

**ICCVAM**

Interagency Coordinating  
Committee on the Validation  
of Alternative Methods

**NICEATM**

National Toxicology Program  
Interagency Center for the Evaluation of  
Alternative Toxicological Methods

# **ICCVAM Perspective on OECD Draft Guidance Document (GD) 34: Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment**

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**Report to the Scientific Advisory Committee on  
Alternative Toxicological Methods (SACATM)**

**October 20, 2004**

**Research Triangle Park, North Carolina**



**ICCVAM/NICEATM**

- ▶ **Brief history of the evolution of GD34**
  - ▶ OECD Solna Workshop (1996)
  - ▶ OECD Stockholm Conference (2002)
  - ▶ OECD Expert Consultation, CPSC, Bethesda (2004)
- ▶ **Revisions of Draft Guidance Document (GD34) on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment**  
(September 2001→October 2003→September 2004→October 2004)
  - ▶ Outline of content and issues
  - ▶ ICCVAM (major) comments on
    - ▶ September 2001 draft GD34
    - ▶ October 2003 draft GD34
  - ▶ GD34 revisions resulting in September 2004 draft
- ▶ **OECD Expert Consultation, October 13-15, 2004**

# Solna Workshop (1)

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- ▶ **October 1994:**
  - ▶ the 5th Meeting of the National Coordinators of the OECD Test Guidelines Program (WNT) agreed that an attempt should be made via OECD to internationally harmonize the various published and advocated concepts for the validation of alternative test methods
- ▶ **January 22-24, 1996:**
  - ▶ OECD Workshop on Harmonization of Validation and Acceptance Criteria for Alternative Toxicological Test Methods, Solna, Sweden
  - ▶ Final report [ENV/MC/CHEM/TG(96)9]: 02-August-1996
- ▶ **Scope of Solna Workshop:**
  - ▶ limited to the area of risk assessment of chemicals and chemical products
  - ▶ emphasis on alternative tests
  - ▶ included aspects of all Three Rs as defined by Russell and Burch in 1959: Replacement, Reduction and Refinement of animal tests

# Solna Workshop (2)

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- ▶ Objectives of Solna Workshop:
  - ▶ to reach international consensus on harmonized principles and criteria for the validation and acceptance of toxicological test methods with emphasis on alternative tests
  - ▶ to develop guidance for validation procedures including the purpose of the validation, selection procedures of tests to be validated, the review process, statistical data analysis, regulatory acceptance and further practical aspects
  - ▶ to discuss general principles concerning strategies for risk assessment which take into account alternative tests, and to reach consensus on certain testing strategies/schemes

# Solna Workshop (3)

- ▶ **Consensus Reached on Principles and Criteria for Validation and Regulatory Acceptance**
  - ▶ **Criteria for a Valid Test**
  - ▶ **Criteria for Regulatory Acceptance**
  - ▶ **Other Considerations**
    - ▶ *Flexibility*: the level of necessary reassurance through validation that is appropriate for a specific purpose varies and needs to be identified on a case-by-case basis
    - ▶ *Battery Approach*: individual test methods within a proposed battery should be validated, but the test battery itself need not be validated
    - ▶ *Adjunct Tests*: to refine the risk assessments, e.g. mechanistic studies may be exempt from validation
    - ▶ *Parallel Submissions* of data from existing and new methods helps facilitate regulatory acceptance of new methods
    - ▶ *Patented* [proprietary] test methods are not permissible as formal OECD TGs and could encounter regulatory agency resistance, and therefore need an avenue for consideration/validation/adoption

# Solna Workshop (4)

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- ▶ **Consensus Reached on the Validation Process**
  - ▶ Issues involving definitions, test development, test method optimization/prevalidation, readiness for validation, the conduct (process) of an (independent) peer review (not participants and prerequisites)
  - ▶ **Validation**
    - ▶ Planning of the validation study
    - ▶ Conduct of testing
    - ▶ Statistical recommendations
  - ▶ **Assessment of the results**
    - ▶ Data analysis
    - ▶ Evaluation of performance of alternative method
  - ▶ **Reporting of results**
    - ▶ In peer-reviewed journal
    - ▶ To regulatory authorities

# Solna Workshop (5)

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## ► Outcome:

### ► September, 1996:

- *Final Report of the OECD [Solna] Workshop on Harmonization of Validation and Acceptance Criteria for Alternative Toxicological Test Methods [ENV/MC/CHEM/TG(96)9]*

### ► September, 2001:

- *Draft Guidance Document [GD34] on The Development, Validation and Regulatory Acceptance of New and Updated Internationally Acceptable Test Methods in Hazard Assessment*

### ► November, 2001:

- Comments on draft GD34
  - ICCVAM/NICEATM comments: 24 pages
  - U.S. comments: ~70 pages (~2X the draft GD itself)

# Noteworthy ICCVAM Comments and Recommendations on Sept 2001 Draft GD34 (1)

- ▶ Hold an international workshop to address issues in the GD [became the Stockholm Conference, March 2002]
- ▶ Draft GD34 does not, and should, comply with many of the recommendations of the 1996 Solna Workshop/Report
- ▶ Draft GD differs substantially from the 1996 Solna Report, principally in content and organization, e.g. Validation Criteria, Acceptance Criteria, Management of the Validation Process, Independent Peer Review Process
- ▶ OECD should not imply itself to be the foremost validation authority and should acknowledge established organizations and their development of nationally and internationally harmonized criteria and processes for the validation and regulatory acceptance of new test methods
- ▶ Append contents of ICCVAM 1997 report where appropriate (*Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods*)
- ▶ Consider previously submitted ICCVAM comments on OECD document [ENV/JM/TG(2001)5] *Validation Issues: Current Practices and Issues For Consideration* as relevant to draft GD34

# Noteworthy ICCVAM Comments and Recommendations on Sept 2001 Draft GD34 (2)

- ▶ Include sufficient guidance for test sponsors regarding the submission of adequate data/information, including usefulness and limitations of the method
  - ▶ Utilize the ICCVAM guidelines for this purpose (*Evaluation of the Validation Status of Toxicological Methods: General Guidelines for Submissions to ICCVAM*, Revised October 1999, NIH Pub. 99-4496)
  - ▶ Adopt a standard submission format to help facilitate harmonization and standardization of necessary documentation and help facilitate the evaluation process and international endorsement of validated test methods
- ▶ The proposed OECD procedure for validating alternative methods is too cumbersome and costly and would yield few validated assays
  - ▶ OECD process should be cited as only one approach
  - ▶ Other (e.g. ICCVAM, ECVAM, ZEBET) approaches should also be described
- ▶ The GD should include a discussion about the importance of understanding the mechanistic relevance of test models

## Noteworthy ICCVAM Comments and Recommendations on Sept 2001 Draft GD34 (3)

- ▶ OECD should retreat from its proposal that it serve as both a formal international methods validation authority and a formal regulatory acceptance authority
- ▶ OECD's role should remain a methods harmonization authority that generates more flexible test guidelines based upon specific, standardized, validated protocols
  - ▶ Need clear lines of separation for validation study conduct, validation status evaluation, and regulatory acceptance
  - ▶ Need to avoid appearance of a potential conflict of interest (i.e. one organization assuming responsibility for validation, "independent" assessment, and regulatory acceptance)
  - ▶ Multilateral OECD roles could foster trade barriers and have significant consequences in light of the treaty obligations requiring mutual acceptance of data from OECD-accepted methods

# Stockholm Conference (1)

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- ▶ OECD Conference on Validation and Regulatory Acceptance of New and Updated Methods in Hazard Assessment, Stockholm, Sweden, March 6-8, 2002
  - ▶ Report of the Stockholm Conference on Validation and Regulatory Acceptance of New and Updated Methods in Hazard Assessment [ENV/JM/TG/M(2002)2/ADD1], September 30, 2002
- ▶ Proposed Aim:
  - ▶ To develop and achieve consensus on “practical guidance on principles and processes for the validation and acceptance of animal and non-animal test methods for regulatory hazard assessment purposes”
  - ▶ Consensus achieved would be used to revise the draft OECD Guidance Document GD34 (*The Development, Validation and Regulatory Acceptance of New and Updated Internationally Acceptable Test Methods in Hazard Assessment*)

# Stockholm Conference (2)

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## ► Specific Objectives

### ► Provide practical guidance on:

- how to adequately address established validation principles and criteria
- the conduct and management of the validation process
- how to adequately address established principles and criteria for regulatory acceptance of validated test methods including the submission of information to support their validity
- the process for independent peer review, regulatory consideration and implementation of new and updated test methods

# Noteworthy Issues and Recommendations of the Stockholm Conference (1)

- ▶ 40 recommendations for changes or inclusions in GD34
- ▶ Append "Solna [validation] Principles" to GD34
- ▶ GD34 should not be a checklist but should provide general guidance on and a structure for test validation
- ▶ GD34 should address aspects of validation of ecotoxicology tests
- ▶ Workshops Recommended:
  - ▶ OECD DIP (Data Interpretation Procedure)/PM (Prediction Model) workshop
    - ▶ Hosted by ZEBET, Berlin, Germany, July 1-2, 2004
    - ▶ To provide guidance and clarification on DIPs and PMs: concepts, terminology, breadth of applicability, facilitating revision of GD34
      - Consensus not reached on these issues
      - + Recommendation that ICCVAM Performance Standards be included in GD34 and included in future OECD Test Guidelines
  - ▶ OECD workshop on acquisition and use of human data as reference data for validation studies where appropriate
    - Workshop did not take place

# Noteworthy Issues and Recommendations of the Stockholm Conference (2)

- ▶ Guidance on role, membership, and operation of VMG (Validation Management Group) needed
- ▶ Peer review process should be fully transparent (including availability for public comment) and separate and distinct from the validation process
- ▶ Independence of peer review process essential
  - ▶ Potential conflicts of interest need be avoided
    - ▶ Peer reviewer panelists must be:
      - ▶ independent of test sponsor
      - ▶ independent of anyone involved in the validation study
      - ▶ devoid of any interests (other than academic) in the test of concern
- ▶ Publication of a validation study in a peer-reviewed scientific journal, though recommended, is no substitute for an independent peer review process

# Noteworthy Issues and Recommendations of the Stockholm Conference (3)

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- ▶ GD should provide guidance on how tests can enter the validation process at different stages, based upon level of development, prior use, available data, proposed use
- ▶ Guidance needed on roles of tests as components of test batteries and testing strategies
- ▶ Guidance needed on validation of (Q)SARs and other computer-generated database systems
- ▶ Explanations/details necessary for certain concepts:
  - ▶ "Catch-up" or "bridging" validation
  - ▶ Retrospective validation vs. prospective validation
  - ▶ Application of similar standards for validation to any test
  - ▶ "Provisionally acceptable" tests (*those tests where relevance could only be partially addressed during validation because the test's endpoint had not been previously considered*)

# Noteworthy Issues and Recommendations of the Stockholm Conference (4)

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- ▶ Chemical selection for validation studies should include input from relevant regulatory authorities
- ▶ Reference chemicals selected should be relevant to the adverse effect or mechanism of concern and the species of concern
- ▶ Relevant good quality human reference data, if available, should be utilized
- ▶ Definitions used should be consistent and harmonized with those in other international documents
- ▶ Other issues addressed: animal welfare, GLP compliance, proprietary methods, regulatory input into validation studies, regulatory justification for acceptance/rejection decisions

# Guidance Document GD34, October 2003 Draft

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- ▶ *Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment* (title revised)
- ▶ Table of Contents
  - ▶ Preamble
  - ▶ Executive Summary
  - ▶ I. Introduction
  - ▶ II. Definition of the Test Method
  - ▶ III. Test Method Development
  - ▶ IV. Test Method Optimization [Pre-Validation]
  - ▶ V. Test Method Validation
  - ▶ VI. Independent Evaluation of a Validation Study (Peer Review)
  - ▶ VII. Regulatory Acceptance of Validated Tests
  - ▶ VIII. New Test Submissions: Supporting Documentation
  - ▶ IX. References
  - ▶ ANNEX I: "The Solna Principles and Criteria"
  - ▶ ANNEX II: Definitions and Glossary
  - ▶ ANNEX III: ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods

# Highlights of ICCVAM Recommendations/ Comments on GD34, October 2003 Draft (1)

- ▶ The purpose and perspective of the GD are not clearly stated. Rather than discussing validation from a general viewpoint, the document appears to speak too much from the perspective of OECD itself performing the validations rather than from the perspective of a general guideline for performing validation-related activities by various groups, sponsors, or organizations.
- ▶ The GD suggests that proof of the ability of a lab to comply with GLP can substitute for demonstrated competence in a specific test method. However, these two concepts are independent and not interchangeable.
- ▶ Potential OECD conflict-of-interest issues reiterated [slide 10]
- ▶ The GD should describe the experiences and processes of the many national and international organizations involved in development of harmonized criteria and processes for the validation and regulatory acceptance of new test methods

# Highlights of ICCVAM Recommendations/ Comments on GD34, October 2003 Draft (2)

- ▶ Chapter V, "Test Method Validation"
  - ▶ The GD should describe and emphasize generic processes that reflect the fundamental principles of high quality scientific validation study approaches common to all validation studies (including those used by ECVAM, ICCVAM/NICEATM and other government and non-government laboratories)
  - ▶ ∴ a description of the procedures OECD recently applied to in vivo endocrine disrupter testing methods is inappropriate
  - ▶ The GD should include a discussion about the importance of understanding the mechanistic relevance of test models, their limitations, and usefulness
- ▶ Chapter VI, "Independent Evaluation of a Validation Study (Peer Review)"
  - ▶ Should provide practical generic guidance for independent peer review evaluation and regulatory acceptance processes for new and revised test methods (recommended for previous [9/2001] draft) that reflect the salient recommendations from the 2002 Stockholm conference
    - ▶ OECD-specific procedures and processes not present in the 9/2001 draft and not addressed at the 2002 Stockholm Conference are now included and should be deleted and replaced with ICCVAM-recommended language

## Highlights of ICCVAM Recommendations/ Comments on GD34, October 2003 Draft (3)

- ▶ It is unlikely that the large majority of the tests used by some regulatory agencies will or could be validated under the OECD procedure outlined
- ▶ It may not be appropriate for some specific methods of limited application to undergo generalized validation
- ▶ ∴ ICCVAM recommends the inclusion of the following language in the GD:
  - ▶ "The guidance in this document is intended to be sufficiently flexible so that it can be used for any type of test, regardless of whether it is an *in vitro* or *in vivo* test, or a screening test or a definitive test. Nevertheless, it should be recognized that other validation frameworks and schemes may be necessary and appropriate for hazard/risk assessment test methods that are commonly used in some agencies, such as those dealing with evaluation of biologics safety and efficacy."

# GD34, September 2004 Draft

- ▶ *Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment* (title maintained as revised, October 2003 draft)
  - ▶ Revised 21 September 2004 by OECD Secretariat
  - ▶ To serve as a working document for the planned OECD GD34 Expert Consultation Meeting (ECM), 13-15 October 2004
- ▶ **TABLE OF CONTENTS**
  - ▶ PREAMBLE
  - ▶ EXECUTIVE SUMMARY
  - ▶ I. INTRODUCTION
  - ▶ II. DEFINITION OF THE TEST METHOD
  - ▶ III. TEST METHOD DEVELOPMENT
  - ▶ IV. **TEST METHOD PREVALIDATION**
    - ▶ *General Considerations*
    - ▶ *Participating Laboratories*
    - ▶ *Conduct of Prevalidation*
    - ▶ *Evaluation of the Prevalidation*

# GD34, September 2004 Draft: Table of Contents (cont'd)

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## ▶ V. TEST METHOD VALIDATION

- ▶ General Considerations
- ▶ Management of the Validation Process
- ▶ Statistical Support
- ▶ Prediction Models and Data Interpretation Procedures (PMs, DIPs)
- ▶ Reference Data
- ▶ Between-Laboratory Validation Phase
- ▶ Definition of Purpose and Objectives of the Test
- ▶ Selection of Participating Laboratories
- ▶ Monitoring of Participating Laboratory Performance
- ▶ Selection of Test Chemicals and Chemical Management
- ▶ Coding and Distribution of Test Samples
- ▶ Testing
- ▶ Data Collection
- ▶ Data Analysis
- ▶ Reporting
- ▶ Record-Keeping/Data Dissemination

# GD34, September 2004 Draft: Table of Contents (cont'd)

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- ▶ V. TEST METHOD VALIDATION—  
Other Considerations
  - ▶ Flexibility
  - ▶ Potential Improvements to an Approved Test
  - ▶ Test Battery and Tiered Testing Strategy Approach
  - ▶ Retrospective Validation
  - ▶ Validation of (Quantitative) Structure-Activity-Relationship Systems (Q)SARs
  - ▶ Patented Methods
  - ▶ Performance Standards for Test Methods

# GD34, September 2004 Draft: Table of Contents (cont'd)

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- ▶ VI. INDEPENDENT EVALUATION OF A VALIDATION STUDY (PEER REVIEW)
  - ▶ General Considerations
  - ▶ Mechanisms for Peer Review
  - ▶ Selection of Peer Reviewers
  - ▶ Charge to Peer Reviewers
  - ▶ Peer Review Process
- ▶ VII. INTERNATIONAL REGULATORY ACCEPTANCE OF VALIDATED TESTS
  - ▶ Validation Study Outcomes
  - ▶ Applicability Domain
  - ▶ Criteria for Regulatory Acceptance
  - ▶ From Protocol to Test Guideline

# GD34, September 2004 Draft: Table of Contents (cont'd)

- ▶ VIII. NEW TEST SUBMISSIONS: SUPPORTING DOCUMENTATION [based upon ICCVAM Submission Guidelines]
  - ▶ Introduction and Rationale for the Proposed Test Method
  - ▶ Test Method Protocol Components
  - ▶ Characterisation of the Substances Tested to Validate the Proposed Test Method
  - ▶ *In Vivo* Reference Data Used to assess the Accuracy of the Proposed Test Method
  - ▶ Test Method Data and Results
  - ▶ Test Method Accuracy
  - ▶ Test Method Reliability (Repeatability/Reproducibility)
  - ▶ Test Method Data Quality
  - ▶ Other Scientific Reports and Reviews
  - ▶ Animal Welfare Considerations (Refinement, Reduction and Replacement)
  - ▶ Practical Considerations
  - ▶ References
  - ▶ Supporting Material

# GD34, September 2004 Draft: Table of Contents (cont'd)

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## ▶ IX. REFERENCES

- ▶ ANNEX I: ~~"The Solna Principles and Criteria"~~  
Definitions and Glossary
- ▶ ANNEX II: ~~Definitions and Glossary~~  
Examples of Test Method Validation
- ▶ ANNEX III: ~~ICCVAM Guidelines for the  
Nomination and Submission of New, Revised,  
and Alternative Test Methods~~
  - ▶ Deleted as an annex and incorporated into text  
in abbreviated (outline) form to provide guidance on  
content and organization of test method submissions  
for evaluation of validation status

# Principle Changes to GD34, Sept 2004 Draft

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- ▶ Attempted to broaden the document and have it express the current thinking on validation of test methods and their subsequent translation into OECD test guidelines
- ▶ Effort to make GD34 a more generic document and less prescriptive
- ▶ Substantially revise the document to be responsive to comments and recommendations of OECD member countries and participants of the 13-15 Oct 2004 ECM
- ▶ Minor changes introduced:
  - ▶ Reorganization of several sections to improve clarity
  - ▶ Terminology changes, e.g., within-laboratory, between-laboratories, and prevalidation
  - ▶ Replacement of figures
  - ▶ References have been updated, but still need further editing

# Principle Changes to GD34, Sept 2004 Draft: Topics Extensively Revised or Newly Introduced

- ▶ Rewritten: Introduction, to mirror comments by OECD member countries
- ▶ Extensively Rewritten: Chapter V, Test Method Validation—
  - ▶ section on the Validation Management Group
  - ▶ section on the management of the validation process
  - ▶ **ICCVAM suggestions on Performance Standards** included
- ▶ Completely Revised: Chapter VI, Peer Review—
  - ▶ Added: portions of **ICCVAM proposal on Independent Evaluation of a Validation Study (Peer Review)**
  - ▶ Deleted: reference to OECD peer review options and related figures
- ▶ Revised: Chapter VIII, New Test Submissions: Supporting Documentation—
  - ▶ **ICCVAM Submission Guidelines** introduced in abbreviated form
- ▶ Deleted: Annex with the Solna Principles
- ▶ Deleted as annex, but incorporated into text: **ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods**
- ▶ Added: New Annex II (Examples of Test Method Validation)—
  - ▶ Template suggested for describing criteria and peer review approaches in a more general way for different types of tests
  - ▶ Includes examples for *in vitro*, *in vivo*, ecotoxicity, biodegradation tests

# Highlights of OECD Expert Consultation Meeting (ECM) on GD34, October 13-15, 2004 (1)

- ▶ Purpose: a "revision meeting" of invited experts from member countries and organizations
  - ▶ to resolve remaining differences between OECD member countries that would allow for finalization of GD34
    - ▶ to consider comments received from OECD member countries plus subsequent comments regarding the October 2003 draft GD34
    - ▶ to discuss the WNT recommendations (May 2004), re. broadening of GD34 to include:
      - ▶ several other types of tests (e.g. biodegradation, ecotoxicology, *in vivo* and chronic testing)
      - ▶ different approaches to validation employed by OECD member countries
  - ▶ to consider proposed modifications to the draft GD34 (21 September 2004) made by the OECD Secretariat and to further rework and improve the draft and ready it for WNT, April/May 2005
- ▶ Hosting Country: U.S. (ICCVAM/NICEATM)
- ▶ Hosting Agency: U.S. Consumer Product Safety Commission (CPSC), Bethesda, Maryland
  - ▶ Dr. Marilyn Wind, Vice-Chair, ICCVAM

# Highlights of OECD Expert Consultation Meeting (ECM) on GD34, October 13-15, 2004 (2)

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## ▶ Day 1:

- ▶ Spent reaching consensus on specific issues identified by the Secretariat as needing resolution, e.g. ECVAM's Modular Approach to Validation, management of the validation process, peer review, flexibility in the validation process, ecotoxicity, reference chemicals

## ▶ Day 2:

- ▶ Identifying additional important elements that needed consideration, areas of controversy, topics in need of clarification or elaboration, consideration of supplementary text and annexes
- ▶ Chapter-by-chapter revision: reorganization of chapters and chapter sections to improve continuity
- ▶ Identifying examples of validation activities—practical guidance: specific examples of test methods that have gone through a validation and the processes employed

## ▶ Day 3:

- ▶ Breakout Groups assigned specific chapters to edit, rework, draft new text as appropriate
- ▶ Next Steps: further revision of the document, drafting assignments (homework) over next 4 weeks, timelines, readying the draft for WNT

# Highlights of OECD Expert Consultation Meeting (ECM) on GD34, October 13-15, 2004 (3)

- ▶ Substantial progress was made in achieving consensus regarding many previously controversial issues
- ▶ Progress made in reorganizing/redrafting/editing of the GD
- ▶ Members of the Expert Consultation Group
  - ▶ worked in concert to generate an acceptable draft
  - ▶ set out to achieve a common goal: to revise and improve GD34
    - ▶ transform it into a document that embraced and complemented the validation principles and guidelines established by recognized validation bodies, but not supplant them
    - ▶ assist OECD in finalizing the GD so as to:
      - ▶ develop a more generic document
      - ▶ capture validation aspects and scientific arenas previously overlooked
      - ▶ meet the needs of member countries
      - ▶ avoid potential incompatibilities between GD34 and the validation principles/guidelines of established international validation bodies
      - ▶ provide guidance that is user-friendly to all stakeholders
  - ▶ left the ECM with more homework than they had anticipated



# U.S. Consumer Product Safety Commission

