# Co-Development of Drug and Test – Is It a Special Challenge with PGx?

## Session 5

## 18th Annual DIA EuroMeeting
## Paris, France – March 8, 2006

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**Office of Clinical Pharmacology**
**CDER/FDA**

# Agenda

1. **The US Perspective**
   Felix Frueh
   FDA, USA

2. **European Perspective and Current Hurdles**
   Michael Doherty
   F. Hoffmann-La Roche Ltd., Switzerland

3. **Home-brew Tests vs. Approved Tests – Considerations**
   Amy Brower, Third Wave Technologies, Inc., USA

4. **Panel Discussion**

# Some questions we'd like to address during this session (1)

- What is the regulatory process for IVD's in Europe? Is the situation with home-brews the same in Europe and the US?
- Why have there been so few new drug launches with diagnostics since Herceptin?
- Does the regulatory environment, as it is today, support or hinder the development of RxDx cross labeled products?
- Looking forward, what is needed in the regulations by the diagnostics industry and pharma industry to encourage the development of RxDx products?
- Does it make good business sense to development a personalized medicine that is linked to a diagnostic that would define sub-populations?
- Does the Rx development process as it is widely implemented today allow for the co-development of a drug and IVD?
- Is it realistic to expect to see a single biomarker that provides adequate definition for stratification?

# Some questions we'd like to address during this session (2)

- What factors are driving diagnostic companies to or away from seeking regulatory approval for their products?
- To what degree are laboratory testing using e.g. FDA approved diagnostics compared to home brew testing?
- How do testing situations differ depending on the test, e.g., CF testing vs. HIV testing vs. UGT1A1 testing?
- When, and to what extent, are new clinical trials necessary for making claims for a diagnostic product?
- How do service labs introducing diagnostics as homebrews present an obstacle to device companies seeking regulatory approval?
- How do technology companies opening CLIA labs shift the use to ASRs and home brews, vs FDA-approved products? Why do they do it?

# Drug-Test Co-Development: Do We Have It Backwards?

## The U.S. Perspective

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# Disclaimer

- The views expressed in this presentation are the ones of the author and may not necessarily reflect the position of the U.S. Food and Drug Administration.

# What I will talk about:

- Need for change (why we have it backwards...)
- Drug-test co-development vs. drug relabeling
- Some remarks about developing biomarkers
- Genomics in drug labels
- Increase in genomic data submission to the FDA
- Why I think change will happen

# Drug Development and Public Health: Why we have it backwards

- The situation today:
  - Drugs are developed and approved predominantly for everyone – the “one size fits all” paradigm appears to persist – yet we know they only work in subsets (to various extents: “hit rates” range from 15 – 80 percent)
  - Tests are developed mainly in cases when drug trials fail to produce statistically persuasive data for approval in all-comers
  - These trials however may already include protocols for genomic studies that can help rescue the drug for approval in subpopulations should the drug fail in all-comers
  - Consequently, from a public health perspective, we have the story backwards

# How to change it: Move towards Personalized Medicine

1. Existing drugs: relabeling ~ can be cumbersome, indirect approach, long process, not necessary for all cases
2. New drugs: (true) co-development ~ direct approach, easier to conduct

- Both are important:
- Relabeling is particularly important to address safety concerns, less used for efficacy issues
- Co-development is probably more relevant to address efficacy questions, but can also be useful for safety concerns

# 1. Relabeling ~ Example: Warfarin, November 14, 2005

*29 mg/wk*

*28 mg/wk*

*24 mg/wk*

*18 mg/wk*

*6 mg/wk*



**Initial Dose: 35 mg/week**

**Age**
**Gender**
**BSA**
**Concomitant Drugs**
**Co-morbidities**

**Stable Maintenance Dose**

2 3

INR

**Repeat INR: Adjust Dose**

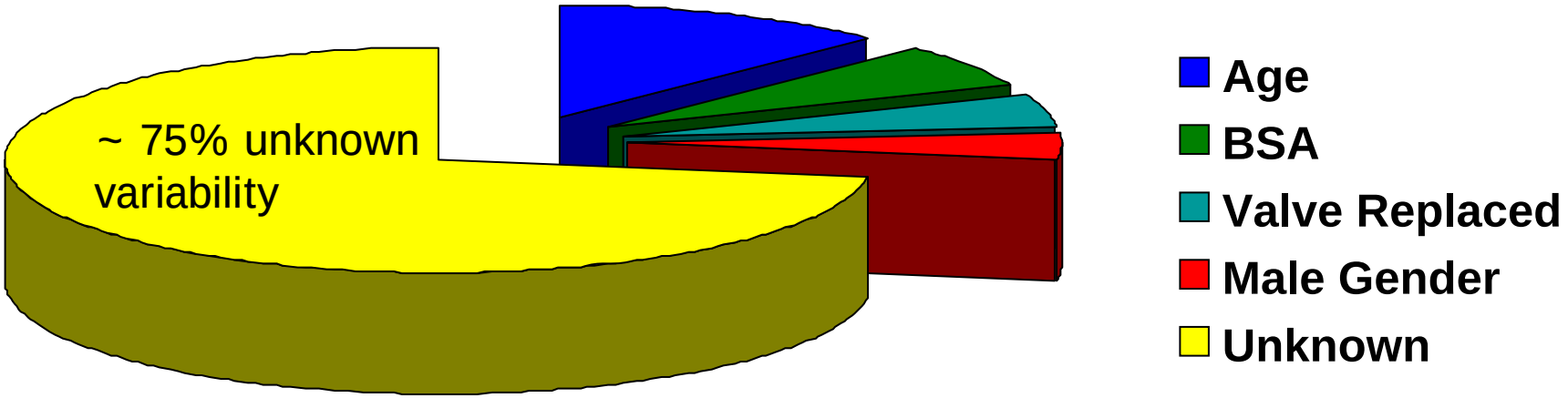
**Increase DOSE Decrease**

**30-35%** 2 3 **20-25%**

INR

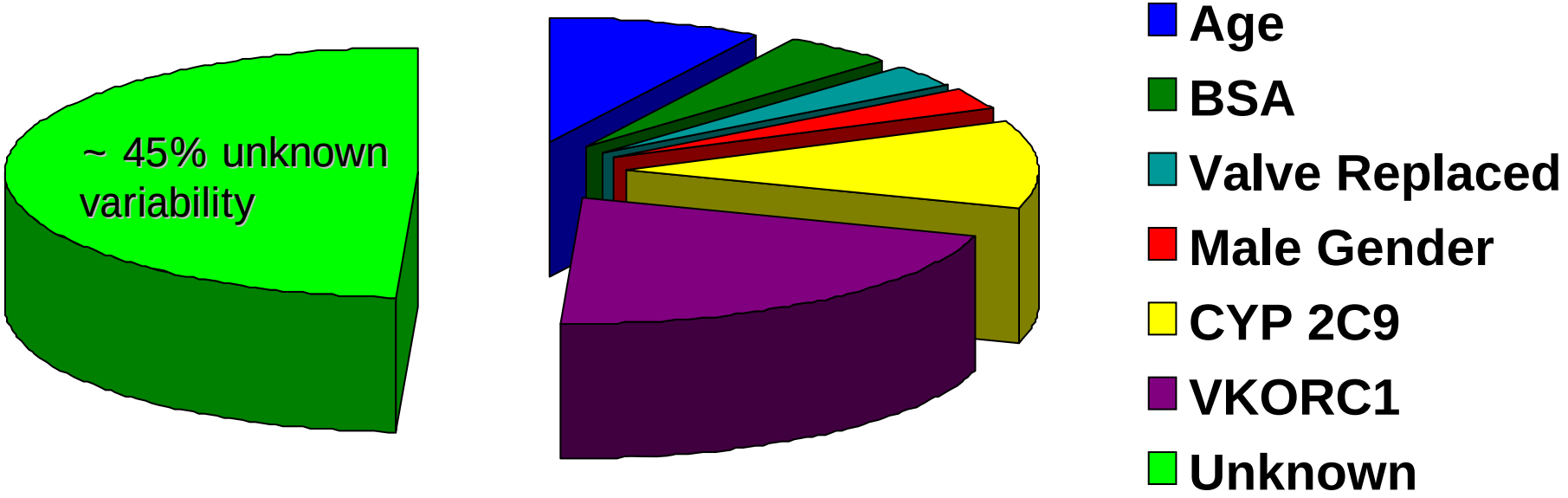
**30 Days**

# Predicting the Stable Dose of Warfarin




*M. Caldwell, CPSC, November 14 2005*

# Predicting the Stable Dose of Warfarin




*M. Caldwell, CPSC, November 14 2005*

# FDA CPSC Advisory Committee Recommendations

- Does the committee agree that sufficient mechanistic and clinical evidence exists to support the recommendation to use lower doses of warfarin for patients with genetic variations in CYP2C9 [VKORC1] that lead to reduced activities?

  10 YES, 0 NO

- Does the committee believe that genotyping patients in the induction phase of warfarin therapy would reduce adverse events and improve achievement of stable INR in patients with genetic variations in CYP2C9 [VKORC1]?

  10 YES, 0 NO

# FDA CPSC Advisory Committee Recommendations, cont'd

- Does the committee believe that existing evidence of the influence of CYP2C9 [VKORC1] genotypes warrants relabeling of warfarin to include genomic and testing information?

  8 YES, 2 NO

# Relabeling Challenges

- New science points out feasibility to update current label:
  - However, most studies are retrospective ~ but this also means that usually a significant amount of data is available ~ powerful for creating genotype – phenotype associations
  - Meta-analyses of such data could be helpful: Coordination of label update with the availability (or approval) of a test
- Interplay between Center for Drugs and Center for Devices is critical (FDA)

# 2. Drug-Test Co-Development ~ What Is It ?

- Drug and test are investigational (biomarkers are “exploratory” or “probable valid”)
- Clinical phase of drug development program will provide evidence of clinical utility (i.e., value) of the diagnostic test
- Claim for test would be for use with drug, drug cross-labeled for use with diagnostic, diagnostic will be required
- Other parts of drug and diagnostic development programs (e.g., analytical validation) would proceed as usual

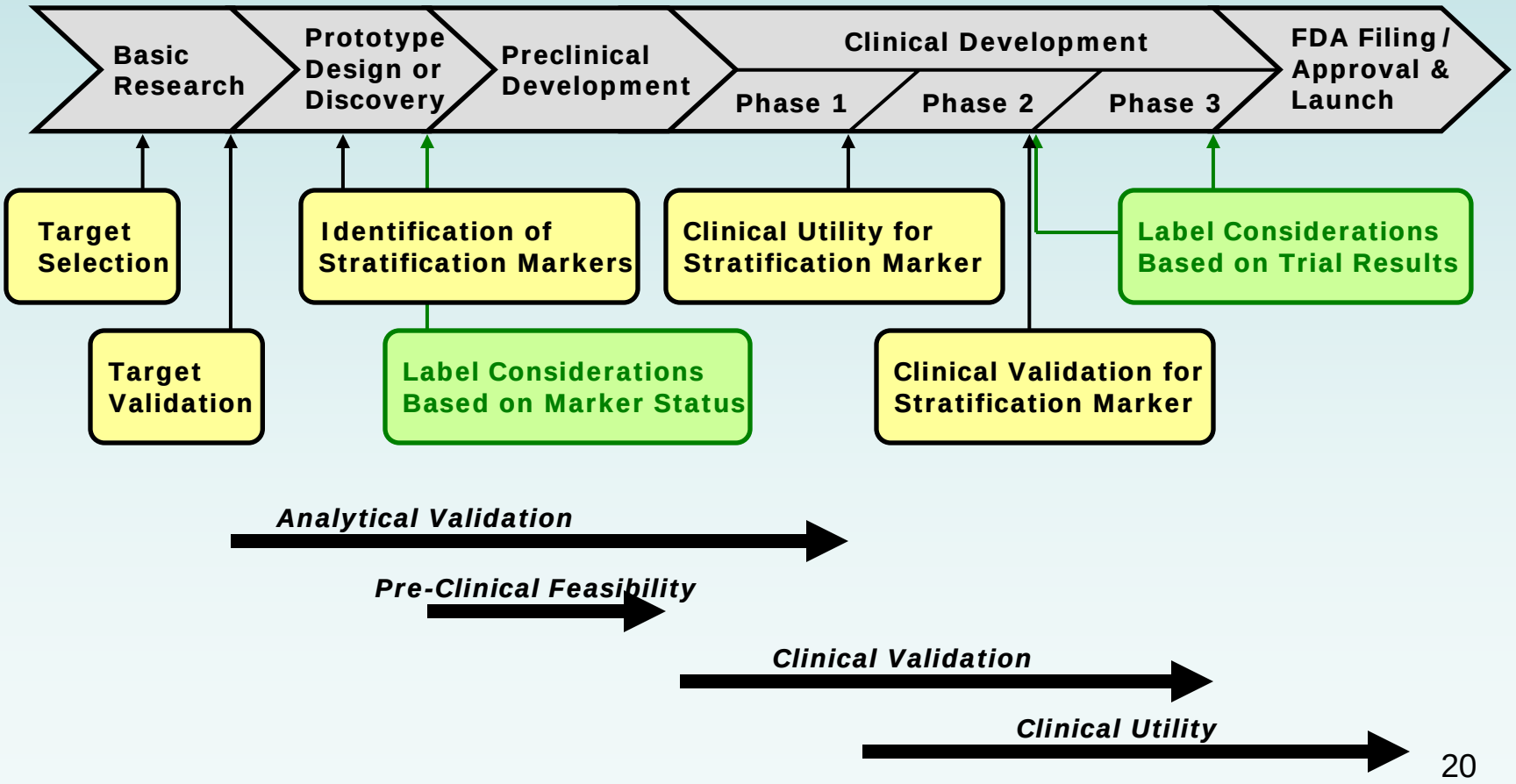
# Why Drug-Test Co-Development?

- Move therapy from non-mechanistic (i.e., trial and error) approach to scientifically based prediction
- Refine definitions of disease (i.e., disease subtypes)
- Avoid certain adverse drug event and therefore improve benefit/risk analysis
- Select patients for therapy based on better predictions of response – or avoidance of non-response and at risk for toxicity

# Guidance on Drug-Test Co-Development

- **Drug-test co-development concept paper**
  - Published Spring 2005
  - Focused mainly on technical/analytical issues, not so much on clinical aspects
  - 90 day comment period ~ 20 comments to docket
  - Proposed timeline and strategy for drug and test developments are ideal, but may not be achievable
- **Drug-test co-development draft guidance**
  - Complete re-write of concept paper, to be published in 2006
  - Focus more on clinical aspects
  - Better integration of test (diagnostic) development into drug development process

# Strategic Milestones for Drug-Test Co-Development



# Test (Biomarker) Development

1. High profile markers (e.g. “known valid” and “probable valid” markers)
2. Lesser known markers, proprietary markers (“probable valid” markers)
3. Marker discovery (“exploratory” markers)

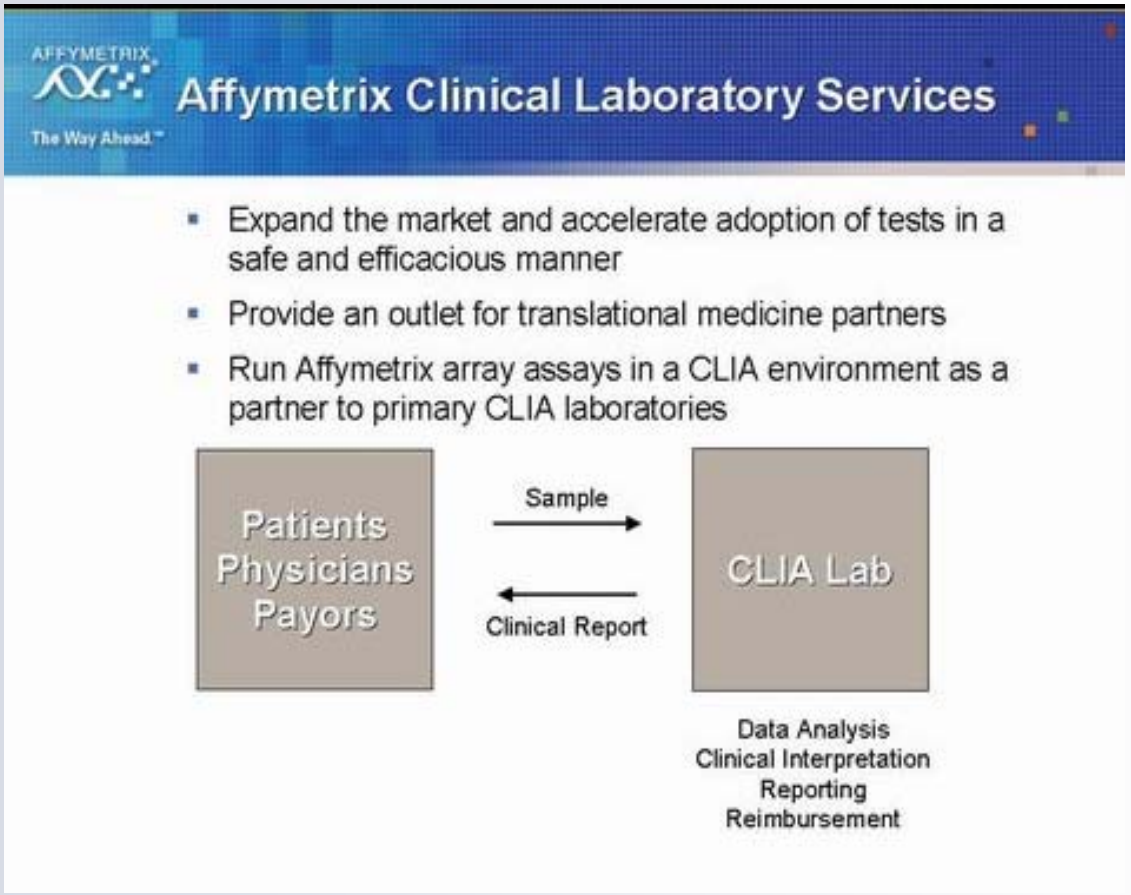
- The problem is that markers need to be developed (qualified) in the context of their intended use
- Therefore, we don’t know how good the marker (or test) is before going into the clinical study
- This makes it difficult to generalize findings.
  - For example: EGFR positivity is relevant for one drug and indication, but may not be relevant for another drug and same indication or not for the same drug and a different indication.

# Pharmacogenomic Test Development is on the Rise: Indicators

1. Market demonstrates flexibility and innovation ~ new business opportunities
2. Number of drug labels with pharmacogenomic information is increasing
3. Number of "Genomic Consults" for INDs and NDAs is increasing
4. Voluntary Genomic Data Submissions are used strategically by industry to set stage for subsequent regulatory submissions

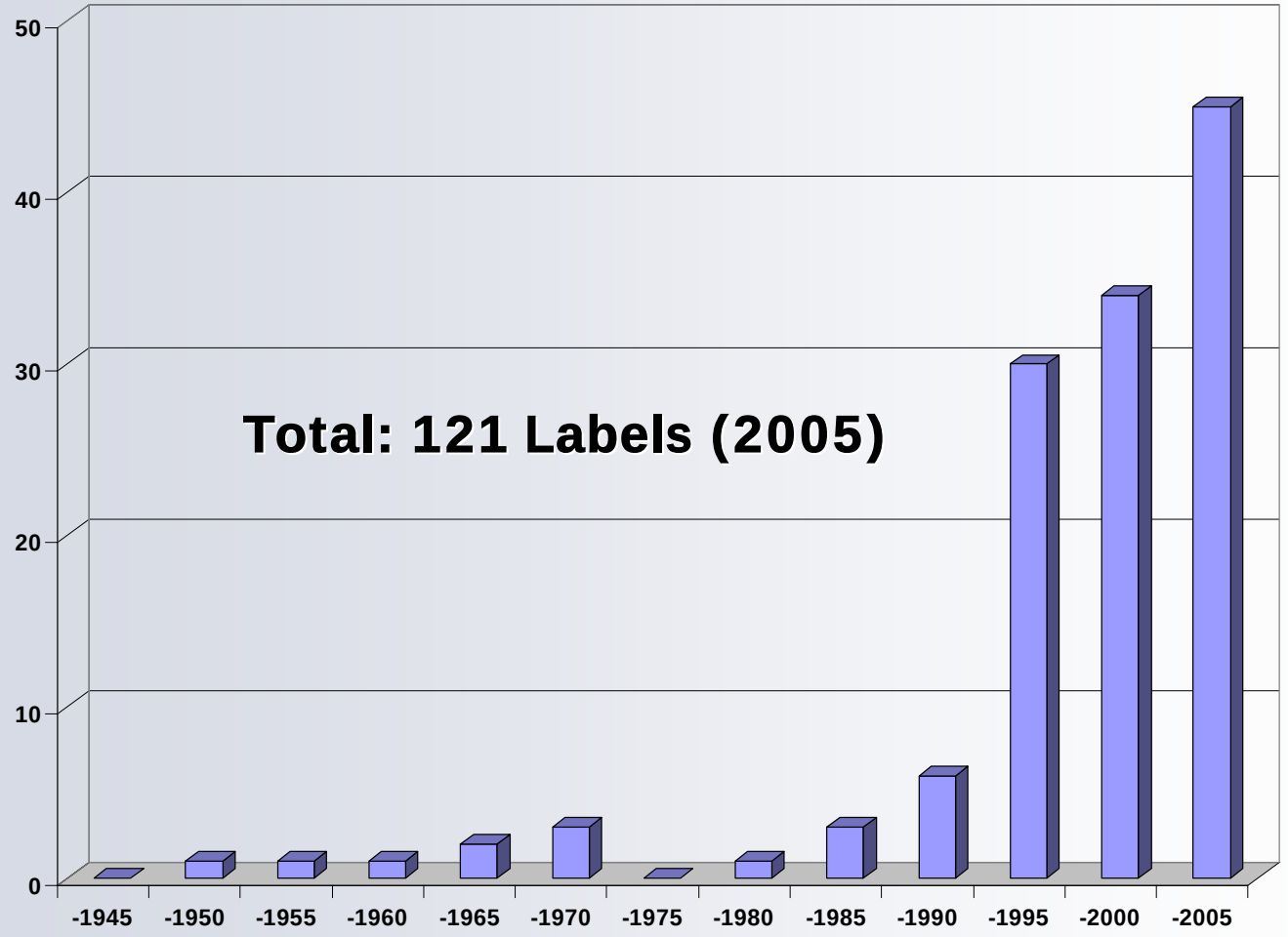
*(→ But can we translate it into clinical practice?)*

# 1. New Business Opportunities

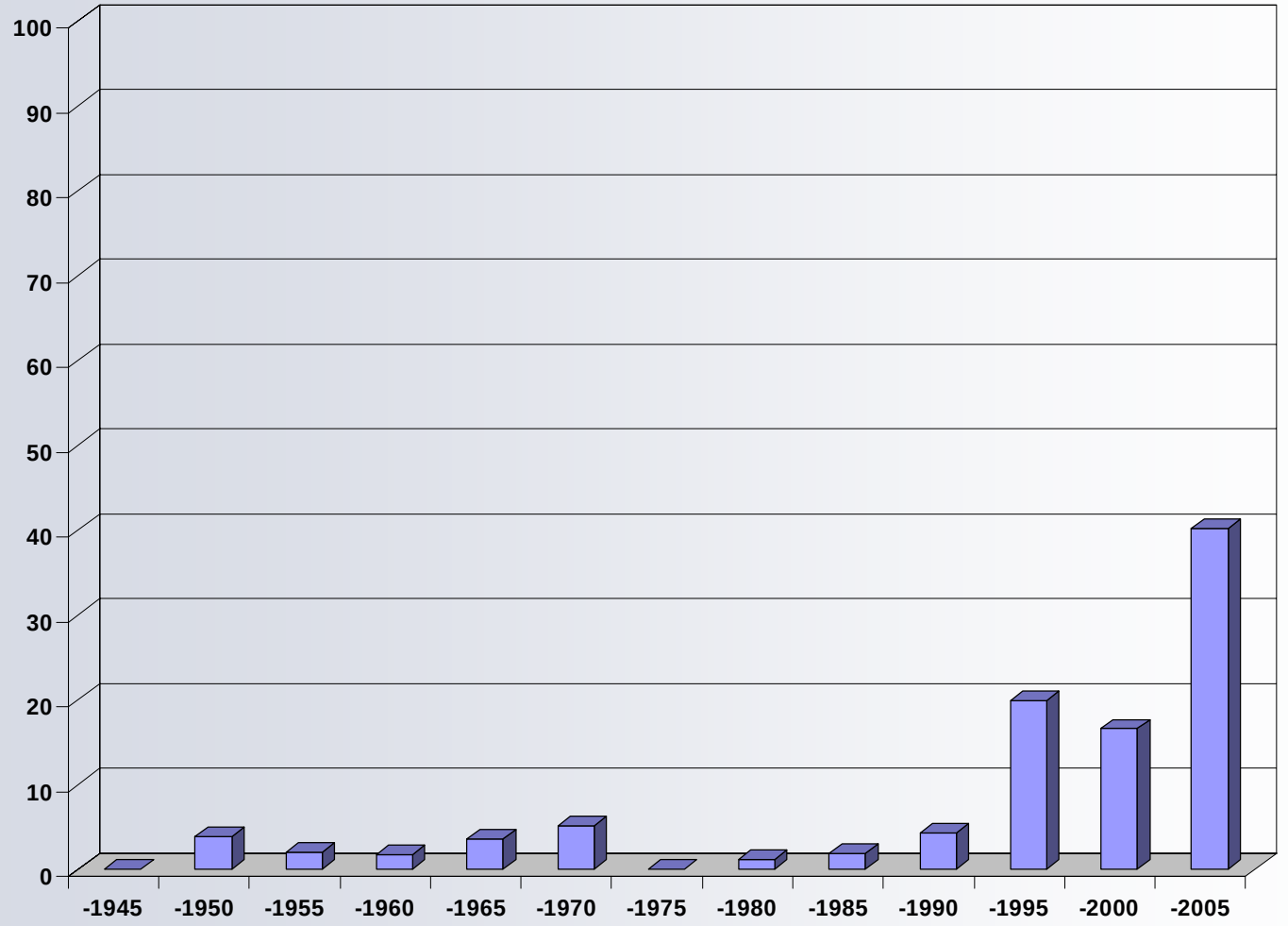



*Steve Fodor, CEO Affymetrix – JP Morgan Conference – Jan 9, 2006*

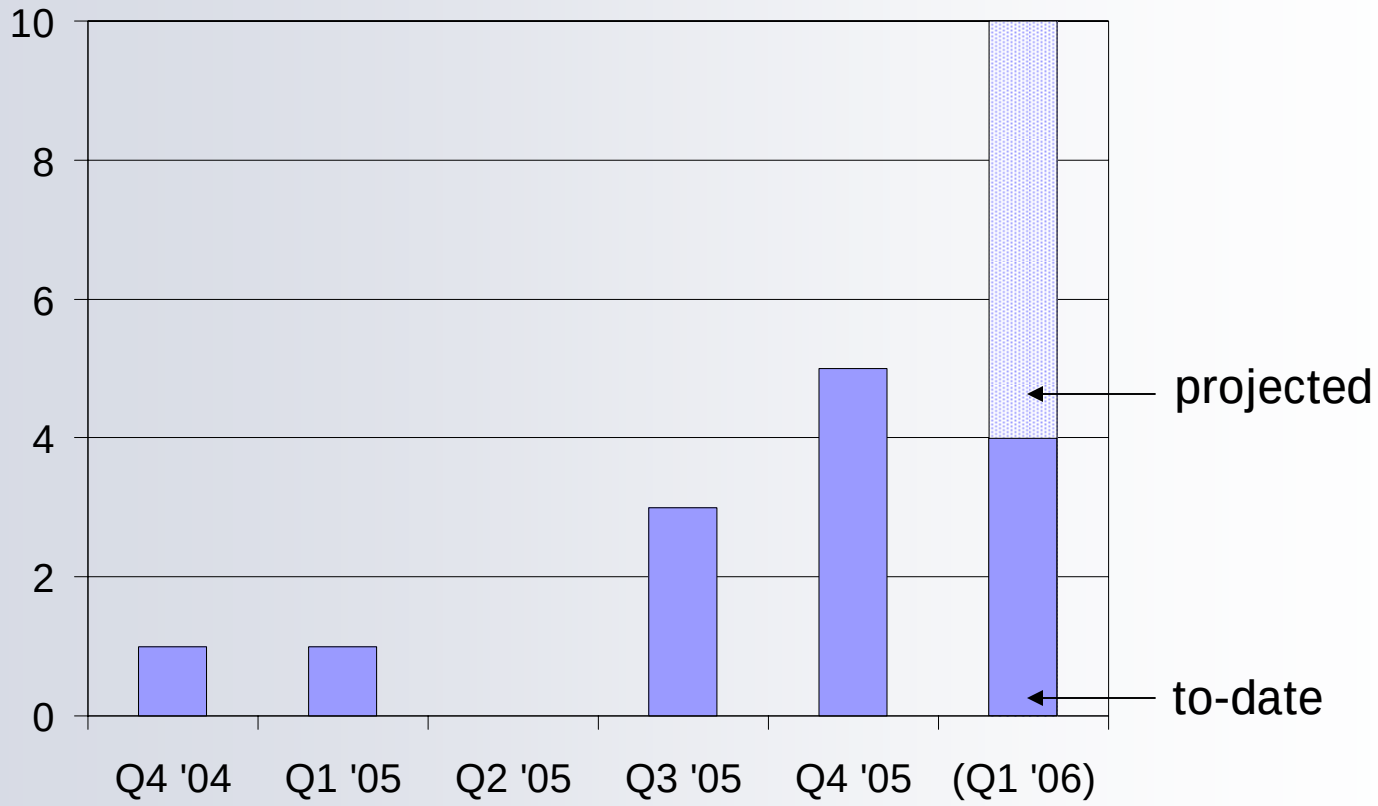
# 2. Number of New Labels with Pharmacogenomic Information



# Percentage of New Labels with Genomic Information Compared to All New Labels



# 3. Increasing Number of Consults Received in OCP Genomics Group



# 4. Voluntary Genomic Data Submission (VGDS) Program at FDA

- **VGDS statistics:**
  - 25 submissions received
  - 15 sponsor meetings held (2 bilateral with EMEA)
- **Impact:**
  - Strategic use of VGDS meetings
  - New policy development, best practices
  - Education
  - New pathway for communication
- **Success Measures:**
  - Overall feedback: 4.5 out of 5 (formal survey)
  - Multiple (and follow-on) submissions from single sponsor

# VGDS Submission Types

- **Therapeutic Areas:**
  - Cancer (multiple types)
  - Alzheimer's Disease
  - Hypertension
  - Hypoglycemia
  - Depression
  - Obesity
  - Rheumatoid Arthritis

- **Scientific and PGx Areas:**
  - Biomarkers
  - Genotyping Devices
  - Microarrays
  - Analysis Software
  - Databases
  - Metabolic Pathways
  - Biostatistics
  - Enrichment design
  - Registry design
  - Toxicology

*Data based on 25 submissions*

# Sounds good, but …

- Drug-test co-development is rarely applied in today's drug development process
- *Why?*
  - Lack of thorough understanding of disease
  - Business model of "one-size-fits-all"
  - Fear of financial/competitive disadvantage
  - Unknown regulatory landscape
- *Will we get there?*
  - Yes, if we change the way we think about public health and the way we do business

# Why don't we see more co-developed medical products on the market?

- Current statistical evaluation for drug approval is based on benefit relative to overall population – the identification of e.g. a responder subpopulation is only required if the signal in overall population does not win
- If we change this paradigm, it would mean that a test is required (existing or newly developed, i.e. co-developed)
  - *Are we ready for this?*
    - Sometimes we are (we know the marker and have successfully used it in a clinical trial)
    - Sometimes we are not (we may not understand the science well enough to make the right decision)
    - (And sometimes we are not getting all the information, even if available, to make the right decision)
- Developing the target (i.e. marker for the test) can be as difficult as developing the drug itself ~ and we have a lot more experience developing drugs

# How to change how we do business

- Encourage to develop biomarkers rigorously and in the appropriate context of use
- Search outside the box for new ways to do this research, e.g. collaborations, consortia, etc.
- Invest in new tools, technical and intellectual (i.e. statistics)
- Create an environment that promotes drug-test co-development (requires change)
- Provide regulatory guidance (FDA concept paper on drug-test co-development published in 2005, draft guidance to be published in 2006)

# Closing Remarks

- We still have only few examples for drug-test co-development:
  - Herceptin® (breast cancer, Her2/neu+, approved 1998 in U.S.)
  - Gleevec® (CML, Philadelphia chromosome (Bcr-abl), 2001; GIST, c-kit, 2003)
  - Erbitux® (colon cancer, EGFR+, 2004)
- Drug-test co-development requires a paradigm change: drugs need to be developed with the intent to identify and treat only patients that benefit from therapy
- To encourage this change, we need a supportive scientific, regulatory and economical environment
- With increasing understanding of the causes of adverse drug reactions and knowledge of mechanisms of drug action, it is reasonable to assume that unnecessary exposure to harm (or lack of efficacy) will be difficult to defend in the future

# www.fda.gov/cder/genomics

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