Interview with Lloyd Sansom, Emeritus Professor, Australia

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Tags: Lloyd Sansom

Would you please introduce the PBAC and the role it plays in Australia’s pharmaceutical sector?

The Pharmaceutical Benefits Advisory Committee (PBAC) is a statutory committee of the Australian government which was first established in the 1940s, and which makes recommendations to the Minister of Health and Ageing regarding medicines which should be considered for funding on the Pharmaceutical Benefit Scheme (PBS) This is an advisory role, and it’s important to differentiate between a statutory committee and a statutory authority. There are only two statutory authorities in Australia: the Reserve Bank and the Civil Aviation Authority, whose decisions bind government. The PBAC, on the other hand, advises the Minister. The Minister cannot list a drug on the PBS unless a positive recommendation is received from the PBAC, It is true that the vast majority of drugs recommended by the committee are in fact listed on the PBS, but it’s not a surety. If the PBAC recommends a medicine for listing but with a Government cost exceeding A$10 million per year, the Minister must take the matter to the cabinet for approval The government will determine whether or not, depending on budget and expenditure priorities, whether a positive recommendation from PBAC will or will not be accepted and the timing of any such funding. In 1991, the National Health Act (under which the PBAC operates) was changed to require the PBAC to take cost-effectiveness into account in its deliberations. Cost-effectiveness has been in Australia for 17 or 18 years, and forms the basis of the PBAC’s decision context. The guidelines for companies to prepare submissions to PBAC have just been updated and are extremely comprehensive. There is a

clear acceptance in the country that cost-effectiveness is the appropriate way to value medicines expenditure. It is my strong personal belief that the cost effectiveness paradigm for subsidy consideration will become common in both developed and developing countries throughout in the world. Increasing demand, coupled with increasing cost, will direct and demand that governments and third party payers, will look at value for money – they have to. Simply examining the percentage of GDP spent on health in the USA, at almost 17%, which compares to an Australian expenditure of approximately 9.8%, (and most European countries which vary from 8.5% to 10-11%),.and comparing health outcomes and health access equity between countries strongly suggests that it is not necessarily how much you spend but the effectiveness of that expenditure. Looking at the paradigms under which healthcare success is evaluated, that is, equity of access, affordability, and outcomes, the US is not the top of the league, even in spending double as any other country as a percentage of GDP. This issue will become more critical with ageing populations and increasing demand for health(and medicine) services. Recent data suggests that a female child born today in the UK has a 1 in 2 chance of living to 100. Looking at the intergenerational report published in Australia two years ago investigating the impact of ageing demographics and new technologies between now and 2042, it shows a projected increase of pharmaceutical expenditure at some seven fold as a percentage of GDP, from 0.5% to 3.5%. Looking simply at the ageing population and demographics, demand for healthcare services will increase in every country, and observing the social milieu, changing dependency ratio,(i.e. percentage of people working and paying taxes to those not working), one cannot separate health issues from the social domains in which it operates.

There is no question that health will become a major issue if it isn’t already, as the population ages, and that demands for assessment of value for money of a health intervention versus alternatives will continue to be more important – i.e. what additional benefit does a given treatment offer compared to the present situation? You mention cost-effectiveness, and the Australian system being exported elsewhere to become the global paradigm. In making such evaluations, how do you value one treatment against another?

Without a cost-effectiveness analysis it is difficult to bring the value concept back to a common metric. One of the advantages of cost-effectiveness is not only determining whether an intervention represents value for money, but in providing a system where equity of evaluation becomes the norm.

How do you compare someone who has a migraine with someone who has terminal cancer?

You bring it back to a common metric and a common outcome from which you can allow relativity. Another way which is sometimes suggested by commentators is apportioning expenditure on the basis of disease burden.

This approach does not provide an equitable framework What is that common outcome?

Wherever possible the PBAC uses the cost per Quality Adjusted Life Year (QALY.) You can't always get to a QALY measure, and in some cases it's not appropriate, and the evaluation must utilise other analyses, depending on context. Some people argue against the use of cost effectiveness analysis. At a recent meeting in Malaysia it was described by one industry representative as , "the enemy of our profit.". Australia has universality of access to health services. In the US, it has been reported that approximately 50 million people have no access to insured healthcare, and this number is 10 million in Canada. If the social fabric is underpinned with an equity of access, then there must be a transparent equity framework, This is in partnership with the population taking greater responsibility for their health, and recognizing the critical importance of preventative measures for issues like obesity, hypercholesterolaemia, hypertension, participation in screening programs appropriate use of vaccines, etc. Preventative health programs must become a much more overt focus of future healthcare models.

What is it about Australia that allows for the easier adoption of this mentality, resulting in better access, equity, and treatment outcomes for half the percentage of GDP spent in the US?

Maybe because in regard to prescription medicines the Australian Government through the PBS is a monopsony.If a drug is not listed on the PBS, the market is generally much less, and is certainly not guaranteed. It's a similar situation to the UK with the NHS: you either do business with us, or you don't do business at all. But having said that, what we've certainly tried to do over the last eight years in Australia, is make the process more transparent and accountable, entering into a dialogue with stakeholders For example, the HPV vaccine was initially rejected by the PBAC, and there was considerable public debate about that decision The reason for rejection included that the PBAC was concerned at the different efficacy of the vaccines in various age groups due to prior sexual activity history and the subsequent impact on the cost effectiveness in the primary cohort(12year olds) and the older catch up cohorts,(12-18 and 19-26 years)concern regarding the duration of the effectiveness, and the impact on outcomes if women did not continue utilising the cervical cancer screening program due to incomplete oncogenic subtype coverage by the vaccines Subsequent to the initial decision ,dialogue with the sponsor addressed each of this issues in a frank manner which included certain undertakings of future activity and commercial matters which enable the PBAC to recommended the listing of the vaccine In terms of why Australia has been successful in

its approach, the country has tried to be transparent as to what sponsors need to do and what are the dataset limitations, and in doing so give sponsors a sense of shared responsibility. One of the issues in Australia is that the subsidy of pharmaceuticals is considered to be part of the National Medicines Policy NMP), of which there are four arms. These 4 arms relate to the following.Safety and Quality (registration).Equity of Access (PBS).Quality use of Medicines (QUM).importance of having a responsible and viable pharmaceutical industryQUM is an interesting concept. The term rational use is often used elsewhere but this implies that if something's not rational then it's irrational and someone/something is to blame. If you want to change behaviour in effective medicines use, it is best to avoid apportioning blame. There's a continuum across these four arms- of a viable industry bringing new therapeutic agents to market, which are then evaluated for safety and efficacy, then whether they contribute affordably, which is equity, and then it's about how we use the medicines properly to achieve best outcomes, i.e. QUM.Australia has the National Prescribing Service(NPS), which is resourced by but independent from the Federal Government and is the effector arm of QUM. When a new drug is listed for subsidy the NPS will produce publications and resource material regarding the appropriate clinical use of the new agent Medicines are seen to be an integral part of the health care system though the NMP The National Medicines Policy talks about stakeholders including patients, patient advocates, medical practitioners, pharmacists, nurses, government, and industry. .

Why has it been successful?

60 years of history, a single purchaser, and I'd like to think that the culture of shared responsibility and ownership by all the stakeholders has also contributed to its successThe basic concept is that the PBAC evaluation takes into account relative clinical benefit and relative costs. I.e. what additional benefit does this new medicine provide against its comparator and what is the cost difference. This simply means that the PBAC examines the cost of any improved health outcomes.What I have realized in my many meetings with companies in the last eight years and particularly the last 12 months, is that companies around the world are living in the past. If we learn nothing from history we are foolish. But If we stay in the past, we cannot be a part of the future. The only thing you can change is the future. It's a simple philosophy. In the past the registration of the medicine by the regulatory agency (e.g. FDA) was seen to be the only barrier to success. While acceptance by independent agencies of the product's quality and safety is a critical step registration is the start of a process. The old paradigm was acceptable when the drugs cost $10-$100/year, but when the costs rise to $50,000-$70,000 per patient per year, it is no longer appropriate.Many of the new agents will only have a market if a third-party payer is prepared to contribute (Government and/or private), and as soon as that's the case, the paradigm of the

evaluation process shifts from registration requirements to requirements for subsidy evaluation.

Talking about some of those more expensive diseases, what is the philosophy behind creating access to drugs at the margins?

Life-saving drugs are unique. There's a group of drugs like the statins, which are highly cost-effective, and at $300-500 per year are very significant drugs and used by a significant proportion of the population The QUM problem with statins is not necessarily the drugs themselves, but rather one of persistence with the medication. This fact may make statins less cost-effective, not because of the drug itself, but because the way in which they're used. It's a compliance, concordance, and adherence issue that's similar with the anti-hypertensives. In both of these examples the cost per patient is relatively low but major QUM issues impede the clinical benefit. In the middle now are drugs that don't treat orphan diseases, or are not lifesaving drugs – but are "so-called" targeted drugs for $30,000-$70,000 per patient per year. This is becoming more common in the oncology arena The issue here is the high cost(which can be increased by screening costs) and often small survival gains(often 3-8 weeks) for a large number of patients, particularly in the more common cancer types. The total cost is high and the cost effectiveness ratios are much higher than generally acceptable Other examples of biologics in diseases such as rheumatoid arthritis demonstrate significant improvements in quality of life over many years without any survival advantage . And then there's the other end of the spectrum, covered under the lifesaving drugs program in Australia, is a number of extremely expensive drugs (A$400K-800K/patient/year for extremely rare diseases where the number of people affected in the entire country amounts to 20 or 30, and these drugs are considered orphan or ultra orphan.

Therefore, is their cost likely to be greater?

The answer is yes, because of the cost of development and the small market size. But studies into these "lifesaving "drugs have often used surrogate outcomes with high uncertainty regarding patient-relevant outcomes. There's an intuitive logic that if you replace an enzyme, it will do certain things, to restore good health. The insulin model is often quoted as a reference point however the relevance to these inborn errors of metabolism is uncertain.

But the question is whether these children should be treated in a special way?

The answer has till now generally been that special arrangements should be used. But in Australia this is not part of the PBS, and is funded through specific budget allocations. The PBAC has to make a positive recommendation to the minister that they are clinically effective but not cost-effective due to the price requested. The PBAC just reviewed one drug for such a disease which as adults will

cost $800,000 per patient per year, and there is no hope that drug will ever be cost-effective in the current paradigm. Recently, I met with representatives of 10 large international companies, many of which are organised with a fragmentation of R&D, trial design, health economics activities. What the PBAC has been saying for some time is that cost-effectiveness and access to market issues start at drug development, not after registration. In the last 12 months I have met many US based senior executives of industry and we have discussed this issue, and I am pleased that there seems to some acknowledgement that issues around subsidy need to be considered upfront, and not at the end of the development process The questions asked in registration are quite different than those for cost-effectiveness. In registration, there is a risk-benefit analysis. The registration process asks for the evidence that allows for the assessment of risk and benefit i.e. about quality and efficacy. That's not the question the PBAC asks. The PBAC accepts the registration, but asks the questions relating to comparative efficacy and toxicity and cost differences (both in terms of direct and indirect costs.) The registration process is invariably non-comparative, while cost-effectiveness, by definition, is comparative. Incremental benefit versus incremental cost In essence, the PBAC examines and evaluates incremental costs and benefits over the comparator.

What companies have to do is start thinking about the nature of possible comparators and how that data may be assesses-direct head to head ,indirect comparisons or ?

. Generally in this country, very few submissions have head to head trials against comparators, instead preferring indirect comparisons against a common comparator, with all the uncertainties involved, including issues around surrogate outcomes and whether they are patient relevant or not, Companies will often approach the PBAC knowing that their data is insufficient or incomplete to address the question of comparative effectiveness and cost, but say, "It's all we've got."

Why should the Australian taxpayer take all the risk around uncertainty?

Uncertainty, can occur in a number of ways. Commonly, it's because of clinical uncertainty, including projected benefits based on surrogate endpoints using convoluted economic analyses.

The question is, how can uncertainty be managed?

And that's the question every instrumentality like PBAC has been trying to deal with. Methods which may be used at the moment is to a) restrict the listing, b) reduce the price. One recent concept proposed to address uncertainty has been coverage with evidence development(CED)concept, This concept was initially proposed in the USA and was recently examined by a paper published by Hutton et al that was published as a result of an HTAi Policy forum conference. In essence it is the initial funding while further data to address the uncertainty is

collected . It’s an interesting concept and has been used in this country two or three times. Australia has some particular issues around it including what is the initial subsidy price. Issues for patients, sponsors and payers are summarised in the paperSome companies are espousing the concept of CED as the answer to uncertainty, with the concept of “Pay us now, we’ll get some more data later,».

But the question is what data? Will the new “data collected be any less uncertain?

Some sponsors have proposed observational data sets, which invariably cause more uncertainty because they are almost always subject to selection bias. The whole question about post-marketing surveillance is an interesting one, and not one that PBAC has shied from, but it’s not just an issue for subsidy agencies, but also for registration. . What the subsidy agencies will need to do is ensure the data collected for registration flows on into the evaluation for subsidy area. What PBAC has also done is identify the areas with the most uncertainty at the moment, and those are indirect comparisons and surrogate outcomes. The PBAC has raised these issues, in international for a. The PBAC has established two working groups examining the issues of indirect comparisons and surrogates, and who will report to PBAC by December 2008, and it is our intention to make those papers public in order to inform the international debate, since the industry is global, and these issues are on interest to all in this arena. There can never be international harmonisation of decisions for subsidy. Decisions, mechanisms, and criteria should and must reside with national/regional governments/private providers. But in terms of what data sets are needed to assess cost-effectiveness, we should be able to have international guidelines. If one agency wants a certain set of data or criteria, it should be able to left that requirement , and convince others internationally, that the specific requirement is a core piece of information needed to make a decision. There is a need for international agencies to have a dialogue, which will often be seen by industry to be conspiratorial, but it’s not – it’s frank, open, and transparent. These are issues for all of us. . And we’ve got to be able to move forward with it. For example on the two working groups there are members of the PBAC , members from its economic sub-committee, external experts and members of industry,.

There is an ICH for registration purposes, and the question is, can we extrapolate ICH into a subsidy scenario?

The HTAi has recently reported on the outcome from a policy forum debate on this issue which will further inform the international debate international covenant.

The question is, can we do the same thing in subsidy?

It’s more. These issues will take some time for the debate to mature but only Superman goes from the ground floor to the top floor in a single bound; all us mortals go up gradually. There needs to be a clear understanding that this is not about usurping in any way an authority’s independence to make decisions on health care expenditure. That would be impractical, inappropriate, and just plain stupid.

The PBAC is willing to continue to be involved in this debate.Other than meeting with industry and being transparent, what other attributes would you point to as lying behind Australia’s global recognition on a health policy front?

Commitment to the equity and sustainability of the system and the recognition that medicines integral part of the health system. The National Medicines Policy states clearly that it’s not a matter of supply of medicines, but rather achieving health outcomes through I get the feedback from companies that they believe the PBAC can respond to relevant issues and is prepared to enter into dialogue with all stakeholders to address issues. We’re just about to form a new working group around compliance, adherence, and concordance, which flows from the recent PBS Reforms and combination product guidelines. PBAC and sponsors do not always agree but the first principle for progress is an open dialogue in which neither party feels threatened.

Talking on the patient side of things, and the general patient profiles and attitudes that influence the ultimate effectiveness of PBAC’s policy recommendations, what role can the PBAC have in influencing the behaviours and attitudes that affect the end outcomes for consumers?

I don’t think that’s the specific role of the PBAC. The NPS in Australia is the effector arm of QUM, and the PBAC and NPS work closely together, if the PBAC considers a drug with which it believes there are likely QUM issues, the sponsors are encouraged to include QUM initiatives as part of the submission process of new medicines. However, generally industry has a poor understanding of what QUM is. QUM is an ethos. It’s those things you should think about if you’re going to use a drug, whether you should use it, and how. It’s a thought algorithm. Industry wants to define many subparts of QUM, that are all in fact QUM activities. It’s important to note the difference between the two terms. The industry in Australia is active in promoting QUM issues and I have seen a significant change in attitude particularly with some individual sponsors Just as companies should think about subsidy as a part of drug development process, so too should they think about QUM at that early stage And how they may be addressed as part of both pre and post marketing activities.To give another example, there was a recent issue with packaging. The drug in question was an effective agent, but the packaging was small containers that the elderly – the drug’s target market – could not easily open. It was silly. But all the drug’s stability data had been gathered in

that container.

Who in the development group thought about patient utilization?

This was a drug for chronic disease, so compliance is going to be an issue.

The next question is obviously to ask: what can we do around packaging with respect to compliance?

QUM is a culture an ethosA lot of this has to do with partnership, accountability, and transparency. One can't ask for more transparency without accepting accountability. You can't have one without the other, and the same thing goes for industry, The work doesn't end at registration, and that's the message companies have to realize, that the future of drug subsidy is going to be quite different than an issue around registration.

What would say as a final message to Pharmaceutical Executive readers about the Australian ethos and the PBAC?

I would say the ethos is that we are all stakeholders. Subsidy is to enable health outcomes at a cost that an individual and community as a whole can afford.Industry has to be viable. The question is about how "viable" is viable,. The scientific efficiency is greater and the risk of drug discovery is, in my opinion decreasing, since most of the unique drug target discoveries are coming out of publicly-funded institutions. On the other hand the cost of drug development has soared while at the same time little clinical data is collected with the issue of data requirements for subsidy in mind .This need to be addressed and the efficiency of this aspect of the industry's activities need to be. The industry in this country has done a good job.

The dialogue between industry and ourselves is mature, vigorous, and positive PBAC doesn't sit there and think, to whom can we deny access today?

" I'm sure some people think that, but it's not our job to deny access, it's to advise the Minister with respect to what pharmaceuticals represent value for money and should be publicly funded. And in doing that, the PBAC takes into account not only the science but societal expectations. The PBAC looks forward to working with all stakeholders including the pharmaceutical industry to ensure that Australians continue to be provided with an access to pharmaceuticals which promotes positive outcomes but at the same time ensuring that the system's equity is sustained into the future by using cost effectiveness as the process for evaluation.

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