Evolution of Data Requirements in the Regulatory and HTA Environments

Glancing Back, Looking Forward

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The Changing Regulatory Environment

- Historical emphasis upon proof-of-concept for a new drug...does it fulfill its claims?
- Changing environment as new safety concerns emerge for many new drugs and biologic agents.
- Recognizing that safety and “real world” effectiveness are of concern to regulators, payers, prescribers, and patients over the entire product life-cycle.

General Limitations of Proof Of Concept Studies

- Limited information on long term use
- Limited information on any but the most frequent safety issues
- Limited information on drug interactions
- Limited information in full target population for the marketed product
- Limited information comparing to existing drugs
- Limited information regarding appropriate utilization

Consequences of Historical Drug Development Regime

- At market authorization, “required” information about a new drug is very limited.
- Outstanding questions at the time a new drug is marketed:
  - Where does the product fit in respect of other therapies?
  - What is the cost-effectiveness of the new drug?
  - How to introduce it into sub-populations not studied in the qualifying CT’s?
  - How to collect information on safety for less common and rare, but serious adverse events?

Evidence Required for Health Technology Assessment

- Requires information about the usefulness of a new drug in the general population:
  - Where does the product fit in respect of other therapies?
  - How to introduce into sub-populations not studied in the qualifying CT's?
  - How to collect information on safety for less common and rare, but serious adverse events?
  - How to collect information on safety for commonly occurring medical events that may be attributable to the new drug? (e.g. M.I.)
- What is the actual cost-effectiveness of the new drug?

How to Resolve the Information Gap for New Drugs?

- Build Safety/Effectiveness into Post Marketing Strategies
  - Appropriate market entry times
  - Use of Registries
    - Drug registry
    - Disease registry
  - Epidemiologic (large) safety studies using public data sets where available – Population Registry
  - Appropriate controls on utilization
    - Both Regulators and Payers are involved
- ***Active comparator studies***
    - Supporting direct comparisons for economic analyses
- Structured life-cycle safety & effectiveness data

Comparator Studies

- New drug vs placebo superiority study
  - Good for assay sensitivity; but affords only indirect comparisons with existing drugs
- New drug vs existing drug superiority study..... highly desirable
- New drug vs existing drug direct equivalence study
  - ***Non-inferiority design*** has special challenges
    - Regulator – assay sensitivity
    - Payer - appropriate non-inferiority margin

Non-inferiority Trials

- Active Comparator needs to be well evidenced
  - "not much worse than" not of much value if comparator is ineffective in study population
- Poor trial execution causes CT to succeed
  - Confounders, poor selection, poor measures, etc., all cause the means to look similar or drive the OR's to 1.0
- Outcome measures need to be clear, easily discriminated, clinically relevant, not normal disease outcome or variation
- Typically require larger N than superiority

Where NI Trials Are Indicated

- Applications based upon essential similarity in areas where bioequivalence studies are not possible, e.g. modified release products or topical preparations;
- Products with a potential safety advantage over the standard might require an efficacy comparison to the standard to allow a risk-benefit assessment to be made;
- Disease areas where the use of a placebo arm is not possible and an active control trial is required to demonstrate the efficacy of the test product.

Note: In cases 2 and 3 above, a non-inferiority trial would not be necessary if superiority could be shown over the active comparator.

NI Margins and Clinical Judgment
(Important take-away messaging)

- The selection of the non-inferiority margin is based upon a combination of statistical reasoning and *clinical judgment*.
- A ***three-armed trial*** with test, reference and placebo allow within-trial validation of the choice of non-inferiority margin and *it should be used wherever possible.*
- It is not appropriate to use effect size, treatment difference divided by standard deviation, as sole justification for the choice of non-inferiority margin.
  - This statistic provides information on how difficult a difference would be to detect, but does not help justify the *clinical relevance* of the difference, and does not ensure that the test product is superior to placebo.

Why Three Arm NI Studies ?

- In a three-arm CT, the performance of the active comparator is not the main consideration;
  - However, if both the test and the active comparator fail to demonstrate a *statistically* significant advantage over placebo this could suggest that the trial is insensitive, or lacks assay sensitivity.
- If both fail to demonstrate *clinically* significant advantage over placebo, the choice of active comparator is problematic and the test product is unimpressive.

Note: A two-arm reference to active comparator NI trial would not have failed; rather, it would have obscured the observation that both products were equally ineffective.

Ongoing Problems With NI Trials

- There are many conditions where established “effective” agents do not consistently demonstrate superiority in placebo controlled trials (e.g. depression or allergic rhinitis).
  - Where this lack of sensitivity exists, a non-inferiority trial which does not include a placebo arm is not appropriate.
- If the performance of the active comparator in the trial is very different from what was assumed when defining the non-inferiority margin then the chosen NI margin is no longer appropriate.
- When the NI is “generous”, is the payer willing to give away benefit of the older drug? (e.g., 10%, 1 in 10)

How to Resolve the Evidence Gap for New Drugs?

- New Regulatory Strategies for Market Authorization
  - Conditional licensing in Europe, Progressive Licensing in Canada
  - New methods required to strengthen information derived from health services linked databases
    - Improved confidence from observational studies
    - Reduced cost of developing data
    - Remove haphazard approach to results reporting
      - Safety, effectiveness
  - Need a strategy to develop new drug evidence within the "real world"
    - Needs to be integrated with needs of "life-cycle" *benefit:harm* assessment
    - Needs to be responsive to HTA at payer level
    - Needs to be responsive to ongoing information needs of prescribers and consumers, i. e., informs decision makers outside the regulatory agency
    - ***Progressive licensing, progressive listing, progressive pricing ??***

Concluding Observations

- Greater confidence (predictability) can be afforded by providing direct comparisons to listed products.
- Active comparator trials that are superiority design are ideal, and perhaps essential when a price premium is expected.
- Non-Inferiority trials will likely dominate equivalence trials where comparator trials are required, particularly for class extensions.
- Non-inferiority trial design (3-arm!) needs Phase 3 drug development advice, and may have significant jurisdictional variability.