

- David Henry
 - CEO Institute for Clinical Evaluative Sciences, Toronto Canada
 - Former Director, WHO Collaborating Centre, the University of Newcastle, Australia
 - Former Chair Economics Subcommittee, Australian Pharmaceutical Benefits Committee 1992-2001

Summary of IQWiG approach

- Independent summary of clinical data
- Analysis confined to superior treatments
- Analysis confined to therapeutic areas: no prioritization across areas
- Analysis by therapeutic comparators
- Value and cost plotted and efficiency frontier generated
- Generation of decision zones and a ceiling price
- Transparent
- Recognition of other factors

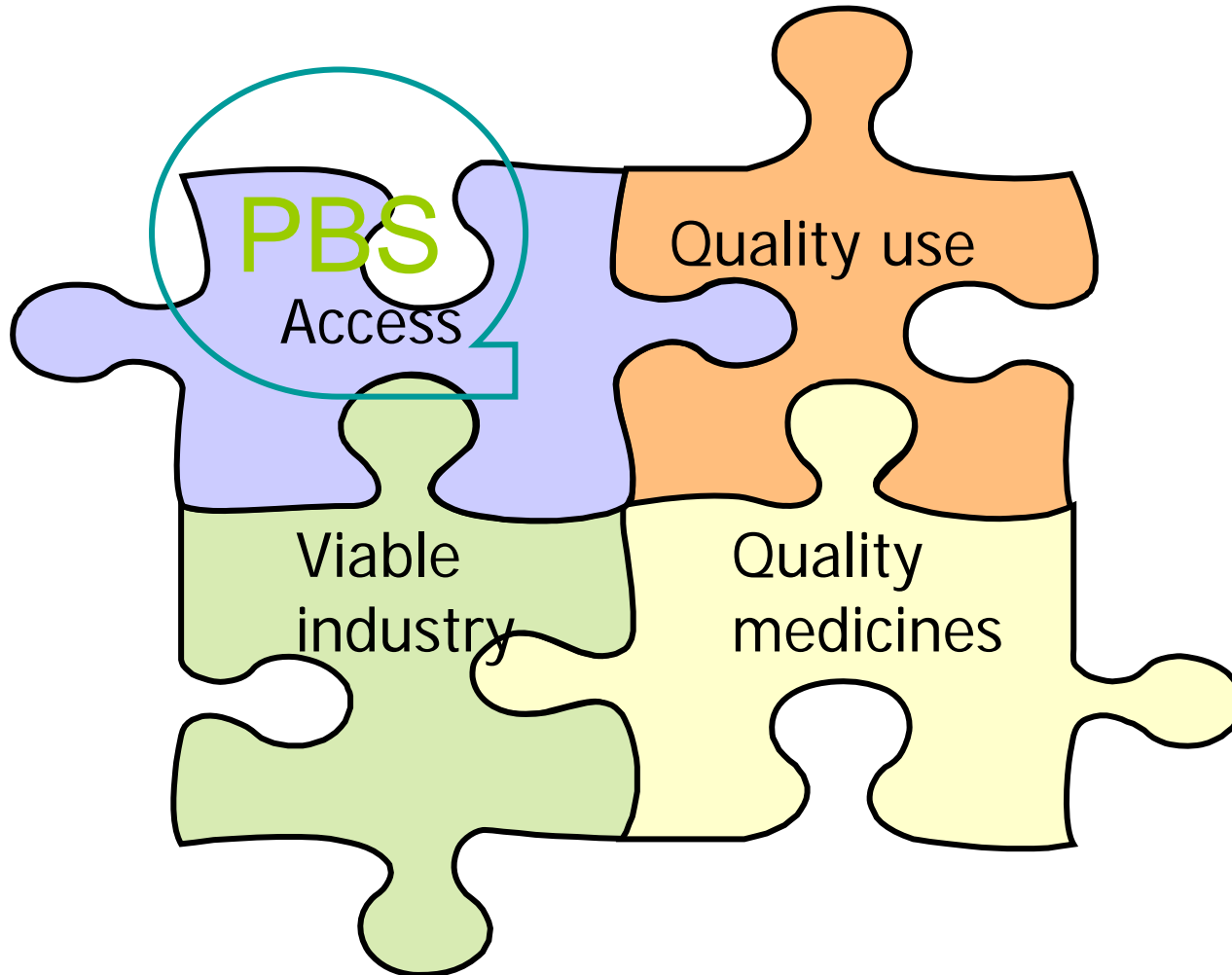
Question

- In a jurisdiction with extensive experience of decision-making based on pharmacoeconomic analyses would the IQWIG approach, based on EBM and efficiency frontiers, be helpful to decision makers?

Plan of presentation

- Details of the Australian PBS
- Experience of using economic analyses in drug reimbursement and pricing decisions: Australia 1993-2007
- How is the Australian experience relevant to the implementation of the IQWIG approach?
- Would the IQWIG approach inform the decisions of the Australian PBAC?

Australian National Drug policies



Australian PBS

- Provides drug benefits for the entire Australian population (population 20 million, per capita GDP \$US 26,000)
- Covers over 650 drug entities
- Underpinned by strong legislation
- Covers mainly community drug use (and use in private hospitals)
- Private health insurance companies provide little drug coverage

Australian Pharmaceutical Benefits Scheme

<http://www9.health.gov.au/pbs/scripts/search.cfm>

- Drugs are placed in different categories – general list, restricted, prior approval (authority required)
- Explicit use of comparative effectiveness and cost data since 1992 *in addition to other criteria*
- 60+ assessments/year
- Explicit guidelines for industry
 - www.health.gov.au/pbs
- Recommendations: list/not list, target use, set prices

The committee and its support

- The committee is independent of government and industry. Supported by strong legislation
- Comprises 12 members; backgrounds in general and specialist medicine, pharmacy and clinical pharmacology
- Economics subcommittee comprises 8 members with backgrounds in health economics, clinical epidemiology, biostatistics and clinical pharmacology
- Both committees are supported by secretariats with very strong technical skills and academic units that evaluate industry submissions

Evaluation

- On average it took 2 person-weeks to evaluate a single submission (sometimes longer)
- Detection of the problems required a team approach with substantial clinical input
- These problems would escape detection in many peer-review systems
- *Beware of published economic analyses*

Context - *negotiation*

- Pharmaco-economic analyses are used as the basis of hard and important decisions
- The committees/government act as *consumers* - ie the customers (not regulators) of the industry
- Decisions are based on an assessment of the ratio of costs to benefits (in natural units)
- The analysis are an excellent basis for price negotiation

The use of cost-effectiveness

- Listing and pricing decisions are based on a formal assessment of cost-effectiveness – ***submissions prepared by pharmaceutical companies. These are evaluated by teams***
- Two situations:
 - Superior drugs *may be offered a higher price* depending on the PBAC interpretation of cost-effectiveness ratios
 - Similarly performing drugs are *offered the same price*. This is a form of reference pricing

EBM issues

- A claim of *superiority* rests usually on a statistically and clinically significant difference based on head to head randomised controlled trials
- A claim of *equivalence* rests on the new drugs being shown to be non-inferior to the existing product
- This case is made by the companies and evaluated by Ministry and academic staff

Decision-making

Factors considered by PBAC

- Clinical significance
- Severity of disease
- Clinical need/ rule of rescue?
- Cost effectiveness
- Cost to government
- Equity
- **Politics!**

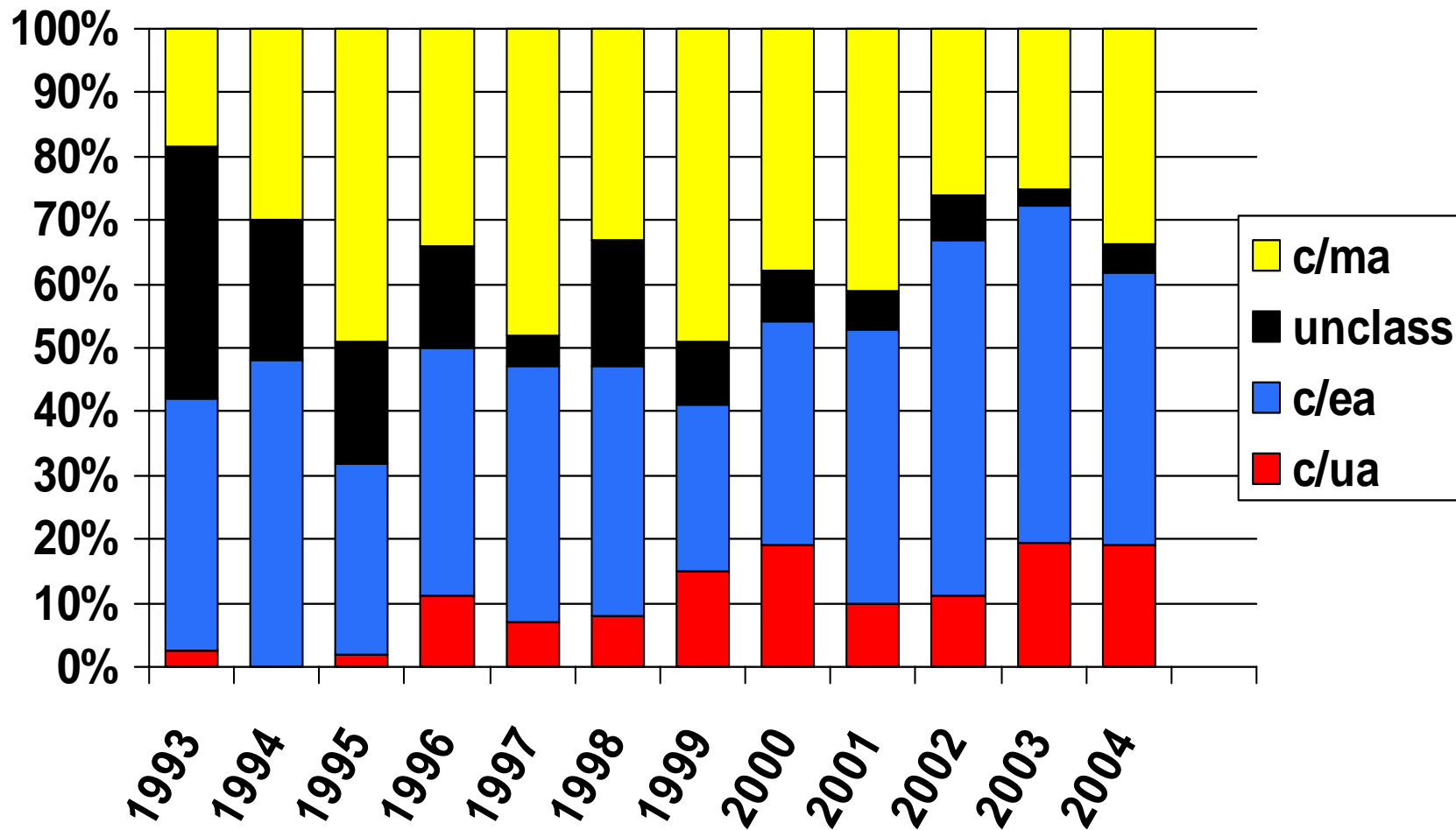
Two stage analysis (based on explicit guideline)

- Stage 1
 - Review of all relevant clinical trial data
 - Synthesis of data
 - Claim of superiority or equivalence against **a single comparator drug** (drug most likely to be replaced in clinical practice)
 - Trial-based economic analysis with limited extrapolation
- Stage 2
 - Modeled economic analysis – at the discretion of the company

Experience

Types of economic evaluation: major submissions

Number: 38 67 47 62 58 61 61 48 51 46 36 **539**



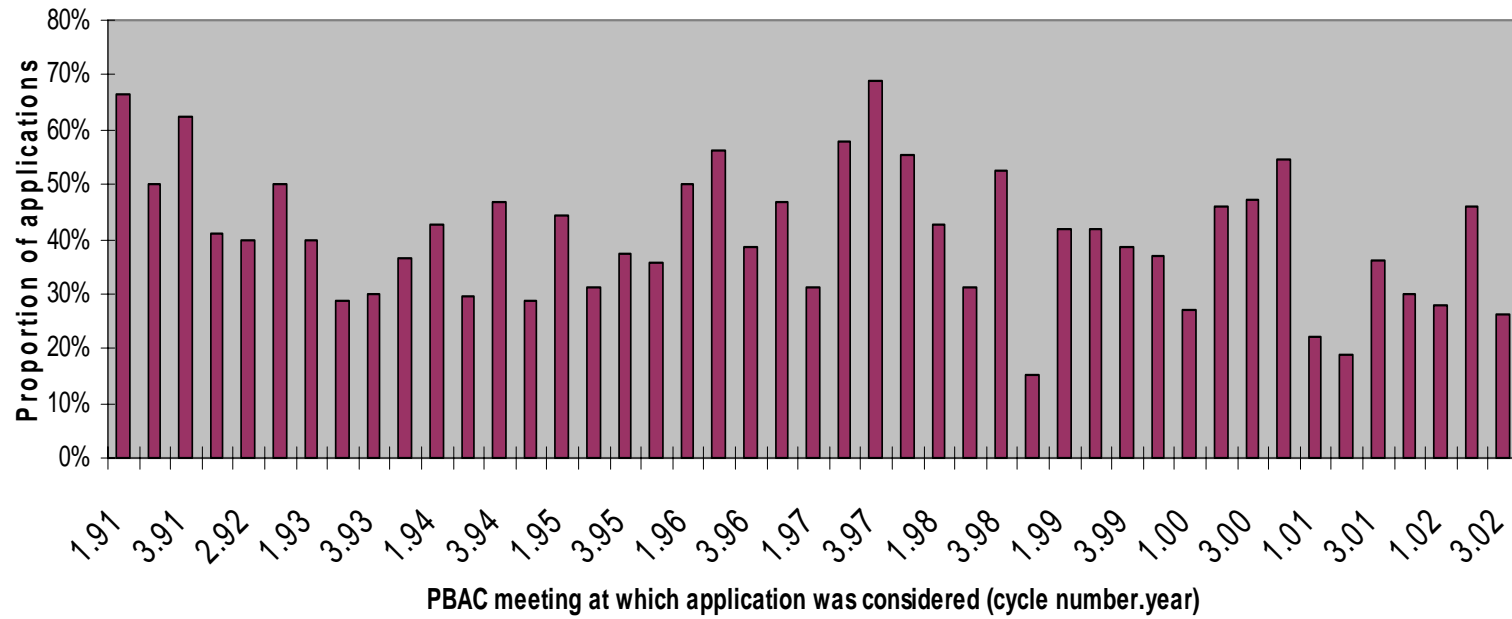
Analysis of superiority based submissions

(Harris, Hill, Chin et al Monash and Newcastle Universities)

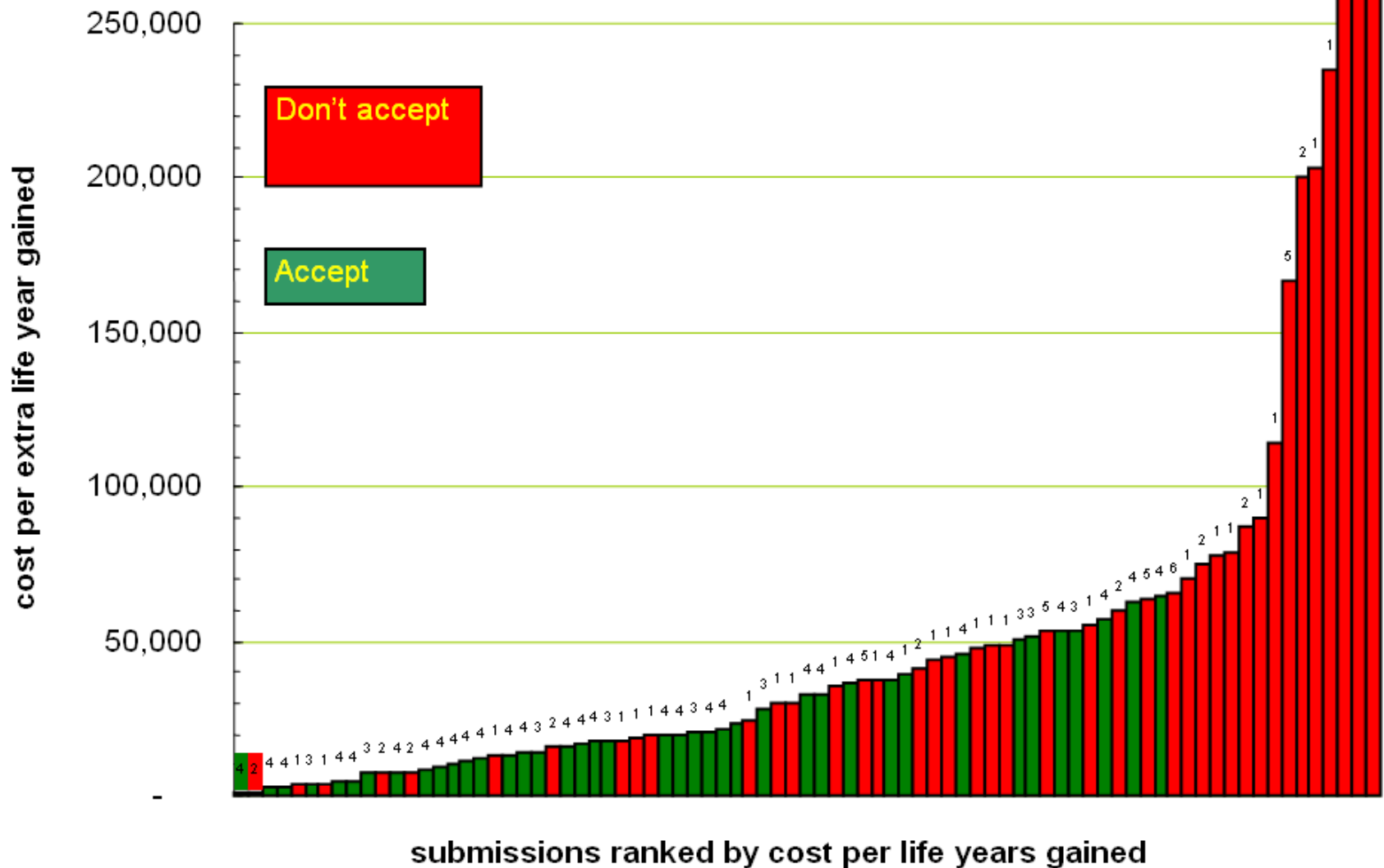
Data-sets

- 858 major submissions to the PBAC between February 1994 and December 2004.
- 116 contained data on cost per QALY
- 138 on cost per life year gained.
- The final sample was 103 decisions with a cost per QALY and 123 with a cost per life year gained.

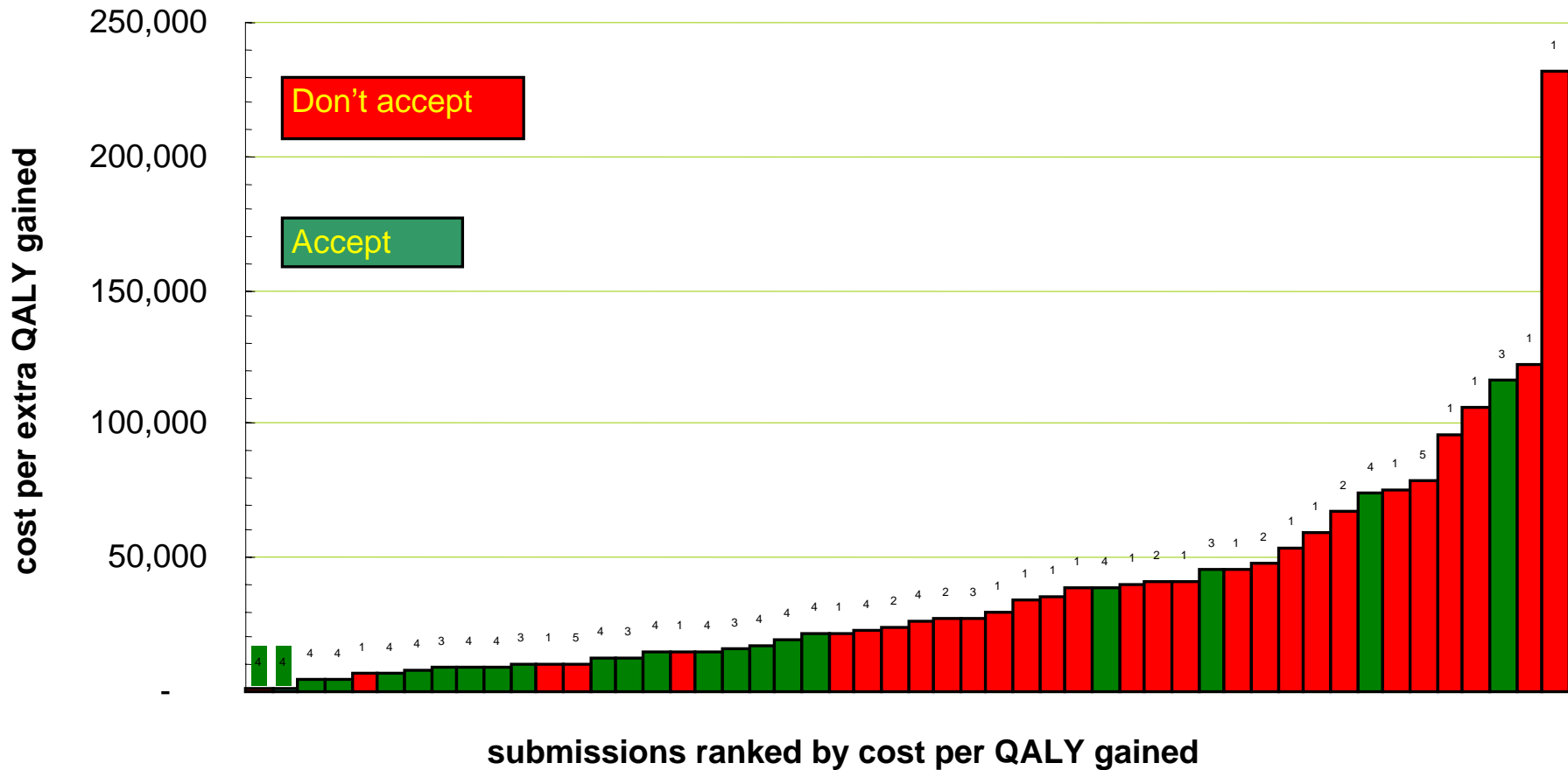
Proportion of Major PBS Applications Approved (Listed) Within a Single Cycle



Recommendation of the PBAC Oct 1992 to Dec 2000 based on cost per life year gained



Recommendation of the PBAC Oct 1992 to Dec 2000
based on cost per QALY gained



Model variables for multivariate analysis

Data item	Description	Scoring
Clinical significance	Did the PBAC consider that the size (point estimate) of the treatment effect to be clinically important	1= Yes 0=No
Precision of clinical evidence	Precision of treatment effect	$P < 0.05 = 1$ $P > 0.05 = 0$
Level of evidence	What is the level of the key clinical evidence presented to the PBAC?	Head to head RCT=3 Indirect comparison RCT=2 Non randomised=1
Quality of studies	12 item checklist on selection and absence of bias in trial design and analysis ²	High quality = 3 Moderate quality =2 Low quality =1
Relevance of evidence	Comparator and population in trial appropriate	1=yes 0= no
Model validity	Model structure	Critically flawed=0 Reliable =1
Modelled outcome	Translation of clinical outcomes to quality of life	Critically flawed=0 Reliable =1
Modelled cost	Cost estimates	Critically flawed=0 Reliable =1
Cost per QALY	Incremental cost per additional quality adjusted life year	\$'0,000 ¹
Cost to government	Annual predicted additional financial cost to government of listing	\$m
Life threatening	Condition associated with premature mortality (<5 year survival)	1=yes 0=no
Last line therapy	Accepted placebo/standard care as comparator)	Last line=1 Not last line=0
Uncertainty of cost per QALY	Upper limit in model sensitivity analysis	\$'0,000
Previously considered	If the drug had been considered before for that indication	Yes=1 No=0

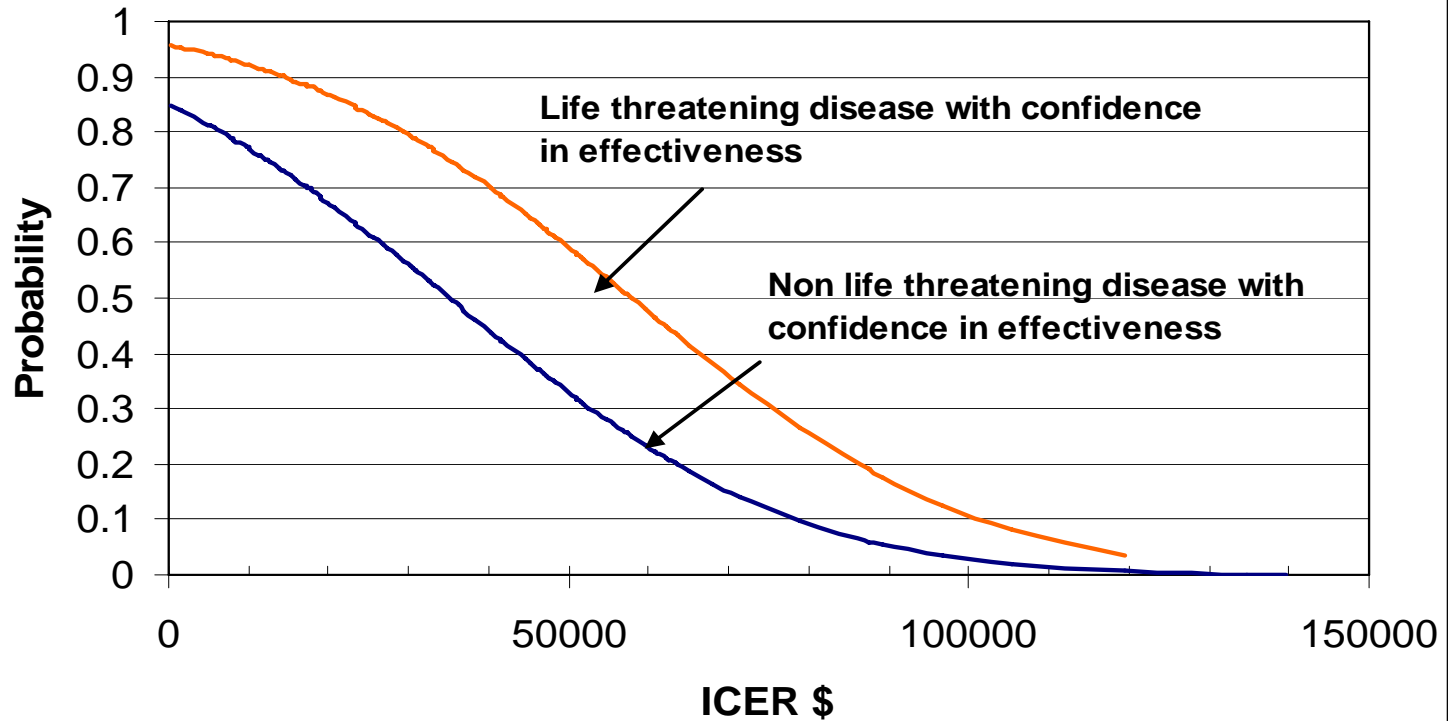
Methods

- The probability of recommending a drug for listing on the PBS Schedule at the price proposed was estimated in a probit multiple regression model.

Results

- Clinical significance, cost effectiveness, cost to government, and severity of disease were significant influences on decisions.
- Confidence in *clinical significance* increased the probability of recommending coverage by 30% (95% CI 13% to 48%).
- An increase in \$10,000 from a mean incremental cost per QALY of \$42,920 reduced the probability of listing by 7% (95%CI. 4% to 10%).
- ***Pseudo R²=0.1574 (LYG) and 0.1917 (QALY)***

Prob. of PBAC recommendation by incremental cost per QALY by severity of condition and confidence in the evidence



From Harris, Hill Chin et al 2007

What about the rest: sample of 400 submissions

- Reliance on surrogate outcomes
 - Of 400 submissions 216 were initial submissions for drug/indication pairs
 - 150/216 [69%] were subsequently recommended for addition to the formulary.
 - Of those recommended for listing, 36/150 [24%] applications presented claims of efficacy that were wholly dependent on surrogate endpoint data, and 68/150 [45%] submissions relied on a combination of surrogate with intermediate and/or clinical endpoint data.

Surrogates

Main Indication	Outcome measure
Asthma	<ul style="list-style-type: none"> ▪ FEV₁ ▪ PEFR ▪ FVC ▪ day and night asthma scores ▪ bronchodilator use
Bladder carcinoma	<ul style="list-style-type: none"> ▪ normal cystoscopic examination, and normal findings on examination of a random biopsy specimen and cytologic analysis of urine ▪ time to termination of treatment due to persistence, recurrence, or progression of disease
Cranial diabetes insipidus	<ul style="list-style-type: none"> ▪ antidiuretic response in healthy volunteers subjected to forced hydration
Dry eyes	<ul style="list-style-type: none"> ▪ mean number of daily instillations
Glaucoma	<ul style="list-style-type: none"> ▪ reduction in IOP ▪ improved compliance ▪ less systemic absorption
HIV infection	<ul style="list-style-type: none"> ▪ CD4 count ▪ viral load
Hypercholesterolaemia	<ul style="list-style-type: none"> ▪ change LDL-cholesterol ▪ change in total cholesterol ▪ change in HDL-cholesterol ▪ change in triglyceride levels
Hypertension	<ul style="list-style-type: none"> ▪ change in sSBP ▪ change in sDBP ▪ change in mean trough seDBP ▪ successful response at 4 or 8 weeks (defined as reduction in trough seDBP >10mmHg) ▪ normalised BP (defined as trough seDBP <90mmHg)
Major depression	<ul style="list-style-type: none"> ▪ change in MADRS¹ ▪ change in CGI² ▪ change in HAM-D³ ▪ CGI score
Menopausal symptoms	<ul style="list-style-type: none"> ▪ plasma oestradiol ▪ plasma FSH ▪ plasma LH
Onchocerciasis	<ul style="list-style-type: none"> ▪ mean skin microfilaria density ▪ non-infectivity as measured by <5 microfilariae/mg of biopsied skin
Paget's disease	<ul style="list-style-type: none"> ▪ normalisation of SAP ▪ change in SAP
Prostate cancer	<ul style="list-style-type: none"> ▪ plasma testosterone level
Schizophrenia	<ul style="list-style-type: none"> ▪ >20% reduction in PANSS⁴ ▪ >20% reduction in BPRS⁵ ▪ change in BPRS ▪ change in CGI ▪ change in HAM-D ▪ change in CPRS⁶ ▪ >50% reduction in HAM-D and/or MADR Score
Testosterone deficiency	<ul style="list-style-type: none"> ▪ mean total testosterone

Error-prone

(Hill et al. JAMA 2000; 283: 2116-2121)

- 218/326 (67%) of submissions to the Australian PBS had problems that would have significantly impacted on decisions had they not been corrected
 - 154 disagreements on estimates of clinical efficacy
 - 71 disagreements on models
 - 15 disagreements on choice of comparator
 - 9 serious calculation errors

Politics - example

- Cervarix – HPV vaccine for girls
- Detailed clinical assessment and modelling
- Committee recommended against listing on the basis of price/cost-effectiveness
- Female Senators petitioned the Prime Minister to overturn the Committee's decisions

AUS PBS: Relevance to IQWIG

- In the real world reimbursement committees DO take account of cost-effectiveness
- But there are a number of additional factors that are included in the final recommendation
- The final analytical models explain only a small proportion of variance in decision making (by the PBAC)
- Cost-effectiveness analyses done by industry are quite error prone

AUS PBS: Relevance to IQWiG

- Only a small proportion are based on QALY analyses and there is considerable reliance on surrogates QALYs are not used in priority setting but as a cost-effectiveness tool
- Cost minimization analyses are common
- Ceiling prices are usually set by cost-effectiveness thresholds
- Most major disagreements with industry concern the clinical claims

Will the IQWiG approach inform decision making?

- YES
 - The clinical data will be sorted prior to the economic analyses using rigorous methods
 - The work is being done independently of industry
 - In real life many decisions are made within therapeutic indications, not across them
 - Cost/QALY appears valuable but is not the definitive variable in many cases

Will the IQWIG approach inform decision making?

- The use of efficiency frontiers is an attractive alternative to the Australian industry-driven approach of single agent/single comparator analyses
- The process is very transparent
- In this setting the practical use of cost-effectiveness analysis is price-setting