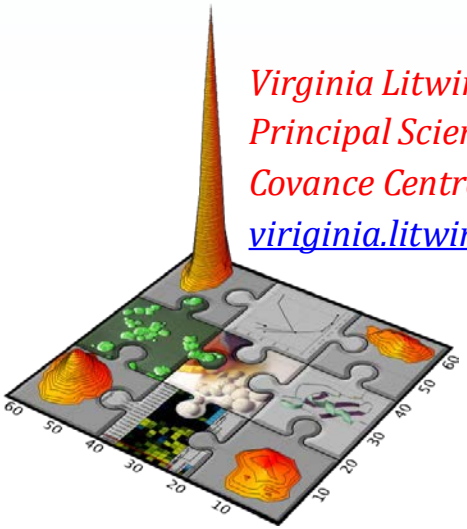
New Recommendations for Clinical Flow Cytometry Laboratory Developed Tests from the International Council for Standardization of Haematology and the International Clinical Cytometry Society

MetroFlow Fall 2014
Union, NJ



Virginia Litwin, Ph.D.
Principal Scientist, Hematology/Flow Cytometry
Covance Central Laboratory Services, Inc.
viriginia.litwin@covance.com

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Acknowledgements

Bruce H. Davis, MD

President, Trillium Diagnostics, LLC

Past President, Clinical Cytometry Society

Treasurer, International Council for Standardization in Haematology (ICSH)

Vice Chair and Past-Chair, CLSI area committee for Hematology

Past Treasurer and Co-founder, International Society for Laboratory Hematology (ISLH)

Teri A. Oldaker, CLS (ASCP), CC

Presentation Overview

Stakeholders for Flow Method Validation

Timeline Flow Method Validation

ICSH/ICCS Recommendations

Late Breaking News!

Next Steps

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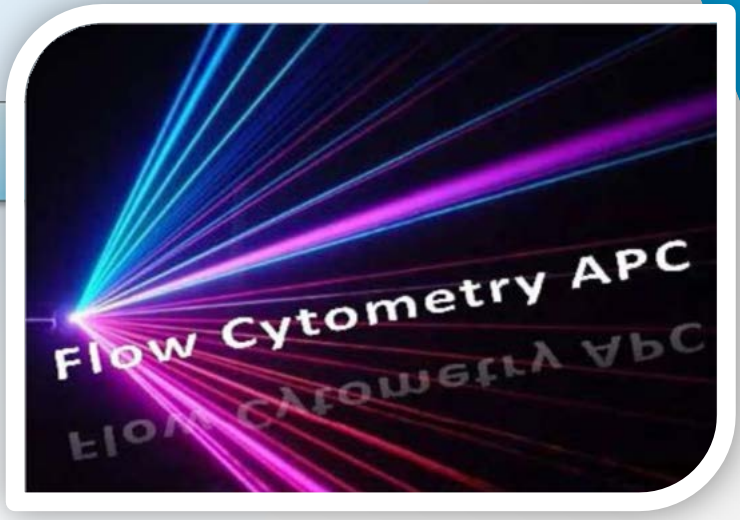
Stakeholders

- Pharmaceutical Industry
- Clinical Laboratory Medicine
- Technology/Scientific Sector

Pharmaceutical Industry

AAPS Flow Cytometry APC

To promote discussion regarding the proper application of flow cytometry in drug development with an emphasis on establishing best practices regarding assay and instrument validation.



AAPS, Bio-Tec Section, Ligand Binding Assay Bioanalytical Focus Group, Flow Cytometry Action Program Committee

LinkedIn/Groups Flow Cytometry Action Program Committee
http://www.aaps.org/Ligand_Binding_Assay_Bioanalytical

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Pharmaceutical Industry

European Bioanalytical Forum

- Objective
- Flow cytometry harmonization
- Increase the use of flow cytometry techniques in drug development programs with an emphasis on biotherapeutics
- Whitepaper
  - The use of flow cytometry in a regulated environment
  - Manuscript in preparation

http://www.europeanbioanalysisforum.eu

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Clinical Laboratory Medicine

ICSH

International Council for Standardization in Haematology

- Founded as a standardizing committee associated with the European Society of Haematology in 1963.
- The ICSH is a not-for-profit organisation that aims to achieve reliable and reproducible results in laboratory analysis in the field of diagnostic haematology.
- The ICSH coordinates Working Groups of experts to examine laboratory methods and instruments for haematological analyses, to deliberate on issues of standardization and to stimulate and coordinate scientific work as necessary towards the development of international standardization materials and guidelines.

http://icsh.org

Clinical Laboratory Medicine

International Clinical Cytometry Society

Dedicated to promoting excellence in clinical applications of flow cytometry through practice, education, and research. Members include all individuals engaged in the practice of clinical flow cytometry, whether on the bench or at the bedside.

http://www.cytometry.org

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Technology/Scientific Sector

International Society for Advancement of Cytometry

- To serve a multidisciplinary community by leading technological innovation, scholarship, and the exchange of knowledge in the quantitative cell sciences.
- Our vision is to advance the impact of cytometry in meeting current and emerging challenges in the life, biomedical, and physical sciences

http://isac-net.org

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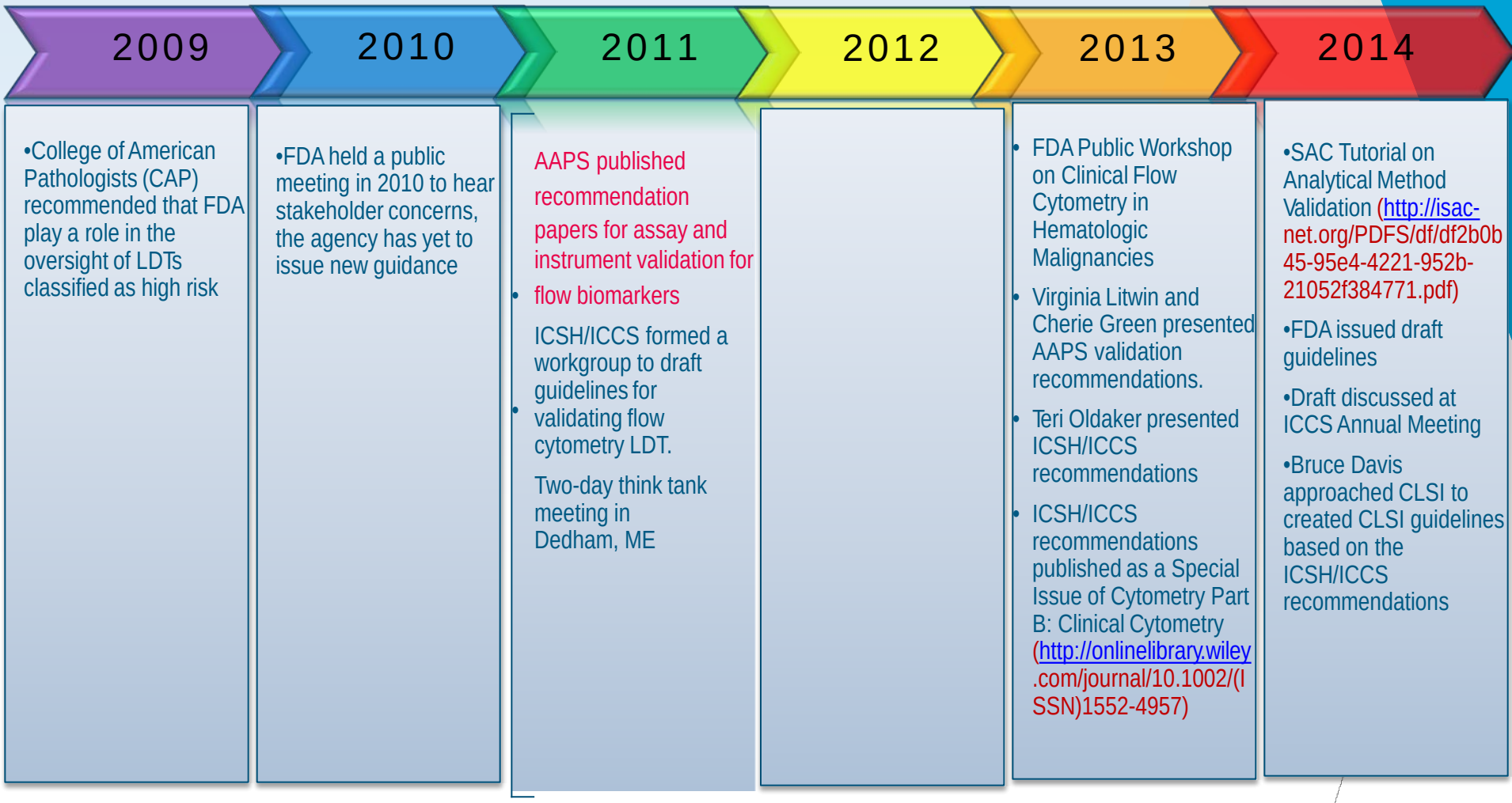
Flow Method Validation/LDT Timeline



http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm334772.htm

Recommendations for the validation of flow cytometric testing during drug development: I instrumentation

Cherie L. Green[a], Lynette Brown[b], Jennifer J. Stewart[b], Yuanxin Xu[c], Virginia Litwin[d], Thomas W. McCloskey[e]*

Recommendations for the validation of flow cytometric testing during drug development: II assays

*Denise M. O'Hara[a], Yuanxin Xu[b], Zhiyan Liang[c], Manjula P. Reddy[d], Dianna Y. Wu[e], Virginia Litwin[f],**

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Public Workshop on Clinical Flow Cytometry in Hematologic Malignancies, February 25-26, 2013

The purpose of this public workshop is to seek input from academia, Government, laboratorians, industry, clinicians, patients and other stakeholders on the role of clinical flow cytometry in hematologic malignancies, ***in order to develop a specific regulatory policy for this class of in vitro diagnostic devices.***

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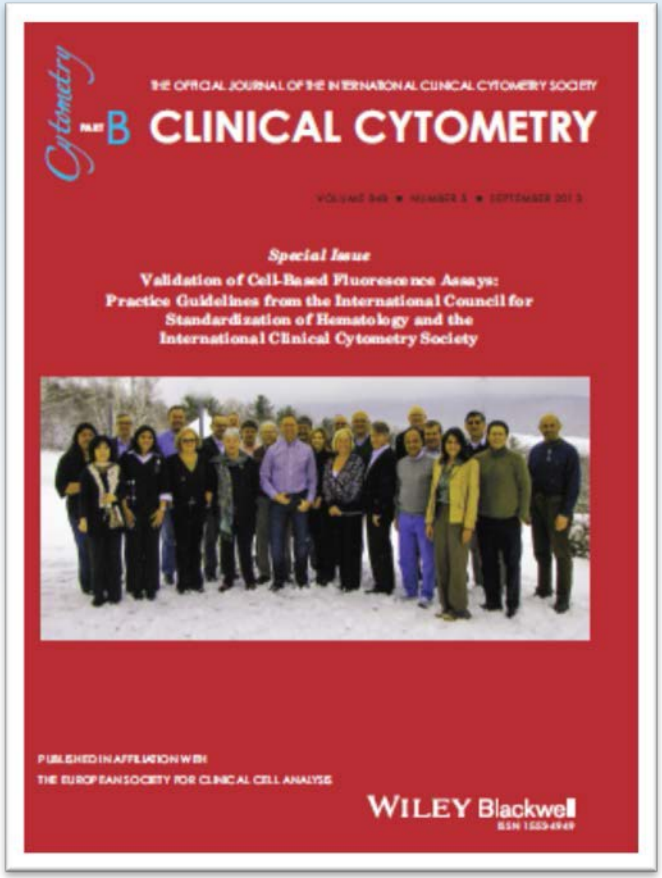
ICSH/ICCS Recommendations



Cytometry Part B (Clinical Cytometry) 84B, 2013

Special Issue

Validation of Cell-Based Fluorescence Assays: Practice Guidelines from the International Council for Standardization of Haematology and International Clinical Cytometry Society

Written by an ICSH/ICCS Workgroup

http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4957

ICSH/ICCS Guidance Document

What

- **Broad, expert -driven guidelines to address the uniqueness of cell based assay validations**
- **Pre-analytical Considerations**
  - Sample storage, stability, transport
  - Cell counts, viability and use of morphology as needed
- **Analytical Performance**
  - Optimization/validation of instrument, sample prep, antibody/reagents, compensation and data analysis
- **Performance Characteristics**
  - Validation samples
  - Detailed criteria to assess required performance specifications
- **Post-analytical Considerations**
  - Resulting categories, data and sample storage
  - Internal and external quality assurance

ICSH/ICCS Guidance Document

Who

- Chairs: Brent Wood (ICCS/ICSH) ,David Barnett (UK NEQAS, UK), Teri Oldaker (ICCS), and Bruce H. Davis (ICSH; CLSI)
- 36 International Experts
  - *USA, UK, France, Spain, Canada, Germany, S Korea, China, Japan, The Netherlands, Australia*
  - *EuroFlow, Pharma Clinical Trials, FDA, Flow Diagnostic Companies, National and International Reference Labs*
- 10 Observers (Corporate Sponsors)
- Experience in the development and/or standardization of cell-based fluorescence assays

ICSH/ICCS Guidance Document

Who

- Bruce H Davis MD, Amar Dasgupta MD, Steven Kussick MD, Jin Han MD PhD, Annalee Estrellado, Patrick O'Neil
- Shabnam Tanqri MD, Horacio Vall PhD, David Kaplan MD, Bob Hoffman PhD, Norman Purvis PhD, Anna Porwit MD PhD, Ben Hunsberger, T. Vincent Shankey PhD
- Brent Wood MD PhD, Dragan Jevremovic MD, Marie C Béné PharmSciD PhD, Ming Yan, Patrick Jacobs, Virginia Litwin PhD
- David Barnett PhD, Raul Louza, Peter Gambell, Jitakski De MD, Teri Oldaker, Curtis Hanson MD

ICSH/ICCS Workgroup

Why

- **Controversy and confusion about regulation of laboratory-developed tests (LDT) in diagnostic laboratories in the USA**
  - *Testing in diagnostic laboratories is regulated by Centers for Medicare and Medicaid Services (CMS)*
  - *Approval for In Vitro Diagnostic Tests is regulated by the FDA*
  - *In 2009, the College of American Pathologists (CAP) recommended that FDA play a role in the oversight of LDT*
- **The FDA had not *at that time* issued guidance documents regarding LDT**
  - *Most current guidance documents were designed for clinical chemistry methods*
  - *There is a need for flow-specific guidelines*
  - *Flow-specific guidelines should be prepared by flow experts*

Laboratory-Developed Tests
CAP Suggests Added Oversight of Homebrews

- CAP recommended →
  - more FDA oversight for high risk LDT
  - Stronger CLIA accreditation for labs with low or moderated risk LDT
- Major change in position
  - Old position
    - The fear was that if the FDA had to approve all LDTs in a manner similar to what it does for drugs and complex devices, it could stifle innovation in lab testing and delay patient access to valuable tests
  - New Position
    - "as more and more LDTs came along, we decided it would be appropriate to restudy the issue
- We believe FDA oversight will preserve safety while allowing innovation."

CAP's Views on LDT

Laboratory-Developed Tests
CAP Suggests Added Oversight of Homebrews

Three-tier System

- low, moderate, or high risk tests

❑High-risk tests

▪Reviewed by the FDA

❑Low-risk tests

▪laboratory accreditor would verify validation procedures and compliance with accreditation standards during normally scheduled inspections.

❑It's the College's view that its regulatory proposal would require modification of CLIA regulations but not new legislation.

CAP LDT Oversight Model

Classification	Determining Factors	Oversight	Examples
Low Risk	The test results is often used in conjunction with other findings to establish a diagnosis. No claim that the test result indicates prognosis or direction of therapy The test presents low risk to patients.	The laboratory performs and reviews validation internally prior to offering the test clinically. The accreditor will verify, during the normally scheduled inspections, that the laboratory performed appropriate validation studies	Cytokeratin Fragile X
Moderate Risk	The test result is often used for predicting disease progression of identifying whether a patient is eligible for a specific therapy. The laboratory may make claims about clinical accuracy or clinical utility The test poses a moderate level of risk to patients	The laboratory must submit validation studies to the accreditor for external review prior to offering the test clinically.	KRAS HER2

CAP LDT Oversight Model

Classification	Determining Factors	Oversight	Examples
High Risk	The test result predicts risk, progression, patient eligibility for a specific therapy.	The laboratory must submit the test to the FDA for review prior to offering it clinically.	Oncotype DX
	The test uses proprietary algorithms for computations such that the test result cannot be tied to the methods used of inter-laboratory comparisons cannot be performed.		
	The test poses potentially significant risk to patients.		

Flow MRD, CLL, infection (CD64), Rh Immune globulin Rx in FMH, Immuno-deficiency

Leukemia and Lymphoma Evaluation; MRD Detection; PNH Diagnosis;

Major factor in decision to use cytotoxic therapies; Rh Immune globulin Rx in FMH; ~ $200K/yr for Solaris Rx in PNH

Why is the a Concern to ICSH/ICCS?

Used for more that 30+ years

Variety of applications

- Simple enumeration assays (CD4, CD34)
- Complex pattern recognition (Leukemia)

Numerous consensus documents and standards

- Published in peer reviewed journals

Established EQA surveys

Regulated by CAP/CLIA

Most are LDT

FDA Involvement

Early 1990

- FDA claimed authority to regulate LDT
- Exercised “enforcement discretion”

2014

- FDA is asserted the right to regulate all laboratory-developed tests but has exercised discretion about which tests to review
- LDT to be subjected to the same requirements as IVD

Cell-based Fluorescent Assays In Flow

FDA Cleared
Lymphocyte subsets(TBNK)
CD34 Stem Cell Counts
FMH by anti-HbF or anti-RhD

LDT
Infection/sepsis
Anti-PMN titer (ANCA)
HLA-B27
Hematopathology and MRD
Genetic immunodeficiency Assays
Allogenic transfusion detection

LDT, CLSI/ICSH Consensus Method
Leukemia/ Lymphoma/ MDS evaluations
PNH screen
Reticulocytes, including IRF
Chronic Granulomatous Disease/PMN dysfunction
Hereditary Spherocytosis and related defects (EMA test)
Immunoplatelet count (CD61, CD42, CD41)
Genetic causes of bleeding or thrombo-cytopenia

Challenges to Flow FDA Clearance

Evolving Technology

- 4 Colors → 5/6 Colors → 8 Colors → >10colors
- More Biomarkers Available - Clinical Utility

Consensus For Leukemia, Lymphoma, and MDS Diagnosis

- Partial at Best
- Apprentice Nature of Medical Training

Cost Prohibitive

- Annual Sales of < $1,000,000

No Existing "Predicate Devices"

- Requires Expertise by Regulatory Reviewers
- Requires Guidelines Appropriate to the Technology

Challenges to Flow FDA Clearance

Specific Concerns Relating to Hematologic Malignancies

Interpretative Nature of Data Analysis

- **Unlike**
  - Simple Chemistry Analyte
  - Nucleic Acid Test Positive/Negative
- **Like**
  - H&E or IHC in Histopathology
  - The Slide/Plots do not Provide the Diagnosis, the Interpreter Does!
- **Flow Is Used In Conjunction With Other Test Results to Make a Diagnosis**

ASR Rule Impact to Constituents

ASR Rule 1997 (2007) to Facilitate Availability of Assays with Unintended Impact

ASR Cocktails

- No longer available for purchase
- Labs must create their own
  - Clinical lab resources are primarily dedicated to testing, not manufacturing, but forced do to so
  - Reduced quality
- Manufacturers cannot promote combining ASRs

Information Restrictions

- Manufacturers cannot provide medical or performance claims
- Manufacturers cannot provide guidance on validation
- Clinical labs are obstructed from access to information

ASR Rule Impact to Constituents

Manufacturers are Reluctant to Sell Non-FDA Cleared Instruments to Clinical Labs, Clinical Labs are Obstructed from New Technology

RUO Antibodies – Not Available to Clinical Labs

Validation of Cell-based LDTs

- No clear guidelines
- Challenges due to lack of available samples

This has impacted the ability of labs to provide patient access to critical and innovative tests leading to the perception that regulatory protection has impeded providing quality care to U.S. patients.

The Regulatory Climate is Changing

- Increased Uncertainty About LDT Regulations and Oversight
- Labs Concern About CLIA vs FDA Requirements for LDT Validations
- Manufacturers Concern About Cell Based 510K and PMA Requirements
- Requests for Guidance from Our Constituents
- We Decided to be Proactive and Develop a Guidance Document

LDTs in Clinical Flow Cytometry

Few FDA Cleared Assay In Clinical Cytometry

- T Cell Subsets with Applications in HIV or AIDS
- FMH Assay Kits with Anti-D and Anti-HBF
- CD34 Stem Cell Counts
- ASR Classification Concept Used as "Back Door", But Limited to One Analyte Per Assay in a Multiparametric Technology, Therefore In Typical Multi-color Practice Are LDTs

LDT Assays In Flow Cytometry Represent Majority of Testing

- Panels for Leukemia, Myeloma, Lymphoma and MDS Diagnosis
- Paroxysmal Nocturnal Hemoglobinuria (PNH) Testing
- Leukocyte Dysfunction Syndromes (CGD, Cd11b/18 Deficiency , Etc.)
- Minimal Residual Disease Studies for Leukemia, Lymphoma, and Myeloma
- Sepsis Detection: Neutrophil CD64 , CD35, And Cd11b

Barriers to FDA Clearance for FCM Testing

Barriers to FDA clearance – LDTs Will Remain

- Lack of consensus for Leukemia, Lymphoma, and MDS diagnosis
- Technology continues to evolve – 4 color, 5/6color, 8 color, 9+ colors
- Interpretative nature of flow cytometry – not simple chemistry analyte or nucleic acid test positive/negative
- ASR regulations not consistent, not understood and may be modified
- No existing “predicate devices” – requires both expertise by regulatory reviewers and flexible guidelines
- 510(k) process revision proposal anticipated for Fall 2011
- Requests for additional information, often on clinical outcomes being requested, along with triplicate sites being requested for each flow cytometer model – **expensive or cost prohibitive**
- Lack of consensus guidelines specific for validation of cell-based assays – shoehorn guidelines for soluble analytes

Regulatory Climate is Changing, Impacting the Clinical Laboratory and Practice of Laboratory Medicine

- FDA intends to regulate laboratory developed tests (LDTs) – FDA hosted a 2 day workshop for public comment in College Park, MD, July 2010; Proposed Guidelines pending Fall, 2011
- FDA is in the process of revising the 510(k) and PMA approval process for in vitro diagnostic devices (IVDs), new rules likely to be implemented in Fall 2011
- FDA has released draft guidelines for use of IUO/RUO labeling instructing industry to develop parental attitude toward “clinical” customers
- FDA released draft guidelines for clearance of companion diagnostics and industry asking for more regulations on clinical lab LDT “me too” assays
- Relevance to cell based fluorescence measurements (FCM) is that currently no guideline exists either for laboratory practice or regulatory assessment (no CLSI or ICSH guidelines)
- European CE mark process likely to evolve as well regarding IVDs
- Russia, South America, Canada and Australia have increasing regulatory oversight of IVDs within the last few years

Dt.aft Guidance 01.. Industi 'Y and Food and n . ug Administi ation Staff

Commet'cially Disti ibute d In Vitt o Diagnostic PI·o ducts Labeled o Reseai ch l Jse Only 01 Inv estigati onal Use Only: FI equently Ask ed Questions

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UOCUJnent issued OR: June·], 2011

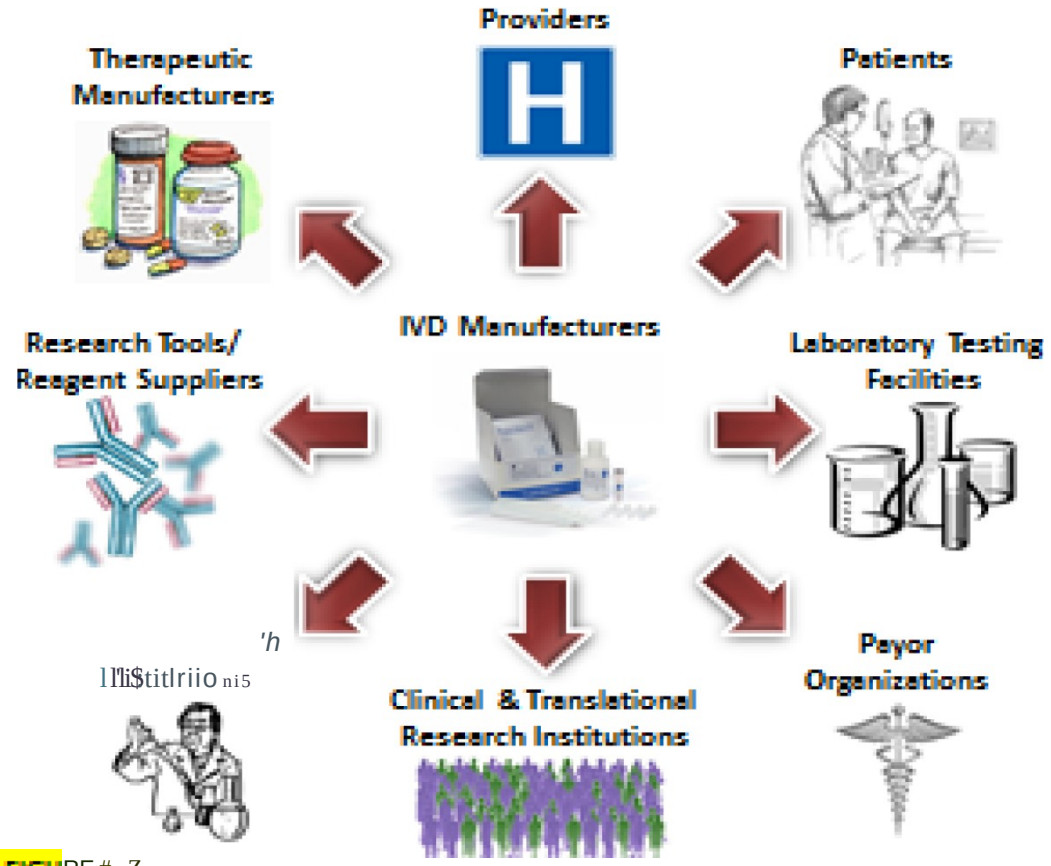
y;ou should submit comn1ents and suggestions regarding tlii.s draft docutll.eDt \vithin 90 days of publication in the *Federal Register* of the notice annooocing the availabillity of the draft guidance. Submit written.comments to the Div:ision ofDookets Management (HFA-305), Food and Drug Adnllnistration, 5630 Fishers Lane, nn. 1061, Rockville, I\ID 20852. Submit electronic comn1ents to b :/lv,rv,rv,r.re ations. ov. ldent:ifv aU conunents \ViJth the docket number listed in

St;akeholdeliS Involved w ith RUO & IUO IVDs

RUO and IUO IVDs are used by several stakeholders in various capacities

Scientia d ISO

KEY STAK EHOLDERS INV O LVED V..'ITH RUOs/ IUOs



KEY TAK EAVc.' Y-A 5

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  - Basic research
  - Clinical research trials
  - Development of lab tests
  - Use in therapeutic manufacturing and development
  - Use in the provider setting
- Htw I t:he:SJet ests. are re;gulated g-oing fOn:'Tard ".1iIl im Jact th e:se stakE holde r :so:me more d ramatically th an oth ers

FIGURE # Z

Source: Scientia analysis

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Draft Guidance for Industry aud Food and Drug Administration Staff

In Vitro Companion Diagnostic Devtces

DR.AFT GCllDA rVCE

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DocwneDt issued oD: Ju)y 14 2011

Ym1 should snbnrit c:onnnents and Slllggesfions regarding this draft doe1.maent Nl!tbim 60 days of public.ation in fue *Federal RRgi.ster* of the notice annnmcing the availability of the draft guidance_Submit 11.1.rite n oonunents to the D!1.risio n of Dockets l\1anagemmt (HF -305) Food and Dn1g }_dm nistra t i 5630 F!shers Lane n n 1061, Rockvil[e MD 20852_Subrmt electroruc comments to http J/l:Tyfilr..regulations_gov_Identify all oonu:nents l\rith the docket number listed *m* the notice of a\lailabiliry tbatp Ubl-Shes m the *F€d€rol Ritgistu_*

FDA Proposes to Revise IVD Review Process

- October 2011: Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health (CDRH), claims his agency is working to make medical device clearance standards more consistent and predictable. Companies have long complained about inconsistent standards and sudden changes in the approval process when applying for 510(k) clearance or pre-market product approval.
- Institute of Medicine of the National Academies Report: Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years
- Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process Board on Population Health and Public Health Practice
- Institute of Medicine of the National Academies
- available from The National Academies Press at http://www.nap.edu/catalog.php?record_id=13150

Where to go From Here?

- Cytometry community experts need to develop guidelines for assay validation that is tailored and appropriate for cell-based assays and provide guidance to practitioners and regulators
- International Council for Standardization in Haematology (ICSH) initiated a project guideline for validation of fluorescent cell based assays. Intended for peer reviewed publication.
  - Organizational meeting 26 -27 March 2011, Dedham, Maine
  - Sponsored by ICSH, ICCS with major support from Abbott, Beckman Coulter, Becton Dickinson, Mayo Clinic, PhenoPath, Clarient, Arista, Biogen, Covance
- Propose Guideline from CLSI through Area Committees of Hematology and I/LA on Cell-based Assays
- CAP should improve efforts to recruit experienced laboratory inspectors from ICCS and ESCCA (long history of education) and accept responsibility for meaningful laboratory accreditation in flow cytometry

The Centers for Medicare & Medicaid Services (CMS) regulates all laboratory testing (except research) performed on humans in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA) (CDC, CLIA 88). The objective of the CLIA program is to ensure quality laboratory testing for approved, marketed drugs. Although technically, clinical trial samples are considered clinical research samples and do not fall under CMS regulations, for the most part, the analysis of clinical trial samples intended for drug safety assessment, diagnostic testing to meet enrollment criteria, and disease monitoring for efficacy assessment, is conducted in CLIA certified laboratories.

Late Breaking News!

FDA Issues 2 Draft Guidance Documents in October 2014

Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories/ Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

Flow Cytometric Devices/Draft Guidance for Industry and Food and Drug Administration Staff

Regulatory Oversight of LDT

Contains Nonbinding Recommendations
Draft - Not for Implementation

Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

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Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: October 3, 2014

You should submit comments and suggestions regarding this draft document within 120 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact LDTframework@fda.hhs.gov. For questions regarding this document as applied to devices regulated by CBER, contact the Office of Communication, Outreach and Development in CBER at 1-800-835-4709 or 240-402-7800 or ocod@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of In Vitro Diagnostics and Radiological Health

Center for Biologics Evaluation and Research

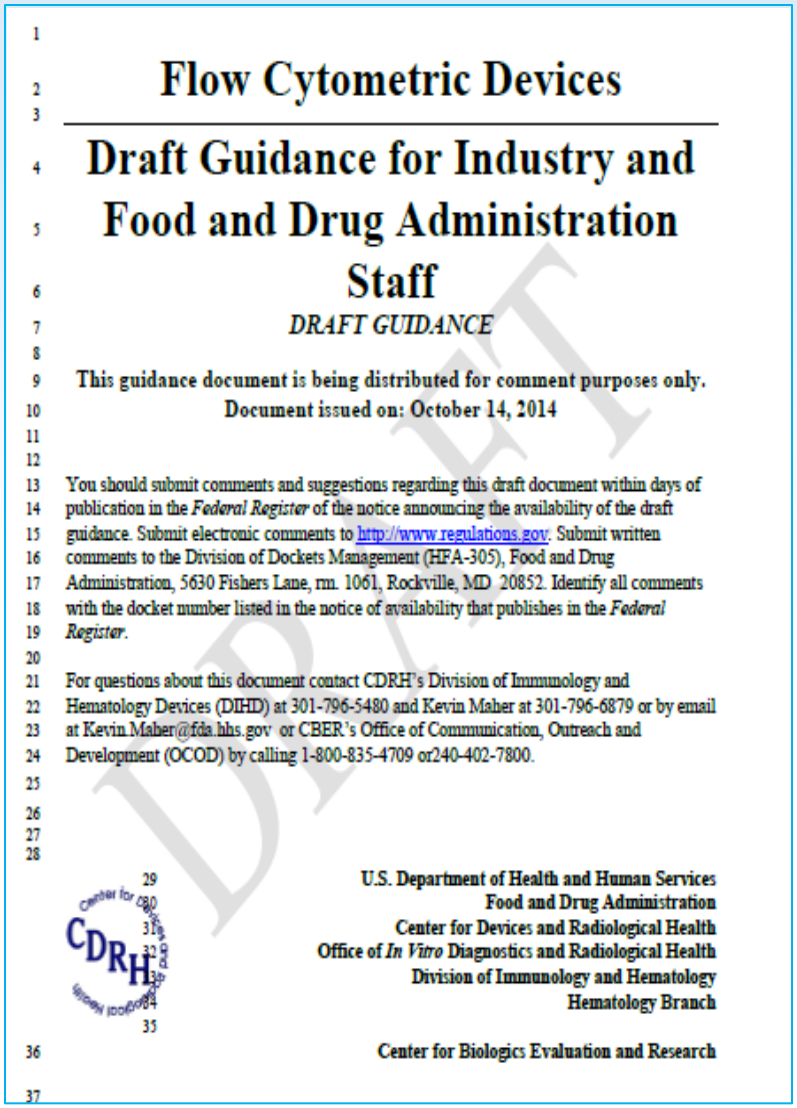
Assay = Device

Defines LDT as an IVD intended for clinical use and designed, manufactured and used with in a single laboratory

Assays designed by entities owning several labs and developing an assay in one lab and transferring the assay to other labs within the network are NOT LDT.

States that CLIA accreditors only evaluate the lab's ABILITY to perform the test but does not evaluate the VALIDITY of the test.

Flow Cytometric Devices



Flow Cytometric Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Document issued on: October 14, 2014

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For questions about this document contact CDRH's Division of Immunology and Hematology Devices (DIHD) at 301-796-5480 and Kevin Maher at 301-796-6879 or by email at Kevin.Maher@fda.hhs.gov or CBER's Office of Communication, Outreach and Development (OCOD) by calling 1-800-835-4709 or240-402-7800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of *In Vitro* Diagnostics and Radiological Health
Division of Immunology and Hematology
Hematology Branch

Center for Biologics Evaluation and Research

- Only addresses IVD, LDT
- Out-of-date
  - Innovative blood collection tubes not mentioned
  - Does not use accepted terminology for analytical categories, i.e. quasi-quantitative
  - Unware of >3-4 color assays
  - Not applicable for digital instruments
- References from publications
  - 7 of 8 are before 2002
  - No reference of AAPS and ICSH/ICCS recommendations
  - No reference to EuroFlow and ERIC consensus for harmonization
  - No reference to >6 color assay design
  - No reference to >6 color assay instrument QA

Next Steps

Request to Clinical and Laboratory Standards Institute to adopt Special Issue into CLSI Flow Cytometry Guidelines

Summary

Two Major Issues:

1. **Validation of Flow Cytometric Methods**
   - Lack of official guidance documents for flow cytometric method validation
     - This affects the Pharma Sector, Clinical Laboratories, and IVD manufacturers
2. **FDA Oversight of Flow Cytometric LDT**