Clinical Trial Outcome Assessments

Characterizing, Adopting, and Applying

Measurement Methods in the Development of Improved Analgesic Treatments
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The views expressed are those of the author, and do not necessarily represent an official FDA position

Outline

- Outcome Assessments in Drug Development
  - Range of uses
  - Effectiveness = Treatment Benefit
  - Characterizing an Assessment
  - Identifying an Outcome Assessment
- Biomarkers
  - Definition
  - Categories
  - Range of uses in drug development
- Accepting biomarkers and other DDTs
- DDT Qualification

Outcome Assessments in Drug Development

- Provide proof of concept evidence
- Guide stepwise development decisions
- Basis for marketing approval and labeling claims
  - Demonstrates a specific treatment benefit
  - Observed effect can be reliably interpreted as a treatment benefit
- Treatment benefit is a favorable effect on a meaningful aspect of how a patient feels, functions, or survives
  - Usually an effectiveness benefit
  - What does the assessment mean to the patient?
  - Survival has well understood interpretation
  - Feels and Functions are more complex

Evidence Supporting Effectiveness

- Evidence from Adequate & Well controlled clinical trials
- The methods of assessment of subject's response are well-defined and reliable (21CFR314.126)
- Effects on the OA can be reliably interpreted as a treatment benefit
  - Understanding what the assessment means in terms of how the patient feels or functions

Feels and Functions as Effectiveness

- Feels
  - A patient's physical sensation or perceived mental state related to health within typical 'daily' life
  - Pain
  - Severely low mood (depression)
- Functions
  - A patient's ability to perform an activity that is a meaningful part of typical 'daily' life
  - Not isolated physiologic processes (eg liver metabolism)
  - Not ability to perform actions not part of usual life

Intrinsic Characteristics of an Assessment

- Patient assessments have certain intrinsic characteristics
- Many independent of how the assessment is used in a clinical trial
- The characteristics do not describe a judgment of whether it is suitable to be used in any particular manner
- Recognizing these characteristics will aid the process of evaluating whether it is well-defined and reliable

Assessment Characterization

Dimension								
Psyche Influence		Psychomodulated Measures						Biomarker
Who Measures		Patient		Clinician		Observer		Instrument
Relationship to Treatment Benefit		Direct	Indirect	Direct	Indirect	Direct	Indirect	Indirect
How Obtained	Naturalistic	10cm Pain VAS	Pain Rescue Medication Use	PANSS	Joint movement spasticity	Observed seizures	Observed infant behavior	HbA1c CMAP measures CT volume
	Artificial Procedure	NONE	Alcohol Presentation Challenge	NONE	9-Hole Peg test, 6-min Walk, FEV1	NONE	?	Endocrine stimulation tests

Characteristics of a Patient Assessment

- Dimensions
  - Characteristics that are largely orthogonal
  - Particularly where dimension consists of mutually exclusive categories
    - Not gradations of a characteristic
  - Raise distinct issues for evaluation
- Is it “Psyche Influenced”?
- What is the relationship to a meaningful aspect of patient status?
- Who is performing the rating?
- What is the setting of the measurement?

Dimensions of an Assessment (1)

- Psyche Influenced?
  - Is the assessment influenced by human choices
  - Conscious or unconscious
  - Rater or patient
  - Judgment, cooperation, motivation
  - Influenced: Psychomodulated
    - As OA most often intended to learn about patient's current state of feels or functions
  - Not influenced: Biomarker
    - As OA often intended to predict a future state of feels or functions
- Framework particularly aids communication regarding psychomodulated assessments

Dimensions of an Assessment (2)

- What is the relationship to meaningful patient feeling or functioning?
  - Direct vs Indirect
  - Indirect means the concept being measured is not the exact directly meaningful concept
    - "indirectness" is graded within the category
  - For OA use the relationship between the measured concept and the intended meaningful concept is important
    - Usually not an important dimension for non-OA use
- What is the setting for measuring
  - Naturalistic vs Artificial Procedure
- Who is performing the rating?
  - Patient, Clinician, Observer, (Instrument)

Dimensions of an Assessment (3)

- Categories are not judging fitness, preferability, suitability; just categorizing an aspect
- Other dimensions exist
  - Not included in these basic dimensions
  - May also influence suitability for a given situation
  - Sensitivity - graded, not distinct categories
    - Sensitivity to differences in the measured concept
    - Change in the meaningful aspect of feels or functions when there is change in the measured concept

Identification of Outcome Asssesments

- Name of actual assessment
- Concept that the OA actually (directly) measures
- Indirect measures:
  - Not evaluating feels or functions directly
  - Therefore also need to name the meaningful aspect of feels or functions intended to be inferred
- Direct measures:
  - Measured concept is meaningful
- Examples
  - Numeric rating scale *for* Pain Intensity
  - ETDRS Eye chart *for* visual acuity *for* vision-dependent activities
- Full identification is an important step in assessing suitability of use as an OA

Identification of OAs

- Essential to identify the meaningful concept that is intended
- Essential to identify the intermediate concept for Indirect measures
- Caution regarding name of tool
  - Name of tool does not make it 'something'; its characteristics do
  - Some indirect tools are given a name not reflecting what is measured; can create confusion and miscommunication

2-D Representation of the Framework

- Multiple possible hierarchy orders to squash four dimensions onto a 2-D drawing
- All are equivalent
- Dimensions can be applied in any order
  - Same end-result description
- Display may be selected to highlight characteristics of particular focus

Assessment Characteristics Chart

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Biomarker Definition & Categories

- An objective patient characteristic that is measured as an indicator of:
  - Normal biologic processes
  - Pathogenic processes (abnormal biologic processes)
  - Biological responses to a therapeutic intervention
- Nomenclature of biomarker types
  - Language used to describe, discuss, biomarkers
  - FDA terminology chiefly relates to uses in therapy development

Types of Biomarkers (1)

- Prognostic biomarker
  - Indicates future clinical course of the patient with respect to some specified clinical outcome, in the absence of a Tx intervention
    - Except Tx interventions incorporated in the data that established the prognostic interpretation
  - No relationship to any particular new Tx
    - But might indicate patients in whom we would be able to discern (measure) a response after Tx
  - Applying a new Tx may invalidate the preTx inference
    - Marker-outcome relationship can change post Tx

Types of Biomarkers (2)

- Predictive biomarker
  - Measured prior to an intervention
  - Identifies patients who are relatively susceptible to a particular drug effect versus less susceptible patients
    - Benefit or harm
    - Exists only for a Tx with some effect
  - Developed Tx by Tx

Types of Biomarkers (3)

- Pharmacodynamic biomarker
  - Response-indicator biomarker
  - Post Tx measurement
    - Stand alone
    - Pre vs post Tx comparison
  - Marker that reveals whether, or how large, a particular biological response has occurred in that particular patient
  - May or may not be Tx-specific
    - Development occurs in a Tx by Tx manner

Types of Biomarkers (4)

- Efficacy-response biomarker
    - Efficacy-surrogate biomarker, Surrogate endpoint
  - Subset of general pharmacodynamic biomarkers
  - Predicts the clinical outcome of the patient at some later time
  - May be Tx specific
    - Developed Tx by Tx at first

Biomarkers in Drug Development (1)

- Patient selection tool for study enrollment
  - Prognostic biomarkers
  - Predictive biomarkers
  - Enrichment studies
    - can greatly increase study power to show an effect
    - Avoid patients with potential for harm without potential for benefit
- Patient stratification tool
  - To ensure balance between randomized groups
    - Help ensure study results are interpretable
  - To statistically separate categories to aid seeing differential effects
  - Prognostic and moderate or unconfirmed major predictive biomarkers

Biomarkers in Drug Development (2)

- Phase 1 study outcome assessment
  - Pharmacodynamic biomarkers
  - Demonstrate drug is bio-active
    - May indicate actions on early cellular effects rather than clinical outcome
    - There may be multiple bioactivity steps to evaluate with multiple biomarkers
  - Aid in initial selection dose / regimen for later studies
  - Justify resources for further development
    - Proof of concept

Biomarkers in Drug Development (3)

- Phase 2 study outcome assessment
  - Pharmacodynamic biomarkers
  - Evaluate dose-response relationship
    - Variation in dose-response across patients
  - Identify response-predictive patient baseline-characteristics
  - Design of A&WC studies
    - Selection of doses
    - Uniform vs. Individualized regimen
    - Selection of patient population
    - Estimation of sample size
  - Can be critical to efficient and successful development program

Biomarkers in Drug Development (4)

- A&WC Studies (Phase 3)
  - Pharmacodynamic biomarkers
  - Secondary endpoint
    - Supportive of primary EP findings
    - Objective, precise
    - Helps decrease uncertainties regarding primary efficacy endpoint results interpretation
  - Primary Endpoint
    - Surrogate endpoint for that *Context of Use*
    - Well established relationship to clinical outcome
      - Conventional marketing approval
    - "reasonably likely to predict…" relationship
      - Accelerated approval provisions of regulations

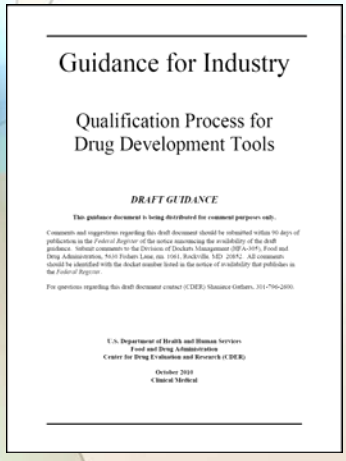
How have Biomarkers Become Accepted?

- Case by case
  - Within a specific IND/NDA/BLA/Labeling Update
  - For a specific drug
  - Driven by a specific drug developer's needs
- General use accepted over extended period
  - Scientific experience accumulates through varied uses
  - Usually very extended time-frame
  - Evidence collection not cohesively directed

How can Biomarkers Become Accepted?

- Previous routes remain available
- Co-development of drug and test
  - Companion diagnostics
  - Policy Guidance – July 2011
    - Others in development
- Biomarker Qualification Process
  - Developing program within CDER
  - Outgrowth of Critical Path Initiative

DDT Qualification Process Guidance (Draft)



Guidance for Industry

Qualification Process for Drug Development Tools

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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

October 2010
Clinical Medical

- Qualification process for drug development tools (DDTs):
  - Biomarkers
  - Clinical outcome assessments (PROs and other rating scales)
  - Animal models
  - Others
- New *and* existing DDTs
- Not required for tool use
  - Intended to ease repeated use

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

DDT Qualification

- A conclusion that within a carefully and specifically stated "context of use" the DDT has been demonstrated to reliably support a specified manner of interpretation and application in drug development
  - Utility in drug development, particularly regulatory decisions, is central to purpose of qualification
  - Particularly for DDTs expected to have application in multiple different drug development programs
- Validation ??
  - Context of Use !
- For biomarkers: Not how IOM decided to use term

Effects of Qualification & Programs

- The DDT can be applied in drug development programs without the need for submission of extensive DDT-supportive information to each IND, and review division re-evaluation to confirm that usage is justified
- Value of DDT being qualified:
  - ➢ May make the DDT more attractive to use
    - ❖Avoid slowing the drug development program
  - ➢ May make developing a therapy for a disease more attractive
    - ❖Development program may appear more tractable
- Value of Qualification Process
  - ➢ Structured process for FDA to work with DDT developers to aid efficient refinement of tool and successful Qualification

Qualification's Place in Therapeutic Development

- Qualification is not required
  - ➢ Case by case approach for accepting use in a single IND/NDA/BLA program remains valuable
  - ➢ Current well established DDTs do not need formal Qualification
- Qualification is voluntary
  - ➢ DDT developer can choose to pursue or not pursue qualification
- Qualification is intended for DDTs that will be used in multiple drug development programs
  - ➢ Public knowledge and availability essential
  - ➢ Consortia or collaborative groups likely to be source of DDTs for qualification

Biomarker: What becomes Qualified?

- Biomarker is a measurement of a substance, analyte, anatomic image, or other describable characteristic
  - Assay methods are needed to measure the biomarker
  - Assay method is not the biomarker
- One biomarker can have multiple assays that are capable of measuring the biomarker
  - Assay method performance characteristics are important
- CDRH clears or approves commercial testing devices for clinical measurements
- CDRH clearance does not equal CDER qualification
  - Different purposes

Context of Use (CoU)

- DDTs are qualified for a very specific *context of use*
- A comprehensive statement of the manner of use and the purpose, including how to apply results to decision making
- Identifies the limits of known reliability as shown by the evidence

- DDT may also have utility outside the currently qualified CoU
  - Accept on case by case (IND specific) basis
  - May expand qualified CoU as further data justifies

Context of Use (CoU)

- When & how the DDT measurement is made
  - How the samples are analyzed for the biomarker
- How the data are analyzed and interpreted
- What decision is made based on the data
- What action, and how, drug development is altered by the DDT results
- Adequately specifying the CoU is often a difficult first step towards qualification
  - Determines what kind of data are needed

DDT Qualification Process
Three Major Parts

- Initial evaluation for agreement to collaborate
  - Would the biomarker in the proposed CoU be important?
  - Is the current state of knowledge sufficient to justify applying Agency resources
- Interactive Consultation and Advice Stage
  - Interdisciplinary working team assembled
  - Ongoing, interactive, discussion and advice to submitter
  - Submitter works to develop remaining needed evidence
- In-depth Review Stage
  - Submission of full data package for working team review
  - Formal Qualification granted if appropriate
- Statements of Qualified DDTs are made public