FDA Review of Biomarkers

OARSI OA BM Workshop III

Imaging Biomarker

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Overview

- FDA Regulatory Definitions
- Pathways for BM review in FDA
  - BM Qualification
  - CDER Review process
  - CDRH Review process
- Resources

Definition: BM

- Biomarker: Objectively measured and evaluated characteristic as an indicator of normal or pathogenic biological process, or biological response to therapeutic intervention.[1]
  - Prognostic
  - Predictive
  - Pharmacodynamic (activity)

[1]Biomarkers Definitions Working Group (2001). *Clinical Pharmacology and Therapeutics, 69,* p.89-95.

Definition: BM (continued)

- Prognostic BM: Baseline patient characteristic which categorizes patients by degree of risk for disease occurrence or progression.
  - Informs natural history
  - Absence of therapeutic intervention
- Predictive BM: Baseline characteristic which categorizes patients by likelihood of response to particular treatment.
- Pharmacodynamic (activity): Dynamic assessment which shows that a biological response has occurred after therapeutic intervention.

Surrogate Endpoint

- Definition: Biomarker intended to substitute for a clinical endpoint.
  - Expected to predict clinical benefit, harm, or lack of benefit or harm.
  - Based on scientific evidence.
  - A subset of pharmacodynamic biomarkers

Pathway: BM Qualification

- Definition: Conclusion that within stated "context of use", BM demonstrates specific interpretation and application in decision-making.
  - Specific interpretation
  - Application in drug development
  - Regulatory decision making

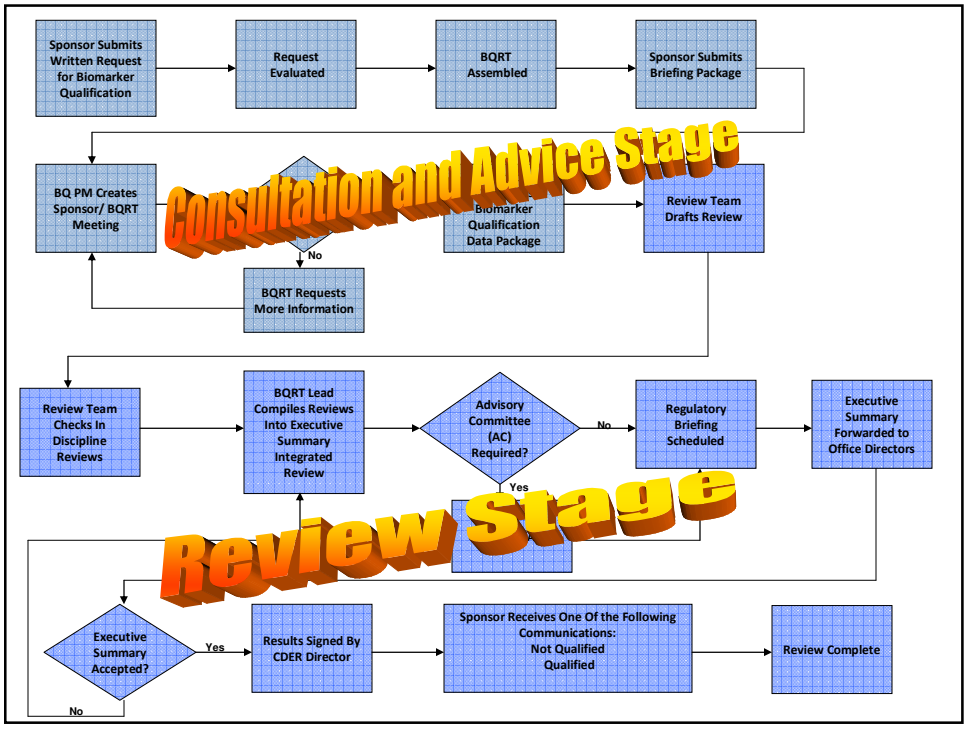
BM Qualification

- Voluntary process
- Advances drug development
- Used by many sponsors
- Collaborative effort
- Promotes development of good BM
- Possibility of personalized therapy
- Central Administrator
- Two stage process

BM Qualification: Context of Use

- Describes manner of use, interpretation, and purpose of BM in drug development encompassing:

1. Identification
2. Species
3. Population
4. General Purpose
5. Specific drug development or regulatory decision addressed
6. Interpretation



Qualified BM Examples

Sponsor	Biomarkers	Context of Use
Predictive Safety & Testing Consortium (PTSC) Nephrotoxicity Working Group (2008)	Urinary kidney biomarkers: KIM-1, Albumin, Clusterin, Trefoil factor-3 → ATN TP, β2-MG, Cysatin C → GLN damage	Detection of acute drug-induced nephrotoxicity in rats to complement BUN and Cr in GLP rat studies
International Life Sciences Institutes (ILSI)/Health and Environmental Sciences Institute (HESI) (2010)	Renal Papillary Antigen 1 Clusterin	Drug induced nephrotoxicity in rats
PJ O'Brien, WJ Reagan, MJ York, MC Jacobsen (2012)	Cardiac troponins T and I	Safety assessment in rats, dogs

Pathway: CDER Review

- Contact individual CDER review divisions
- Exploratory BM generally not qualified or cleared/approved
- Case by case basis for BM intended for patient selection or enrichment
- Review divisions: CDER/OND/ODE II/DPARP for disease modifying drugs in OA
- CDER/OND/ODE II/DAAP for symptom treatment in OA

Pathway: CDRH Review

- Most BM “cleared” via 510(k) process
- High risk BM “approved” via PMA process
- Review Group is CDRH/OIVD for both serum and radiographic BM

What is a Medical Device?

Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is –

- recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them;
- intended for use in the *diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease,* in man or other animals, or
- intended to *affect the structure or any function* of the body of man or other animals, and which does *not achieve its primary intended purposes through chemical action* within or on the body of man or other animals and which is *not dependent upon being metabolized* for the achievement of its primary intended purposes.

Risk-Based Paradigm

- Class I: simple, low risk devices
  - **General controls**
  - **Most exempt from pre-market submission**

- Class II: more complex, higher risk
  - **Performance standards**
  - **Pre-market Notification[510(k)]**

- Class III: most complex, highest risk
  - **Clinical data needed**
  - **Pre-market Application [PMA]**

What is an IVD?

- Reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health.
- Intended to *cure, mitigate, treat, or prevent disease* or its sequelae.
- Collection, preparation, and examination of specimens *taken from the human body*.
- These products are devices and may also be biological products.
- 21 CFR 809.3

Companion Diagnostics

- Defined as essential for safe and effective use of therapy
- Identify patients most likely to benefit from a particular therapy
- Identify patients at increased risk for SAE
- Monitor response to treatment

Example: HER-2 testing for Herceptin therapy in metastatic breast and gastric cancer

Resources

- DDT Guidance Document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf
- BM Qualification Information: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm2840

Resources Continued

- Clinical Trial Imaging Endpoints Guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM268555.pdf
- Companion Diagnostic Devices Guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM268555.pdf

Thank You!

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