Bioequivalence and Interchangeability: Implications for a Provincial Formulary

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Bioequivalence

- *"a high degree of similarity in the bioavailabilities of two products (of the same galenic form) from the same molar dose, that are unlikely to produce clinically relevant differences in therapeutic effects, or adverse effects, or both"*

  (Conduct and Analysis of BA and BE Studies, Part A, Health Canada)

- *"a Notice of Compliance issued in respect of a new drug ..... shall state the name of the Canadian Reference Product referred to in the submission and shall constitute a declaration of equivalence for that new drug"*

  (Subsection C.08.004 (4), Food and Drug Regulations)

Interchangeability

- *"decisions respecting interchangeability and drug lists remain in the domain of the institution responsible for the costs of the product which includes hospitals, provincial governments and other third party payers"*

  (Canada Gazette, Part II, September 6, 1995)

- *interchangeability requires consideration of whether or not the generic drug exactly fulfills the purposes of the brand name drug, achieves all the beneficial results the brand name drug would have achieved and has no negative side-effects that the brand name drug would have avoided ..... and that in every way, the generic drug 'does no harm' when used interchangeably in the individual or in the target population*

Harmonization Efforts

- *in principle, all provinces support harmonization e.g. development of a list of 'core submission requirements'*
- *in reality, interchangeability is a provincial accountability issue*
- *for subsequent-entry products, in some provinces if a 'declaration of equivalence' has been made for Report A drugs and the Canadian Reference Product is identical to the Ministry's original product, less information is required; comparative bioavailability data is still reviewed for Report B and C drugs*

Burden of Proof :
The Standard *In Vivo* Bioequivalence Trial?

- *Inclusion Criteria:*
  - *objective is the reduction of intrasubject variability*
    - *age range 18-55 yrs*
    - *height/weight ratio within 15% of normal*
    - *healthy adult males*
- *Study Design:*
  - *objective is to minimize variability and bias*
    - *exercise, diet, smoking, alcohol use*
    - *administration of food and fluid*
    - *posture and physical activity*

Population Covered by the Alberta Health Sponsored Drug Programs 1995/96

Age in Years	Female	Male	Total	% of Total Population
< 1	526	579	1,105	0.25%
1-4	2,699	2,908	5,607	1.28%
5-14	9,745	10,498	20,243	4.60%
15-24	11,535	11,063	22,598	5.14%
25-44	17,257	13,773	31,030	7.07%
45-64	57,257	31,280	88,537	20.14%
65-74	83,186	74,229	157,415	35.81%
75 +	69,167	43,809	112,976	25.71%
Total	251,490	188,139	439,629	100%
% of Total Population	57.2%	42.8%	100%	

Burden of Proof:
The 90% Confidence Interval?

- *Current Standards:*
  - ***Relative Mean AUC:***
    - *the 90% CI of the relative mean AUC of the T to the R formulation should be within 80-125%; AUC may be evaluated by determining AUC_T provided that $AUC_T/AUC_I \geq 0.80$*
  - ***Relative Mean C_{max}:***
    - *the relative mean measured C_{max} of the T to the R formulation should be between 80-125%*

Average vs Individual Bioequivalence

- ***Average Bioequivalence:***
  - *does not address the right question i.e. 'switchability'*
  - *does not take into account subject by formulation interaction*
  - *no incentive to create a less variable T formulation*
  - *does not encourage use of subjects that are representative of the target population*
- ***Individual Bioequivalence:***
  - *attractive from a clinical point of view but practical and methodological issues must be overcome*

Number of Brand Name Authorizations for the Alberta Health Sponsored Drug Programs 1993-1997

Year	Brand Name Requests	Approved	Declined	Approval Rate
1993 (3 months)	167	121	46	72.5%
1994	431	260	171	60.3%
1995	186	96	90	51.6%
1996	185	65	120	35.1%
1997	87	38	49	43.7%
Total	1056	580	476	54.9%

- ***Is there evidence to support a problem with the current interchange of drugs?***

From the Formulary Perspective:

- *do equivalent plasma concentrations mean equivalent therapeutic effect and safety?*
- *to what extent are minor differences in formulations exaggerated in special populations?*
- *should bioequivalence be determined at only one point in a product's lifetime i.e. formulation creep?*
- *to what extent should the legislators and policy makers be involved?*