mutagenicity | ✓ | ✓ | ✓* | ✓* |
| Skin Sensitisation | ✓ | ongoing | ✓* | ongoing* |
| Reproductive & Developmental | ✓ | ✓ | ✓* | ongoing* |
| Toxicokinetics / Metabolism | ✓ | ✓ | | |
| Carcinogenicity | ✓ | ongoing* | | |
| Subacute & Subchronic Toxicity | ✓ | | | |

* Reduction / refinement alternatives

# Actions taken within the JRC to improve the situation

# Actions taken: International Collaboration and Regulatory Process

**Memorandum of Collaboration between the international 'VAMs' – in finalisation**

**Discussions between EC and OECD to speed up the process – the JRC will second a Staff Member from January 2009 for at least 6 months**

**Discussions between EC, USA, Canada and Japan (ICATAM)**

**Establishment of website showing the regulatory status of methods (TSAR)**

# Actions taken: ECVAM and the JRC/IHCP

**ECVAM Business Plan**

**Annual Work Programme 2009**

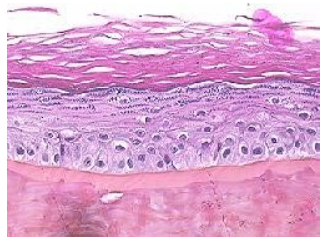
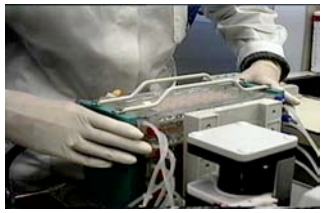
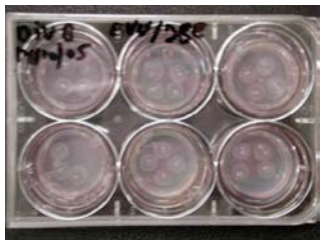
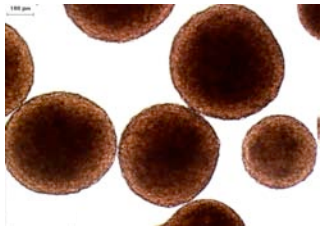
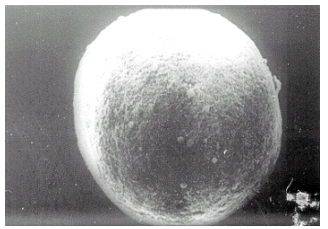
**Restructure of the JRC-Institute for Health and Consumer Protection**

**ECVAM will be treated as a horizontal (policy support) ACTION across the JRC-IHCP (no longer in one Unit only)**

**Set-up and Implementation of Integrated Testing Approach in IHCP**

# What expertise is available at JRC-IHCP

- Validation of alternative methods ('classical ECVAM') and method validation in general
- In-vitro methods and in-silico methods
- Automated systems for screening
- Nanosensors
- Omics (needs to be enlarged from metabonomics and toxicogenomics to proteomics)
- Databases

# Immediate Actions to be taken: Method validation

***Analysis, restructure and consolidation of processes for:***

- **Test method submission**
- **Test method evaluation and validation**
- **Confidentiality issues**
- **'Me-too' methods**
- **Peer review process**
- **Establishment of Stakeholder Experts Group for prioritisation of methods**
- **Revision of duties of ECVAM's Scientific Advisory Board (ESAC)**
- **Setting up new advisory structure of ESAC in line with Commission procedures for scientific committees within 2009**

# Immediate Actions to be taken: Method validation

***Validation and post-validation of available robust methods***

- **As outlined in ECVAM Business Plan and 2009 JRC Action Work Programme**

- **Training of Staff Members to become Study Directors**

- **More focus on method validation and optimisation of integrated testing approaches, less on method development respectively optimisation of single test approaches**

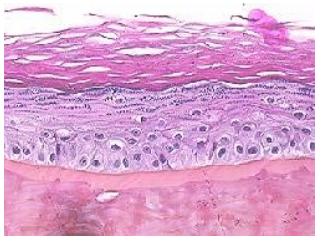
- **Increase knowledge management activities in line with (complementary to) EPAA activities**

# Immediate Actions to be taken: In-house Method Assessment

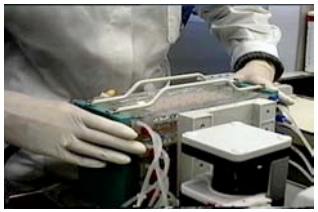
## *ECVAM's Laboratories*

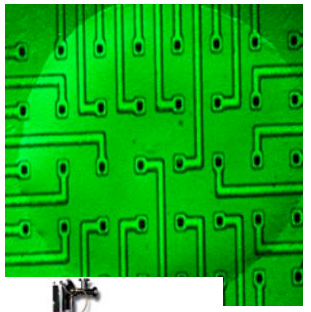
- **Restructure the IHCP laboratories**
- **GLP certification and ISO accreditation of in-house validaiton laboratory**
- **Prepare laboratories for training purposes**
- **Alignment of research activities (proactive method optimisation)**
- **Establish a repository of chemical substances**

# Concluding remarks

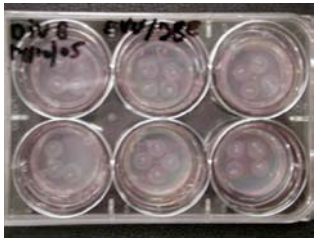


- ECVAM's prime role is validation of sound and valid alternative methods

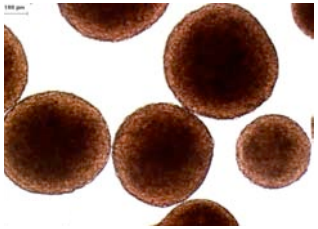


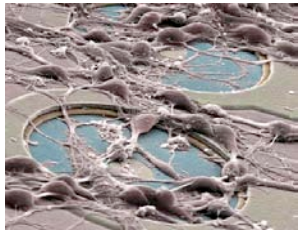


- Without good methods ECVAM cannot make the process faster – the main bottleneck is non available of methods to-date

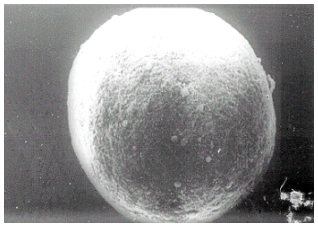


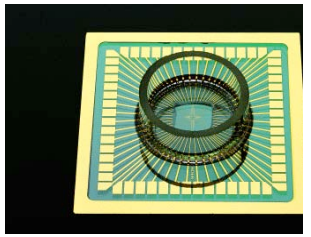
- 2009 Most deadline methods may be met, at least for scientific validation





- Difficulties to be expected for 2013 deadline methods





- ECVAM will strengthen its activities on integrated testing approaches with focus on robustness testing and validation


A successful ECVAM
requires
working together and interdisciplinarity
Thank you for your attention!