



Including the Patient Voice in Drug Regulatory Risk- Benefit Decisions

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Treatment Benefit

- *Treatment benefit* — The impact of treatment on how a patient *survives, feels, or functions*.
 - The benefit of treatment on other concepts are not direct measures of treatment benefit
- Treatment benefit may be measured as
 - Comparative efficacy (e.g., an improvement or delay in the development of symptoms or decrements in function compared to placebo or an active comparator)
 - Comparative safety (e.g., a reduction or delay in treatment-related toxicity or other safety-related concern compared to placebo or an active comparator)

Treatment Benefit Claims (Effectiveness)

- May be found in...
 - Indications section of labeling
 - Other sections of labeling
 - Clinical Studies section
 - Clinical Pharmacology section
 - Dosage and Administration section
 - Advertising and promotion
- Same evidence standards apply for all

Treatment Benefit Claims: Evidence Required

- A statement of drug benefit (i.e., a claim) needs to be based on substantial evidence
- Substantial evidence demands adequate and well-controlled studies of the benefit
- Adequate and well-controlled studies demand, in addition to many other considerations, well-defined and reliable assessments
- Well-defined and reliable assessments of the concept represented by the claim are judged in the context of use (“fit for purpose”)
- An assessment is adequate if it measures the claimed concept in the target population in a well-defined and reliable way

Two Categories of Drug Development Studies

STUDIES TO LEARN

- Phases 1 and 2
- NOT necessarily adequate and well-controlled
- Do not support labeling claims
- Learning by exploratory analyses
- Interim analyses – *potentially* more liberal

STUDIES TO CONFIRM

- Adequate and well-controlled
- Prospectively defined key endpoints consistent with study objectives
- Phase 3, usually
- Blinded treatment assignment (everyone blinded)
- Interim Analyses – pre-planned, tightly controlled
- Replicate or otherwise confirm results from previous studies
- Key endpoints may support claims

Reporting of Negative Findings as Benefit

- A negative finding can be reported if the absence of the adverse reaction is convincingly demonstrated in a trial of adequate design and power
- A concept must be convincingly measured before it can be reported as a negative finding

Assay sensitivity: Studies to Show an Absence of an Adverse Event

- To interpret the result, one must know that, if the study drug had caused an adverse event, the event would have been observed. Ordinarily, such a study should include an active control treatment that does cause the adverse event in question
- *Absence of evidence is not evidence of absence*

Example: “Abuse liability”

What is the **CONCEPT** measured?

Does the **CONCEPT** match the targeted **CLAIM**?

PRO:

- Liking ratings
- Symptoms (e.g., blurred vision, spaced out, euphoria)
- Take again/street value/monetary worth
- Categorization of effect to be like known drug class
- Drug strength assessment

ClinRO:

- Muscle-relaxation, posture
- Impaired speech
- Observed confusion
- Overall strength of drug effect
- Global based on DSM-IV-TR

Objective Tests:

- Motor speed, coordination, and reaction time
- Cognitive performance
- Memory
- Pupillary dilation/constriction
- Heart rate, blood pressure
- Skin temperature
- Urine drug screens

Composites:

- Drug attractiveness

“Misuse/Abuse Liability” Measurement

- A multidomain concept
- Claiming “no liability” implies:
 - (1) measurement of all important domains
 - (2) no liability in any important domain.
 - (3) claim is limited to the population studied

Labeling and Risk: Guidances for Industry

- Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf>
- Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf>

Adverse Reactions and Labeling (I)

- Undesirable effects, reasonably associated with the use of a drug
- May be prospectively measured or spontaneously reported
- May occur as part of the pharmacologic action of the drug or may be unpredictable in occurrence
- Do not include all adverse events observed during use of a drug; only those for which there is some basis to believe there is a causal relationship
- May include signs and symptoms, changes in lab values, changes in other measures of critical body function (e.g., vital signs, ECG)
- Clinical trials experience and postmarketing experience listed separately in labeling

Adverse Reactions and Labeling (II)

- Adverse events are included in labeling depending on
 - Seriousness of the event
 - Number of reports
 - Strength of causal relationship to the drug
- Because spontaneously reported events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious ARs

- *A serious* adverse reaction results in any of the following outcomes:
 - Death
 - Life-threatening adverse experience, inpatient hospitalization
 - Prolongation of existing hospitalization
 - Persistent or significant disability or incapacity
 - Congenital anomaly or birth defect
 - Other effect that jeopardizes the patient deemed serious in medical judgment
 - Medical or surgical intervention needed to prevent one of the above

Typical Reasons to Suspect Causality with Spontaneously Reported Adverse Events

- Timing of onset or termination with respect to drug use
- Plausibility in light of the drug's known pharmacology
- Occurrence at a frequency above that expected in the treated population
- Occurrence at a rate that exceeds the placebo rate
- Existence of challenge and dechallenge experience
- Occurrence of an event typical of drug-induced adverse reactions (e.g., liver necrosis, agranulocytosis, Stevens-Johnson syndrome)

Comparisons of Adverse Reactions Is a CLAIM Requiring Substantial Evidence

- Comparisons of adverse reactions between drugs in terms of frequency, severity, or character must be based on adequate and well-controlled studies

Example of a CLAIM in the AR Section

- *In trials in which **valsartan [angiotensin II receptor blocker]** was compared to an ACE inhibitor...the incidence of **dry cough** was significantly **greater in the ACE inhibitor group** (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129 patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received **valsartan**, HCTZ, or lisinopril were **20%**, 19%, and 69%, respectively ($p < 0.001$).*

Interpretation of ARs

- Results of significance testing should be omitted unless they provide useful information AND are based on a prespecified hypotheses in an adequately designed and powered study

Example of a violative claim in promotion based on comparisons of adverse reaction rates (see DDMAC letter, 5-26-09)

- Claim: *Drug A is “A Safe Alternative to Drug B” with a table that compares the risk of neuropathy of the two drugs.*
- DDMAC: *This presentation misleadingly suggests that Drug A has a superior safety profile compared to Drug B, when this is not supported.... FDA is not aware of any adequate and well controlled, head to head clinical trials designed to compare the safety of these two products or of any substantial clinical experience to support this claim.*

Example of a violative claim in promotion (see DDMAC letter, 8/28/2008)

- Claim: *Favorable tolerability profile with a low incidence of beta blocker related side effects*
- DDMAC: *The above claim misleadingly implies that the tolerability profile of Drug C is better than the tolerability profile of other beta-adrenergic receptor blocking agents when this has not been demonstrated by substantial evidence or substantial clinical experience.*

Maximize Benefit--Minimize Risk

- FDA approves a product to treat a specific condition, based on a comparison of benefit with risk when used in the intended population and use.
- A safe medical product is one that has reasonable risks, given the magnitude of the benefit expected and the alternatives available.

Including the Patient Voice when Choosing a Treatment

- Labeling explains how the product should be used to maximize benefits and minimize risk.
- The prescriber is central to managing risks and benefits for the individual patient.
- The patient voice is important when defining the most appropriate balance between benefits and risks of a medical product