Personalized Medicine Update

FDA-Industry IVD Roundtable Meeting
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Overview

- FDA & Personalized Medicine
  - Overview of activities
- Companion Diagnostics
- Co-development of Diagnostics and Therapeutics
- Enrichment Strategies for Clinical Trials
- Next Gen Sequencing

FDA's View of Personalized Medicine

- Commissioner Hamburg
  - Committed to Personalized Medicine program
- Office of Medical Products and Tobacco (OMPT)
  - Manages three medical product centers
  - Direct interest in personalized medicine
  - Initiating OC coordination of personalized medicine in product centers
- CDRH/CDER/CBER
  - Working together to identify issues, create solutions
    - Internal practices
    - External guidance

CDRH's Role in Personalized Medicine

- PM a priority for CDRH
  - Personalized Medicine Staff
    - 6 dedicated staff in PM
    - Chief Medical Officer
    - ~10 review staff in review divisions
  - Current scope is IVDs, with other device issues as needed
  - PM requires careful approach within current laws/regulations

Current PM Activities

- Guidances for Industry
- Changes to Internal Practice & Policy
- Approaches to Emerging Technologies

Current PM Activities: Guidances

- Companion Diagnostics
  - Draft guidance published July 2011
    - http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262292.htm
  - Plan to finalize “very soon”
- Process of Codevelopment of Diagnostics and Therapeutics
  - Plan to publish draft in 2013
- Clinical Trial Designs Employing Enrichment Strategies
  - Draft guidance published December 2012
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf
- Others in the works
  - Next Generation Sequencing -- Points to Consider
  - Investigational IVD devices used in therapeutic product studies

Current PM Activities: Intercenter Policies & Communications

- Different Centers have different laws, regulations, cultures, and needs
- Process becoming established as “normal”:
  - Working in close proximity with each other
  - Inviting each Center to others’ meetings
    - See the full picture
  - Identifying issues together and creating draft policy
- Regular internal interactions on broader scope

Current PM Activities: Additional Intercenter Advances

- Creating agreed-to ways of working together
- Recognizing each Center's role in process
  - Including limitations
- Creating streamlined regulatory communication methods
  - Different centers use different systems to archive, track submissions
- Increasing recognition of status of tests in INDs

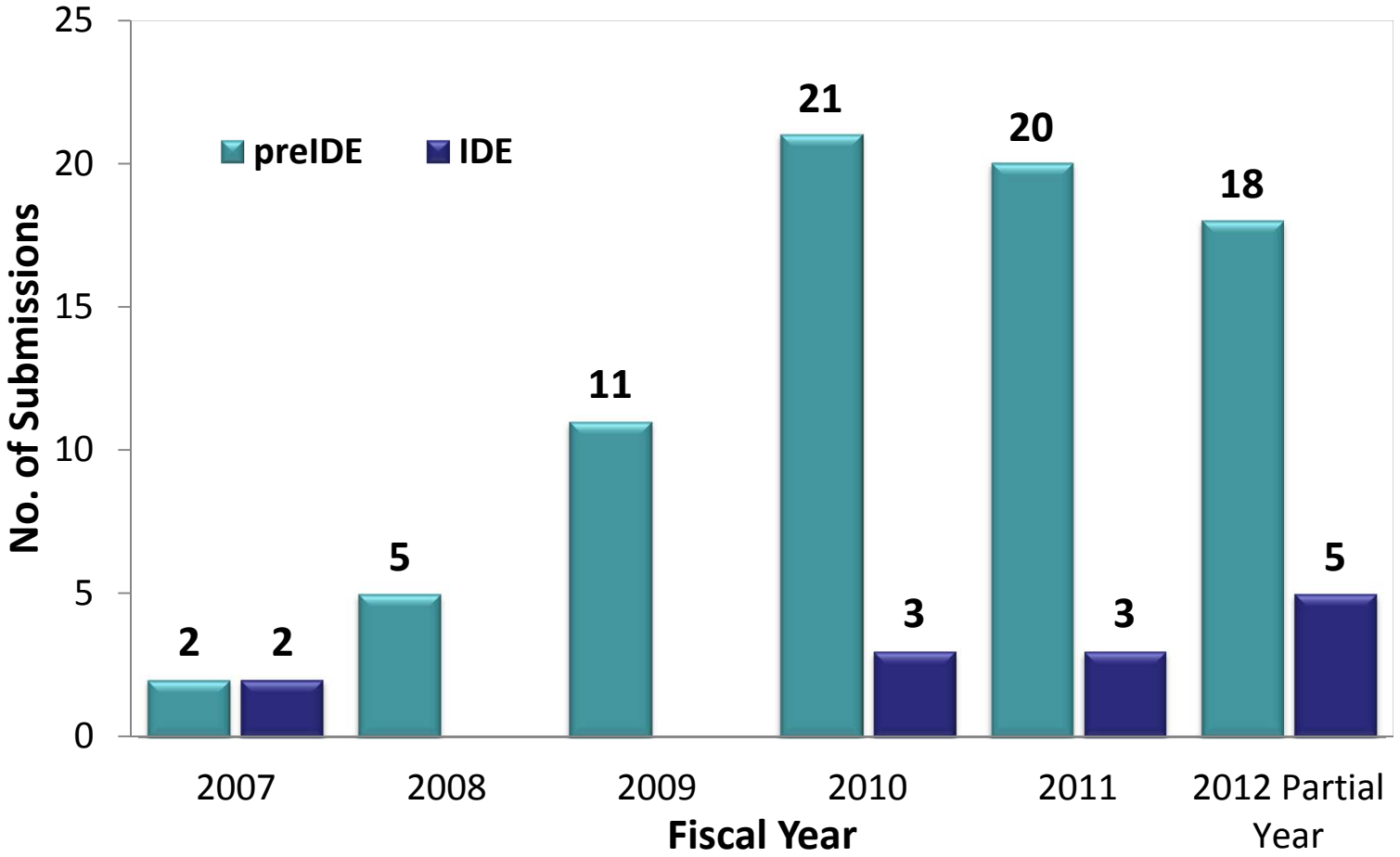
Current PM Activities

- Emerging Technologies
  - Next-gen sequencing
  - Array-based testing (CNV)
  - Proteomics
  - Innovation Pathway

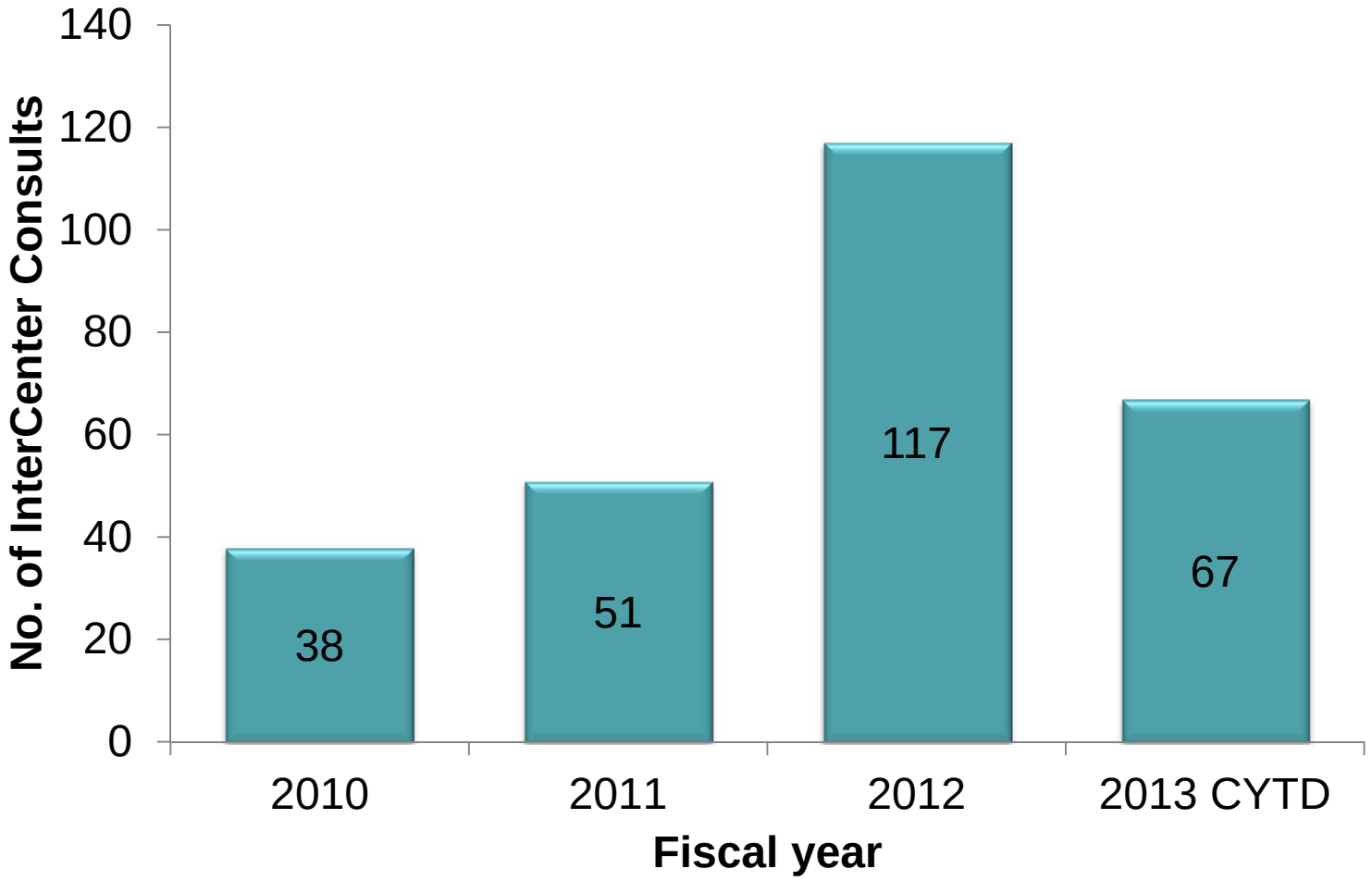
Companion Diagnostics

- Defined as being essential for the safe and effective use of a corresponding therapeutic product
- Running list of approved IVD companion diagnostics
  - www.fda.gov/companiondiagnostics
- Many more in the pipeline
  - Increase in submissions related to companion diagnostics

Increase in Companion Dx-related Pre-IDE and IDE submissions



Increase in InterCenter Dx Consults



Lessons Learned from Companion Dx Approvals

- Intercenter communication now highly effective and review staff working well together
  - Co-attendance at meetings
  - Questions/consults transmitted in timely manner
  - Approvals and press well-coordinated
  - *Recognize impending changes to model: NGS, "basket" trials*
- Accelerated drug approval does not significantly change when companion Dx needed
- Drug and Dx sponsors should carefully define expectations for each other
- Modular PMA process for Dx highly preferred over traditional
- Codevelopment has passed first tests

The Process of Codevelopment

- FDA has reviewed >15 companion Dx applications and many therapeutic development programs with potential companion Dx
- No two programs or products are exactly alike
  - Preference, timing issues, disease state, intended use, etc.
- Loud calls for a guidance on the codev process

Guidance on the Process of Codevelopment

- Guidance will:
  - describe general principles of the codevelopment process
  - describe points to consider in both therapeutic and diagnostic development programs
  - describe FDA preferences for certain elements
  - not prescribe any particular development pathway

Enrichment Strategies for Clinical Trials

- Draft guidance Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products.
  - Published December 2012
  - Guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf
  - Webinar: http://www.fda.gov/Drugs/ucm343578.htm

Enrichment Strategies for Clinical Trials

- Enrichment is defined as the prospective use of any patient characteristic –demographic, pathophysiologic, historical, genetic, and others – to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population.

Enrichment Strategies for Clinical Trials

- Guidance discusses three enrichment strategies:
  - Decreasing heterogeneity (noise); choosing an appropriate population, i. e., patients who definitely have the disease
  - Finding a population with many outcome events, i. e., high risk patients, or patients with relatively severe disease -- prognostic enrichment
  - Identifying a population capable (or more capable) of responding to the treatment -- predictive enrichment

Enrichment Strategies for Clinical Trials

- The guidance discusses
  - general clinical trial design considerations
  - examples of potential clinical trial designs for enrichment
  - regulatory considerations when using enrichment strategies
  - predictive enrichment designs
    - Performance characteristics of the selection criteria (i.e., test accuracy, precision, cutoffs)
    - Study of marker-negative patients

Next Generation Sequencing

- Approaches to Regulation
  - Evaluation of analytical performance
  - Clinical significance of rare variants identified by NGS
- Efforts to Speed Transition to Clinic
  - Reference standards
    - Development of reference materials – FDA/NIST collaboration (human, microbial RMs)
  - Unified resource of clinically relevant variants
    - Leverage other efforts, NCBI, NHGRI, ACMG, ICCG

What's Changing

- NGS now in play
  - Diagnostic and companion diagnostic uses
- Greater interest in "basket" trials and combination drug trials
- "Breakthrough" therapy designation
- Rare mutations/markers gaining ground
  - Need systematic approach to gathering evidence

Summary/Outlook

- Progress is rapid, but still has its unpredictable moments
- Everyone playing well together
  - Each center learning a lot from the other
  - Greater internal uniformity already in place
- Sense that system will work
  - New lessons from every new model
  - Guidance lagging submissions as we learn
- System operational but still needs some refinement
- Sponsors “getting it”
- Constantly changing technology – we are preparing
- Process is evolving – contact the Agency early and often

Thank you!

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