

Track A: Considerations for Design of Equivalence Studies

Moderators: Colin Reisner*(Pearl)
Richard Ahrens (Univ of Iowa)
Sanjeeva Dissanayake (MHRA)

Scribe: Sue Holmes (GSK)



General Considerations for Design of Equivalence Studies (1)

1) When are pharmacodynamic safety / efficacy studies required, and why?

Consensus: If systemic PK data shows BE, safety PD not required

Debate: Considerable debate over whether pulmonary PK BE alone acceptable in the absence of a PD study

Further research: Generally agreed that combined PK/PD/scintigraphy study required to ascertain whether:

- PK studies can discern regional deposition
- Whether 'similar' *in vitro* formulations with equivalent PK can exhibit different PD
- Whether different PD effects are seen with deposition of similar lung doses of commercial formulations to different lung regions

Debate: Some support for widening PK limits given idiosyncrasies of OIP PK, to obviate the need for subsequent 'less sensitive' PD studies. In this scenario, a PK fail = end of development utilizing an equivalence pathway. Some discomfort with doing away with the need for PD studies in the absence of more PK-PD correlation data.

2) What is of fundamental importance when designing an equivalence study?

Consensus: Universally agreed that assay sensitivity was the key. Whatever is required should be permissible in terms of enriched populations, dose, dose separation, duration, population.

Consensus: Development of half-strength T presentations not appropriate for such studies. However, regulatory authorities may occasionally request such development.

Consensus: Volunteers acceptable for PD safety; patients usually required to evaluate efficacy (asthma or COPD population, not both)



General Considerations for Design of Equivalence Studies (2)

3) When is paediatric data required, and why?

Consensus: Paediatric data may be required in certain circumstances, particularly for generic DPIs.

Likely to be required where relative performance of devices (in terms of APSD) differs across the flow rate range.

Debate: A more conservative view was expressed that similarity of devices (look, mechanism, operation) is required to waive the requirement for paediatric data.

4) Definition of equivalence margins for 'effect-axis' comparisons / Effect axis or dose axis (relative potency) comparison?

Very few opinions expressed on this, possibly given the lack of statistical representation

Consensus: Relative potency using 0.8-1.2 too conservative & unfeasible. 0.67 – 1.50 appears appropriate, although more data required to determine feasibility / sample sizes.



Efficacy Considerations for Design of Equivalence Studies (1)

Assuming you have to do a PD Study:

1) What are the basic elements of a PD study?

Consensus: Cross-over design is essential, since parallel design will require a sample so large that the study will not be feasible.

Need as steep a dose-response as possible. The power of a study to discriminate between the potency of different formulations is a function of the ratio (s/b) of within subject variability (e.g. root mean squared error = s) to the slope of the dose-response ($=b$).

Debate: FDA position - Estimation of relative potency (ratio of doses of T and R formulations that will produce equal response) is an acceptable approach that will provide the most informative comparison of T and R. Reliability of the study will be reflected in the width of the confidence interval around the estimate of relative potency. EU position – Both relative potency and comparison of responses to equal doses in the presence of sensitivity (= significant dose-response) can provide reliable comparisons of drug delivery by T and R.



Efficacy Considerations for Design of Equivalence Studies (2)

2) If you are developing a SABA formulation, which study model would you choose to use?

Consensus: This is a well developed field, with well defined pathways for successful studies.

Both studies of bronchoprotection against methacholine or histamine challenge and carefully done bronchodilation studies can be used.

Debate: Which is the better model?

BRONCHODILATION: Advantage: Technically easier to do. Disadvantage: easy to fail if subjects aren't well selected and study isn't meticulously conducted.

BRONCHOPROTECTION: Advantage: Greater probability of success. Disadvantage: Technically more difficult to conduct.

Unanswered questions: Methacholine is the currently favored bronchoprovocation agent. Could study designs using exercise, AMP, or mannitol be more statistically powerful?



Efficacy Considerations for Design of Equivalence Studies (3)

3) Is the choice of models different for a LABA?

Consensus: No, can use same approach as SABA (single agent and combination formulations containing LABA)

Need some modification for time points of measurement (SABA peak effect at ~30 min.; LABA peak is later).
Need longer washout before study to avoid tolerance to LABA bronchoprotective effect.

4) If you are developing an inhaled corticosteroid, which study model would you choose to use?

Consensus: This is a less mature field where it is less clear which approach is optimal.

Debate: Which is the better model? Each has pluses and minuses.

CLASSIC STUDY OF IMPROVEMENT IN LUNG FUNCTION in asthma that is suboptimally controlled at baseline: Advantage: Clearly clinically relevant Disadvantage: Concern about carry-over between treatment arms prevents cross-over design.

ASTHMA STABILITY MODEL: Advantage: Clearly clinically relevant; sufficiently steep dose-response. Disadvantage: Technically difficult to conduct; large screen failure rate to identify suitable subjects.



Efficacy Considerations for Design of Equivalence Studies (4)

EXHALED NITRIC OXIDE: Advantage: Easy to measure. Disadvantage: Clinical relevance less clear than asthma stability model or classic study of improvement in lung function. Unclear whether dose-response slope between high and low doses is sufficiently steep.

AMP OR MANNITOL CHALLENGE: Advantage: Easier to conduct than asthma stability. Disadvantage: Clinical relevance uncertain. Unclear whether dose-response slope between high and low clinically relevant doses is sufficiently steep.

SPUTUM EOSINOPHILIA: Advantage: Easier to conduct than asthma stability. Disadvantage: Clinical relevance controversial. Unclear whether dose-response slope between high and low clinically relevant doses is sufficiently steep.



Safety Considerations for Design of Equivalence Studies (1)

- 1) PK defines requirement for safety studies
 - Without PK match development program will be more complex.
 - If T/R point estimate near unity, but CIs too wide, repeat PK study with larger sample size
 - If point estimates different, consider altered dose of T as needed (e.g., if substantial differences) and repeat PK study, or proceed to safety PD studies



Safety Considerations for Design of Equivalence Studies (2)

- 2) What are the safety parameters that need to be assessed for development of beta-agonists, antimuscarinic agents and inhaled steroids?
- Beta agonists: well defined in guidance, including serum potassium, glucose and ECGs to coincide with known maximal effect. Assess safety parameters in fasting state to avoid food effect.
 - Antimuscarinic: Guidance not available, PK similarity desirable given difficulty of justifying safety based on PD. For PK comparisons therefore aim for upper limit of 90% CIs for the T/R ratio < 125%. Pragmatic approach to PD safety may be to assess biochemical parameters, hematology and ECG at maximal effect (fasting state), but acceptability of this approach needs to be discussed with regulators on case by case basis.
 - ICS: Conduct assessment for adrenal suppression and bone growth as outlined in guidance.



Safety Considerations for Design of Equivalence Studies (3)

- 3) What are the appropriate populations for safety assessments of these classes of compounds?
- Healthy volunteer reasonable surrogate for systemic exposure.
- 4) When is assessment in the paediatric population required?
- Comments specific to DPI's
- Design of device different (general agreement not reached)
 - Change in FPD at lower flow rates, even if T/R similarity demonstrated at higher flow rates