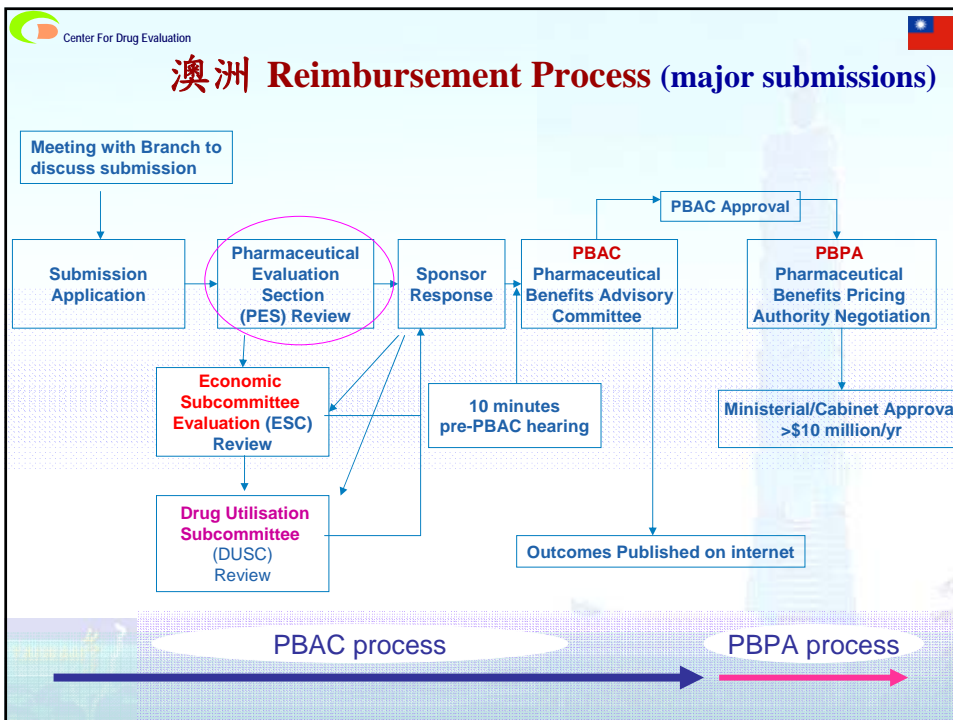


Center For Drug Evaluation 

Andrew S. MITCHELL

Strategic Adviser, Evaluation
 Pharmaceutical Evaluation Branch
 Department of Health and Ageing
 Australia



1

Applying pharmacoeconomic information to drug subsidy decisions: an Australian perspective

Andrew S Mitchell
Strategic Adviser, Evaluation
Department of Health & Ageing



3

Overview

- ◆ Australian health care system
- ◆ Subsidising drugs on the PBS
- ◆ Using economic evaluations
- ◆ 2006 PBAC Guidelines
- ◆ Basis for harmonisation

4

Australia



5

Population overview

- ◆ 20.8 million people
- ◆ Most people live around the coast
- ◆ Challenges in rural and remote areas
 - skilled workforce, access
- ◆ Challenges with ageing population
 - decreasing birth rates and longer life expectancy

6

Australian health care system

- ◆ Federal government
 - subsidises community-based services
 - rebates private health insurance
- ◆ State/territory governments
 - provide public hospital services
 - at no charge to patients
- ◆ Promote coordinated care

7

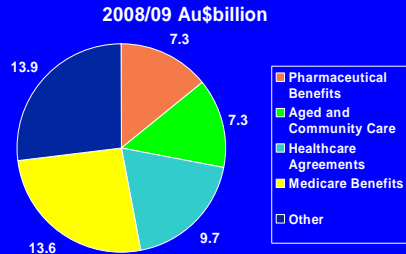
Major DoHA programs

- ◆ **Medicare Benefits Schedule**
 - medical, pathology, diagnostic, imaging
 - fee for service
 - some co-payments
- ◆ **Pharmaceutical Benefits Scheme**
- ◆ **Australian Healthcare Agreements**
 - helps fund public hospitals
- ◆ **Aged and Community Care**



8

Forecast DoHA Expenditure



9

The PBS

- ◆ **In operation >50 years**
- ◆ **708 different drugs (June 2008)**
- ◆ **168 million scripts (06/07)**
- ◆ **Au\$7.0 billion cost to government (07/08)**
 - 16% of government health budget
- ◆ **4.3% growth from 05/06 to 06/07**



10

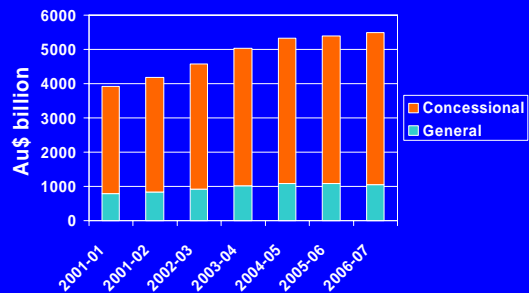
PBS objective

- ◆ **to provide timely, reliable and affordable access for the Australian community to necessary and cost-effective medicines**
 - equity of access
 - value for money



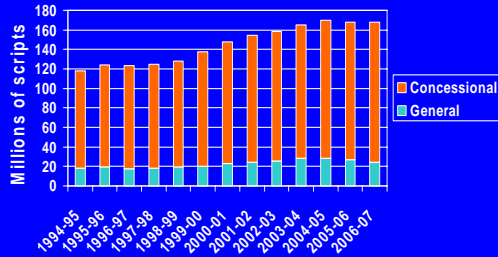
12

PBS cost to government



13

Volume of PBS prescriptions



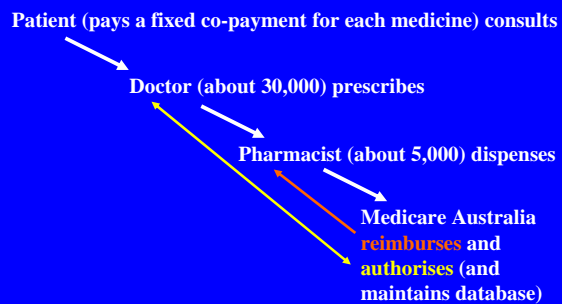
14

Usual supply amounts

- ◆ For acute treatment: enough for a course
- ◆ For chronic disease: enough for a month
 - see pharmacist monthly
 - three months where stable doses (eg OC)
- ◆ Repeats for chronic disease: 5
 - see doctor 6-monthly
 - twelve months where stable and not managed by a specialist doctor

15

The PBS in operation



16

Control of access to the PBS

- ◆ Approved prescribers only
 - doctors, dentists, optometrists (2008)
- ◆ Approved dispensers only
 - pharmacists, ~60 rural dispensing doctors
- ◆ Approved hospitals
 - for certain section 100 programs
 - other supply arrangements

17

Fixed copayment for patients

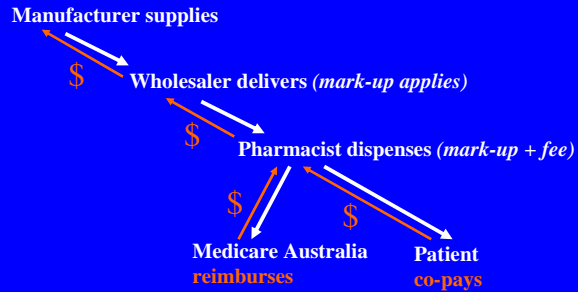
- ◆ General beneficiary: Au\$31.30/script
- ◆ Concessional beneficiary: Au\$5.00/script
- ◆ General beneficiary safety net
 - Au\$1141.80/calendar year for a family
 - then Au\$5.00/script
- ◆ Concessional beneficiary safety net
 - Au\$290.00/calendar year for a family
 - then Au\$0.00/script

18

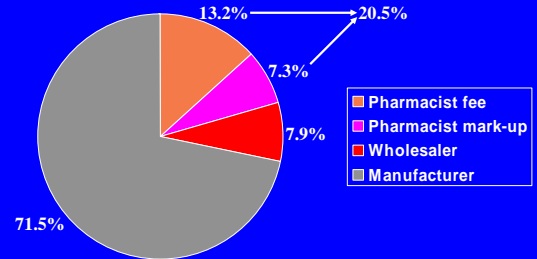
Pharmacy arrangements

- ◆ PBS medicines are largely delivered through community pharmacy
- ◆ Rules limit locations
- ◆ Fourth Community Pharmacy Agreement
- ◆ Incentives for pharmacists to use PBS

Paying the PBS supply chain



Share of PBS costs (04/06-03/07)



Choosing drugs for subsidy

- ◆ Prerequisite: TGA “registers” drug
 - efficacy, safety, quality
- ◆ PBAC “recommends”
 - comparative effectiveness, comparative safety, comparative costs
- ◆ Minister “declares”

Cost-effective PBS drugs

- ◆ Cost-effectiveness requirements phased in 1991 and 1992; mandatory since 1993
- ◆ Percent of drugs which have been subject to cost-effectiveness requirements
 - >50% all 708 PBS drugs

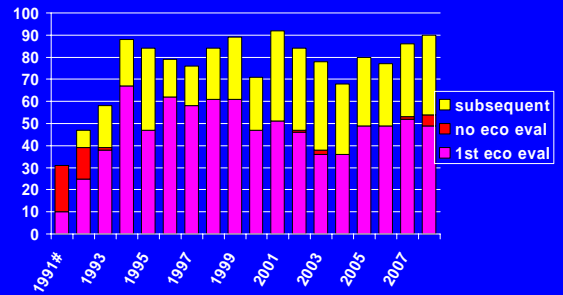
Handling a major submission

- ◆ Each major submission is
 - prepared by a sponsor (consultant)
 - evaluated in-depth by PES (9 weeks)
 - reviewed by Economics Sub-Committee
 - used by PBAC
- ◆ A re-submission is
 - prepared by a sponsor to resolve major disputes

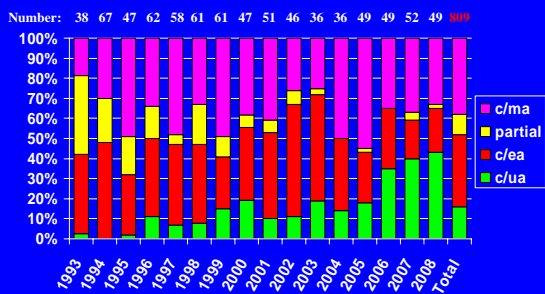
Types of major submissions

- ◆ New drug
- ◆ Major change to current restriction
- ◆ Re-submission
- ◆ Referred/deferred submission

Major submissions 1991-2008



Types of economic evaluation



PBS listing insights (1)

- ◆ Subsidising drugs in Australia
 - adding systematic consideration of economic evaluations is established and sustainable
- ◆ Scientific basis of major submissions
 - achieve and maintain scientific credibility

PBS listing insights (2)

- ◆ PBS use of economic evaluations is consistent with
 - an efficiency criterion
 - influence of other relevant factors
- ◆ Insights require further work

C/E: need to have

- ◆ Separate licensing and subsidy decisions
- ◆ Positive list
- ◆ Price negotiations
- ◆ Ability to restrict indications
- ◆ Adequate guidelines for submissions
- ◆ Competent evaluations of submissions
- ◆ Consistent and informed decision-maker

31

C/E: nice to have

- ◆ Legislative framework
- ◆ Equity across beneficiaries
- ◆ Independent committee
- ◆ Single subsidy program
- ◆ Transparency for all stakeholders
- ◆ Clear division of roles
 - eg post-listing pricing reviews



32

C/E: warnings

- ◆ Cost-effectiveness is not necessarily a cost-containment tool
- ◆ Impact is in long-term
- ◆ Difficult to apply retrospectively unless part of a wider review
- ◆ Requires shift
 - from purely opinion-based decision-making
 - towards evidence-based decision-making



33

C/E: benefits

- ◆ “Outcomes-based reward system”
- ◆ Cost-justification
- ◆ Robust decision-making
- ◆ Basis for greater transparency



34

Scarce skills management

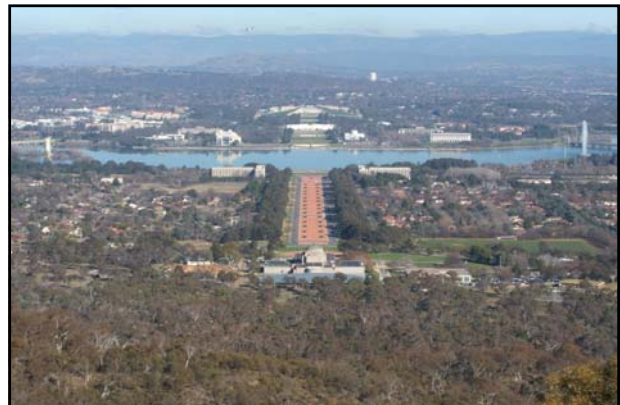
- ◆ Scarcity of skills an ongoing issue
 - preparers, evaluators, users
 - evidence-based and multi-disciplinary
 - clinical epidemiologists, biostatisticians, health economists
 - clinicians, pharmacists, psychometricians
 - committee members respected by peers, but not necessarily representative



35

Accommodate negotiation

- ◆ Cost-effectiveness is not fixed
- ◆ Negotiate eligible population
 - restrict to those who benefit most
- ◆ Negotiate price
 - reduce price of proposed drug
- ◆ Negotiate transparency
 - rebate arrangements allow an “effective” price that is less than published price



37

Current PBAC Guidelines

Current PBAC Guidelines URL:

- <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacguidelines-index>

- ◆ Context of decision-making process
- ◆ Main design principles
- ◆ Key elements and developments

38

Context

- ◆ PBAC recommends whether drugs should be subsidised on national formulary
- ◆ Legally required to consider comparative cost-effectiveness since 1987
- ◆ Guidelines for submissions by companies
- ◆ First substantive revision since 1995 released in December 2006

39

Design of PBAC Guidelines

- ◆ Based on information needs of PBAC
 - not a “how to do” manual
- ◆ Responses to requests for information
 - identify key matters for specific circumstances
 - provide for a transparent presentation
 - promote PBAC confidence in submission

40

Design of PBAC Guidelines

- ◆ No minimum standard
- ◆ Promote comparability across submissions
 - but not prescriptive
 - flexibility remains
- ◆ Minimise uncertainty where possible
- ◆ Subject to regular review
 - provides for introduction of new methods
 - established and accepted methods will influence future updates

41

Experience-based

- ◆ Acknowledges international trend towards c/e information by large third-party payers
- ◆ Seeks to influence drug development
- ◆ Distils multi-disciplinary influences
- ◆ Benefits from extensive consultation
- ◆ Reflects >1,150 PBAC c/e decisions
- ◆ Order of evidence integration is crucial

42

6 sections to a major submission

- ◆ A: context
 - restriction and comparator
- ◆ B: clinical evaluation
- ◆ C: translating between evaluations
- ◆ D: economic evaluation
- ◆ E: utilisation and financial implications
- ◆ F: optional
 - quality use of medicines, risk-sharing arrangements and other relevant factors

A: context of submission

- ◆ Requested restriction (**extended guidance**)
 - many ways to identify eligible patients
 - more c/e in those likely to benefit most
 - varying levels of reinforcement
- ◆ Main comparator (**clarified guidance**)
 - pragmatic: “the therapy prescribers would most replace in practice”
 - not necessarily “most c/e” or “most prescribed”
 - clinical management algorithms may help

What comparator for trials?

- ◆ Availability of randomised trials does not determine selection of comparator
- ◆ Prefer active-controlled randomised trials
 - support noninferiority claims
 - demonstrate superiority claims
- ◆ Placebo for last-line trials only
 - recruit “refractory” patients
 - support “niche” indications

B: clinical evaluation (clarified)

- ◆ Hierarchy of preferred sources of evidence
 - direct randomised trial(s)
 - indirect comparisons: two sets of randomised trials involving common reference
 - non-randomised studies
 - expert opinion
- ◆ Minimise systematic and random error
 - conventional EBM approach to appraisal
 - all relevant randomised trials, not a selection
- ◆ No minimum standard

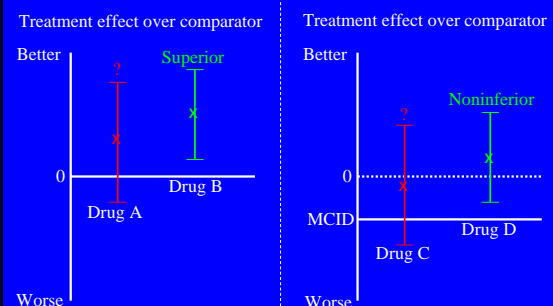
Harmonisation? (1)

- ◆ Typically the same dataset for each new drug and each new indication
- ◆ Determined by each company’s response to regulatory agencies
- ◆ Reviewed internationally by both regulatory and subsidy agencies
- ◆ Similar assessment of strengths and weaknesses

B: Noninferiority and c/ma

- ◆ Not legal for PBAC to recommend a more expensive drug unless it is more effective or less toxic for some patients
- ◆ Rely on noninferiority design (**extended**)
 - show new drug is significantly better than MCID below treatment effect of its comparator
 - this approach is relevant even when no prospectively noninferiority trial data is available
 - often applies to indirect comparisons

Superiority vs noninferiority



C: Translating trial evidence

- ◆ **New guidance**
- ◆ Request a more explicit set of connections between the clinical and economic evaluations

 1. Identify whether translation issues arise
 - (applicability, extrapolation or transformation)
 2. Investigate each in a premodelling study
 3. Facilitate independent verification
 4. Relate results to the economic evaluation

Guidance on translation

- ◆ **New guidance**
- ◆ **Applicability** to other patients and circumstances
 - assessment of treatment effect variation
 - subgroup analyses where justified
- ◆ **Extrapolation** beyond trial horizon
 - time-to-event analyses
- ◆ **Transformation** of trial outcomes
 - surrogate to final outcomes
 - post-trial utility valuation

Harmonisation? (2)

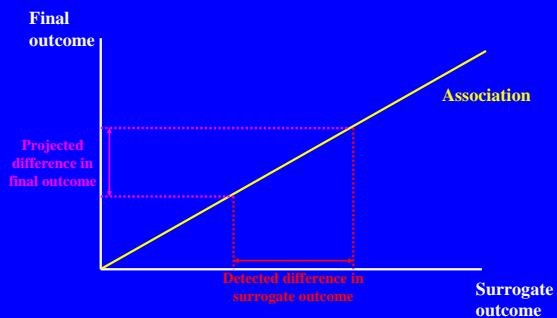
- ◆ **Common and recurring set of translation issues**
- ◆ **Working on a set of methods to maximise confidence in translation**
- ◆ **Relies on common acceptance of EBM hierarchy and approach to clinical evaluation**

Surrogate to final outcomes

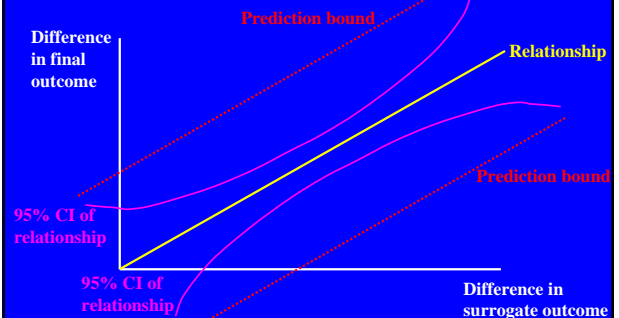
- ◆ **3 steps to a more convincing transformation**

 1. **Association** between surrogate and final
 - typically epidemiological (longitudinal) studies
 - plus biological reasoning
 2. **TE on surrogate predicts TE on final**
 - requires randomised trials
 - prefer >1 mechanism of action on surrogate
 3. **Rationale to accept this prediction given the mechanism of action of the proposed drug**

Association



Trial-based predictions



What implications? (1)

- ◆ Needs direct randomised trials to quantify treatment effects with confidence
- ◆ Measure both surrogate and final outcomes
 - unequivocally defined (eg extent, duration)
 - applies also to clinical surrogates (eg TTP)
 - what methods of analysis of prediction?
 - applying across mechanisms of action?
 - how relate to specifics of a model?

What implications? (2)

- ◆ Randomised trials should more adequately support quantitative predictions of final outcomes for each new mechanism of action
- ◆ Unless seeking to claim superiority, subsequent drugs with same mechanism of action (“me-too’s” or same drug class) could rely on surrogates only
 - ie Step 3 is not needed

What implications? (3)

- ◆ Competing trend and enthusiasm for biomarkers as surrogate outcomes
 - is this the right trend for the long-term?
 - what insights from CAST and anti-arrhythmics (1989); ILLUMINATE and torcetrapib (2006)?
 - should classification of benefits of harms ethically trump quantification and cost-effectiveness?
 - who should decide this?

What implications? (4)

- ◆ Disincentive for novel mechanisms?
 - more expensive, delays to access?
- ◆ Variation on “Coverage with Evidence Development” (CED), with initial decision on surrogate outcome and confirmation on final outcome?
 - unidirectional cross-overs and drop-ins?
 - ethical justification to continue?

D: economic evaluation

- ◆ Select between noninferiority and superiority
 - for noninferiority
 - » *select between cost-minimisation and cost analysis*
 - for superiority
 - » *select between purely trial-based, stepped evaluation (new) and purely modelled*
- ◆ More extensive sensitivity analyses
 - broad assessment of uncertainty (**extended**)
 - probabilistic sensitivity analysis has a role (**new**)

Preferred base case analysis

- ◆ **Focussed guidance**
- ◆ Considers material increments in
 - health outcomes (prefer utility framework - **new**)
 - provision of health care resources
- ◆ Allow base case to be respecified including re-running all sensitivity analyses (**new**)
- ◆ Supplementary analyses allowed (**new**)
 - monetary framework
 - nonhealth outcomes (eg production changes)
 - provision of other resources

61

Valuation of outcomes

- ◆ Appendix 6: utility valuation (**extended**)
 - trial-based (typically a repeated MAUI)
 - post-trial (scenario-based, “mapping”, “matching”, literature-based)
- ◆ Appendix 7: monetary valuation (**new**)
 - cost-benefit framework less preferred
 - can present as a supplementary analysis

62

Present cost-utility analysis

- ◆ Transforming to QALYs is not always helpful
 - gain in comparability from QALY might be outweighed by loss of confidence in results
 - eg recent decision on HPV vaccine “Gardasil”
 - » *PBAC relied on incremental life-years gained, not submitted incremental QALYs gained*
- ◆ Should present cost-utility analysis when
 - quality-adjusting incremental life-years gained
 - trial-based MAUI reported

63

Other supplementary analyses

- ◆ Appendix 8 (**extended**)
 - nonhealth outcomes
 - » *production changes*
 - » *carer impacts*
 - provision of other resources

64

Summary: major c/e changes

- ◆ Clarify noninferiority pre-c/ma
- ◆ ‘Translation’ issues, premodelling studies and stepped economic evaluations
- ◆ Guidance on ‘translation’
 - ‘application’, ‘extrapolation’, ‘transformation’
 - ‘transforming’ surrogate to final outcomes
- ◆ Base case and supplementary analyses
- ◆ Guidance on valuing health outcomes

65

Some remaining controversies

- ◆ Whether cost-utility analysis is invariably useful
- ◆ Whether monetary valuation and cost-benefit analysis should remain supplementary
- ◆ The complementary roles of “stepped” economic evaluations and PSA in assessing uncertainty
- ◆ Does EVFI have a role in designing subsequent data collection to resolve decision-maker uncertainty?

66

Harmonisation?

- ◆ Common clinical evidence base
 - agree hierarchy to maximise confidence
- ◆ Common translation needs
 - develop common methods
- ◆ Accommodate variations in
 - eligible population and circumstances of use
 - comparator
 - affordability
- ◆ Recognise sovereignty of decisions