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Companion Diagnostics in Personalized Medicine Worldwide

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Definition: Personalized Medicine

Personalized medicine **uses new methods of molecular analysis** to better manage a patient's disease or predisposition toward a disease. It aims to achieve optimal medical outcomes by helping physicians and patients choose the disease management approaches likely to work best **in the context of a patient's genetic and environmental profile**. Such approaches may include genetic screening programs that more precisely diagnose diseases and their sub-types, or help physicians select the type and dose of medication best suited to a certain group of patients.**(source: Personalized Medicines Coalition)**

A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.

(source: National Cancer Institute)

Definitions: Personalised Medicine in the EU

Personalised Medicine is providing the right treatment, to the right patient at the right time by using modern biology's new methods and tools.

Practically, this approach **combines diagnostic** and **therapeutic** tools to create predictable outcomes and tailor medical treatment to the individual characteristics of each patient.

(source: EuropaBio Personalised Medicine Task Force)

… at the right dose…

(source: CDxWG update)

Personalized Medicine

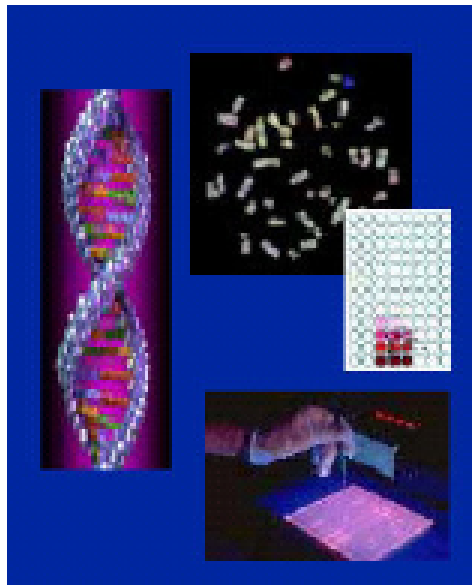
- Applies modern genomic and molecular data
  - to better target health care delivery
  - facilitate drug discovery and clinical testing
  - determine a person's predisposition to disease or condition.
- Linking a drug (or therapy) with a diagnostic test
  - Particular to a stratified patient population

Diagnostic Paradigm Shift

From

Clinical definition of disease

To



Molecular definition of disease

It’s in the genes…

Definition: Companion Diagnostics

Companion diagnostics are assays (a test or measurement) intended to assist physicians in **making treatment decisions** for their patients.

They do so by elucidating the **efficacy and/or safety** of a **specific drug** or class of drugs **for a targeted patient** group or sub-groups.

(source: Amgen website)

Companion Diagnostics

- a.k.a. CDx, or Theranostic - is a diagnostic test,
  - specifically linked to a drug or therapy,
  - in order to assure the safety characteristics and
  - provide data to optimize the effectivity of the drug or therapy.
  - use Biomarkers critical to safety or efficacy of the therapy
- Can include
  - Pharmacogenomics
  - Molecular Diagnostics (all the other “–omics”)
  - Traditional and modern Dx linked to the therapy
  - Imaging and molecular imaging technology

Breaking New Ground with Companion Diagnostics

CDx in Personalized Medicine to:

- **Identify** patients with the disease requiring treatment
- **Determine** the particular drug **therapy** suited for which patients
- Determine most **effective dosage** form for patient genetic / metabolic makeup
- Reduce **Adverse Events** and effect safety of treatment
- **Evaluate course** and effectiveness of patient therapy

Breaking New Ground with Companion Diagnostics

CDx in Development and CT Applications:

- Companion **development** of the Diagnostic with the Drug
- Improved controls during **Clinical Trials**
- Better CT **Endpoint** with Biomarker determination utility
- **Risk Mitigation** factor for patients and clinical trial subjects
- Product compatibility at **launch**
- Synchronized and **integrated Regulatory Submissions**

Genetic Tests Improved Drug

"FDA Clears Test for Patient DNA to Screen for Drug Effectiveness"

Wall Street Journal, January 11, 2005

- Affymetrix GeneChip System / Roche AmpliChip CYP450
  - Measure all 29 alleles of CYP2D6 and two alleles of CYP2C19
  - Reduce over- and under- dosing
  - Reduce adverse events by ~20%
- Third Wave Technology's Invader® UGT1A1 Molecular Assay
  - Measure UGT1A1*28 allele
  - Diagnostic kit for Camptosar (Irinotecan)

Borrowed from FDA presentation

FDA Chronology with CDx

2004

- FDA clears EGFR IHC test for Erbitux treatment in Metastatic CRC
- FDA clears Affymetrix GeneChip System 12/23/04,

  with Roche Molecular CYP450 AmpliChip

2005

- Drug–Diagnostic Co-development Concept Paper DRAFT
- FDA clears UGTIA1 genetic test for Irinotecan in CRC

FDA Chronology with CDx

2006

- FDA approves Vectibix for EGFR IHC Metastatic CRC

2007

- FDA clears Mamaprint, 1st IVDMIA, breast cancer
- FDA updates warfarin label: re CYP2C9, VKORC1 status
- FDA clears genetic test for warfarin sensitivity
- Celecoxib, ATomoxitine, 6MP: drug label genetic information
- FDA approves Maraviroc for CCR-5 tropic HIV-1
- Carbamazepine- label added screening for HLA-B* 1502 for prevention of SJS in Asians

FDA Chronology with CDx (Guidances)

2006

- Draft Guidance on “IVDMIA” published

2007

- PharmacoGenetic tests and genetic tests for Heritable Markers Guidance published
- FDA-EMEA Joint VGDS Guiding Principles

FDA Chronology with CDx

2008

- Abacavir label warning, test HLA-B*5701 prior to therapy
- Public meeting on Critical Path- Lumiracoxib and genetic risk for Drug Induced Liver Injury
- Sponsors seek FDA input for imaging amyloid in the CNS for the diagnosis and monitoring of Alzheimer's disease
- Sponsors for Vectibix and Erbitux jointly seek to limit efficacy indication of EGFR targeted drugs in CRC to wild type KRAS tumors in meeting of Oncology Drugs Advisory Committee (ODAC)

FDA Chronology with CDx

2009

- Drug Diagnostic Co-Development Strategies – A Summary of FDA/Industry Dialog is published
- FDA Industry IVD Companion Diagnostic Drug Roundtable
- FDA revised labels indication and usage of Vectibix and Erbitux re KRAS to include information that Patients with KRAS mutations did not respond to treatment and “that the use of the drugs is not recommended for the treatment of colorectal cancer patients with these mutations.”

FDA Chronology with CDx

2010

- Drug Diagnostic Co-Development Strategies – A Summary of FDA/Industry Dialog is published
- FDA Industry IVD Companion Diagnostic Drug Roundtable
- FDA Proposes New Rx-CDx Guidance within Year
- FDA Announces New Boxed Warning on Plavix- CYP2C19 allele yielding poor metabolizer
- FDA ODAC halts ChemGenex Omapro Leukemia drug approval due to inadequate CDx availability

ODAC Meeting with ChemGenex

Meeting Minutes:

- The **lack of** having a uniform **i**n **v**itro **d**iagnostic test creates uncertainty
  - about patient selection both **in this trial** and,
  - more importantly, **in a post-approval** setting.
- Performance characteristics of an assay should be known prior to widespread use of the assay and drug use based on this assay.
- Information for the assays … has not been submitted to FDA's Center for Devices and Radiological Health (CDRH).

CDx Labeling: Testing required by FDA

• Herceptin/breast cancer	Genentech/Roche	FISH/IHC Her 2
• Erbitux/colon cancer	Imclone	IHC EGFR +/- and Kras
• Vectibix/colon cancer	Amgen	EGFR, KRas mutations
• Selzentry/HIV AIDS	Pfizer	CCR5 tropism

CDx Labeling: Testing recommended by FDA

• Imuran/autoimmune	GSK	Thiopurine methyltransferase
• Camptosar/colon cancer	Pfizer	UGT1A1 variant
• Ziagen/ HIV AIDS	GSK	HLA-B 5701 variant
• Tegretol/epilepsy & bipolar	Various	HLA-B 1502 Asian variant
• Tarceva/NSCLC	Genentech/OSI	IHC EGFR +/-

CDx Informational tests

• Plavix/CV event prevention	Sanofi/BMS	CYP2C19
• VFEND/fungal infections	Pfizer	CYP2C19
• Prozac/depression	Eli Lilly	CYP2D6
• Strattera/attention deficit	Eli Lilly	CYP2D6
• Tamoxifen	Astra-Zenica	CYP2D6
• Warfarin	Osmetech, dx	CYP2C9/VKORC1
• Xeloda/cancer	Roche	Dihydropyrimidine DH'ase
• Gleevec/cancers	Novartis	Philadelphia chromosome, c-KIT
• Cetuximab/colon cancer	BMS/ImClone	IgE antibodies

Growing Biomarker Requirements

- FDA and EMEA encouraging greater use of biomarkers and diagnostics in drug development
- 10% of drug labels contain pharmacogenomic information
- FDA just beginning to « require » biomarker tests
- Of 28 biomarkers, only four are currently “required” to be used prior to using the companion drug
- Of 24 remaining biomarkers, a test is only “recommended” or for “information only”

Growing Biomarker Requirements (2)

- More than 100 EMEA approved drug have biomarkers on drug labels
- 11 EMEA drugs now « require » biomarker testing
- It is likely that the FDA will « insist on » rather than « encourage » the use of biomarker-based diagnostic to guide drug development and use

Biomarker

- Biomarkers can provide a link between the Companion Diagnostic and its designated drug or therapy.
- Single biomarkers may not tell the whole story, need an algorithm to stratify subject population in CT
- Clinical trial design should take biomarker into account
  - use it early & throughout the clinical process
  - to enhance randomization
  - development of control & test group populations for the adjuvant therapy trials.
  - biomarker should not be used as primary endpoint

(Source: FDA-NCI Workshop on Therapeutic Cancer Vaccine / Biomarkers in CT)

Companion Dx – Obstacles to Address

- Rx and Dx follow widely different regulatory processes
- Pharma companies do not grasp subtleties of Dx development requirements or clinical process
- Difficulties synchronizing integrated regulatory submission processes to coordinate timing
- Manufactured IVD's and proprietary LDT's follow widely different regulatory requirements
- Managing the Co-Labeling of Rx and Dx product

Industry Organizations Respond

- Companion Diagnostics Working Group of AMDM
  - Founded at AMDM meeting 2009
  - White Paper recommendations to FDA
  - Sponsored by Association of Medical Diagnostics Manufacturers

- EuropaBio Personalised Medicine Task Force
  - EU Pharma and Dx members
  - 2010 Workshop presentations to EMeA

- Personalized Medicine Coalition
  - Requested Guidance from FDA, December 2009
  - Collaborate with policy and stake holders
  - AMDM CDxWG is Strategic Partner

Companion diagnostics working group formed

The Association of Medical Diagnostics Manufacturers (AMDM) has created a working group specifically for issues related to the regulation of companion diagnostics. The group's chairman is Eric Lawson, project director for medical devices at Voisin Consulting Inc. (Cambridge, MA) and a member of AMDM. Lawson proposed the formation of the group in April of this year, in response to a request by industry colleagues who had been experiencing difficulty with submissions of companion diagnostics to FDA. Formation of the group was also prompted by acting director of OIVD Don St. Pierre's request for industry input in his drafting of a new FDA guidance on companion diagnostics.

Membership in the Companion Diagnostics Working Group (CDx WG) is varied and "energetic," says Lawson. It includes such big-time diagnostics players as Abbott and

drug/biologic and diagnostics manufacturers—should work together in the advancement of personalized medicine." Lawson hopes the paper will be completed by the end of this year.

The issues surrounding oversight of companion diagnostics are many.

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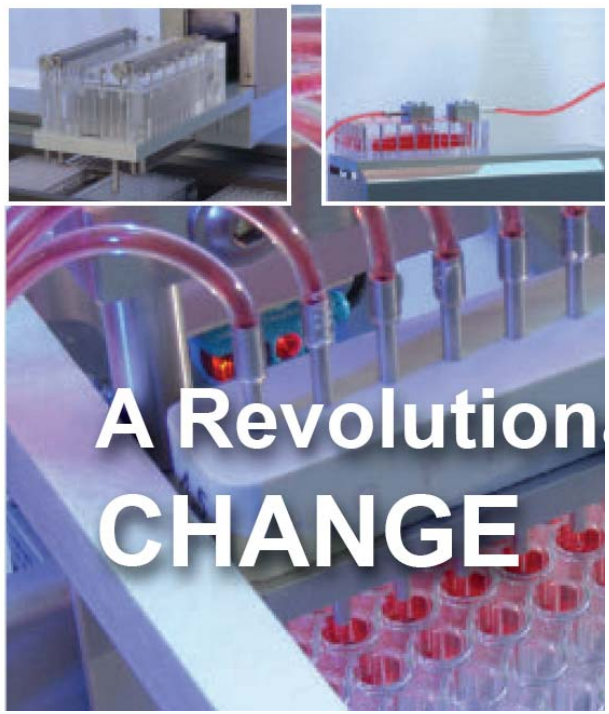


IVD Technology Journal Article

Elsevier BusinessIntelligence

"The Gray Sheet®"

MEDICAL 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.

Diagnostics Association Weighs In

The Association of Medical Diagnostics Manufacturers, which recently established a companion diagnostics working group, is also putting together a white paper to give FDA detailed recommendations for the draft guidance.

"What we want to do is present what roadblocks we have seen in the industry, and what we perceive would be better tools to use for the review and clinical trials and the whole regulatory approach to companion diagnostics," AMDM working group chair Eric Lawson, of Voisin Consulting, said in an interview.

For one, the group would like better communication between FDA, drug firms and diagnostic makers.

"There has sometimes been a problem where CDER [FDA's drug review center] or the pharma company will make decisions that affect the diagnostics company without them knowing what was going on," Lawson noted. "If there were a better formal communication structure, that wouldn't occur."

FDA Organizational Response

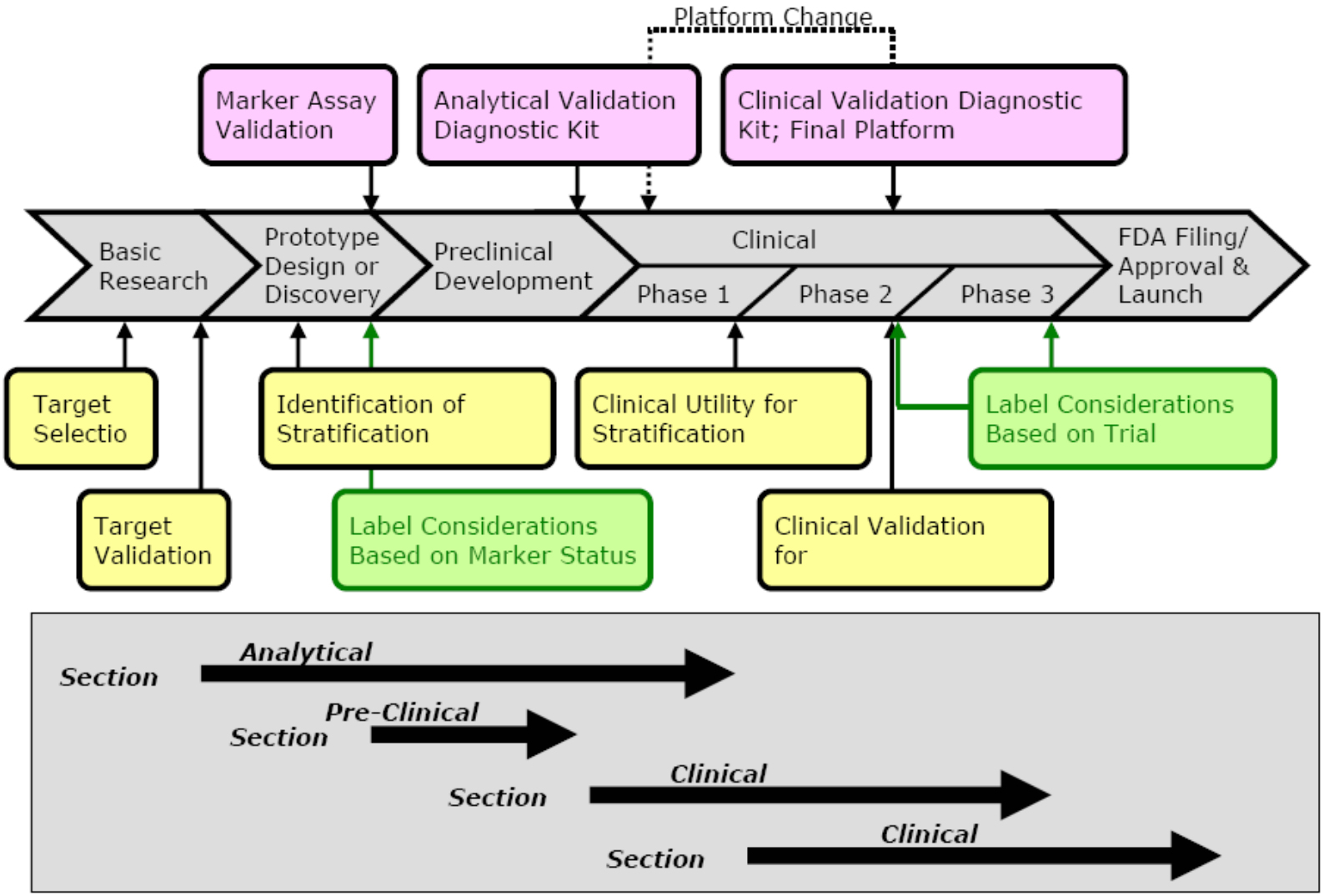
- 2009- Diagnostics & Personalized Medicine Network Leader
  - Francis Kalush, Ph.D
  - To integrate CDRH through 13 cross-Office networks, creating a culture of collaboration for information sharing and informed decision making that provides timely risk identification, analysis risk relative to benefit and public health responses to issues.
  - Work with CDER/CBER personnel on co-development programs and harmonization

- 2010- Sr. Director, Genomics and Personalized Medicine
  - Elizabeth Mansfield, Ph.D.
  - Make a common understanding across all centers throughout the agency about when a test result is being used to shape a drug trial, or drug approval or relabeling.
  - FDA Office of the Commissioner

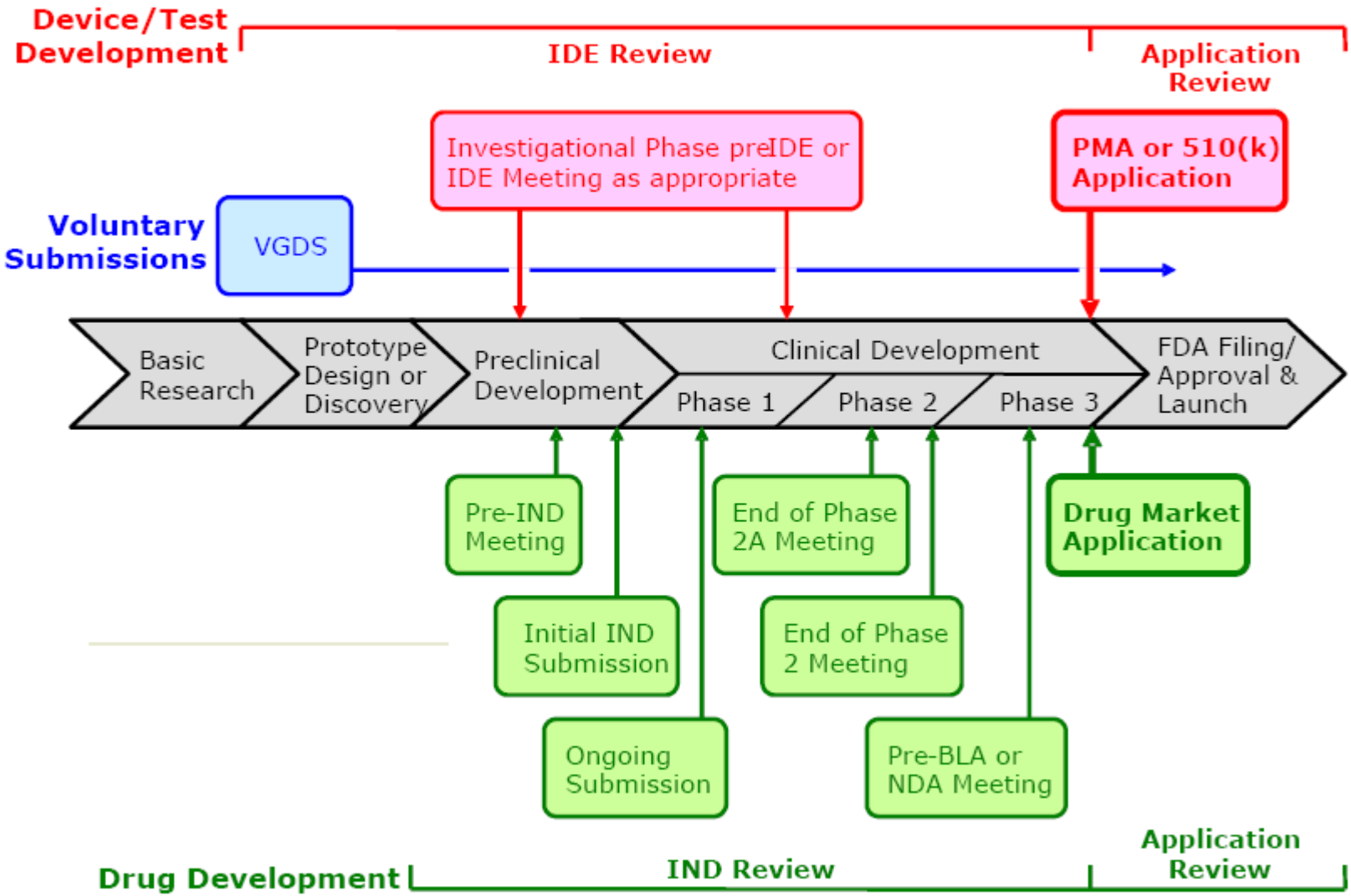
AMDM CDx WG – Suggestions on Key Issues

- Co-Development of Drug and Diagnostic
- Coordination of Rx and Dx in Clinical Evaluations
- Co-Submission of Rx and Dx registration and Market Authorization
- Coordinated agency meetings and review process
- Coordinated approval and launch
- Co-Labeling of Drug and Diagnostic product

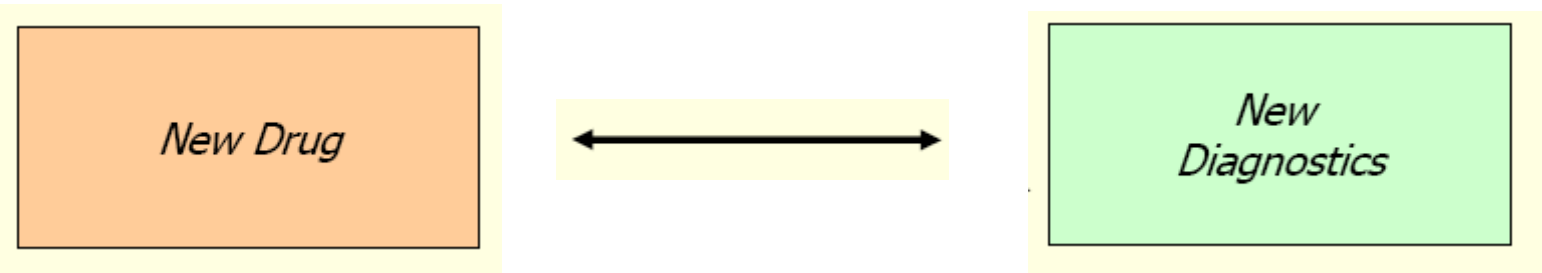
Drug-Device Co-Development: FDA View Key Steps



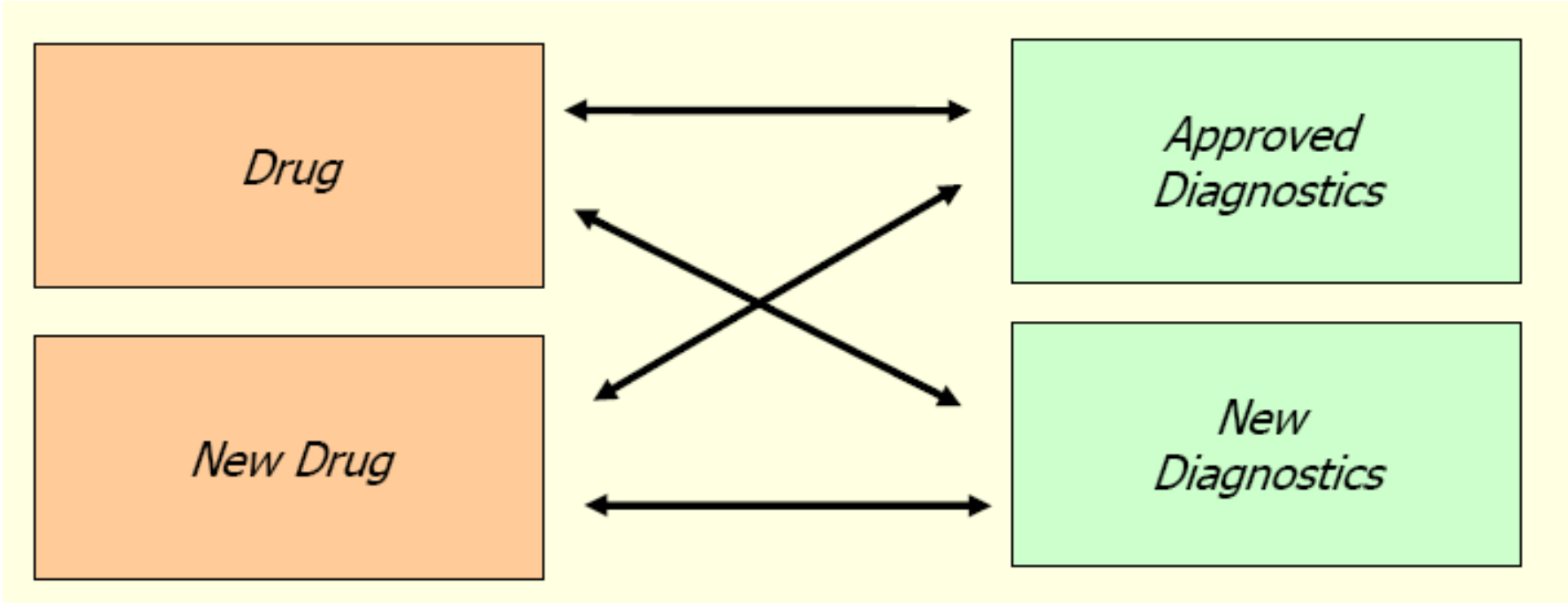
Rx-Dx Co-Development: Formal Industry-FDA Interactions



Rx-Dx Co-Development: FDA 2005 Concept Paper DRAFT

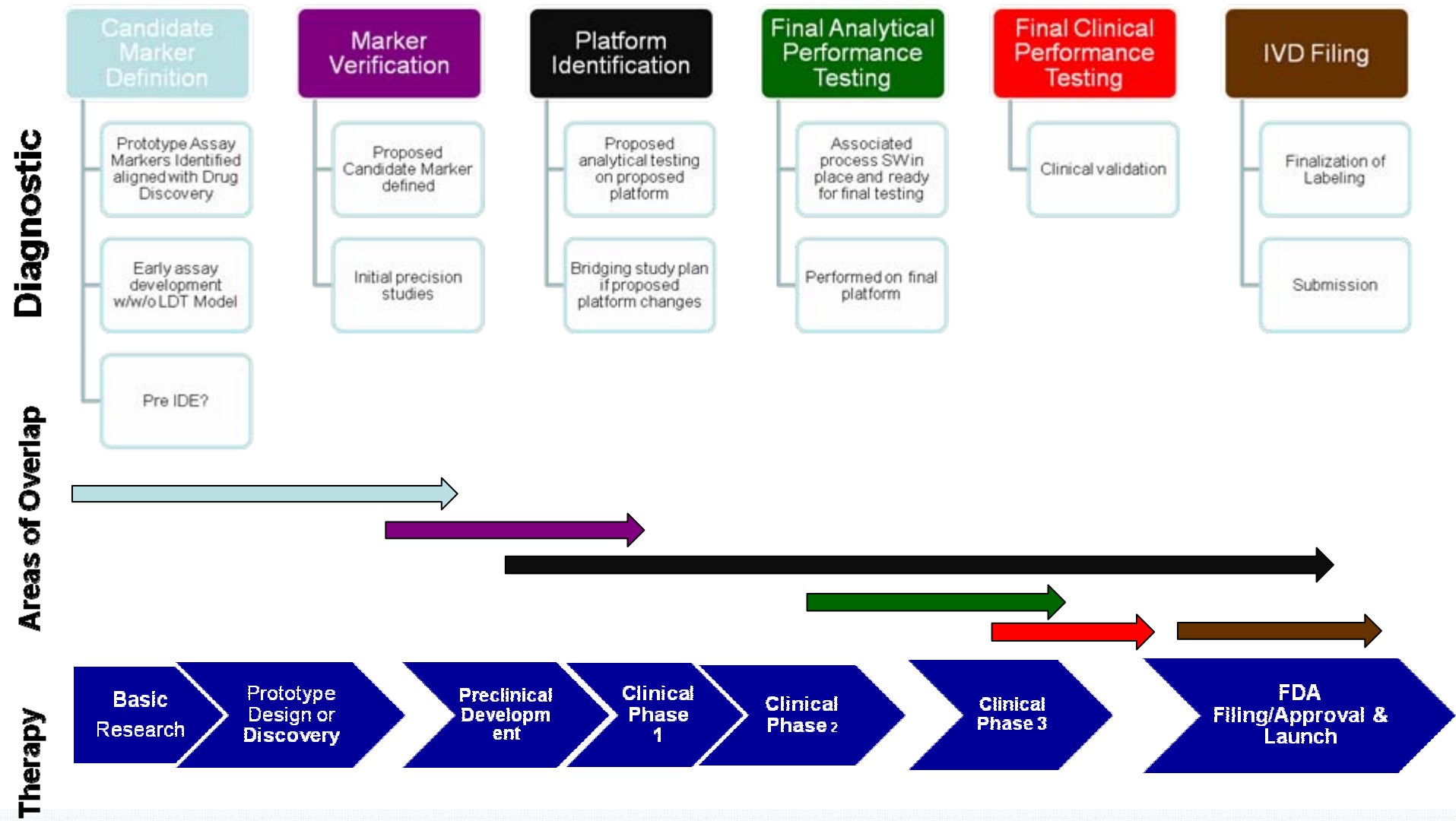


Rx-Dx Co-Development: Actual Interactions Encountered



Source: Francis Kalush, Ph.D, FDA

Analysis: IVD with Therapy



AMDM CDx WG – Suggestions on Modular Issues

- Mis-categorization As A Combination Product
- How Best To Use Ocp, Offiece Of Combination Products
- Coordination And Formalization Of Meetings
- Labeling Standardization
- Regulation Level of CDdx Assays (LDT Issue)
- Incentives For The IVD Manufacturer To Pursue A CDx
- Rx Industry Partner Understanding Dx Process
- Submission Timing And Conclusion
- Acknowledgement Of Conclusion For Diagnostic Partner
- Regulatory Process Standardization

Companion Dx – Goals for Success

By improving the process of

coordinating the co-development of Companion Diagnostics with its Pharmaceutical ally

and streamlining the regulatory submission, review, and approval processes,

the goal can be achieved -

to bring the right drug at the right dose to the right patient at the right time.

Additional Support Provided to the Companion Diagnostics Working Group by

Judi Smith (Judi Smith LLC), Cathy Craft (Siemens),
Chris Bentsen (Bio-Rad), Sheri Hall (BD), Donna Link (TechLab),
Joseph McMullen (Nanogen), Jonathan Kahan (Hogan & Hartson),
Mark Del Vecchio (Liposcience), Pamela Weagraff (T2Biosystems),
Steve Binder (Bio-Rad) Maria Chan (FDA), Mary Gross (Abbott),
Christina Yang (Gen-Probe), Maureen Dawson (Gen-Probe),
Sam Orr (Thermofisher), Richard DING (bioMerieux),
Connie Finch, (BD), Patricia Schrader (BD), Mary Lou Ellwood (BD),
Rick Naples (BD), Shan Thever, Mya Thomae,
Emmanuelle Voisin (Voisin Consulting), Jason Fisher (Roche),
Karen Richards (Novartis).

Team Members:
Companion Diagnostics Working Group

Leif Olsen – Hogan & Hartson	Martin Mann -- Phadia US Inc.
Kristin Godfredsen -- Gen-Probe	Charlene Knape – LabCorp
Rose Romeo -- XDx, Inc.	Pamela Swatkowski – Abbott Molecular
Thomas F. Soriano – DOCRO	Elizabeth Stafford – FDA / OIVD
Francis Kalush -- FDA / CDRH	Karen Bijwaard – FDA / OIVD
Susan M Schneider – Celera	Susan Tiedy-Stevenson – Hogan & Hartson
Jack Rogers -- Roche Diagnostics	Meredith Tallas – Siemens
Karin Hughes – Biosite	Louise Peltier -- Caris Dx
Séverine Marconi -Voisin Consulting	Vipin Adhlakha -- Canon US Life Sciences
Paula E Martin – Abbott Diagnostics	Tracy Bush – Roche Diagnostics
Thomas Flynn -- Abbott Diagnostics	Don Kafader – LabCorp
James Kelly -- Roche	Evelyn Mckeegan -- Abbott
Lisa Brown -- AMDM	Eric Lawson – Voisin Life Sciences

END OF SLIDES