Regulatory Pathways for CPTR Drug Development Tools and Methodologies

March 20, 2017

Outline

Critical Path to TB Drug Regimens

Accelerating the Drug Discovery and Development Timeline

- Qualification: A formal process of review and acceptance
- Biomarker qualification overview

Regulatory Interactions on the Hollow Fiber System of TB (HFS-TB)

- Value of data integration
- Evidenced-based methodology evaluation

Regulatory Interactions on Lipoarabinomannan (LAM) Biomarker Effort

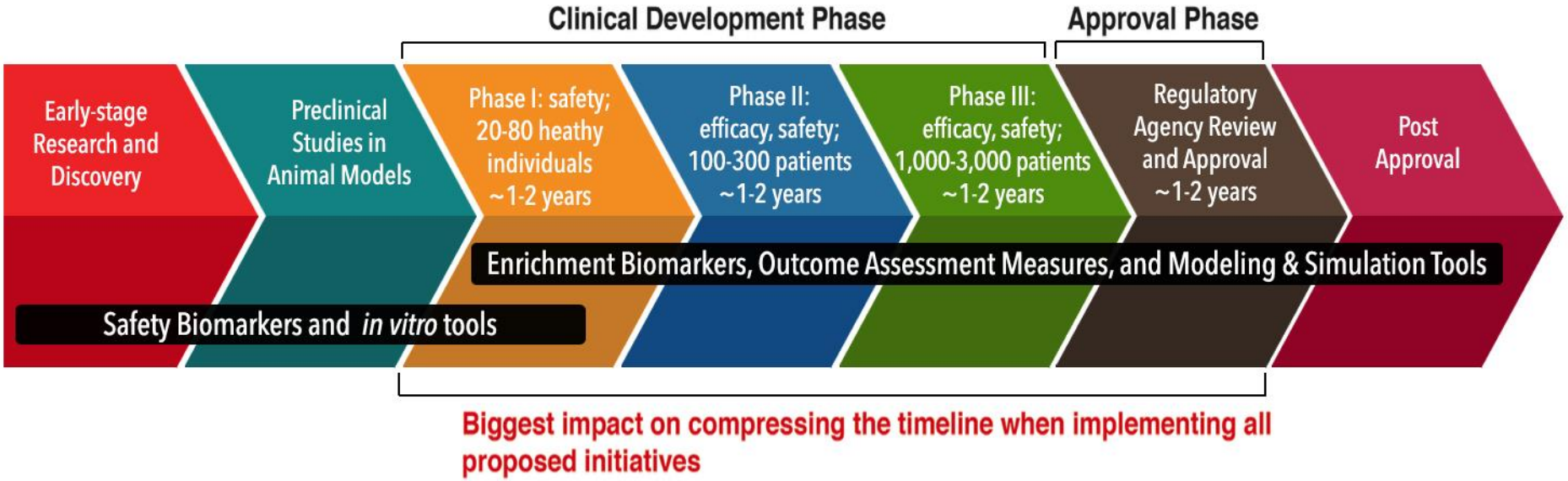
- LAM as a pharmacodynamic biomarker
- Critical Path Innovation Meeting (CPIM) process

Summary and Conclusions

Accelerating the Timeline

Critical Path to TB Drug Regimens

- ✓ Data Standardization and Sharing
- ✓ Biomarker Development and Qualification
- ✓ Outcome Assessment Measures
- ✓ Modeling and Simulation Tools

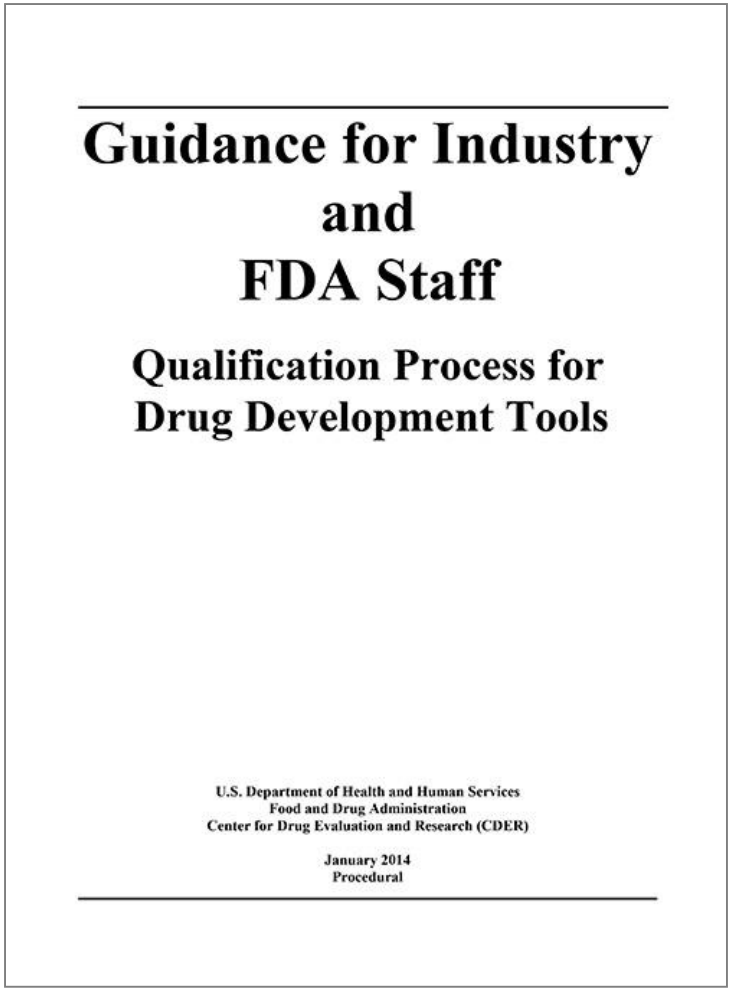


Shared Learning Can Shorten the Timeline

Adapted from *"A virtual space odyssey"*, Cath O'Driscoll (2004) http://www.nature.com/horizon/chemicalspace/background/odyssey.html

FDA and EMA Qualification

A Formal Process of Review and Acceptance

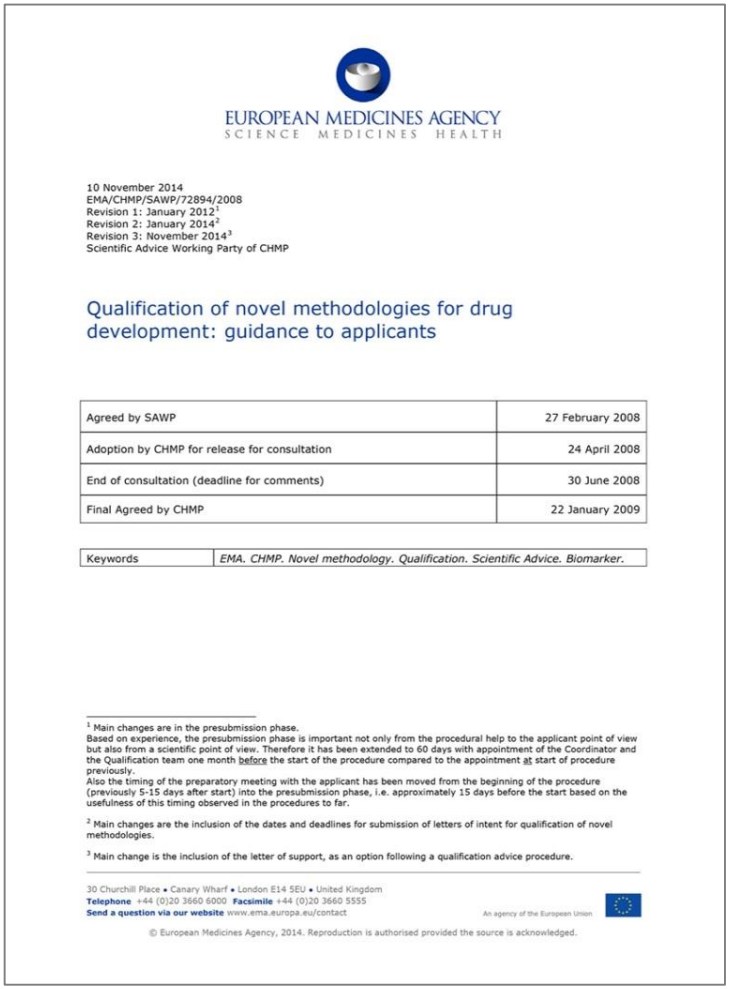


Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2014
Procedural



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Keywords	*EMA. CHMP. Novel methodology. Qualification. Scientific Advice. Biomarker.*

[1] Main changes are in the presubmission phase.
Based on experience, the presubmission phase is important not only from the procedural help to the applicant point of view but also from a scientific point of view. Therefore it has been extended to 60 days with appointment of the Coordinator and the Qualification team one month before the start of the procedure compared to the appointment at start of procedure previously.
Also the timing of the preparatory meeting with the applicant has been moved from the beginning of the procedure (previously 5-15 days after start) into the presubmission phase, i.e. approximately 15 days before the start based on the usefulness of this timing observed in the procedures to far.

[2] Main changes are the inclusion of the dates and deadlines for submission of letters of intent for qualification of novel methodologies.

[3] Main change is the inclusion of the letter of support, as an option following a qualification advice procedure.

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Send a question via our website www.ema.europa.eu/contact

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

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf

Biomarker Qualification

Critical Path to TB Drug Regimens

- Qualification is a formal regulatory review and acceptance process of biomarkers for their use in drug development

- "Qualification is a conclusion that within the stated context of use, the biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory review."

Biomarker Qualification

Critical Path to TB Drug Regimens

Qualification results in scientific acceptance and regulatory certainty of the biomarker

- Once qualified the information pertaining to the acceptable use of the biomarker in drug development will be publicly available
- Biomarker qualification not just biomarker discovery or clinical validation, it the formal acceptance of the biomarker by health authorities for use in drug development

Qualification does not denote that a biomarker is acceptable for use in clinical practice as an *in vitro* diagnostic or otherwise

Objectives of Qualification

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- To qualify and make DDTs publicly available to be used for a specific context of use in drug development
- To streamline drug development and review of regulatory applications
- To facilitate integration of qualified DDTs in regulatory review
- To provide a framework for scientific collaboration to facilitate DDT development

Biomarker Qualification Concept

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Start at the end approach: Up-front conversations around the context of use (COU) since the COU drives the level of evidence needed

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Summary and Conclusions

CPTR Evidence-Based Roadmap

Critical Path to TB Drug Regimens

Degree of Evidence Required

Pre-CPTR Stage

1. DDT Identification

- Identify candidate *in vivo* models as possible DDT
- Determine data needs

2. Exploration

- Proof of concept
- Find best candidate and assay
- Determine data needs

3. Demonstration

- Probable or emerging model/DDT
- Scientifically validated
- Define model performance, sensitivity and reproducibility; predictivity

CPTR

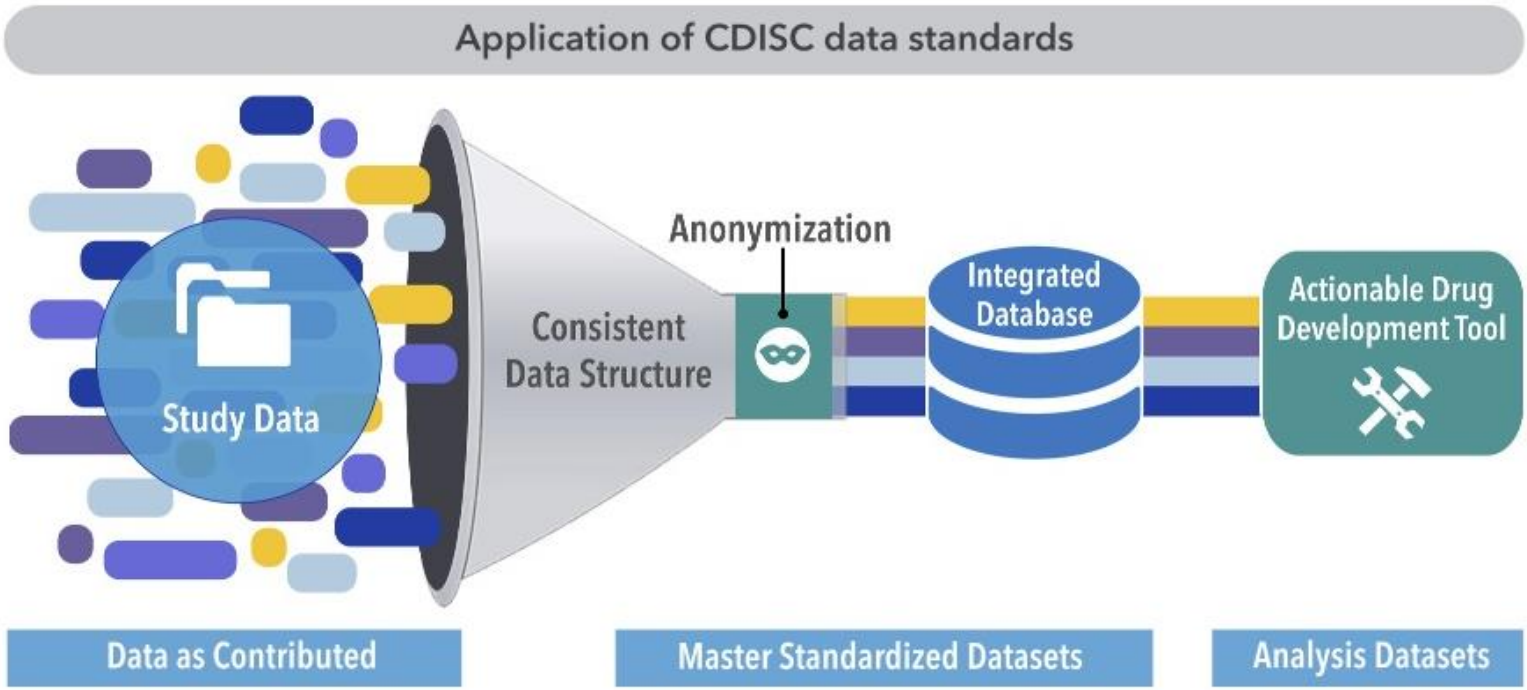
4. Characterization

- Type of DDT
- DDT CoU
- Qualification Strategy

Drug Development Pipeline

Target Validation → Lead Optimization → Translational Medicine → Phase I & II → Phase III → Commercial

Value of Data Integration



Past Regulatory Interactions

Critical Path to TB Drug Regimens

Hollow Fiber System of TB(HFS-TB) Qualification

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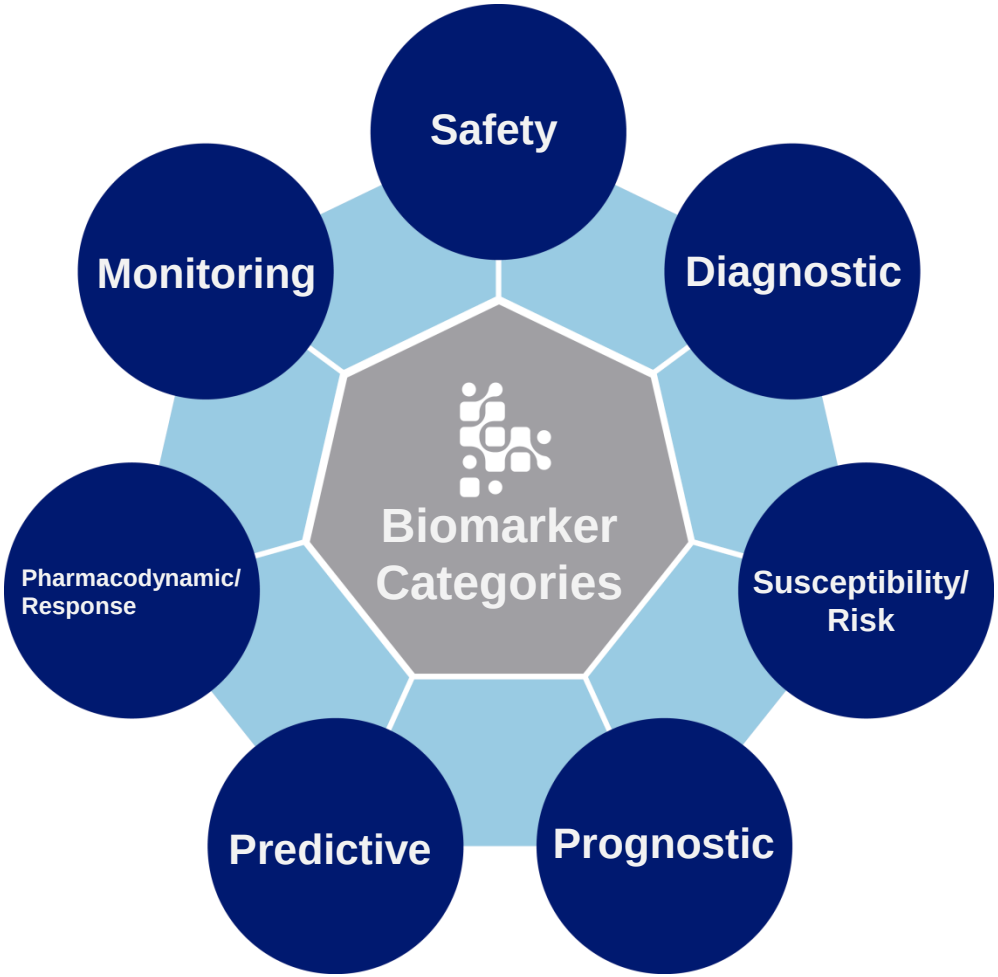
Biomarker Categories



LAM Biomarker Effort

Critical Path to TB Drug Regimens

- An expert sub-team was convened to develop and implement a strategy for regulatory engagement on lipoarabinomannan (LAM) as a pharmacodynamic biomarker for quantitative measurement of bacterial load in sputum.

- This is the first pharmacokinetic biomarker C-Path has advanced to a proposed Context of Use discussion with FDA.

Critical Path Innovation Meeting

Critical Path to TB Drug Regimens

- CPIMs are administered through the FDA's Office of Translational Science, within the Center for Drug Evaluation and Research
- A CPIM is broad in scope and serves as an opportunity for general discussion of challenges in drug development and innovative strategies to address them
- Purpose is to foster discussion of the science, medicine, and regulatory aspects of innovations in drug development
- Requests for CPIMs may come from anyone with a role in drug development (industry, government, PPP, academia, advocacy)
- Appropriate FDA experts from CDER offices and other Centers will participate as resources and time permit
- Meeting discussions are nonbinding on FDA and other participants

CPIM Details

Critical Path to TB Drug Regimens

Examples of CPIM Topics

- Potential biomarkers not ready for formal Qualification Program
- Emerging technologies (non-manufacturing) or new uses of existing technologies
- Novel clinical trial designs and methods

A CPIM does **not** provide

- Advice or a discussion of the regulatory pathway of a particular product
- Discussion of the qualification of particular biomarker, clinical outcome assessment, or animal model

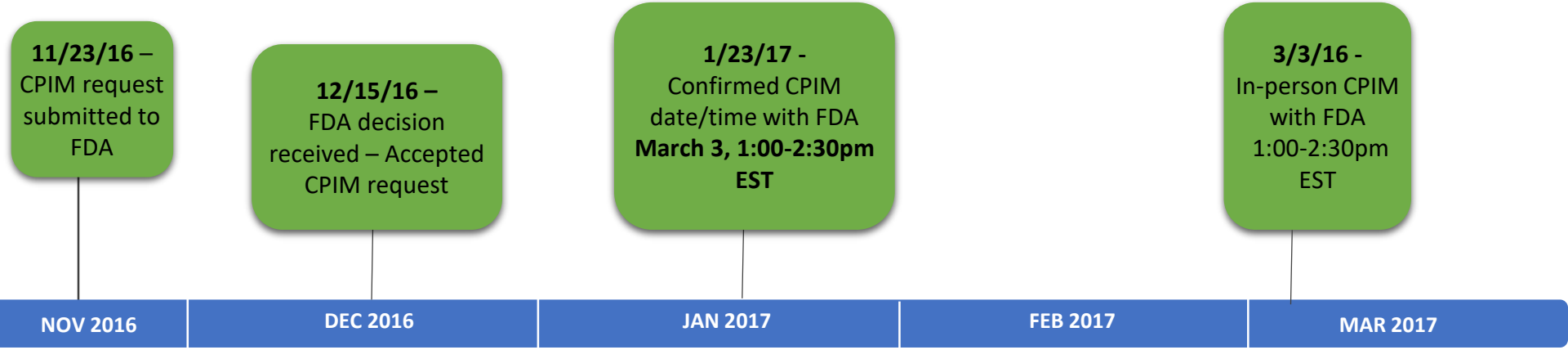
CPIM Details (continued)

Critical Path to TB Drug Regimens

- The CPIM is expected to provide FDA with exposure to innovative methods and techniques that may have value in drug development
- Information package containing the meeting objective, proposed agenda, presentation slides, and attendees is submitted to FDA in advance of the CPIM
- Meetings are typically held in person at FDA and are 60-90 minutes in length
- Outcomes include CDER's perspectives and advice on:
  - Potential for use of proposed new tools and methods in drug development
  - Issues to consider in pursuing the work
  - Pursuing joint efforts through existing consortia, or the potential to form new consortia
  - Recommendations for public workshops or other avenues for engaging with the wider scientific community
- CPIM summary issued by FDA within 60 days of meeting

CPIM Information from FDA: http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm395888.htm

LAM CPIM Request Timeline



Next Steps:

- Feedback from FDA is expected by May 3, 2017.
- Input received from FDA in the meeting will be used to inform future qualification plans for this biomarker.

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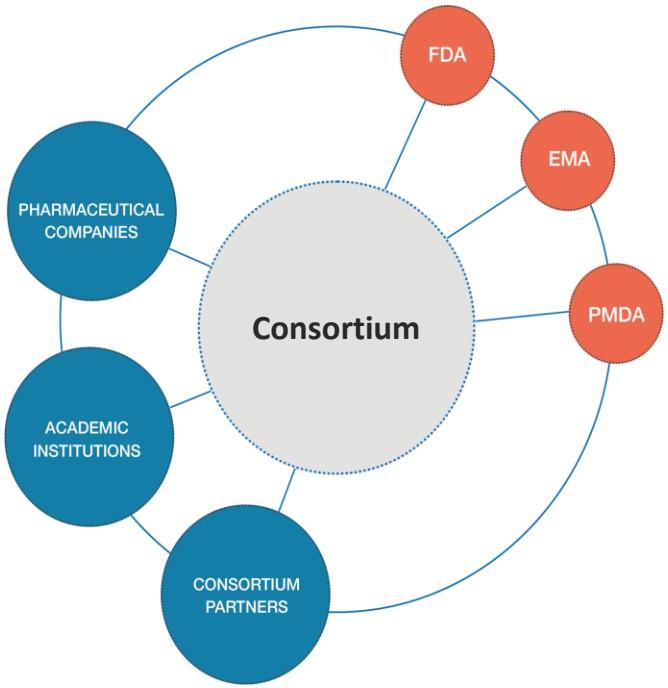
- Novel biomarkers can provide better insight into new chemical entities progressing through drug development
- However, in order to routinely and consistently use novel biomarkers across multiple drug development programs regulatory acceptance is needed (Biomarker Qualification)
- It is difficult for a single organization or stakeholder group to qualify a biomarker in a reasonable amount of time; thus, collaboration is required
- Furthermore, we must all work together to define the optimal scientific and regulatory path for biomarker qualification (Evidentiary Considerations for Biomarker Qualification)



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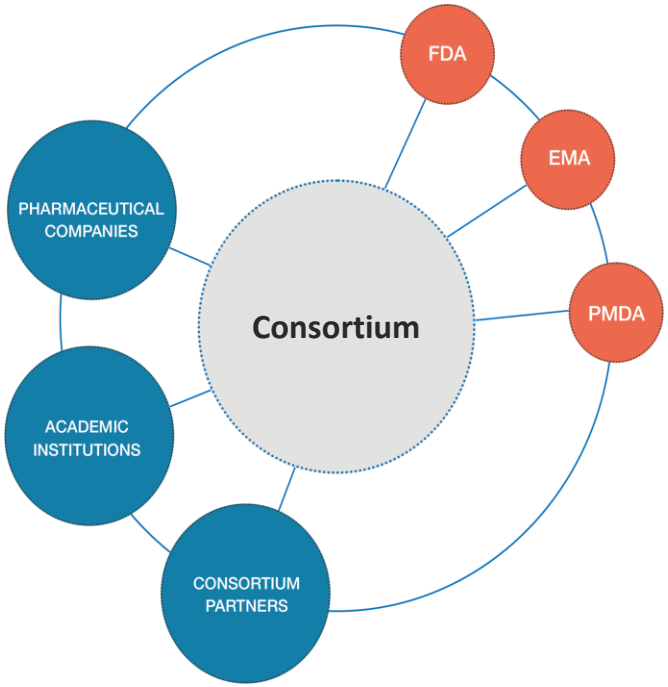
Critical Path to TB Drug Regimens

- Data sharing by key stakeholders (academic investigators and pharmaceutical companies) is required for many of our qualification goals
- Likewise, novel biomarkers will need to be included in late phase clinical development programs by pharmaceutical companies
- Finally, a collaborative relationship with health authorities must be established and maintained



Thank you