

CLINICAL STUDIES TO ASSESS INHALED CORTICOSTEROID BIOEQUIVALENCE

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The Task

- (a) **Generic Equivalents:**
Determine whether the innovator and generic inhaled corticosteroids (ICS) deliver bioequivalent quantities of drug to the site of action in the lungs

- (b) **Reformulations that are not pharmaceutically equivalent:**
Determine the ratio of doses required to deliver equivalent quantities of ICS to the site of action

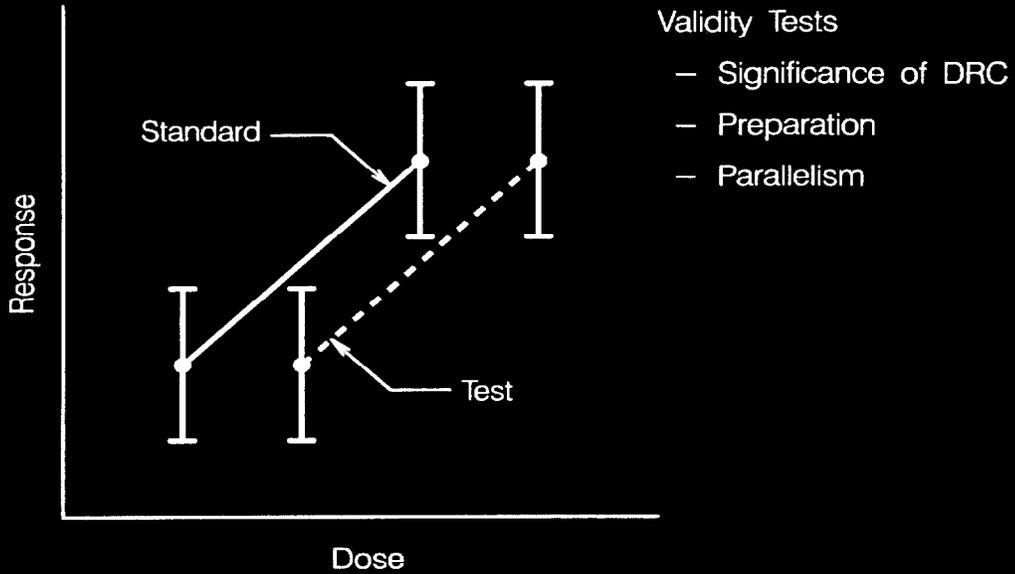
The Concept

- (a) Comparison of formulations along “dose-axis” rather than “response axis”
- (b) Pharmacodynamic response is used to bioassay the quantity of drug delivered to the site of action

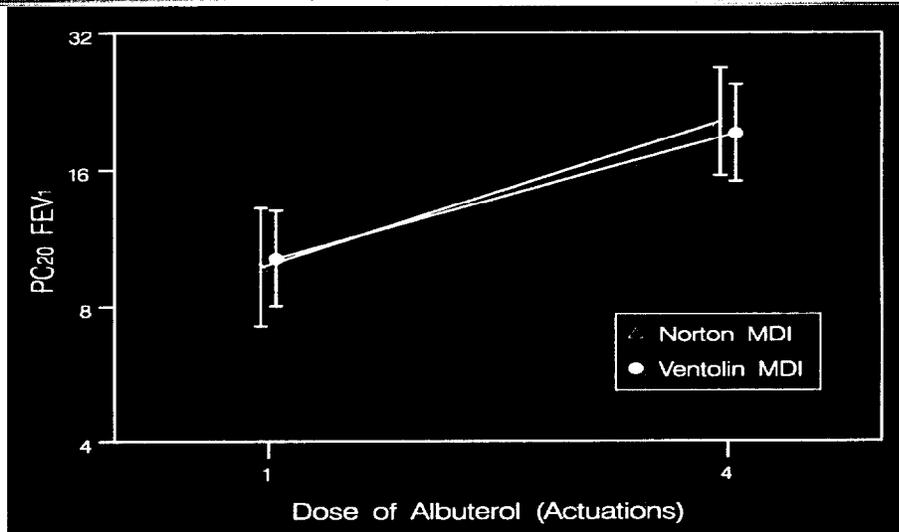
FDA Experience With Generic Albuterol

- | | |
|------------------|--|
| 1989 | Albuterol off patent |
| 1992 | Initial bronchodilation studies could not identify a significant dose-response for reference inhaler |
| 1992-1995 | Search for acceptable, valid methodology |
| 1995 | First generic albuterol inhaler approved using bioassay method |

Overall Study Design – (2,2) Bioassay



Potency of Norton MDI Relative to Ventolin 1 puff Norton = .95 puff Ventolin (90% C.I. 0.69 - 1.40)



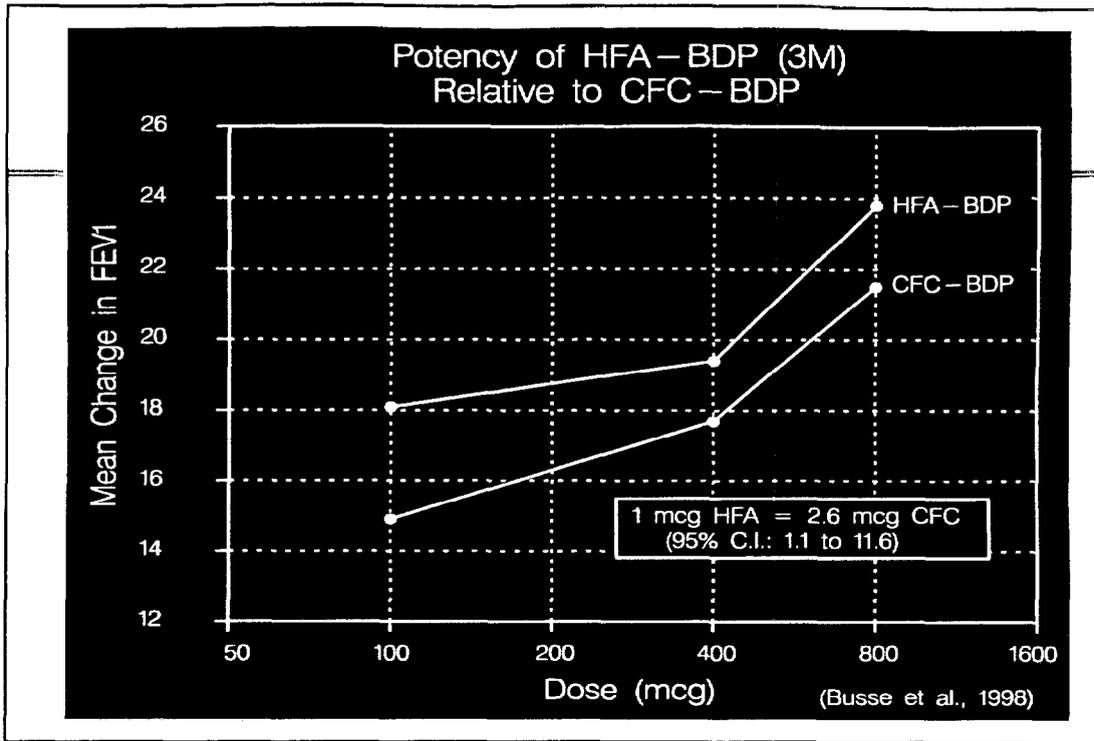
Finney vs. FDA “Dose-Scale” Approach to Bioassay Analysis

	<u>Traditional</u>	<u>FDA</u>
Study Design	2 by 2 3 by 3	2 doses ref. 1 dose test
Curve Fitting	log-linear	E _{max}
Confidence Interval	Fieller's Theorem (normal theory)	Boot Strap (normality not required)

The Problem

This bioassay concept has rarely been applied to inhaled corticosteroids.

When it has been applied to inhaled corticosteroids, it has met with limited success.



This concept has not been successfully applied to inhaled corticosteroids

“Although a substantial number of comparative studies have been performed, it is difficult to draw firm conclusions about the comparative efficacy of different inhaled corticosteroids. This may be partially explained by differences between the designs of studies, the flat dose-response relationship for inhaled corticosteroids, the differences between inhalers, and the lack of control over important confounding factors in many studies. Additional well-designed comparisons, perhaps examining different outcome parameters, are required before any definite conclusions can be made.”

Barnes et al. AM J RESPIR CRIT CARE MED 157;S11, 1998

Common Wisdom r.e. Inhaled Corticosteroids

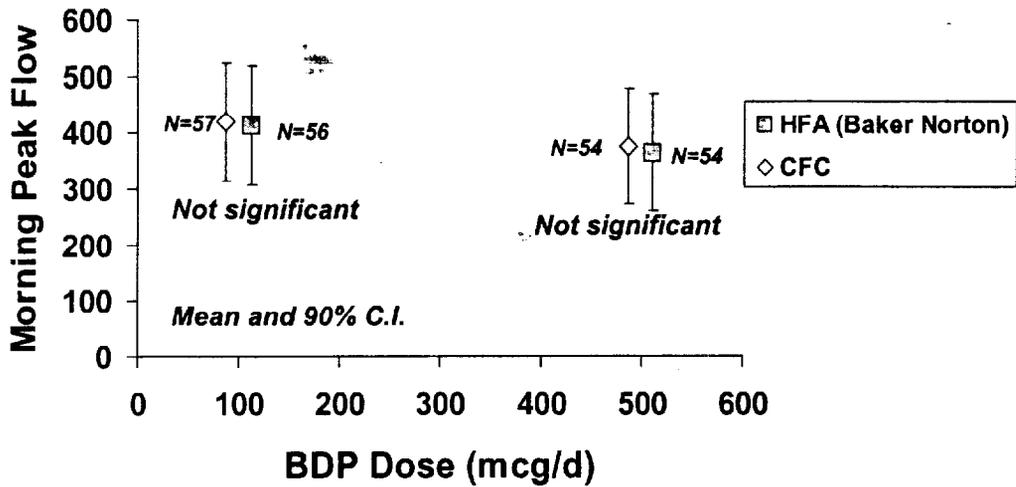
The problem with inhaled corticosteroids is:

**The dose-response curve is just
so darn flat!**

If the ICS dose-response relationship is incredibly flat, then:

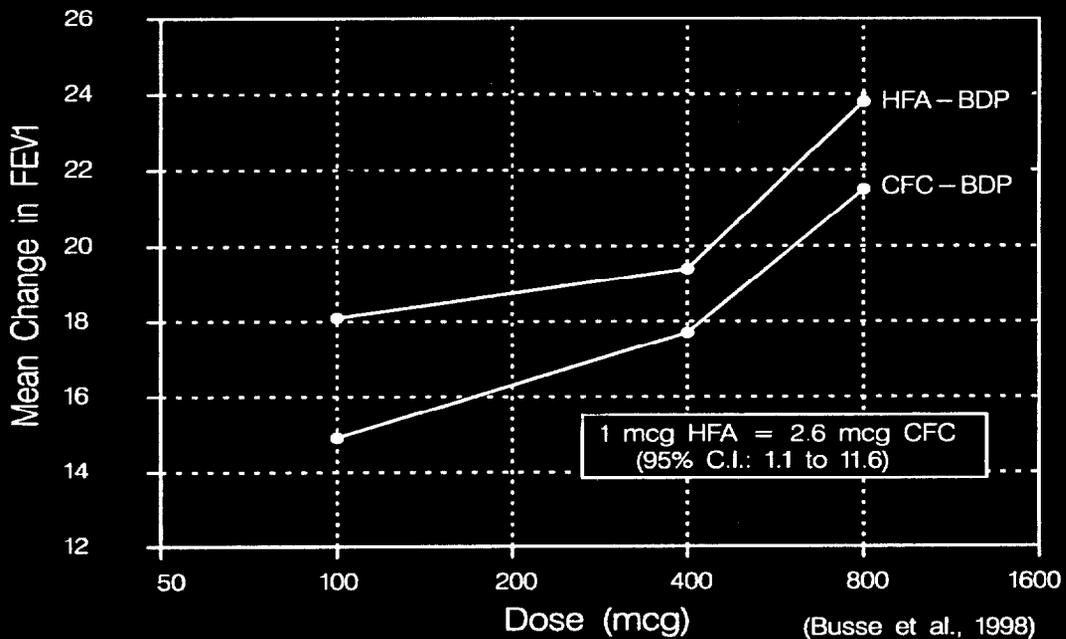
- (a) the dose delivered does not really matter clinically
- (b) do not need to (and in fact can't) use bioassay to demonstrate bioequivalence
- (c) could use clinical trial showing that no two formulations yield similar responses

EFFICACY OF CFC & HFA BECLOMETHASONE MDI'S



Milanowski et al, Respir Med 1999

Potency of HFA – BDP (3M) Relative to CFC – BDP



The ICS dose-response curve is just so darn flat!

But is it really true?

An Asthma Clinician's Paradox

- Clinical studies with hundreds of patients show ICS dose-responses that are flat to non-existent.
- Asthma clinicians think they see ICS dose-response every day in individual patients.

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Which is illusion, which is reality?

Typical ICS Study Design

Parallel Treatment Groups
1-12 Months of Treatment

Baseline → ICS → Improvement in
PFT, Sx, etc. PFT, Sx, PK Flow, etc.

- (a) high variability (S)
- (b) shallow sloped DRC (B)
- (c) carry-over (prevents cross-over)

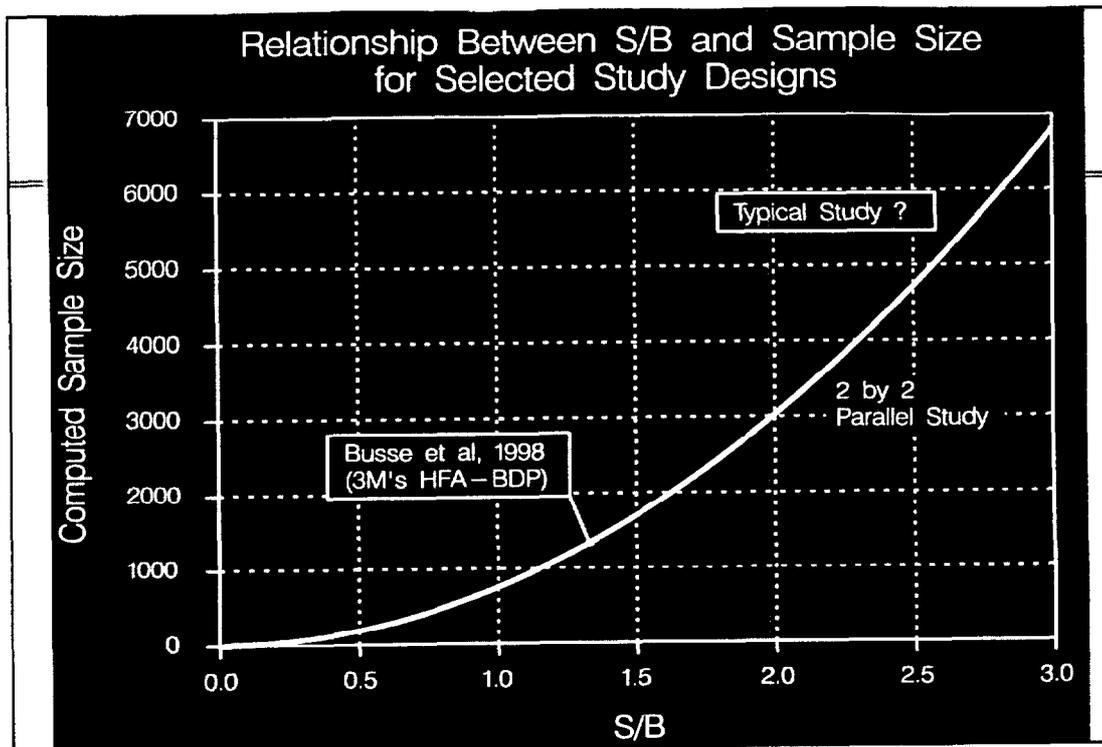
Statistical Power Associated with a Bioassay Study

Related to:

- Variability of responses (S)
- Steepness of dose-response slope (B)
- S + B **do not** function independently, but in concert as the ratio of S/B
- The smaller S/B, the more powerful the study

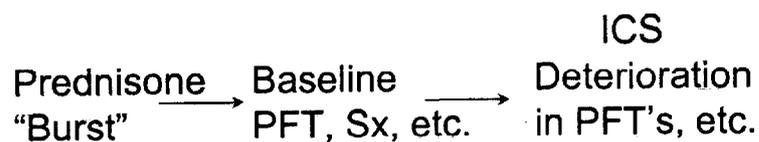
Bioassay Sample Size Computations

- Assume:
 - demonstrate that generic is between 0.5 and 2.0 times as potent as the innovator
 - alpha error = 0.05
 - power = 0.9
 - 2 by 2 bioassay study design

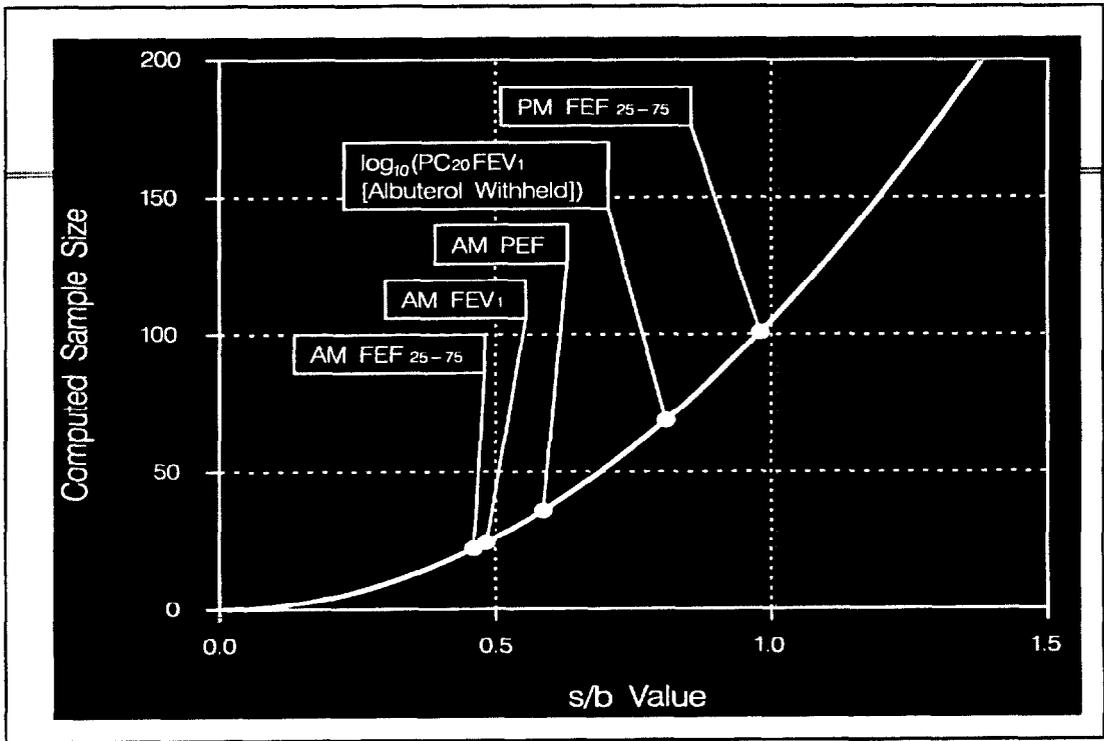
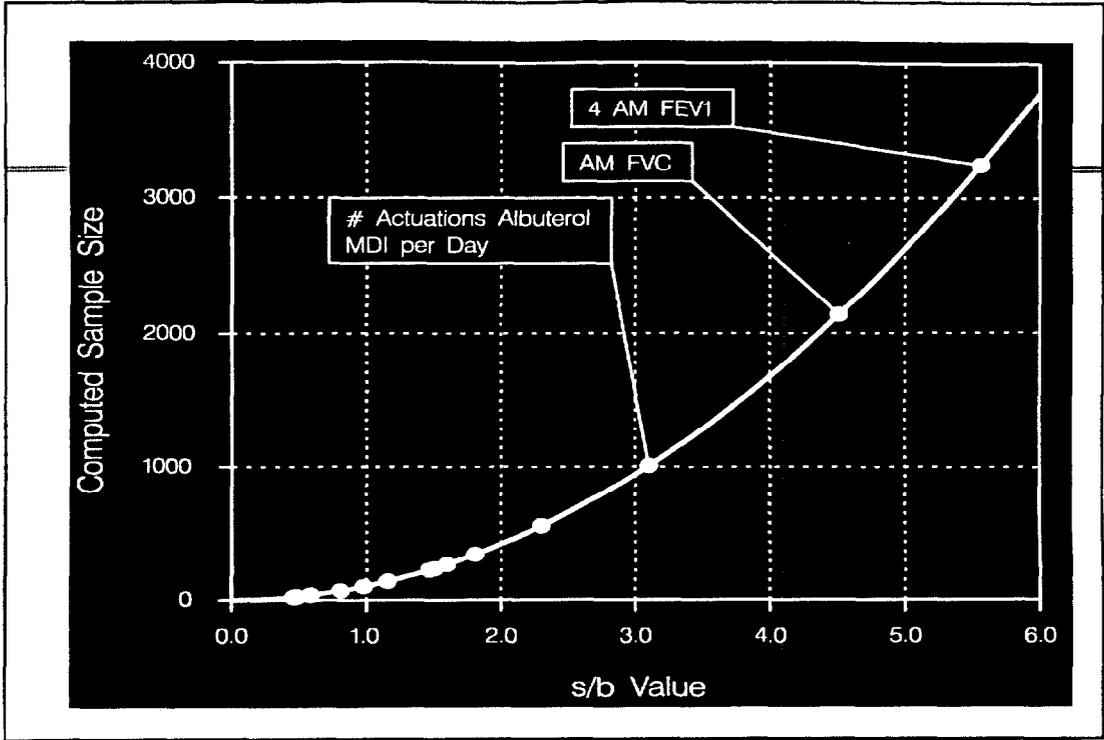


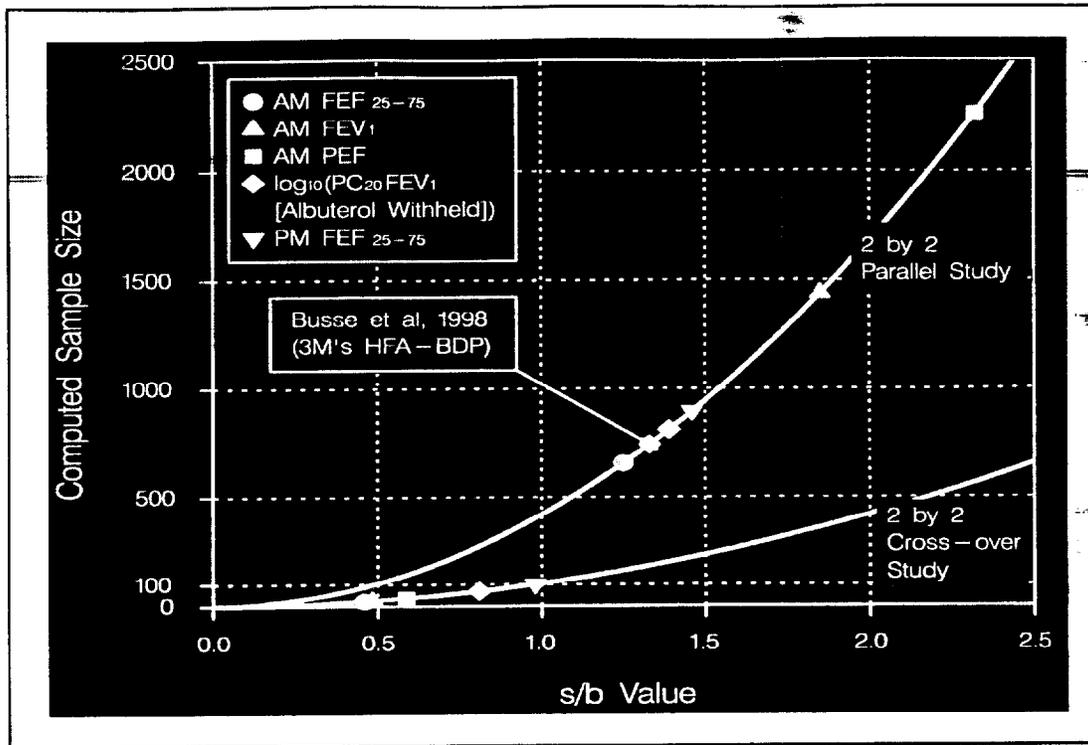
Asthma Stability Following Prednisone "Burst"

1. 100 and 800 mcg/d HFA-BDP
2. Cross-over

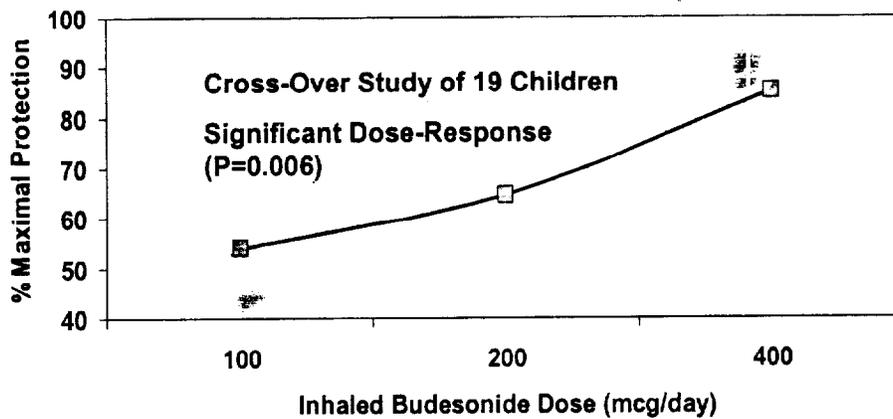


3. Multiple variables examined (58)
4. Estimate S/B for each
5. The lower S/B, the better





Protection Against Exercise-Induced Bronchospasm



Pedersen and Hansen; J Allergy Clin Immunol 1995;95:29

SUMMARY

- The task** -- Develop a method capable of demonstrating *in vivo* bioequivalence for ICS
- The concept** -- Clinical bioassay study: "dose-axis comparison"
- The problem** -- The dose-response curve for is too flat (common wisdom)
-- Use of parallel study design hides the dose-response in individuals (iconoclastic alternative)

SUMMARY

- The solution?** -- Control carry-over
-- Do cross-over study
- *Should* allow accurate assessment of bioequivalence with 10's to 100's of patients (not 1000's)
 - Hasn't been done *yet*