Analysis and Impact of the FDA Guidance on Companion Diagnostics

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VP Regulatory Affairs and Compliance,
Metamark Genetics, Inc.

Chairman, Companion Dx Working Group,
Association of Medical Diagnostics Manufacturers

Metamark GENETICS, INC.

Path for Personalized Medicine in 2010:

"To make progress, the NIH and the FDA will invest in advancing translational and regulatory science, better define regulatory pathways for coordinated approval of codeveloped diagnostics and therapeutics, develop risk-based approaches for appropriate review of diagnostics to more accurately assess their validity and clinical utility, and make information about tests readily available."

The Path to Personalized Medicine, by Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.; N Engl J Med 2010; 363:301-304, July 22, 2010

FDA Intent and Industry Hopes

- FDA to produce related guidances
  - Guidance on Companion Diagnostics
  - Recast 2005 Draft Guidance on Co-Development
  - Further guidance updates

End of slide show, click to exit.

Good Guidance Practice (GGP) Refresher Course

- Documents prepared for CDRH staff, regulated industry and the public
- Guidances relate to:
  - the processing, content, and evaluation of regulatory submissions
  - the design, production, manufacturing, and testing of regulated products
  - the inspection and enforcement procedures
- Contain Nonbinding Recommendations, do not establish legally enforceable responsibilities
- Submit comments within 90 days of publication

What guidance documents is CDRH considering for development during fiscal year 2011?

CDRH is considering developing a variety of guidance documents in fiscal year 2011:

- Guidance Related to FDAAA or General Premarket Issues
- Guidance on Postmarket and Compliance Issues
- Device Specific Guidances
- Radiation Emitting Products Guidances
- Global Harmonization or Standards Related Guidances
- Cross-Cutting, Process, and Other Guidances

Specific topics are listed below:

Guidance Related to FDAAA or General Premarket Issues

- Tracking Pediatric Device Approvals
- 30-Day Notices and 135-day PMA Supplements
- Annual Reports for PMAs
- Medical Device Premarket Clinical Studies: Levels of Evidence

Guidance on Postmarket and Compliance Issues

- Manufacturing Site Change Supplements: Content and Inspectional Considerations
- Medical Device Reporting for Manufacturers
- Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act
- "510k Actions"-FDA and Industry Actions on Premarket Notification Submissions
- Research Use Only
- Distinguishing Medical Device Enhancements from Product Recalls and Corrections
- Electronic Medical Device Reporting

Device Specific Guidances

- Topical Oxygen Chamber for Extremities
- Quality Systems for Laboratory Developed Tests
- Medical Device Appeals and Complaints: Guidance on Dispute Resolution
- Medical Devices Containing Materials from Animal Sources (except IVDs)
- Medical Device Home Use

List of guidance documents CDRH is considering for development this year (2011):

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109196.htm

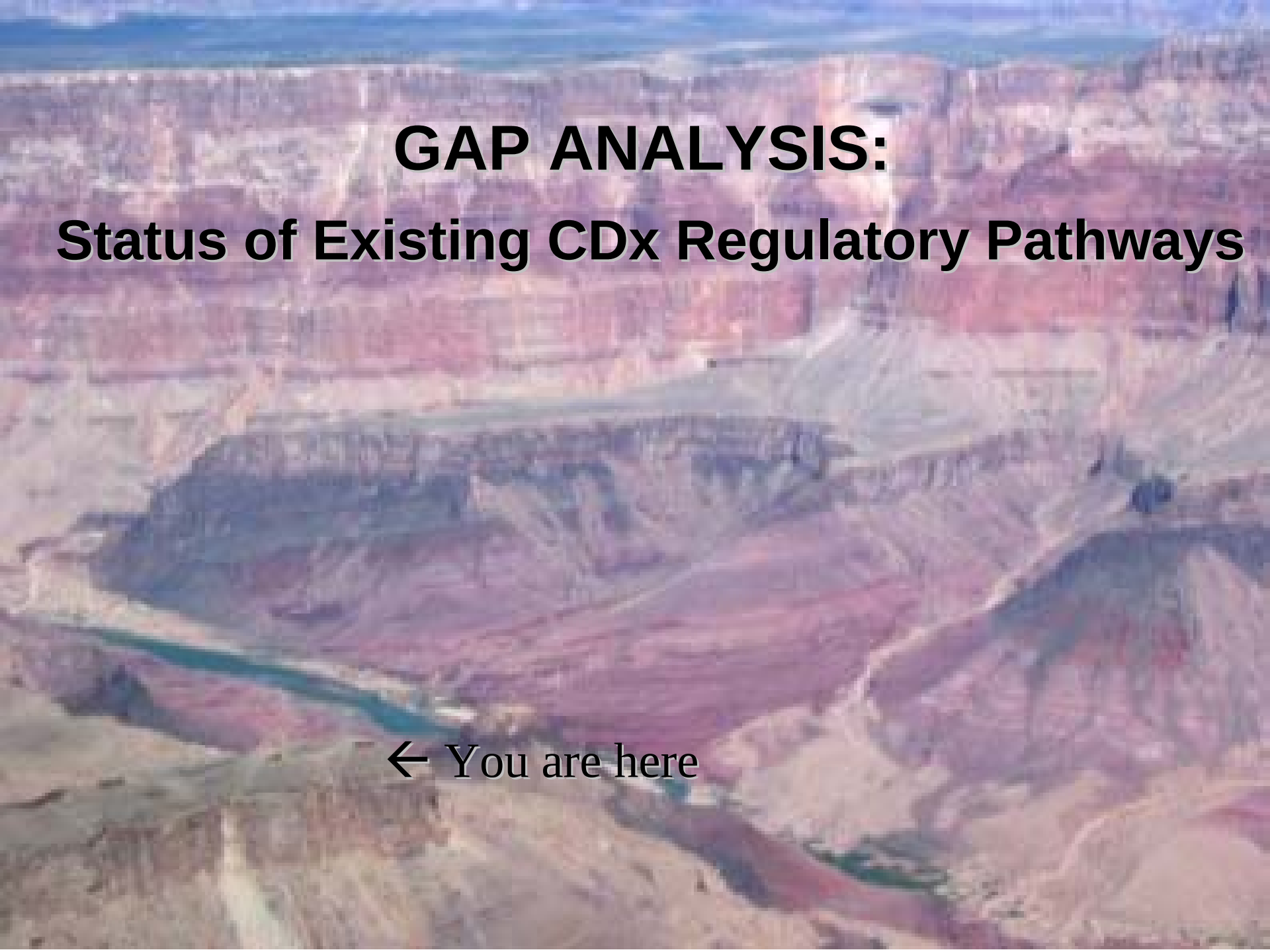
- "510k Actions" - FDA and Industry Actions on Premarket Notification Submissions
- Research Use Only
- Quality Systems for Laboratory Developed Tests
- … and …
- Suggestions?

FDA Encourages Industry Input:

- “You may submit written comments or suggestions for new guidance,”
- to the Division of Dockets Management (HFA-305), Food and Drug Administration, 563 0Fishers Lane, rm. 1061, Rockville, MD 20852.
- Submit electronic comments to http://www.regulations.gov2.
- Identify comments with docket number FDA-2007-N-0270.

AMDM Companion Diagnostics Working Group Membership

- Voisin Life Sciences
- Hogan Lovells
- XDx, Inc.
- DOCRO
- FDA / CDRH
- Celera
- Roche Diagnostics
- Roche Molecular
- Biosite
- AMDM
- Phadia US Inc.
- Micell
- Gen-Probe
- FDA / OIVD
- Abbott Molecular
- Abbott Diagnostics
- Siemens
- Caris Dx
- Canon US Life Sciences
- LabCorp
- Metamark Genetics, Inc.

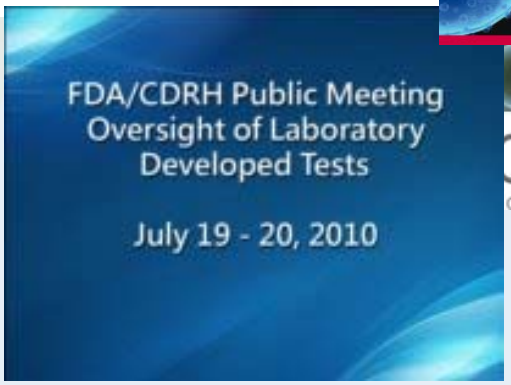

GAP ANALYSIS:
Status of Existing CDx Regulatory Pathways
← You are here

Companion Diagnostics - The Regulatory Hurdles

a panel discussion of Industry and FDA

Barcelona, Spain

th January 2011



"The Gray Sheet"

ICAL DEVICES, DIAGNOSTICS & INSTRUMENTATION

January 11, 2010 Volume 36 Number 2 Page 20

Dx Groups To FDA: Time For Companion Diagnostics Guidance Is Now

Industry groups representing test manufacturers, labs, drug firms and others are redoubling their pressure on FDA to clarify the regulatory requirements for co-development of diagnostics and drug treatments.

White Paper
Table of Contents

- CLARIFIED DEFINITION REQUIRED
- BEYOND GENETIC TESTING
- MOVING BEYOND ONCOLOGY AS THE FOCUS OF CDx
- APPLICATIONS
- LABELING STANDARDIZATION
- REGULATION LEVEL OF CDx ASSAYS (THE LDT ISSUE)

White Paper
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Dr. Lawrence Lesko, RAPS Focus, March 2011

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- THE COMBINATION PRODUCT MISNOMER - MIS-CATEGORIZATION AS A COMBINATION PRODUCT
  - HOW BEST TO USE OCP, OFFICE OF COMBINATION PRODUCTS
- COORDINATION AND FORMALIZATION OF MEETINGS
- SUBMISSION TIMING AND CONCLUSION
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Other Types of Combinations of FDA Regulated Products

A combination product as defined in 21 CFR § 3.2(e), is a product comprised of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product .

Some products are used together in a way that does not meet the regulatory definition of a combination product, but that may raise similar development or regulatory issues.

These kinds of products may include the concomitant use of drugs, devices, and/or biological products that are not "individually specified" in the product labeling (see 21 CFR 3.2(e)(3)); and combinations of drugs, devices and/or biological products with other types of FDA-regulated articles, such as dietary supplements, cosmetics, or foods.

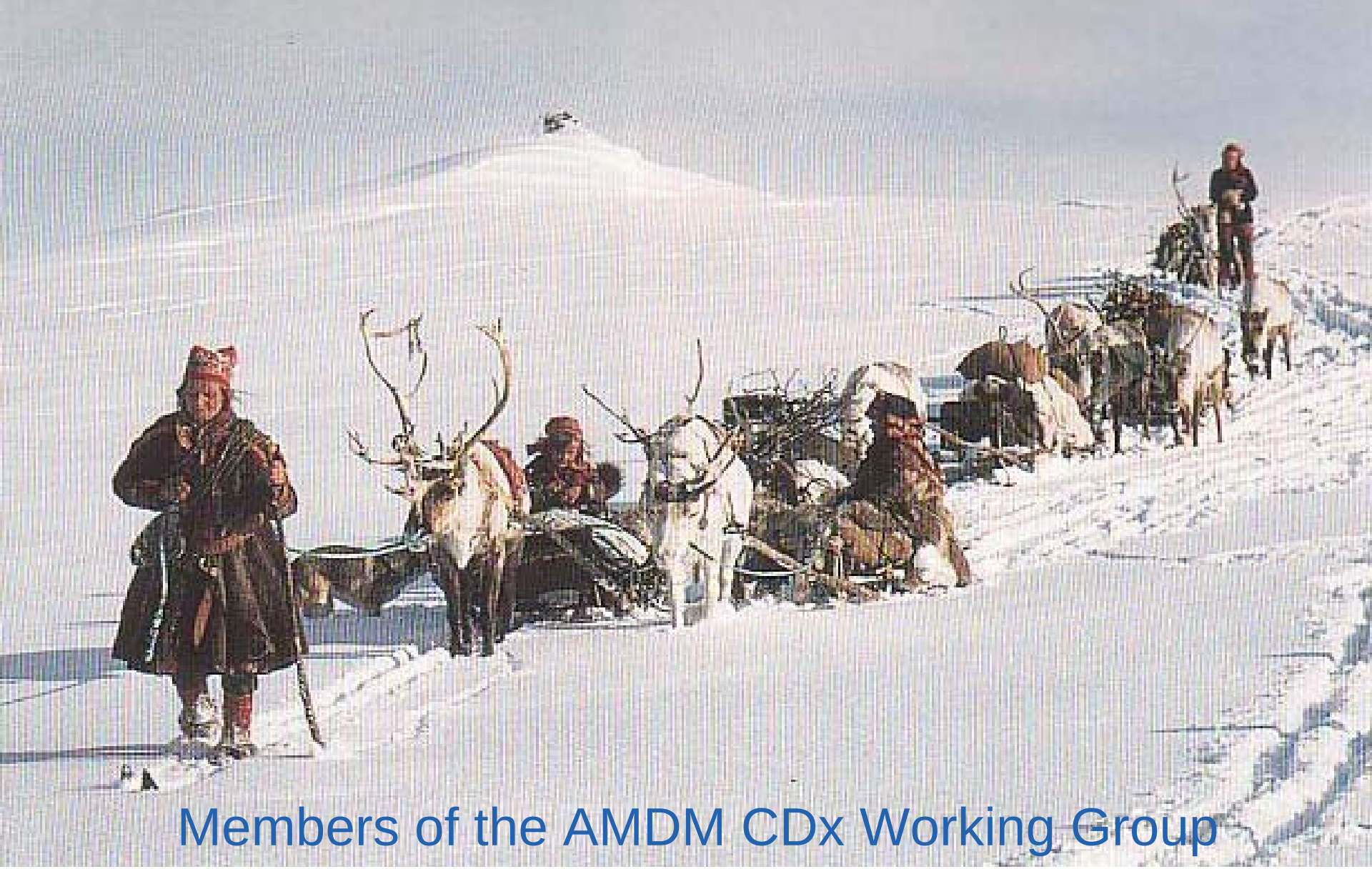
This website will provide links to information on recently approved products of this type and other related information in an effort to keep stakeholders informed.

Examples of These Types of Products

- FDA Approves First Head & Neck Cancer Treatment in 45 Years Data Shows Treatment with Erbitux Extends Survival
- Actonel with Calcium Supplements
- Vectibix (panitumumab) and EGFR pharmDx(r) Test Kit
- DakoCytomation's c-Kit (9.7) pharmDx and Gleevec

White Paper
Table of Contents (cont.)

- COLLECTION OF SAMPLES, CLINICAL TRIAL DESIGN
- INCENTIVES FOR AN IVD MANUFACTURER TO PURSUE A CDx
- INDUSTRY PARTNER UNDERSTANDING Rx/Dx
- BIOMARKER APPROVAL, COLLABORATION, CO-UTILIZATION



Members of the AMDM CDx Working Group continuing on the path

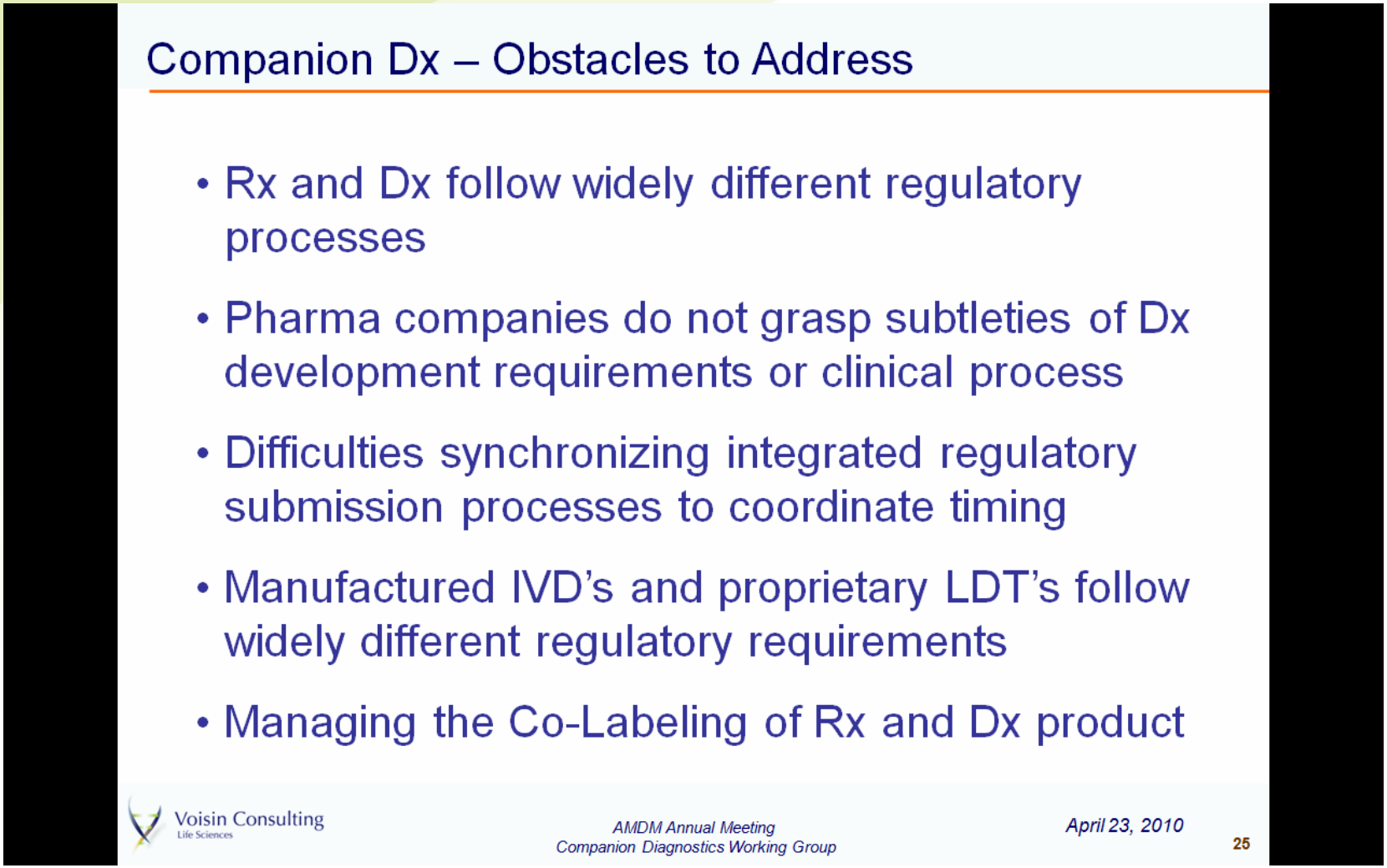
Path for Personalized Medicine per NEJM

To make progress, the NIH and the FDA will

- invest in advancing translational and regulatory science,
- better define regulatory pathways for coordinated approval of co-developed diagnostics and therapeutics,
- develop risk-based approaches for appropriate review of diagnostics to more accurately assess their validity and clinical utility, and
- make information about tests readily available.

The Path to Personalized Medicine, by Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.; N Engl J Med 2010; 363:301-304, July 22, 2010

Last Year AMDM Annual Meeting Request:



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Center Responsibilities Within the FDA

Therapeutic Focus-

- CDER
- CBER
- ODE/CDRH

Diagnostics Expertise-

- OIVD
- OBRR

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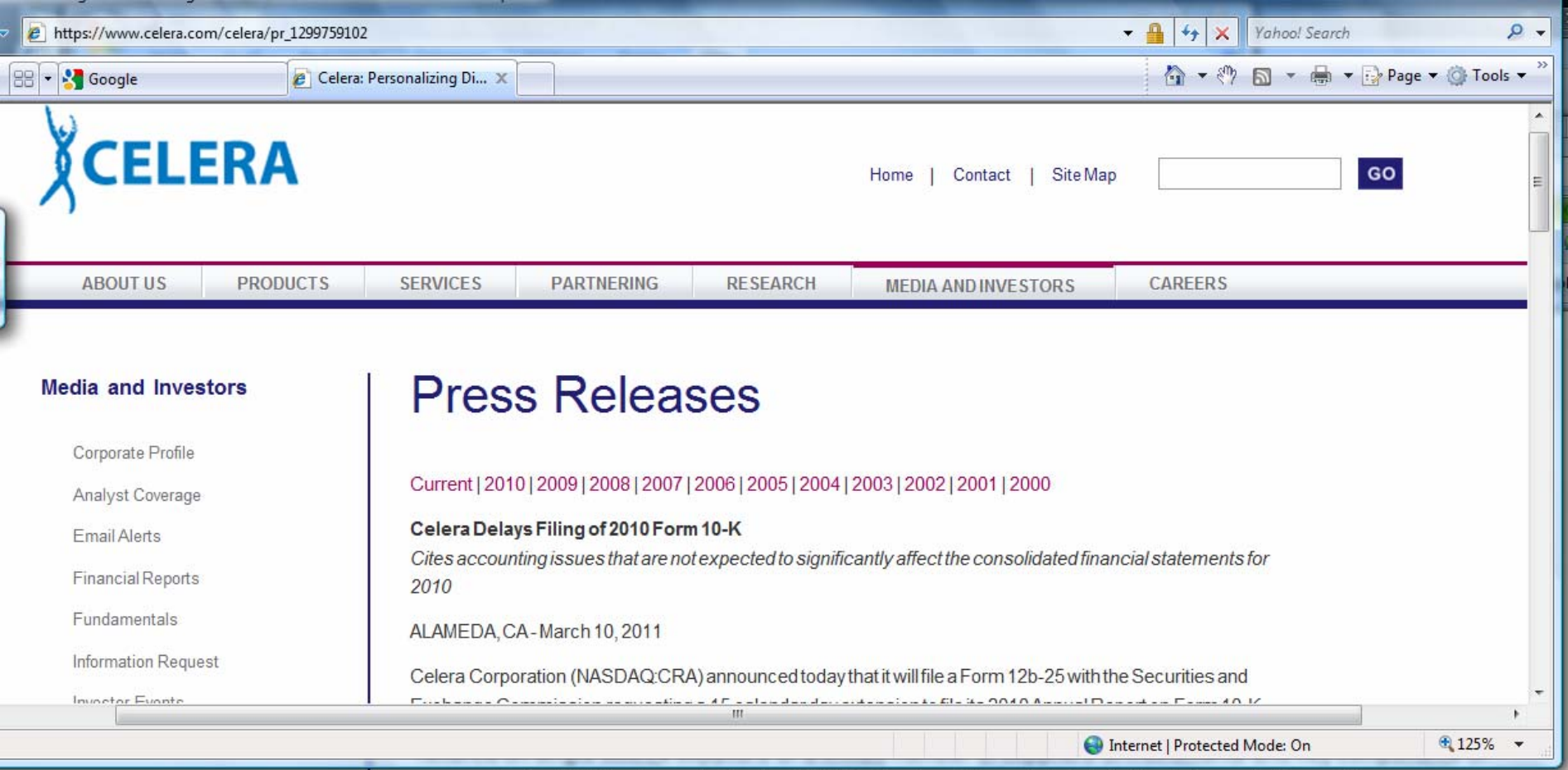
Alberto Guterriez, AMDM Annual Meeting, 4-28-2011


FDA
LDT

OIVD Enforcement Discretion

Dr. Jeff Shuren, Director of the Center for Devices and Radiological Health (CDRH) introduced changes in “enforcement discretion” by stating that:

[the] “**failure to validate** the accuracy, reliability, and clinical implications of a test can **result in patient harm** from misdiagnosis, failure to treat, delay in treatment, inappropriate treatment, or avoidable adverse events”



our products; (12) the impact of potential U.S. Food and Drug Administration interpretations of the regulations governing the sale of Analyte Specific Reagents because the interpretation may require regulatory clearance or approval for some existing products that to date have been sold without clearance or approval; (13) the FDA draft guidance on a new class of complex laboratory-developed tests may require our clinical laboratory and our licensees to obtain regulatory clearance or approval before it or they can perform these tests; (14) our scientific discoveries may not be replicated in studies by other investigators, which may

CDER PGx DRAFT Guidance

Guidance for Industry- Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies, February 2011, DRAFT.

- Footnote #3- Currently, FDA expects that if a diagnostic test is essential for the safe and effective use of a therapeutic product, **that there be a cleared/approved test** with the appropriate intended use available concurrent with the drug label change.

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Guidance from CDER PGx DRAFT

Pharmacogenomics Studies-

Genomic **tests** (i.e., diagnostics) **can identify individuals** who

- (1) are most likely to have an efficacious response to an investigational drug,
- (2) are more at risk for drug-induced adverse events,
- (3) are unlikely to benefit from treatment, and
- (4) are in need of a genotype-modified dose or dosing interval.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243702.pdf

Clinical Investigation Coordination

- CDRH has protocol requirements for the
  IDE →PMA (or 510(k) with or w/o de novo)
- CDER has protocol requirements for the
  IND → NDA
- Coordinate and confirm same protocol so IVD and Rx can use the same data sets leading to the approval pathway

Meeting Coordination

- CDRH has Pre-IDE, non-binding
- CDER has Pre-IND meeting, Class C meetings, binding consequences
  - SPA Special Protocol Assessment
- Need to combine with binding statements

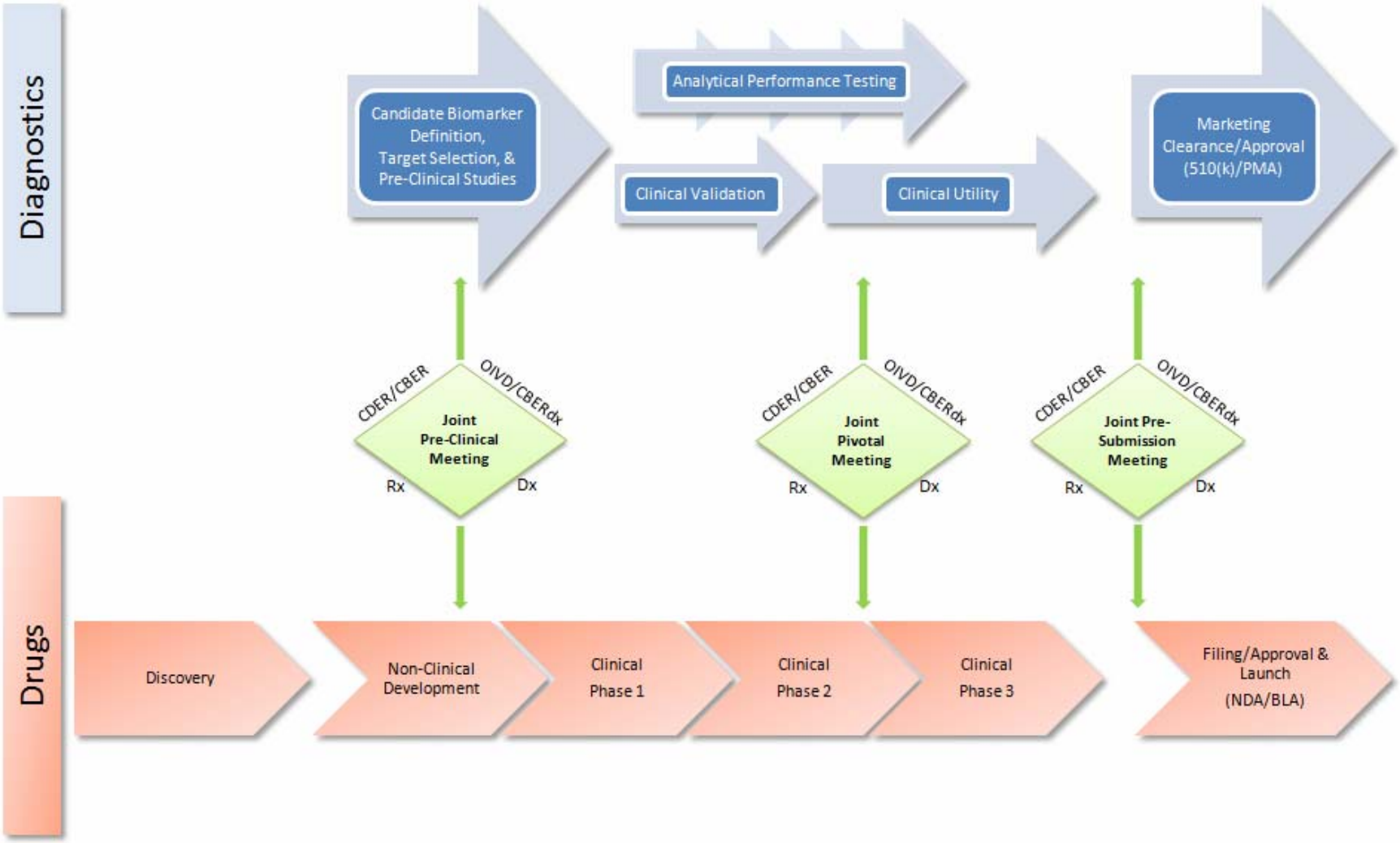
Recommended Advisory Process for a Companion Diagnostic

CDER, CBER

Diagnostic Partner

Pharma Partner

OIVD, OBRR



Proposed Meeting Points for Joint discussion with FDA

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Levels of Risk Assessment for CDx

- FDA has suggested- that a CDx determining the **selection of therapeutic pathways** should automatically be **Class III**, highest risk
- FDA has discussed- modifying the Risk Classification system to include a **Class 2b**, as a vehicle to enhance the **de novo** 510(k) process

- Industry Response- the CDx **should not** be automatically considered as Class III, and must be evaluated against the impact on the patient for therapeutic choices and physician controls

Diagnostic Assay Types

Risk Level	Classification	Pre-Market Review
High	III	PMA
Moderate	II	510(k)
Low	I	Listing and Registration
Unkown	LDT	None

Opportunity with FDA

New FDA Indication for MammaPrint Preps Agendia's Labs to Boost Supply

February 23, 2011

By Kirell Lakhman

The FDA has cleared Agendia's MammaPrint breast cancer-recurrence assay to be used with two additional Agilent microarray scanners and two Agilent bioanalyzers.

The additional indication — MammaPrint's fifth to date — will enable Agendia's two clinical labs in Irvine, Calif., and Amsterdam to expand their capacity if they experience an increase in demand for MammaPrint, TargetPrint, and BluePrint test orders.

The fourth indication, awarded in December 2009, cleared the test to be used on women of all ages.

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Inconsistency vs. Standardization

- **Plavix Label** – Black box warning includes CDx
- **Warfarin Label** – a reference table “makes it easier for physicians to apply the knowledge of the genetic test to inform them on which dose is likely to be best for patients,” said Lawrence Lesko, Ph.D., Director of the FDA’s Office of Clinical Pharmacology.
- **Vectibix Label** – CDx only mentioned as used in Clinical Trials; referred to in study methods; and cryptically under “EGF Receptor Testing”; but not in the indications for use

Companion Diagnostic Labeling Definition

Label for A CDx should indicate it as a diagnostic test:

- whose **information is valuable** to ensure the **Safety and/or Efficacy** of a specific **targeted therapeutic** treatment (drug) used in Personalized Medicine,
- Whose therapeutic drug is specifically identified in the diagnostic label intended use statement,
- and where the need for an approved/cleared IVD is CLEARLY and consistently indicated in the drug label

… to be used to assist physicians in making treatment decisions for their specific patient or a targeted patient sub-group

Recommendations for Levels of Criticality: a Labeling Approach for CDx

- **High Risk -** Drug labeling ***requires*** the use of a Companion Diagnostic as identified in its labeling to ensure Safety and Efficacy of the Drug
  - The CDx test **must be an FDA cleared/approved IVD** assay, not an LDT
- **Medium Risk -** Drug labeling ***recommends*** the use of a Companion Diagnostic as identified in its labeling to ensure Safety and Efficacy
  - The CDx test **must be an FDA cleared/approved IVD** assay, not an LDT
- **Low Risk -** the Therapeutic includes **For Information Only** the use of a Companion Diagnostic identified in its labeling
  - The test is recommended to be an FDA regulated and FDA Listed IVD assay

In summary:

The real value of CDx in personalized medicine

1. "It really does estimate disease risk,
2. It helps categorize a disease diagnosis,
3. It allows selection of the best medicine for that individual, and
4. Choosing the best dose."

Lawrence J. Lesko, PhD, director, Office of Clinical Pharmacology, CDER; in Regulatory Focus, March 2011, Vol. 16, No. 3.

Targeted
Therapeutic

Companion
Diagnostic

Thank you!

Eric Lawson

Metamark™ GENETICS, INC.

DETERMINED TO CONQUER CANCER™

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