Thoughts on Biomarker Development Efforts

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What we said in 2004:

A new product development toolkit — containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques — is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product. We need superior product development science to address these challenges — to ensure that basic discoveries turn into new and better medical treatments. We need to make the effort required to create better tools for developing medical technologies. And we need a knowledge base built not just on ideas from biomedical research, but on reliable insights into the pathway to patients.

What we said in 2006:

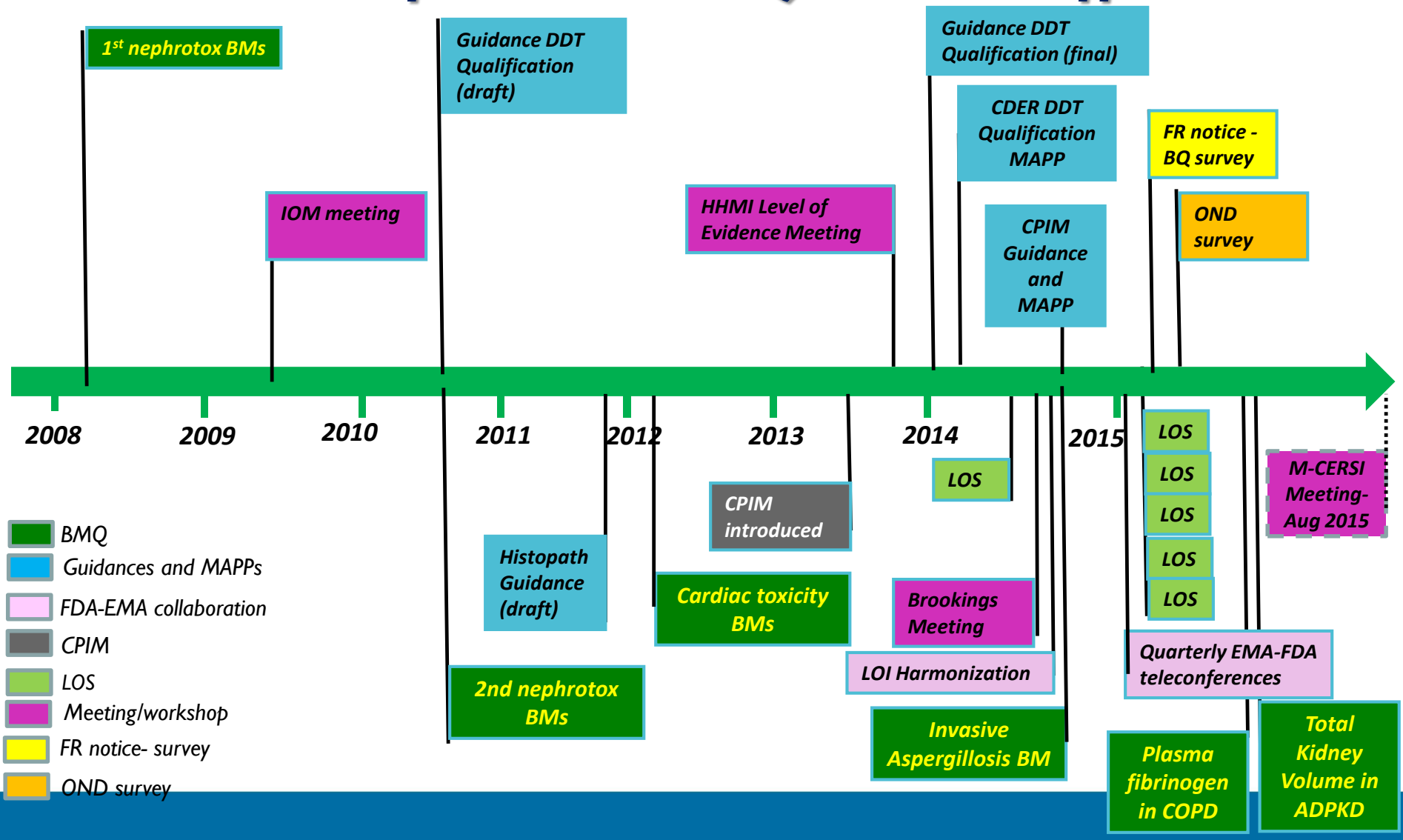
1. Biomarker Qualification. The process and criteria for qualifying biomarkers for use in product development should be mapped. Clarity on the conceptual framework and evidentiary standards for qualifying a biomarker for various purposes would establish the path for developing predictive biomarkers. Stakeholders, including industry, researchers, and patient groups would have a clear idea of what needs to be done to adopt a new biomarker for regulatory use. Such a framework could stimulate biomarker development and, consequently, shorten the time necessary to develop a successful marketing application.

Identifying the framework and evidence needed to qualify biomarkers for different purposes would put an emphasis on correlative and predictive science to accompany the current emphasis on biomarker discovery. Consensus on the following types of questions is needed to put such a framework in place:

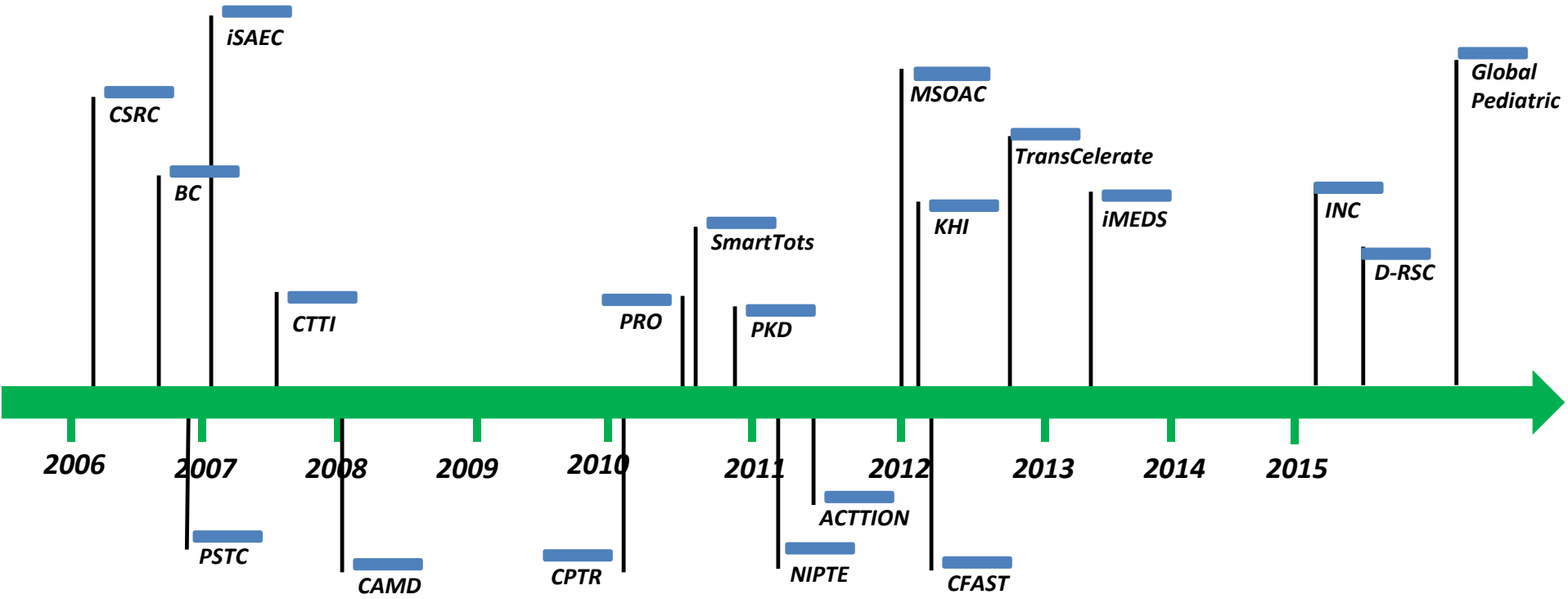
- How can biomarker evidence help demonstrate that a candidate product is not too toxic to test in humans?
- How can biomarkers be used to select dose ranges for initial human testing?
- How can biomarkers be used most effectively to evaluate dose response in later trials?
- What biomarker evidence is appropriate to guide selection of patients for clinical testing?
- What types and levels of evidence are needed to accept a biomarker as a surrogate endpoint for product efficacy?

What has happened since then?

Timeline for Salient BQ-related Efforts



Examples of Consortia



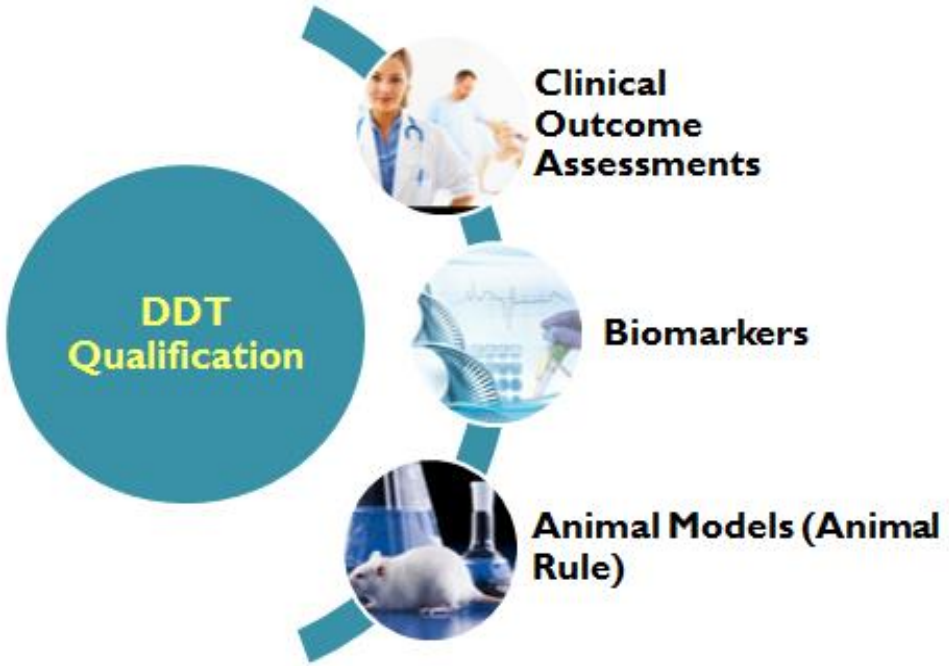
*Cardiac Safety Research Consortium (**CSRC**), Biomarker Consortium (**BC**), Predictive Safety Testing Consortium (**PSTC**), Clinical Trials Transformation Initiative (**CTTI**), Coalition Against Major Disease Consortium (**CAMD**), Critical Path to TB Drug Regimens (**CPTR**) Consortium, Patient Reported Outcomes (**PRO**) Consortium, Polycystic Kidney Disease Outcomes (**PKD**) Consortium, National Institute for Pharmaceutical Technology and Education (**NIPTE**), Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks Initiative (**ACTTION**), Multiple Sclerosis Outcome Assessments Consortium (**MSOAC**); Kidney Health Initiative (**KHI**), Coalition For Accelerating Standards and Therapies (**CFAST**), Innovation in Medical Evidence Development and Surveillance (**IMEDS**) Program, International Neonatal Consortium (**INC**), Duchenne-Regulatory Science Consortium (**D-RSC**), Global Pediatric Clinical Trials Network Pre-Launch Consortium **(Global Pediatric)***

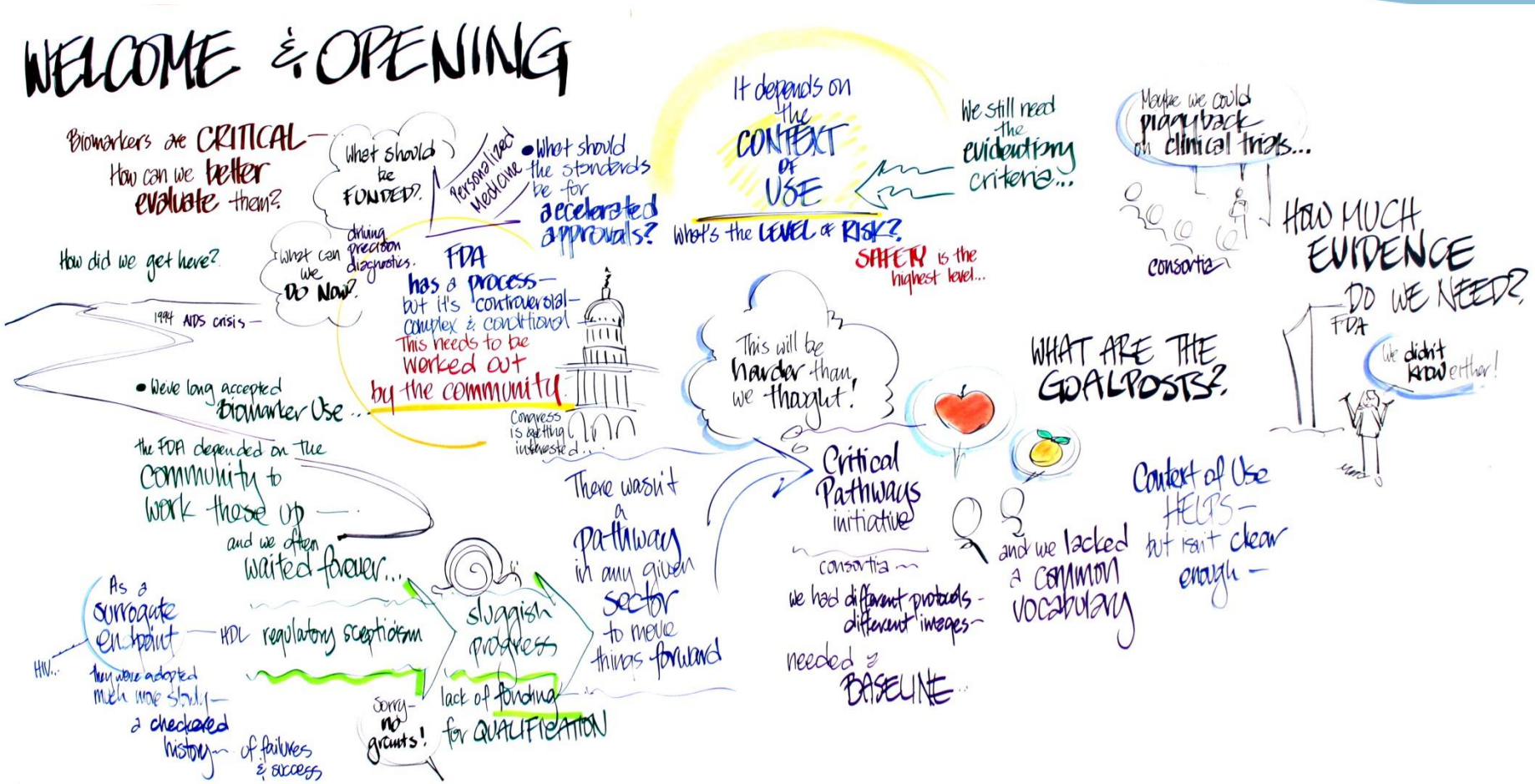
Drug Development Tool Qualification Program

Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools

http://www.fda.gov/downloads/Drugs/GuidanceComplicanceRegulatoryInformationi/Guidances/UCM230597.pdf




WELCOME & OPENING
Biomarkers are CRITICAL — How can we better evaluate them?
What should be FUNDED?
Personalized Medicine
What should the standards be for accelerated approvals?
It depends on the CONTEXT of USE
We still need the evidentiary criteria...
What's the LEVEL of RISK?
SAFETY is the highest level...
Maybe we could piggyback on clinical trials...
consortia
HOW MUCH EVIDENCE DO WE NEED?
FDA
We didn't know either!
How did we get here?
What can we DO Now?
driving precision diagnostics.
1994 AIDS crisis —
FDA has a process — but it's controversial — complex & conditional
This needs to be worked out by the community.
Congress is getting interested...
• We've long accepted Biomarker Use...
the FDA depended on the community to work these up — and we often waited forever...
This will be harder than we thought!
Critical Pathways initiative
consortia
we had different protocols - different images - needed a BASELINE...
WHAT ARE THE GOALPOSTS?
and we lacked a common vocabulary
Context of Use HELPS — but isn't clear enough —
There wasn't a pathway in any given sector to move things forward
As a surrogate endpoint — HDL — regulatory scepticism
HIV...
they were adopted much more slowly — a checkered history — of failures & success
sluggish progress
Sorry — no grants!
lack of funding for QUALIFICATION

Current Challenges

- Lack of standardized methods for measuring new biomarkers and often a lack of reliable evidence about their performance
- Lack of generally-accepted evidentiary standards for qualifying new biomarkers for particular contexts of use
- Inadequate prioritization and coordination of the limited public and private resources available to identify and qualify biomarkers in areas of greatest unmet need
- Inadequate scientific information on the causes, biochemical pathways, and natural histories of many diseases, making identification of disease-specific biomarkers difficult
- Lack of public access to existing research and information on potential biomarkers

What Are We Hearing from Submitters?

- The process takes too long
- We don't have quick wins
- We don't know where the goal line is
- We are getting tired
- We are hearing conflicting views from the Review Divisions in CDER about whether qualification is even needed
- These are multi-million dollar efforts pulled together with tentative resources and we cannot afford to waste time…
- We want clearer timelines and deliverables

So, what are we doing about it?

- Leadership changes for the BQ Program
- Streamlining steps in the process for BQ
- Increased focus on communication with submitters
- Increased focus on communication with CDER staff on the BQRTs
- Harmonization of LOI requirements with EMA
- Setting clear expectations
- Surveys to understand where biomarker development is needed
- Front loading Context of Use discussions
- Letters of Support
- CPIM
- Convening workshops

Opportunities for Collaboration

- Develop evidentiary standards for context-of-use-specific biomarker qualification
- Prioritize specific diseases and respective biomarkers whose development and qualification would advance drug development and satisfy unmet medical needs
- Expand qualification by developing and maintaining an accessible database for collecting biomarker data, and a repository for samples
- Develop standards for biomarker measurement tools…Reproducibility initiatives…
- Encourage and fund biomedical research that is necessary as the basis for development of new biomarkers
- Coordinate existing partnerships and consortia so that they effectively direct their efforts toward development and qualification of priority biomarkers
- Train investigators on regulatory considerations for biomarker development

Development & Approval Process (Drugs)
Drug Development Tools Qualification Program
Animal Model Qualification Program
Biomarker Qualification Program
Clinical Outcome Assessment Qualification Program

Resources for You
- Biomarker Qualification Context of Use
- Biomarker Qualification FAQ
- Biomarker Qualification Contacts and Submitting Procedures
- Biomarker Qualification Templates and Examples
- Additional Resources

Letters of Support

What is a Letter of Support?

This is a letter issued to a submitter that briefly describes CDER's thoughts on the potential value of a biomarker and encourages further evaluation. This letter does not connote qualification of a biomarker. It is meant to enhance the visibility of the biomarker, encourage data sharing, and stimulate additional studies.

Why Issue a Letter of Support?

Encouraging the identification and qualification of new drug development tools has been recognized as one of the approaches to overcome hurdles in drug development programs. This approach has the potential to enhance the availability of useful information about drug safety and efficacy. To encourage further development of promising biomarkers which are not yet ready for qualification, FDA may issue a Letter of Support to submitters who have assembled this information about promising biomarkers.

Where Can You Find Issued Letters of Support?

Letters of Support are made publicly available on the FDA's DDT-Biomarker Qualification Program Website.

For more information, please contact CDER-BiomarkerQualificationProgram@fda.hhs.gov.

Issued Letters of Support

Submitter	Biomarkers	Area(s) for Further Evaluation	Issuance Date with Link to Letter of Support	Additional Information
Predictive Safety Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Urinary Biomarkers: Osteopontin and Neutrophil Gelatinase-associated Lipocalin (NGAL)	Early Clinical Drug Development	8/20/2014: Letter of Support (PDF)	Refer to Predictive Safety Testing Consortium Web Site for more information.

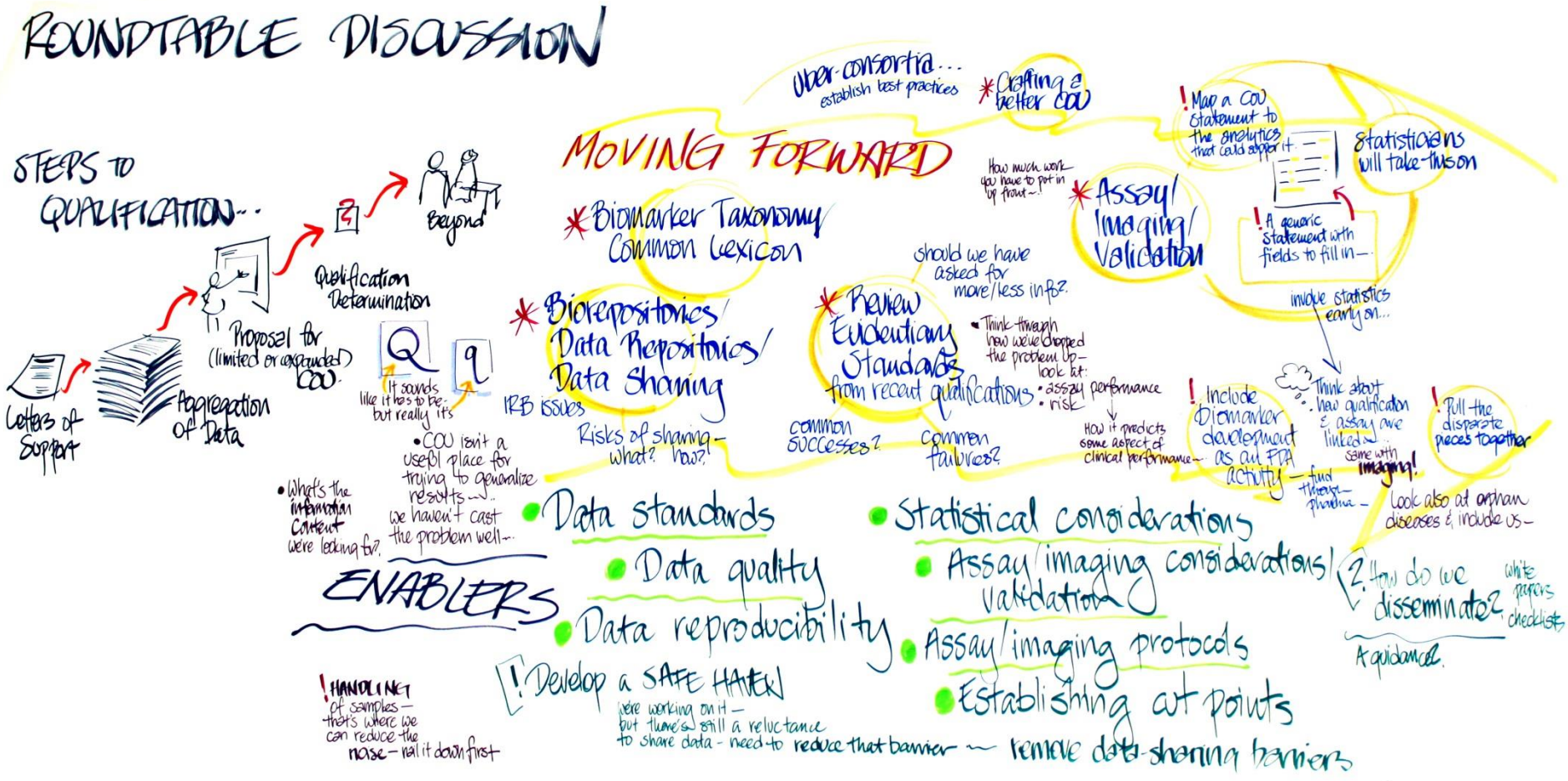
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm412833.htm

Critical Path Innovation Meetings

- Promotes understanding challenges in drug development and innovative strategies to address them
- Potential biomarkers and clinical outcome assessments (COAs) not ready for DDT Qualification Program
- Natural history study design and implementation
- Emerging technologies or new uses of existing technologies
- Novel clinical trial designs and methods
- Nonbinding on FDA and other participants
- No advice on specific approval pathways

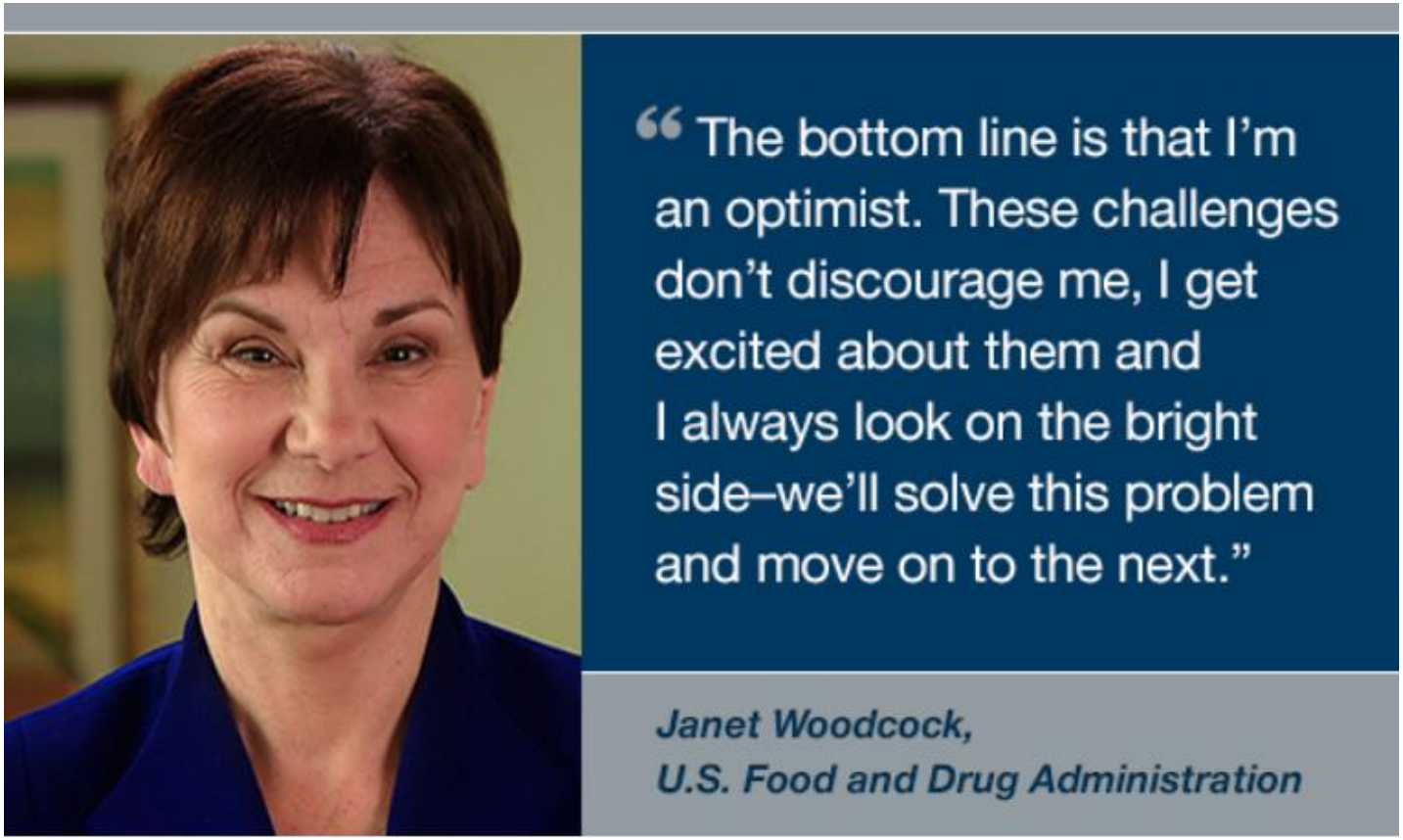
Next Steps…What is Needed

- Enhanced data sharing and collaborative efforts among consortia
- Qualification packages that don't try to "boil the ocean"
  - Limited vs Expanded Context of Use
- Data/specimen repositories which can support expanded contexts of use for biomarkers once additional data is aggregated
- Up front conversations around context of use—which drives the level of evidence needed
- More communication about the value and progress made by consortia efforts
- Greater clarity around levels of evidence for qualification—this takes the entire scientific community—not just FDA
- Patience…we are learning as we go…


ROUNDTABLE DISCUSSION
STEPS TO QUALIFICATION...
Letters of Support
Aggregation of Data
Proposal for (limited or expanded) COU
Qualification Determination
Beyond
MOVING FORWARD
Uber-consortia... establish best practices
*Crafting a better COU
*Biomarker Taxonomy/ Common Lexicon
*Biorepositories/ Data Repositories/ Data Sharing
IRB issues
Risks of sharing – what? how?
common successes?
common failures?
*Review Evidentiary Standards from recent qualifications
should we have asked for more/less info?
Think through how we've chopped the problem up – look at:
• assay performance
• risk
How it predicts some aspect of clinical performance –
How much work you have to put in up front –!
*Assay/ Imaging/ Validation
! Map a COU statement to the analytics that could support it
! A generic statement with fields to fill in –
Statisticians will take-it-as-is
involve statistics early on...
Think about
• how qualification & assay are linked in same with imaging!
! Include Biomarker development as an FDA activity – fund therapy-pharma –
! Pull the disparate pieces together
Look also at orphan diseases & include us –
? How do we disseminate?
white papers
checklists
A guidance?
It sounds like it has to be, but really it's
• COU isn't a useful place for trying to generalize results –
we haven't cast the problem well –
• What's the information content we're looking for?
ENABLERS
• Data standards
• Data quality
• Data reproducibility
! Develop a SAFE HAVEN
we're working on it – but there's still a reluctance to share data – need to reduce that barrier – remove data-sharing barriers
• Statistical considerations
• Assay/imaging considerations/ validation
• Assay/imaging protocols
• Establishing cut points
! HANDLING of samples – that's where we can reduce the noise – nail it down first

Current Efforts

- Internal biomarker survey *(done)*
- External biomarker survey *(published)*
- PhRMA survey
- Inventory of biomarkers used in pivotal trials for approved drugs (2007-present) (being compiled)
- Meeting with University of MD and Cpath on evidentiary standards *(done)*
- Proposal to the Biomarker Consortium to host an evidentiary standards workshop *(next year)*
- ConsortiaPedia, data/specimen repository, proposal to coordinate around a disease specific area *(discussions underway)*


“The bottom line is that I’m an optimist. These challenges don’t discourage me, I get excited about them and I always look on the bright side–we’ll solve this problem and move on to the next.”
Janet Woodcock,
U.S. Food and Drug Administration

- Shashi Amur
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- Suzie McCune
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