



Biomarkers Validation in Clinical Trials: Development of Personalized Medicine

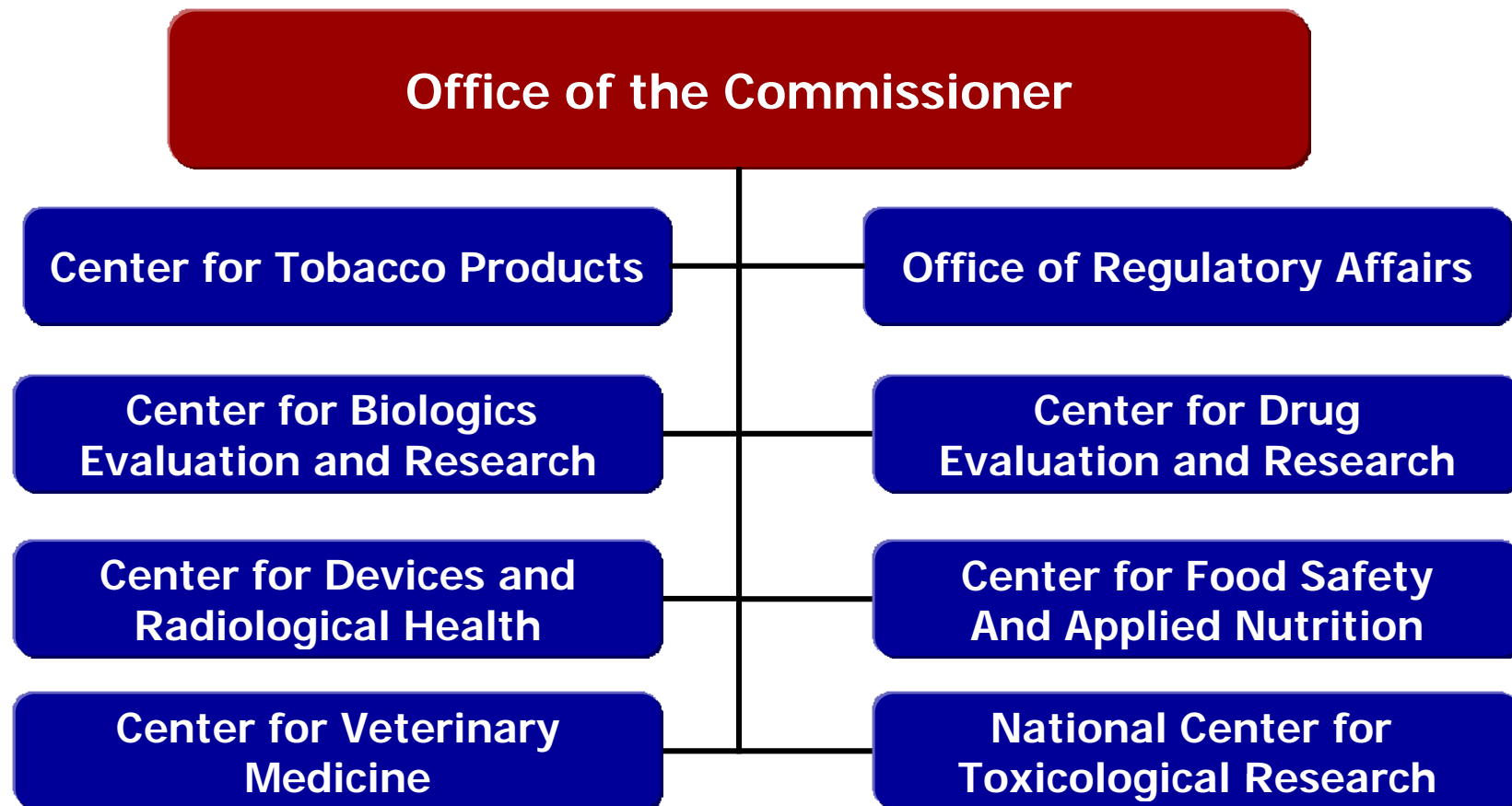
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Irish Biomarker Network
November 4, 2010
Dublin, Ireland

Outline

- FDA Activities and Initiatives for Personalized Medicine (PM)
- Regulatory Framework to Accommodate Companion Dx-Rx
 - Strategies and Examples
 - Translating Biomarkers into the Clinic
- Streamlining the Co-development Process
 - Co-development principles
 - Consultation opportunities
- Summary.

FDA Organization



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“Personalized Medicine”

Refers to the tailoring of medical treatment to the individual characteristics of each patient.

It is not the creation of drugs or medical devices that are unique to a patient, **but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment.**

Genomics Revolution Meets Regulatory Evolution

FDA Commissioner Hamburg notes challenges of changing regulatory models to advance personalized medicine during AAAS/FDLI colloquium. But "we will establish a clear and illuminated pathway for product approval."

The genomics revolution has not yet unleashed a wave of newly targeted therapies in part because regulatory science has to catch up with the breakthroughs of basic science, FDA Commissioner Margaret Hamburg suggests.

"When everything has changed our thinking must change as well. Shifting Paradigms and creating new models is not easy, but I believe that a future that provides safer and more effective therapies for all of us is well worth the effort," she concluded

October 27, 2009

FDA Activities/Initiatives to Date in PM

2007 (cont)

- *Celecoxib, ATomoxetine, 6MP: drug labels gain genetic information
- *FDA-EMA Joint VGDS Guiding Principles
- *FDA approves Maraviroc for CCR-5 tropic HIV-1
- *PharmacoGenetic tests and genetic tests for Heritable Markers Guidance published
- *Asians screening for HLA-B* 1502 for Carbamazepine added to label- Prevention of SJS

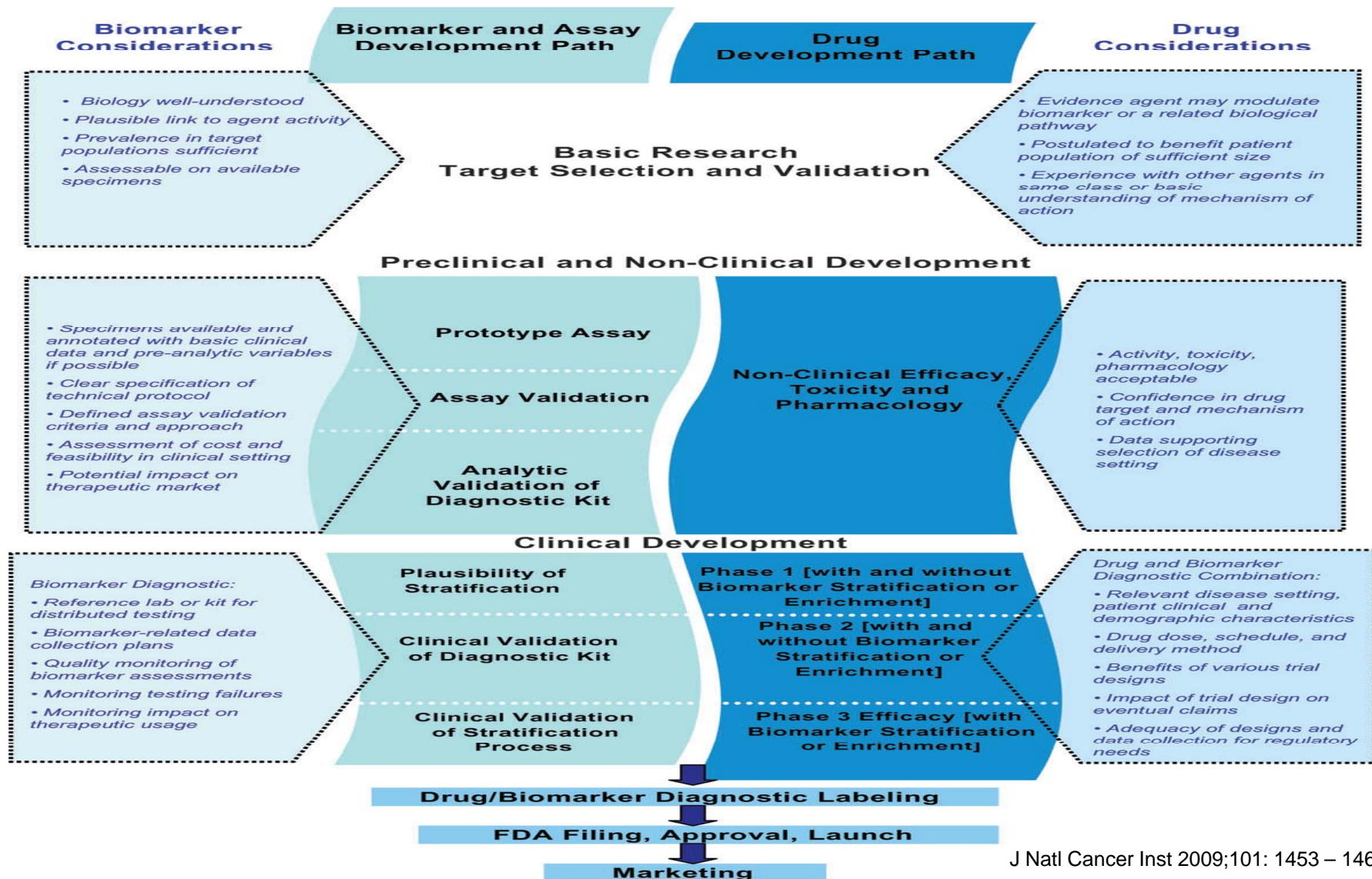
2008

- *Abacavir drug label -warning added to screen for HLA-B*5701 prior to therapy initiation
- *Public meeting on Critical Path-Lumiracoxib and genetic risk for Drug Induced Liver Injury
- *FDA-Industry IVD Companion Diagnostic Drug Roundtable
- *Sponsors seek FDA input on development plans for imaging amyloid in the CNS for the diagnosis and monitoring of Alzheimer's disease
- *Meeting of Oncology Drugs Advisory Committee (ODAC)
- ✎ Sponsors seeking to limit EGFR targeted drugs (Vectibix, Erbitux) in CRC to wild type K-ras tumors

2009

- *Drug Diagnostic Co-Development Strategies – A Summary of FDA/Industry Dialog at the 4th FDA/DIA/PhRMA/PWG/BIO PGX Workshop is published
- *FDA-Industry IVD Companion Diagnostic Drug Roundtable
- *SACGHS Oversight Report recommendations:
 - Require more proficiency testing for genetic tests
 - Establish a mandatory registry for genetic tests
 - Have FDA address clinical validity of all laboratory tests
 - Increase research efforts to generate clinical utility information for genetic tests

A Perspective on Challenges and Issues in Biomarker Development and Drug and Biomarker Co-development (NCI-FDA Workshop)



Benefits/Risks Ratio for Personalized Medicine

- **Patients-**
 - *If helps/hurts, influence compliance/clinical outcome*
- **Health Care Provider-**
 - *Is it too prescriptive or not enough?*
- **Pharma Company-**
 - *Reduced Market Share or add market value*
- **Diagnostics company-**
 - *Poor/non reimbursement for test*
- **Health Care Payer-**
 - *Add to cost without benefit to patient*



Model for Personalized Medicine

- Parameters to consider for a “good medicine and diagnostics”:

Good Medicine

- **Safety and Efficacy**
- **Patients Quality/Quantity of Life improved**
- **Reduction of Cost Care**

Good Diagnostics

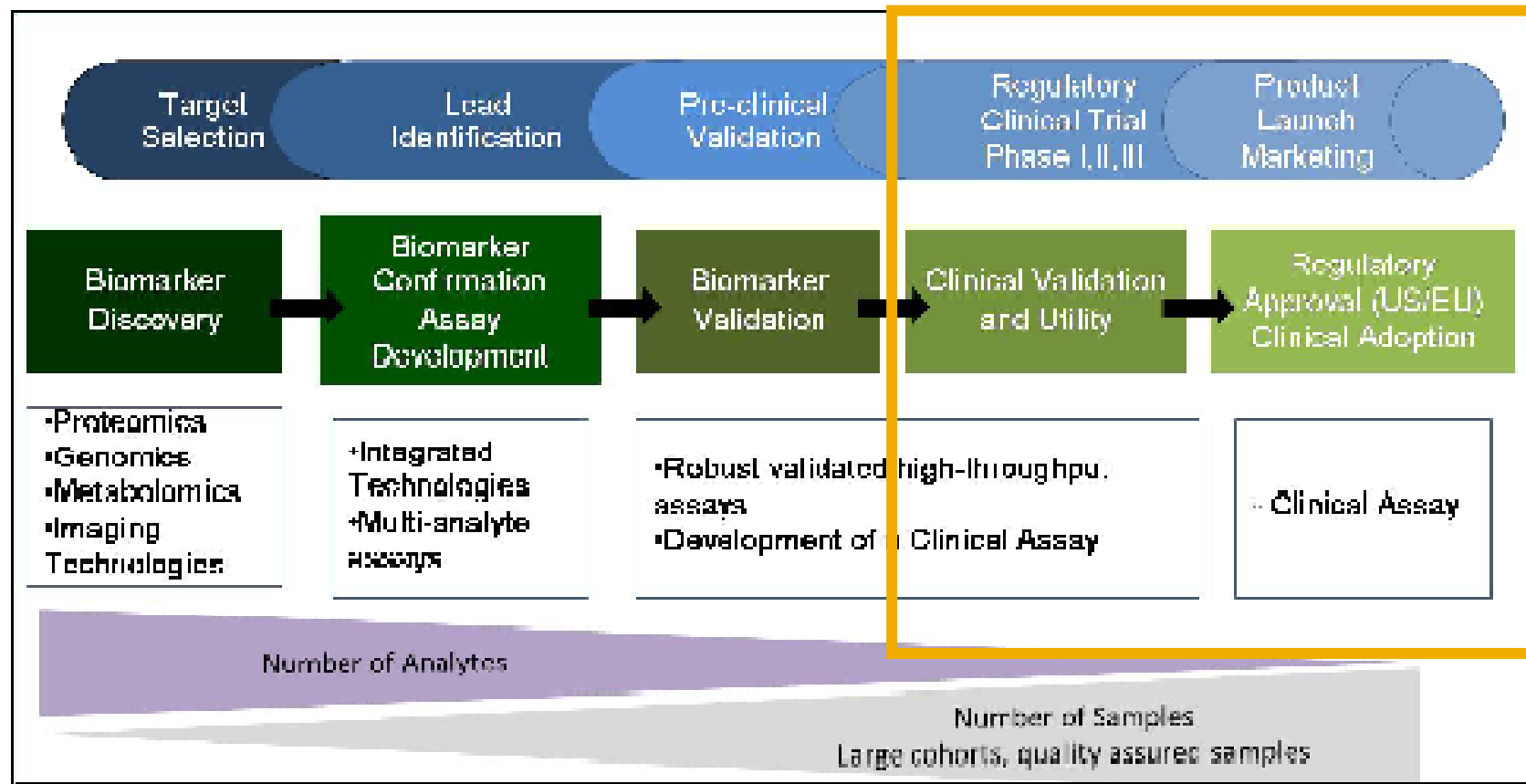
- **Safety and Effectiveness**
- **Patients are diagnosed correctly**
- **Proper subsequent clinical treatment decision**

Improved Health Care Outcomes/Adherences based on Diagnostics to Select Right Drug/Dosage. Eliminating/Decreasing Wasteful Spending

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Translating Biomarkers into The Clinic



Adapted from Workshop Website

Labeling Regulations

“If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, the labeling shall describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug.”

- 21 CFR 201.57(a)(3)(i)

Regulatory Mechanisms Medical Devices

Pre-Market Programs

- 513(g)-Classification information request
- Pre-IDE- Informal consult
- IDE- Investigational device exemption
- 510K- Pre-market notification
- 510K de novo
- PMA- Premarket Approval
- HDE- Humanitarian device exemption

Risk-Based Regulation



Determine potential risks of assay (inappropriate decisions?) e.g. if positive – more tests, surgery, drugs?

Hazard= possibility of harm to patient

Risk = Hazard X Likelihood

Class I 510(k) exempt

**Risk-Based
Regulation**

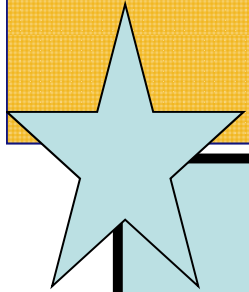
Lower likelihood
of Harm when it
is preventable or
mitigation is
possible

Safety

No Information

Higher likelihood
of Harm when it
not possible to
prevent or
mitigate

Class III PMA



Types of Biomarkers†

- **Risk assessment** leading to preventive interventions for those at sufficient risk
- **Early detection**, enabling intervention at an earlier and potentially more curable stage than under usual clinical diagnostic conditions
- **Prognosis**, allowing for more aggressive therapy for patients with poorer prognosis
- **Prediction** of response to a therapy, thereby providing guidance in choice of therapy
- **Monitoring of disease** response during therapy, with potential for adjusting level of intervention (e.g. dose) on a dynamic and personal basis
- **Early detection of recurrence**

†From AACR-FDA-NCI Cancer Biomarkers Collaborative, Biomarker Assay Validation Subcommittee

Table 1. Biomarker based therapy in Oncology.

Drug/Biologics	Drugs/Biologics TM	Cancer Types	Biomarkers/Device Classification*	Types of Evidence
Trastuzumab	Herceptin	Breast	Her2/neu-Class III	Adjuvant, first-line metastatic and advanced metastatic breast cancer. Detection of Her2/neu overexpression is required for treatment and patients selection.
Cetuximab	Erbitux	Colorectal, Head and Neck	Epidermal growth factor receptor-Class III	Metastatic colorectal cancer and head and neck cancer EGFR positive patients in clinical trial were tested for safety and efficacy. Patients with head and neck cancer are not required to be tested.
Panitumumab	Vectibix	Colorectal	Epidermal growth factor receptor-Class III	Metastatic colorectal cancer EGFR positive patients in clinical trial were tested for safety and efficacy.
Denileukin	Ontak	Cutaneous T-cell lymphoma	CD25 Class III	B-cell Non-Hodgkin's lymphoma patients are required to be tested for CD25 expression.
Imatinib mesylate	Gleevec	CML, ALL, MDs, MPD, GIST, ASM, HES, CEL, DFSP	Philadelphia chromosome, PDGFR c-Kit-Class III	Biomarker tested patients were mostly included in the regulatory clinical trials. The clinical trial size varied based on the disease prevalence.
Dasatinib	Sprycel	CML, ALL	Philadelphia positive chromosome	Phase 2, single-arm studies were conducted in patients with CML and Ph+ ALL resistant to or intolerant of imatinib.
Nilotinib	Tasigna	CML	Philadelphia positive chromosome	A single open label study was conducted in patients with Ph+ CML resistant to or intolerant of imatinib.
Lapatinib	Tykerb	Breast	HER2 Class III	A randomized phase 3 trial of lapatinib with capecitabine in HER2 over expressing breast cancer patients.

*Risk-based Device classification. Philadelphia Chromosome test have not been cleared or approved by the FDA.

Table 2. Biomarker based dose adjustment in cancer treatment.

Drugs/Biologics	Drugs/Biologics TM	Cancer Types	Biomarkers/Device Classification*	Types of Evidence
6-Mercaptopurine	Purinethol	ALL	TPMT	Patients with little or no TPMT activity are at increased risk for sever toxicity from conventional dose and generally require substantial dose reduction. Literature information provided support for label recommendation.
Irinotecan	Camptosar	Colorectal	UGT1A1- Class II	Reduction of the starting dose by at least one level should be considered for patients carrying UGT1A1*28 allele. A number of phase I study provided evidence for label recommendation.

*Risk based classification. TPMT test has not been cleared or approved by FDA.

Possible Scenarios for Incorporation of Test in Drug Development

- **Exploratory** – sponsor explores the options of evaluating the drug with or without use of an assay
- **Real Co-development**– sponsor, prior to initiating clinical development program, uses a new diagnostics to select patients or direct therapy
- **Refine** – sponsor proposed to add a diagnostic after a drug has undergone “stand alone” evaluation to some level and will not be able to advance in development unless efficacy is improved or an adverse event avoided

Examples of Relabeling Pathways for Drugs Safety

- The **sponsor submits data** and requests for the label update. FDA reviews the data and updates the label, if the evidence is adequate (e.g., abacavir)
- **Academia brings experience** / recent developments to FDA's attention. FDA updates the label based on the level of evidence and advisory committee recommendations (e.g., 6 Mercaptopurine)
- **FDA trend-watching:** Based on recent literature that shows added benefit of using a biomarker (panel) to increase efficacy or decrease risk, FDA initiates relabeling efforts (e.g., warfarin)

Dawn for Personalized Medicine

Test recommended/required in drug label

Efficacy

- Herceptin- Her 2
- Gleevec- Bcr-abl
- Gleevec- c-Kit
- Erbitux- EGFR
- Tamoxifen- 2D6
- Rituxan- CD20
- Maraviroc- Tropism

Safety/Dosage

- Carbamazepin- HLA B1502
- Abacavir- HLA B5701
- Warfarin-2C9, VKORC1
- Camptosar- UGT1A1
- 6MP- TPMT
- Codeine- 2D6

Pharmacokinetic / Mechanistic-Pharmacodynamic

Personalized Medicine for In Vivo Diagnostics?

Efficacy

- EEG-(Depth of Anesthesia)
 - Response to Certain Anesthetic Agents
- EEG-(ID depression)
 - Predict Response to SSRIs
- PET Scan
 - Response to Schizophrenia drugs

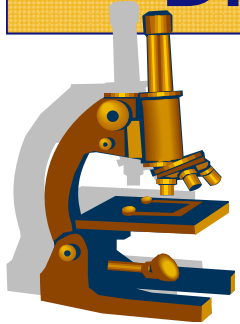
Safety

- ECG (Long QT)
 - Procainamide
 - Cisapride
 - Terfenadine

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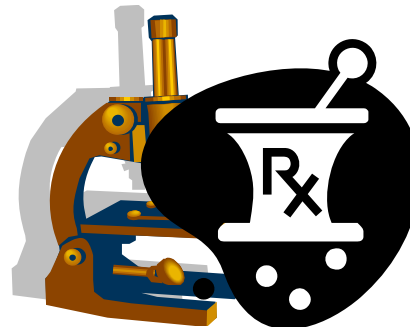
Drug-Diagnostic Developmental Paths



Key Principle



When a diagnostic test is identified as important in selecting which patients receive or avoid a new drug or receive an altered dose of a drug, **the efficacy/safety of the drug** becomes inextricably linked **to the effectiveness and safety of the diagnostic.**



FDA expects that if a test is needed to correctly use a drug, the **diagnostic should be approved with the drug**, and its use will be included in the labeling

Test Performance

- **Analytical validity of the test(s)**
 - Does my test measure the analyte(s) suppose to measure?
 - Correctly?
 - Reliably?
- **Clinical validity of the test(s)**
 - Does my test result correlate with the expected clinical presentation?
 - How reliably?

Challenges for Validating Cancer Biomarkers

- **Factors impacting reproducibility**
 - Tumor heterogeneity
 - Skill of operator (e.g. staining)
 - Lack of common specimen handling
 - May be an even bigger issue post-market (ref vs local labs)
- **Patient heterogeneity**
Stage of disease; gender, age,.....
- **Choice of assay method including technology**

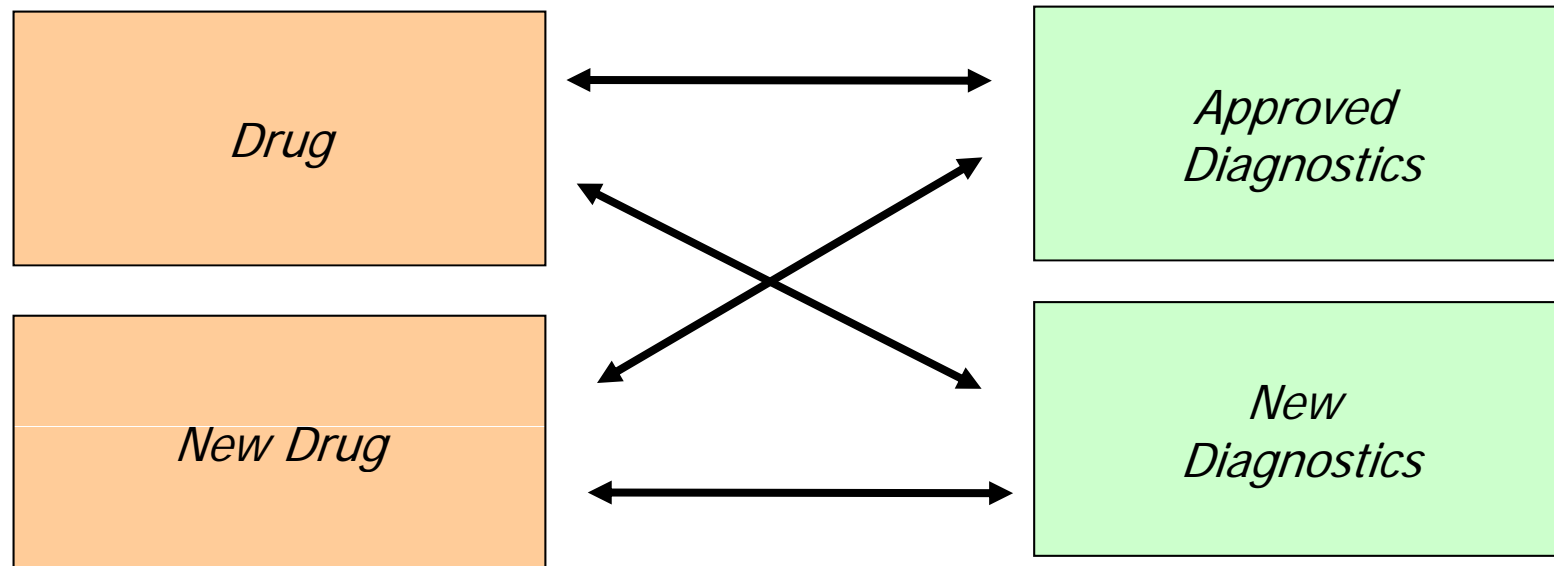
Herceptin and Her2

HercepTest,	HER2 protein (A085 polyclonal antibody), IHC;	Dako, Carpinteria, CA.
Pathway	HER2 protein (CB11 monoclonal antibody), IHC	Ventana Medical Systems , Tucson, AZ
PathVysion	<i>HER2</i> gene, FISH	Abbott Laboratories, Abbott Park, IL
INFORM	<i>HER2</i> gene, FISH	Ventana Medical Systems, Tucson, AZ
SPoT-Light	<i>HER2</i> gene, chromogenic in situ hybridization-ISH	Invitrogen, Carlsbad, CA
EnzMet GenePro	<i>HER2</i> gene, silver-enhanced ISH	Ventana Medical Systems, Tucson, AZ

What is the optimal test?

What is the potential efficacy of drug in patients who do not express Her-2?

Drug – Diagnostics Collaboration Scenario



Iterative nature of science causes an established or new drug associated with an old diagnostic test to be used with an improved diagnostic test. Changes are possible in either the drug or diagnostic and a variety of interactive changes may be established each requiring unique attention to study design.

Clinical Performance

- **Retrospective studies**
 - The study supports the intended use of the test
 - Samples were collected and stored appropriately
 - No sampling bias
- **Literature to support device**
 - Should be analyzed, summarized, organized
 - All published studies are different

Speed up Introduction of Innovative Products: Overcoming Potential Regulatory Barriers

- Harmonization between FDA Reviewing Centers
- Adequate guidance to clarify options from FDA
- Increased dialogue between FDA and Industry
- Encourage sponsors to work with FDA as science develops
- Least burdensome and creative FDA review and approval process
- Make regulatory process transparent, efficient and still preserve FDA's public health mandate

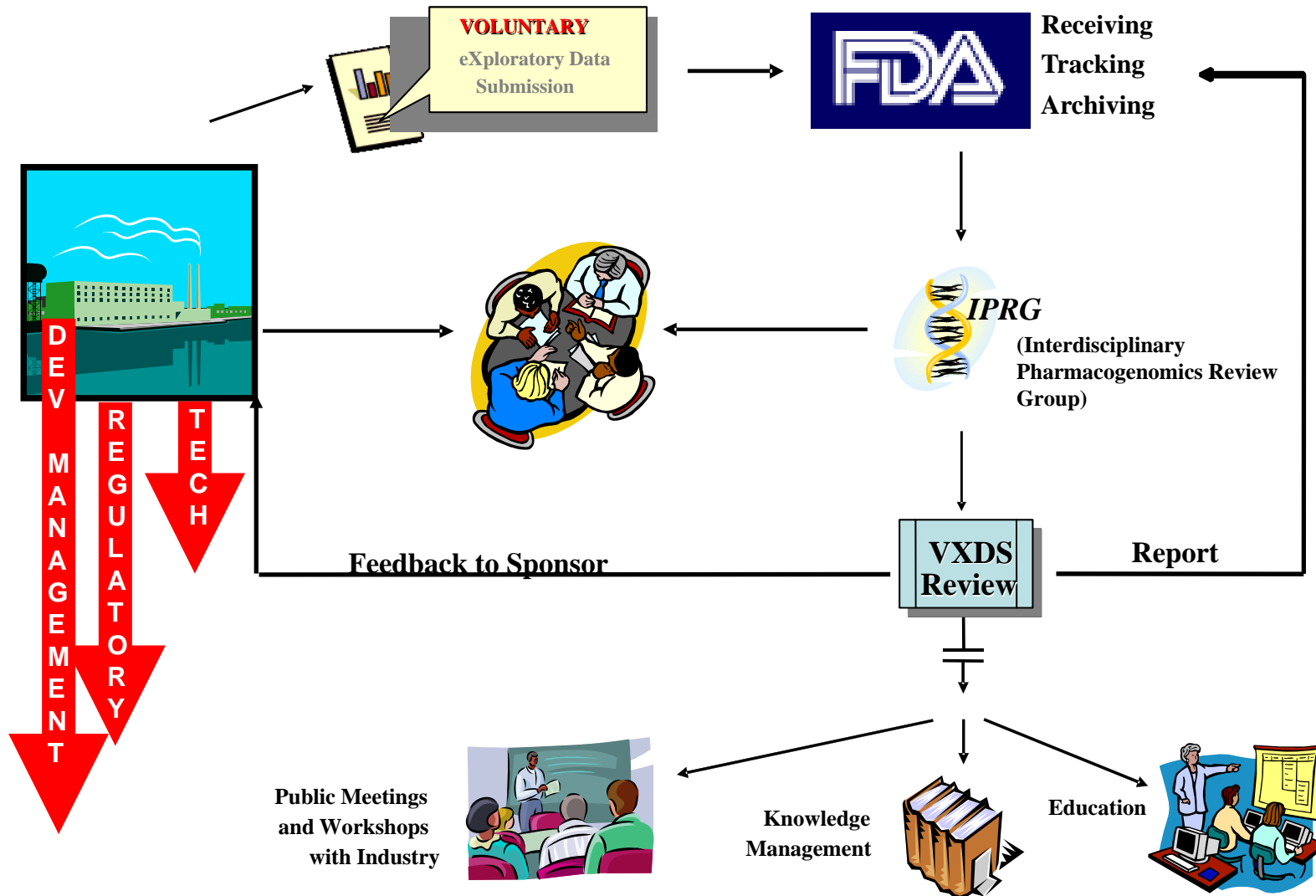
When the Diagnostic Becomes Integral to Approval of the Drug

- Diagnostic approval is needed in parallel with the drug (labeling implications).
- **FDA review centers (CDER/CBER/CDRH/OCP) work with collaborating sponsors (drug-diagnostics companies) to coordinate review processes and tandem approval.**
- “Predictive” claims for companion diagnostics rely on understanding the effect of the drug in both biomarker positive and biomarker negative patients.
- **Companion diagnostics are at the heart of personalized medicine, and carry the same risk profile as the drug.**

Consultation Programs/ Interactions with Regulators

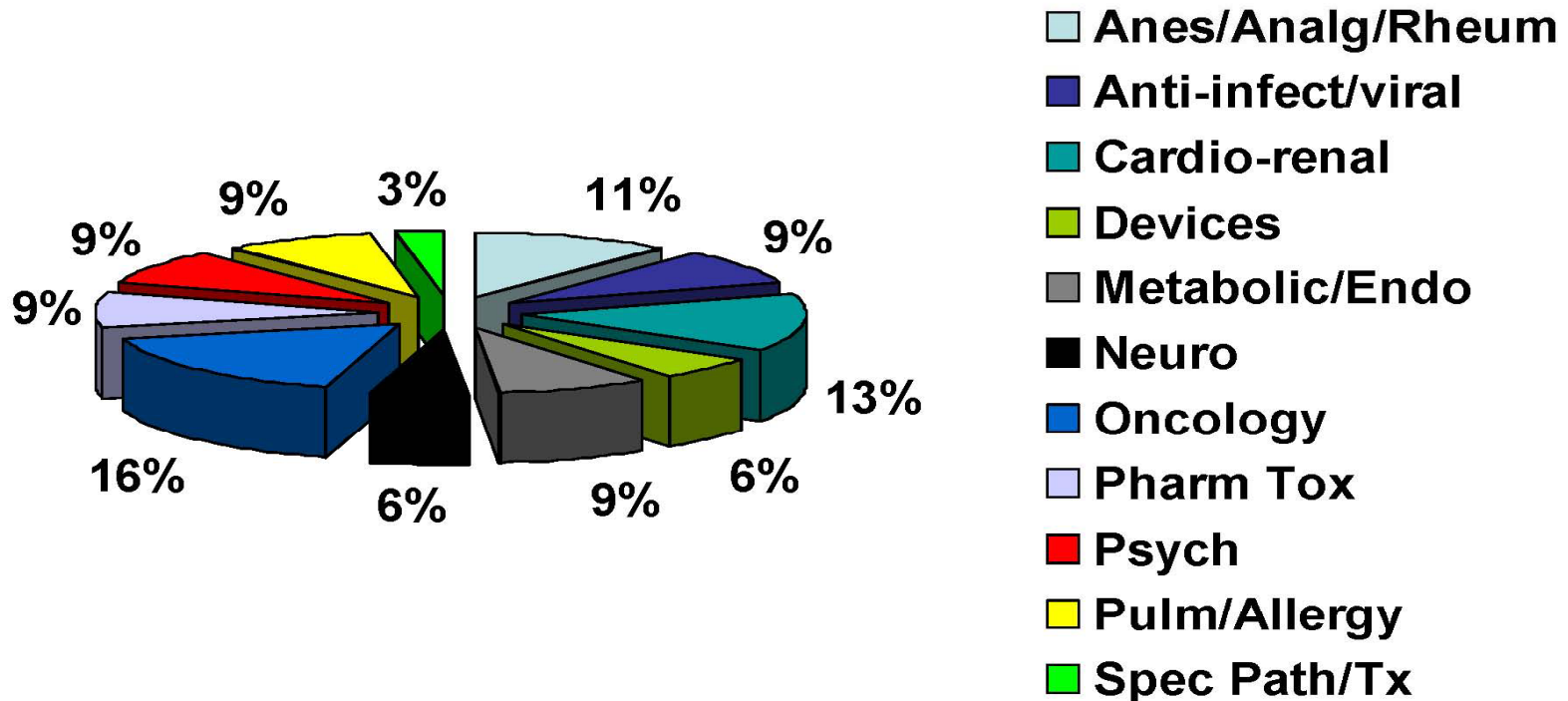
- Early interactions
 - VXDS – Voluntary Data Submission
 - Pre-IDE – Non-binding planning discussions
 - Pre-IND – Per CDER/CBER practice
- Middle interactions
 - IDE – Investigational device exemption
 - IND – Investigational new drug
- Pre-market submissions
 - PMA – Pre-market approval application
 - NDA – New drug application
 - BLA – Biologic license application

Introduction of Exploratory Biomarkers: *Voluntary eXploratory Data Submissions*



Clinical Divisions

VXDS Submissions to 2008



When do I file a pre-IDE for protocol review?

- New product involves cutting edge technology and it will be helpful to familiarize FDA with the technology in advance
- Assistance is needed in defining possible regulatory paths
- The studies involve complex data and statistical approaches and assistance is needed in defining appropriate analyses
- Study designs are complex and you are seeking advice on ways to simplify and focus them on the studies needed to support your claim

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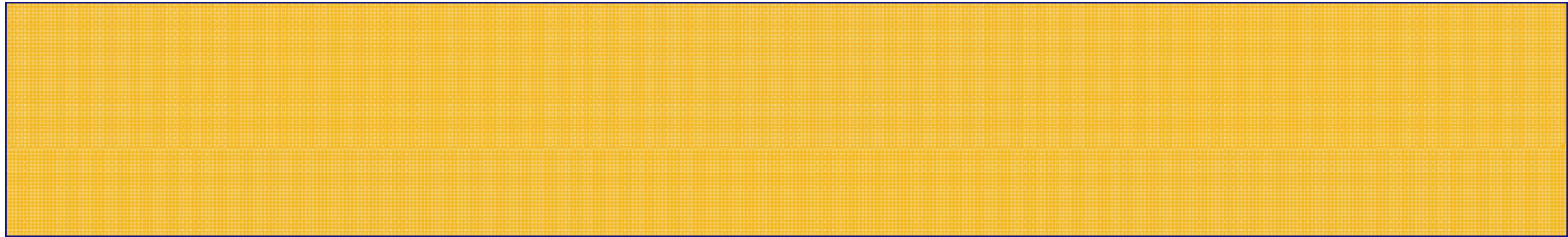
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Current Challenges

- Regulatory framework for companion drug-diagnostics is nascent and evolving.
- Clarity on IVD regulation of medical devices, ie LDTs
- Still a great deal of confusion and controversy about evidence base needed for adoption of an individualizing test into clinical practice-
 - Clinicians dislike information without instructions
- PM success depend on safe and effective Dx-Rx

Future Challenges

- Drug and Diagnostics: better understanding of regulatory framework and product development life cycles
- Create Personalized Medicine (Dx/Rx coordinated) consultation programs to harmonize practices
- Development of a feedback loop to capture outcome on innovative targeted medicines (comparative effectiveness)
- Will regulatory incentives be created for personalized medicine
- Cumulative process approval based on growth of data for Diagnostics/Therapeutics
- Recognize multi drug-diagnostics strategies- eg. bundle
- Facilitate development of “preventive medicine” rather than “treatment medicine”



“The young physician starts life with 20 drugs for each disease, and the old physician ends life with one drug for 20 diseases”

William Osler
The Father of Modern Medicine
(1849-1919)



Thank you!

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