Voisin Life Sciences
Consulting

Personalized Medicine Proposal

Presented by:

Eric Lawson

•Director, Regulatory Affairs
Voisin Consulting Life Sciences

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

Voisin Life Sciences Consulting

Innovative Regulatory Strategy & Product Development for Life Sciences Companies

We design innovative regulatory strategies
We interact with regulators & Key Opinion Leaders to "*validate*" strategies
We prepare & submit high quality regulatory files

We help developing:

- **Innovative** products
- **New classes** of products
- **Products at border between or combining** drugs, biologics, medical devices, diagnostics…

We focus on innovative products for:

- Unmet medical needs
- Rare and/or life-threatening diseases

We help fertilizing & bridging:

- Regulatory & Science
- Multidisciplinary concepts
- Areas that usually don't communicate

Definition: Personalized Medicine

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

This process coordinates **diagnostic** and **therapeutic** tools to **tailor** medical **treatment** to the **individual** characteristics of each **patient**.

Targeted
Therapeutic

Companion
Diagnostic

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
- Difficulties managing the Co-Labeling of Rx and Dx

IVD Technology Journal Article

Companion diagnostics working group formed

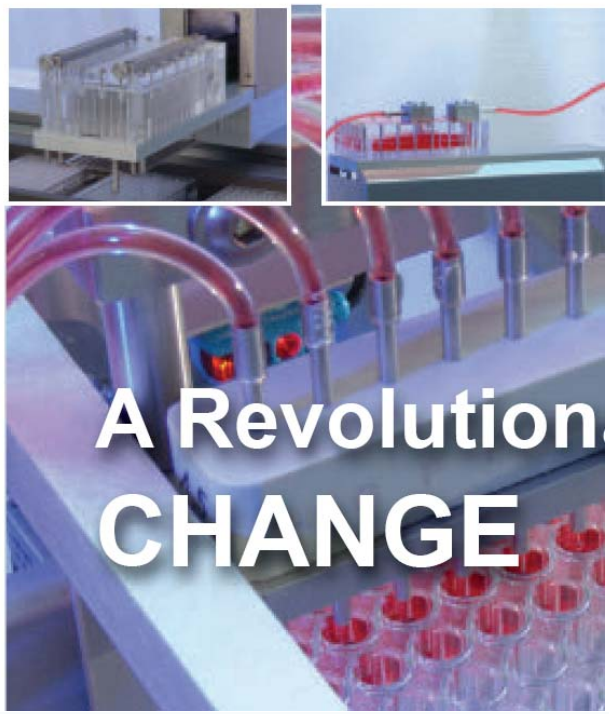
The Association of Medical Diagnostics Manufacturers (AMDM) has created a working group specifically for issues related to the regulation of companion diagnostics. The group's chairman is Eric Lawson, project director for medical devices at Voisin Consulting Inc. (Cambridge, MA) and a member of AMDM. 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.

Reg
abou
diag
says
fere
appı
abou
cent
diffi
coor
the



AMDM Companion Diagnostics Working Group

Leif Olsen - Hogan Lovells

Kristin Godfredsen - Gen-Probe

Rose Romeo - XDx, Inc.

Thomas F. Soriano – DOCRO

Francis Kalush - FDA / CDRH

Susan M Schneider - Celera

Jack Rogers - Roche Diagnostics

Karin Hughes - Biosite

Séverine Marconi - Voisin Consulting Life Sciences

Paula E Martin - Abbott Diagnostics

Thomas Flynn - Abbott Diagnostics

James Kelly - Roche

Lisa Brown - AMDM

Martin Mann - Phadia US Inc.

Charlene Knape - Micell

Pamela Swatkowski - Abbott Molecular

Elizabeth Stafford - FDA / OIVD

Karen Bijwaard - FDA / OIVD

Susan Tiedy-Stevenson - Hogan Lovells

Meredith Tallas - Siemens

Louise Peltier - Caris Dx

Vipin Adhlakha - Canon US Life Sciences

Tracy Bush - Roche Diagnostics

Don Kafader - LabCorp

Evelyn Mckeegan - Abbott

Eric Lawson - Voisin Consulting Life Sciences

Companion Diagnostics - The Regulatory Hurdles

a panel discussion of Industry and FDA

Bio International Convention
The Global Event for Biotechnology

convention.bio.org

May 3-6, 2010 • Monday–Thursday • Chicago, IL USA

A SERVICE OF: Bio BIOTECHNOLOGY INDUSTRY ORGANIZATION

Voisin Consulting Life Sciences

Industry Organizations Develop

- Association of Medical Diagnostics Manufacturers
  - Companion Diagnostics Working Group
  - White Paper recommendations to FDA
- EuropaBio Personalised Medicine Task Force
  - EU Pharma and Dx members
- Personalized Medicine Coalition
  - Collaborate with policy stake holders
- MassBio
  - Bringing Biotech to the healthcare market

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
Table of Contents (cont.)

- 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
- ACKNOWLEDGEMENT OF CONCLUSION FOR DIAGNOSTIC PARTNER

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
- BIOMARKER APPROVAL, COLLABORATION, CO-UTILIZATION

Initial 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)

Companion Diagnostic Updated Definition

A CDx is a diagnostic test:

•whose **information is critical** 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 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

Companion Diagnostic Requirements

- Require **close collaboration** between drug company and diagnostic manufacturer during development
- **Labeling requirements** for drug and IVD must be **coordinated**
- CDx assays, if not analytically proven, could lead to **misuse of the drug** and thereby **potential harm** for patient

It’s in the genes…
CYP450 ARRAY

Companion Diagnostics: Mode of Operation

- Pharmacogenomics
  - Genome of Patient
  - Genome of Infectious Agent
- Molecular Diagnostics (all the other "–omics")
- Traditional and modern Dx linked to a specific therapy
- Imaging and molecular imaging technology

Companion Diagnostic Applications

- **Identify patients** with the disease requiring treatment
- **Determine** the particular drug **therapy** suited for which patients, or stratified patient population
  - Based on patient genotype or phenotypic expression
  - Based on specific disease serotype
- Determine most **effective dosage** form appropriate for patient genetic / metabolic makeup
- Reduce **Adverse Events** that may be caused by mis-application of the therapeutic treatment
- **Evaluate course** and effectiveness of patient therapy

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	AstraZeneca	CYP2D6
Warfarin	Osmetech, dx	CYP2C9/VKORC1
Xeloda/cancer	Roche	Dihydropyrimidine DH'ase
Gleevec/cancers	Novartis	Philadelphia chromosome, c-KIT

Labeling

- Location and Language of Drug Label Information
  - Dako test (Dx) indicates Vectibix in its Indications for Use statement
  - Vectibix (Rx) only casually mentions Dako test as used in CT on page 3, then referred in study methods on page 4, and finally cryptically on page 7 “EGF Receptor Testing”, but not in the indications for use

Recommendations for
Risk Based Labeling Approach
of Drug with 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 IVD assay, not an LDT

LDTs and Companion Dx

- **The Targeted Therapeutic Drug or Biologic requires clinical data submitted to FDA for review**
  - An LDT does not require independent outside review for approval
  - An IVD requires analytical and clinical validation data reviewed by FDA
- **The Targeted Therapeutic Drug must be approved by FDA before widespread use**
  - An LDT does not
  - An IVD requires FDA clearance or approval before it is available for sale

LDTs and Companion Dx

- **The Targeted Therapeutic must meet strict FDA regulations for labeling, claims, and vigilance to report adverse events to FDA**
  - An LDT is not currently subjected to FDA oversight
  - An IVD requires FDA oversight of labeling, claims, and MDR reporting to FDA of adverse events
- **The Targeted Therapeutic Drug must meet FDA cGMP requirements for manufacturing consistency**
  - An LDT is not required to meet GMP or QSR regulations
  - An IVD is manufactured to the FDA Quality System Regulations, 21 CFR 820

Limitations of LDTs in a CDx context

- **No transparency** to public regarding claims
- **No** opportunity for **FDA input or review**
- FDA has **not evaluated** analytical or clinical data
- **Lack of** FDA oversight on clinical interpretation
- Lack of coordination of **labeling claims** for both drug and CDx assay
- No possible **coordination of** CDRH and CDER/CBER **centers**
- **No mechanism** for adverse event reporting

Recommendation Regarding LDTs in a CDx context

- We feel that **when a diagnostic** assay will be used **to make important** therapeutic decisions (a CDx), **then LDTs are not the appropriate format**

- We propose that Companion Diagnostic tests **must be cleared/approved by FDA**

THE COMBINATION PRODUCT MISNOMER

- The definition of Combination Products described in the 21 CFR Part 3.2(e) states:

- (1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, **that are physically, chemically, or otherwise combined** or mixed and produced **as a single entity**;

- (2) Two or more separate products **packaged together in a single package** or **as a unit** and comprised of drug and device products, device and biological products, or biological and drug products;

THE COMBINATION PRODUCT MISNOMER

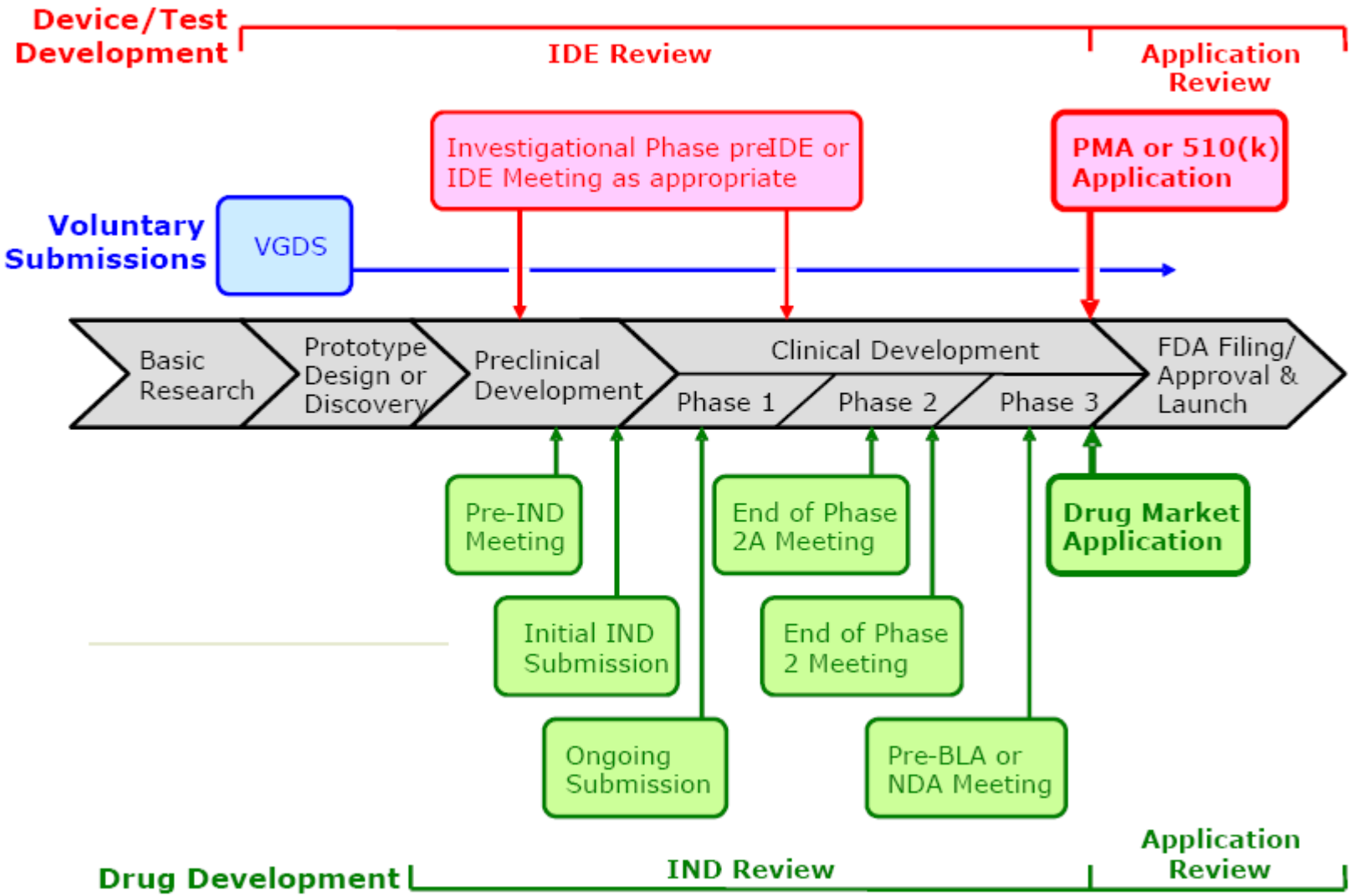
- (3) A drug, device, or biological product **packaged separately** that according to its investigational plan or proposed labeling is intended for **use only with** an approved individually specified drug, device, or biological product **where both are required** to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

- (4) Any **investigational** drug, device, or biological product packaged separately that according to its proposed labeling is for use only **with another individually specified investigational** drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

From FDA OCP Web Page

- "A combination product as defined in 21 CFR § 3.2(e),"
- "Some products are used together in a way that does not meet the regulatory definition of a combination product"
- "Examples of These Types of Products:"
  - Vectibix (panitumumab) and EGFR pharmDx(r) Test Kit
  - DakoCytomation's c-Kit (9.7) pharmDx and Gleevec

Formalized Meetings: Industry-FDA Interactions



Recommended Review Process for a Companion Diagnostic

CDER/CBER

Diagnostic Partner

Pharma Partner

OIVD

Meeting Coordination

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

Clinical Trial Samples

- CDRH has protocol requirements for the IDE →PMA
- CDER has protocol requirements for the IND → NDA
- Coordinate and confirm same protocol so IVD can use the same data set

Other Concerns

- Incentives – how can IVD hurdles be streamlined: timing, time-out clocks, user fees, processes
- VxDS – how could/should CDx utilize this process
- Reimbursement – Payor involvement

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, approval processes,

the goal can be achieved -

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

Voisin Life Sciences
Consulting

675 Massachusetts Ave.
Cambridge, MA 02139
USA
eggimann@voisinconsulting.com

Milton House Level 1
25 Flinders Lane
Melbourne, VIC 3000
mudge@voisinconsulting.com

3, rue des Longs Prés
92100 Boulogne
voisin@voisinconsulting.com

Espace Performance
Bâtiment J
Saint Grégoire Cedex
dupraz@voisinconsulting.com

2nd floor, "Hara House"
#1 Gutte Anjaneya Temple Street
Hosur Main Road, Wilson Garden
Bangalore 560027
vcbangalore@voisinconsulting.com

PSE Building C - EPFL
CH-1015 Lausanne
Switzerland
alvarez@voisinconsulting.com

Singapore
chan@voisinconsulting.com

Please, feel free to contact me or members of the CDx Working Group with your Questions.

Eric Lawson

lawson@voisinconsulting.com

617-386-9953

Thank you!