Australian Government

Department of Health

LIFE SAVING DRUGS PROGRAMME POST MARKET REVIEW

ISSUES PAPER

APRIL 2015

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Introduction

This paper discusses the issues identified by the Life Saving Drugs Programme (LSDP) Reference group in its review of the LSDP. The issues and a number of options are proposed for discussion.

The Department of Health invites interested parties to make written submissions on the issues raised in this paper by 30 April 2015.

This Issues paper should be read in conjunction with the

(i) community, industry and clinician submissions on the LSDP Post Market Review terms of reference; and

(ii) LSDP Review: Technical Assessment Report to terms of reference 1-3, 5 and 7 by the Evaluation Group (the Evaluator's report).

Both documents can be accessed at http://www.pbs.gov.au/info/reviews/life-saving-drugs.

The Department of Health notes the Therapeutic Goods Administration's Orphan Drugs Programme discussion paper released in January 2015.

Written submissions should be sent to PBSpostmarket @health.gov.au.

For accessibility reasons, please submit responses by email in Word, RTF or PDF format. Please note that, unless requested otherwise, written comments submitted to the Department of Health may be made publicly available on our website and may be disclosed to other Commonwealth agencies, including, but not limited to, the Department of Industry.

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Submissions should be received no later than 30 April 2015

Background to the Post Market Review

On 9 April 2014 the Minister for Health announced the Government would review the Life Saving Drugs Programme (LSDP).

The review is examining the current Programme to ensure that Australians with very rare conditions continue to have subsidised access to much-needed, expensive medicines. The Review will look at important issues such as access and equity, value for money and the future administration of the programme.

Patients on the Programme should be reassured that significant changes will not be made to eligibility for the LSDP during the course of the Review. New patients with rare diseases that are eligible for existing drugs can continue to apply for access to treatment and applications for new medicines seeking LSDP listing will continue to be considered.

The public were invited to comment on the terms of reference from 11 August 2014 to 10 November 2014. Submissions received can be found on the PBS website at http://www.pbs.gov.au/info/reviews/life-saving-drugs

The terms of reference (ToR) are

- Review the clinical effectiveness and safety of medicines currently subsidised through the LSDP.
- Review the emerging clinical treatments and diseases, including those that identify sub-groups by molecular target, which could potentially seek subsidisation through the LSDP in the future.
- Conduct an international comparison of subsidisation of drugs for rare diseases and the definitions for a rare/ultra-rare disease.
- Compare the subsidisation and equity principles of the PBS and the LSDP.
- Assess the value for money of the medicines subsidised on the LSDP by evaluating the benefit of each drug's treatment outcomes, including in terms of quality of life achieved through the programme and their cost.
- Review the administration of the LSDP including the Guidelines with which the programme is administered for each condition and assess alternative administrative systems.
- Establish a framework for data collection on rare diseases in Australia and assess how this could function internationally.

An expert reference group was established to provide advice and steer the Review. This issues paper has been prepared by the reference group to seek public comment into the issues identified, to ensure the final report represents views of a wide range of people and these views inform the discussions about future options.

The reference group has additional technical information on each term of reference provided through:

- A health technology assessment report by the University of Adelaide Health Technology Assessment group (terms of reference 1-3, 5 and 7), (the Evaluator's report);
- A research report into consumer perspectives undertaken by the Consumer Health Forum of Australia(terms of reference 4 and 7); and
- A report on the current administration of the Programme provided by the Department of Health.

Parties interested in providing comments to this Issues paper should provide their submissions no later than 30 April 2015.

Further information about post market reviews can be found at http://www.pbs.gov.au/info/browse/reviews

Overview of the LSDP

The LSDP provides subsidised access for eligible patients to expensive and lifesaving drugs for serious and rare medical conditions, under Section 32B (s32B) of the *Financial Framework (Supplementary Powers) Act 1997* (FF(SP) Act) and Schedule 1AA (Part 4) of *the Financial Framework (Supplementary Powers) Regulations 1997* (FF(SP) Regulations), Item number 415.009 (Targeted Assistance – Pharmaceuticals).

Under item number 415.009 the Minister for Health or her delegate, the Secretary of the Department of Health, must seek funding approval of a new medicine before including the new medicine in the LSDP.

The LSDP currently subsidises ten medicines for eligible patients with one of seven rare and life threatening diseases.

In 2013-14, the Programme treated 257 patients at a cost of approximately $77.3 million. Currently 268 patients are being treated on the Programme. On average costs over $300,000 annually to treat a patient through the programme.

Process to list LSDP drugs

Submissions for a drug to be considered for inclusion in the LSDP must be lodged in conjunction with submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) for Pharmaceutical Benefits Schedule (PBS) listing. Submissions are received three times a year; March, July and November by the Department of Health. If the PBAC accepts that the drug is clinically effective for the proposed indication but considers the drug not cost effective and therefore rejects it for listing on the PBS, the Sponsor may then request the application be considered for inclusion in the LSDP.

To be included in the LSDP, the drug must satisfy all of the LSDP criteria for the funding of a drug and the patient conditions for initial and ongoing eligibility (LSDP criteria and conditions).

An important component of the LSDP criteria is the requirement for the submission of evidence to support a conclusion that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug. In addition the Chief Medical Officer (CMO) advises the Minister for Health on drugs proposed to be included on the LSDP.

Information on LSDP criteria and conditions is available at http://www.health.gov.au/internet/main/publishing.nsf/Content/lsdp-criteria

2014 administrative changes

Prior to 1 May 2014, five Disease Advisory Committees (DACs) were responsible for assessing patient applications and making clinical recommendations to the Department of Health delegate regarding initial and continued eligibility for individuals to receive Government subsidised treatment through the LSDP..

The five DACs were the Gaucher Disease Advisory Committee, Mucopolysaccharidosis Disease Advisory Committee, Fabry Disease Advisory Committee , Infantile-onset Pompe Disease Advisory Committee , Paroxysmal Nocturnal Haemoglobinuria Disease Advisory Committee.

Each committee comprised a Chair and four or five clinical experts in the relevant disease area. Some experts were members of multiple committees. Some members of the DACs were also clinically managing and caring for patients receiving treatment under the LSDP. A few members declared advisory positions in drug companies.

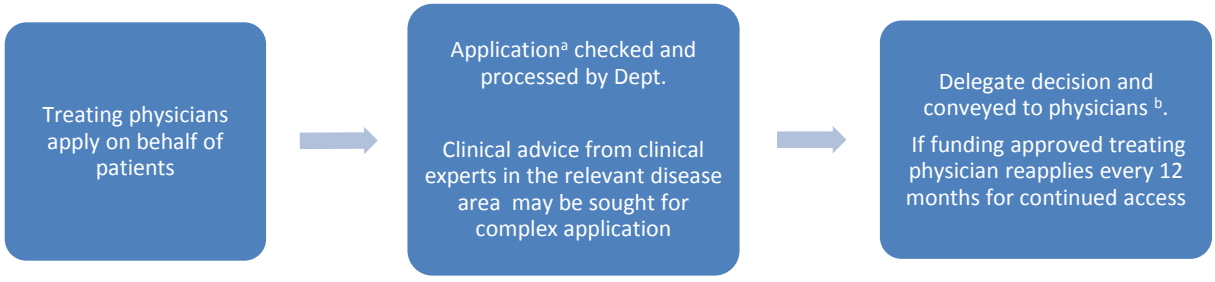
In March 2014 as part of the Government's deregulation agenda, the Minister for Health approved streamlining of the LSDP administrative processes at the same time the post-market review of the LSDP was announced.

Streamlining reduced the administrative burden on all DAC members and allowed members to freely advocate on behalf of their patients, and to share their expertise with colleagues directly rather than through the DAC. Discontinuing the DACs removed the real or perceived risk of conflicts of interest posed through committee membership. The new arrangements enabled advice from medical specialists with clinical expertise in the relevant disease area to be retained on an as needed basis and allowed applications for subsidies to be assessed directly rather than through a committee process.

Information on the ceasing of the DACs was posted on the LSDP website on Friday 21 March 2014.

Process to supply LSDP drugs

Patient Application Process



[a] Application eligibility as per Guidelines

[b] If the application is complete, notification of decision is provided within 30 days.

Ordering and Supply of Drugs

[c] Includes information to the pharmacy, tracking documents and ensures the pharmacy is aware of its responsibility for stock once they take delivery

[d] Processing of invoices can take up to 5 working days to prepare. Drug orders can take up to 5 business days to prepare taking into consideration the drug dispensing audit. Prior to paying the invoices, expenditure documents and tracking documents are updated. The Department coordinates temporary and permanent relocation of drug, on a per patient basis, following doctor approval.

Orphan Drugs and Rare Disease

Australia's orphan drugs programme is administered by the Therapeutic Goods Administration. The programme was established to encourage drug manufacturers to develop and market medicines affecting small populations. Regulation 45(12) of the *Therapeutic Goods Regulation 1990* (the Regulation) provides a waiver of fees for applications seeking orphan drug designation. Orphan drug designation also results in a waiver of fees for drug applications submitted to the PBAC for consideration of PBS funding. Orphan drug designation by the TGA does not mean that the drug will be automatically considered for inclusion in the LSDP.

Regulation 16 H defines an orphan drug as

(1) a medicine, vaccine or *in vivo* diagnostic agent is an orphan drug if it complies with this regulation.

(2) It: (a) must be intended to treat, prevent or diagnose a rare disease; or

(b) must not be commercially viable to supply to treat, prevent or diagnose another disease or condition.

(3) It is not an orphan drug if any of the following persons or bodies has refused to approve it for use for the disease for a reason related to the medicine's safety:

(a) the Secretary;

(b) the Food and Drug Administration of the United States of America;

(c) the Medicines Control Agency of the United Kingdom;

(d) the Bureau of Pharmaceutical Assessment of Canada;

(e) the Medical Products Agency of Sweden;

(f) the Medicines Evaluation Board of the Netherlands;

(g) the European Agency for the Evaluation of Medicinal Products.

(4) It is not an orphan drug if it has been registered for use for the disease or condition before 1 January 1998.

(5) However, it may be registered before 1 January 1998 for another use or indication.

Current definition of rare disease in the Therapeutic Goods Regulation 1990

'Rare disease' is defined in Regulation 2 as "a disease, or condition, likely to affect not more than 2,000 individuals in Australia at any time. Regulation 16H 2(a) specifies that the drug must be intended to 'treat, prevent or diagnose a rare disease".

Regulation 16 I(4) requires applications for vaccines or *in vivo* diagnostic agents requesting designation as an orphan drug, to state that "the vaccine or agent will be

administered in Australia to not more than 2,000 people in each year after it is registered for use for the disease or condition."

Definition of rare disease in other countries

There is no consistent definition of rare disease in comparable countries. In Australia rare disease is defined as a disease affecting less than 2,000 Australians or a prevalence of less than about 1 in 10,000. Table 1 provides examples of the definitions.

Table 1- Definition of rare and/or ultra-rare diseases in certain countries

Organisation / Region	Definition of rare diseases
Australia: Therapeutic Goods Administration (Australian Government 1990)	Affects ≤2,000 Australians, *i.e.* prevalence of about < 1 in 10,000
Ontario, Canada (Ontario Public Drug Programs) (Canadian Agency for Drugs and Technologies in Health 2013)	Incidence rate of < 1:150,000 live births or new diagnoses per year
Alberta, Canada: Alberta Human Services (Alberta Health and Wellness 2008; Canadian Agency for Drugs and Technologies in Health 2013)	Genetic lysosomal storage disorders occurring < 1 in 50,000 Canadians
European Medicines Agency (Canadian Agency for Drugs and Technologies in Health 2013)	Prevalence of < 5 in 10,000
Sweden: Swedish National Health Service (Visschers, van Gemert & Olde Damink 2011)	Prevalence of < 1 in 10,000
United Kingdom: National Institute for Clinical Excellence (Picavet, Cassiman & Simoens 2013)	Affects < 1000 people in England and Wales, *i.e.* prevalence of < 1 in 50,000[a]
United States: Food and Drug Administration (Visschers, van Gemert & Olde Damink 2011)	Affects < 200,000 Americans, *i.e.* prevalence of < 1 in 1,500
Japan: Ministry of Health, Labour and Welfare (MHLW) (Gao, Song & Tang 2013)	Affects <50,000 people in Japan, *i.e.* prevalence of < 4 in 10,000
South Korea: Ministry of Food and Drug Safety (MFDS), formerly known as the Korean Food and Drug Administration *(KFDA) (Gao, Song & Tang 2013)	Affects <20,000 people in Korea, *i.e.* prevalence of < 4 in 10,000
China (Ma et al. 2011; Song et al. 2012)	Rare diseases not been clearly defined by legislation. Consensus on the definition of rare disease: prevalent of < 1 in 500,000 or neonatal incidence of < 1 in 10,000

(Source: Table 137, Life Saving Drugs Programme Review : Technical Assessment, April 2015, page 231)

Reference Group interim report

ToR 1. Review the clinical effectiveness and safety of medicines currently subsidised through the LSDP.

1.1. The reference group considered the report of the Evaluation Group to have comprehensively assessed the available published research on the currently listed medicines.

1.2. For each disease and medicine class the Reference Group considered whether there was more recent evidence from that considered at the time of inclusion in the LSDP to be found in the Evaluator's report that showed:

- the medications were effective or ineffective,
- the clinical benefits were less than what was claimed when the drug was originally evaluated for inclusion on the LSDP,
- the risks or side effects were greater than what was claimed when the drug was originally evaluated,
- there was therapeutic equivalence where there is more than one medication in the same class, and,
- there was additional evidence on whether individuals were or were not responding to treatment.

1.3. Overall, for all the medications included on the LSDP, long term efficacy data other than on biochemical or other markers, has not increased substantially since the listing of the drugs. Equally, there is no new data from which to conclude that the original recommendation to include the medication on the LSDP was wrong i.e. that the medicines are conclusively ineffective.

1.4. None of the LSDP drugs have been shown to cure the disease. The evaluation showed that in each of the seven diseases studied all the drugs slowed progression of the disease in some patients but did not reverse progression. Clinical experience with the medications has identified patients where there is a continued deterioration in the patient's condition despite the continued administration of the relevant medication. Under this circumstance it would appear that continuation of drug therapy where there is no substantial patient benefit is not good use of public monies. Treating physicians should be supported in decisions to cease treatment in such cases, for example, by reference to clear expert endorsed stopping rules. Patients and their carers

should be supported through explicit communication of expected outcomes based on the evidence.

1.5. Due to the rarity of these conditions the health outcomes that define success or failure of treatment are poorly defined at the time initial subsidy was established. These definitions have not been made clearer through more experience gathered from treating more patients in real clinical practice. The lack of clearly defined health outcomes has implications for considering Managed Entry* types of arrangements to support the future funding of any such medicines. Quantifiable entry and continuation criteria must be established upfront for transparent and clear decision-making.

1.6. For several of the rare disease conditions more than one medication of the same class is now available. There is limited but increasing data on the relative effectiveness of the different medications and rationale for differing dosage regimens. These are based on biomarkers i.e. surrogate indicators only. If the available evidence does not show any relative effectiveness differences, then there are limited reasons as to why a less expensive medication within the same class should not be the treatment of choice and therefore preferred for any subsidy.

1.7. The Reference Group considered that there needs to be explicit and pre-agreed criteria for continued funding of drugs. These criteria specify the types of additional new information that the sponsor will provide and the time frame for this to justify continued funding at the time of inclusion on any subsidy programme. This additional information could provide confirmatory evidence of the original benefits or provide supplementary evidence that the surrogate or biochemical markers used in original approval, convert to real health outcome improvements or maintenance of health. Where sponsors fail to provide the agreed information, there should be an automatic and substantial decrease in the price (e.g. of the order of a 50% reduction in the first instance and cessation of subsidy if evidence is not subsequently provided within 12 months).

*Managed entry schemes are mechanisms whereby the reimbursement authority may recommend a drug at a price justified by the existing evidence, pending submission of more conclusive evidence of cost-effectiveness to support listing of the drug at a higher price.

1.8. For **Type 1 Gaucher Disease**, there was weak additional evidence of benefit (based on biomarker data only). Available data identified by the Evaluation Group in a systematic literature review indicates that miglustat is not as effective as imiglucerase and velaglucerase. Miglustat is associated with increased bone disease and adverse side effects (Trial OGT 918-004, Elstein, D et al 2007, Evaluator's report, p60). No Australian patients were listed currently as receiving this medication. Imiglucerase, velaglucerase, and (yet to be subsidised) taliglucerase appear to have similar effectiveness.

1.9. For **Type 1 Gaucher Disease**, continued neurological deterioration in the patient is an indication that therapy is highly unlikely to have long term benefits.

1.10. For **Fabry Disease**, no additional substantive evidence beyond that considered in the original evaluation was found for efficiency in the existing subsidised drugs. The available evidence indicates that agalsidase alfa and agalsidase beta are similar in effectiveness (Vedder et al 2007, see Evaluator's report, p23 and p94).

1.11. For **Infantile Onset Pompe Disease**, there is weak additional evidence of benefit (Kishnani et al, 2009; Nicolino et al 2009, Chien et al 2009, Evaluator's report, p114-115). There is clear evidence of the need for documentation of Cross Reacting Material Status (CRIM status) as this is a predictor of indication for therapy, response to therapy and usually of the patient. There is evidence for the need for dose escalation and rduced efficacy over time.

1.12. For the **Mucopolysaccharidoses** (MPS I, II and IV), there was no significant additional evidence of efficacy for existing subsidised drugs' effectiveness or ineffectiveness (Evaluator's report,, p150-151). There is only one available medication for each disease type. For MPS II clinical experience indicates that neurological deterioration is likely to be a marker of non-response to medication (Evaluator's report, p152, p174). Although there may be early but non-sustained response of airway obstruction and organomegaly to therapy.

1.13. For **Paroxysmal Nocturnal Haemoglobinuria** (PNH), there is additional weak evidence of effectiveness (Kelly et al 2007). There is only one drug, eculizumab, that is available and this is subsidised through the LSDP. Clinical experience suggests that people with PNH have varying levels of response to

eculizumab and that all patients may not need to be on continuous therapy. The Reference Group considered there should be a formal assessment of the potential for patients on eculizumab for PNH to trial periods without the medication. Unlike the other drugs on the LSDP eculizumab is not exclusively used for PNH but is subsidised on the PBS for atypical haemolytic uraemic syndrome. As a consequence, the Reference Group considered it should be reconsidered for listing on the PBS, and potentially subsequently removed from the LSDP.

Issue 1:

The LSDP provides access to drugs but this is usually before there is clear evidence that the drug is effective in the medium and long term. Consequently, the manufacturer may be being paid for a drug that is subsequently shown to be ineffective or less effective than originally claimed. Theoretically the drug could be more effective than originally claimed.

- Should the Government expect some further evidence to support a continued benefit for patients through mechanisms like managed entry schemes and pay for performance mechanisms when the relative effectiveness of a drug is not clear?

- Should the Government expect that sponsor companies share the uncertainty of the benefit through risk share arrangements or similar mechanisms?

- What criteria should Government use in determining what is a reasonable cost to pay for such drugs?

Issue 2:

The Reference Group concluded that none of the drugs subsidised through the LSDP have been shown to cure the disease for which they are subsidised. With all of the drugs progression of the disease may be slowed, though not reversed. Experience with the medications has identified patients where there is a continued deterioration in the patient's condition despite the continued administration of the relevant medication.

The review of evidence and published literature shows that some patients continue to deteriorate despite receiving continued relevant medication.

- Is it reasonable to continue therapy when the patient's disease progressively deteriorates as assessed by clinical parameters and clinical assessments?

- Who should decide to continue therapy if the disease and/or the disease symptoms are not stable or improving (i.e. the disease is progressing)?

- Under what circumstances would a patient or clinician consider that the person has a benefit even when their disease is progressing?

Issue 3:

Clinicians and patients currently agree to certain conditions including discontinuation of the LSDP subsidy if the patient ceases to benefit from administration of the drug, prior to the approval of the funding.

- Should such decisions be binding on all decision makers i.e. the prescriber, the consumer and the Government? If not, why not?

ToR 2. Review emerging clinical treatments and diseases, including those that identify sub-groups by molecular target, which could potentially seek subsidisation through the LSDP in the future.

2.1. There are in the order of 6,000-7,000 single gene disorders, although not all are likely to be responsive to enzyme or similar replacement therapy, and many are very rare. However, through advancement in research and technology, there is likely to be an increase in the diversity of treatments available to treat diseases of largely genetic origin or with a genetic component such as those currently funded under the LSDP. This will include new medications for currently listed diseases and medicines for other rare genetic diseases, such as stem cell therapies, and other approaches to gene modification and modifying the cellular or gene replication machinery (e.g. Stop codon over-ride in Duchenne Muscular Dystrophy).

2.2. The types of medicines currently funded through the LSDP are qualitatively different but overlap with medicines that are targeted at specific genetic variations in common diseases, such as specific

mutations in some breast cancers. These developments in pharmacogenomic research, referred to as genetically stratified or 'personalised medicine', can lead to situations where a relatively small group within the total population with a relatively common disease may be identified as being uniquely responsive to a particular medication. In general, however, these patients may also have recourse to other effective medications and therapies for the broader population with the disease unlike those with the diseases currently included in the LSDP. It is evident that there will be a large growth in tests and medications that enabled stratification of patients within a larger disease or condition. This development may require future modification to the guidelines for submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) and is not considered further in this report.

2.3. It is likely that treatments similar in nature to those currently listed on the LSDP will be available for a range of genetic diseases as rare as those currently listed but also for much more common genetic conditions such as Cystic Fibrosis and Duchenne Muscular Dystrophy.

2.4. The current name of the programme 'Life Saving Drugs Programme' appears to be poorly descriptive. Many drugs subsidised on the PBS have evidence that they improve patients' survival and their quality of life, and could be considered to be 'life saving'. Based on the available evidence of comparative effectiveness, the extent to which some LSDP listed drugs are life saving is still questionable.

2.5. From an ethical perspective there is little basis for distinguishing rare genetic diseases from other rare conditions. Indeed, doing so may distort the overall reimbursement process, as companies may price drugs so that they are not cost-effective and therefore referred to a special high subsidy programme like the LSDP.

2.6. The rationale for determining drug subsidy varies between many countries with similar economies. The rarity of conditions is one factor (see 3.1 below). In some cases, such as the USA, the medicines special access programme was developed primarily to draw attention to diseases that conventional pharmaceutical development programmes would ignore because of the perceived lack of profitability;

so called ‘orphan’ diseases. In other countries the medicines access programme was a way of putting boundaries around high cost medications that would not meet standard comparative effectiveness or cost-effectiveness criteria of existing funding programmes.

2.7. There is confusion in policies between the concept of orphan drugs and drugs for rare diseases. The concept of orphan drugs referred to medicines for diseases where there was little business interest in developing or continuing production of medicines because they were unlikely to be commercially attractive. Size of the potential market, that is the number of potential patients, was one factor in defining ‘orphan’.

2.8. The Reference Group noted that some countries would confer orphan drug status on drugs with more than one indication and is of the view that a drug can only be classified as an orphan drug once: that is the drug associated with treatment of more than one disease or condition should not qualify as orphan for a subsidy programme. This may be different to the view of regulatory agents who have different perspectives (see 2.11).

2.9. As noted at item 3.1, there is no one definition of rare disease. From an economic perspective, it is theoretically possible to conceptualise a disease frequency based on the cost recovery plus profit margin: that is, how many patients treated for how long at a standard price of drug would it require to cover cost to the company for drug development and manufacturing.

2.10. The Reference Group noted that in January 2015, the Therapeutic Goods Administration (TGA) published a discussion paper on the Orphan Drugs Programme which considers limiting indications and disease subsets as an option.

2.11. It is important to note that the criteria used by the TGA in approving a medicine for market are different to those used by the PBAC in recommending the drug for subsidy. In essence, the TGA is required to determine whether the quality, safety and efficacy of the medicines for the purposes for which they are to be used have been satisfactorily established, whereas the PBAC needs to take into account the comparative size of the effect and the cost-effectiveness of the drug.

Issue 4:

Many drugs subsidised on the Pharmaceutical Benefit Scheme (PBS) could be considered to be life-saving. In contrast the extent to which some of the LSDP listed drugs are life-saving is questionable. Many new therapies are emerging on the market. These new drugs may treat the rarer subgroups of more common disease.

Some of the new treatments emerging for genetically inherited diseases such as those currently treated on the LSDP will not be drugs in the conventional sense. Some may be tailored to the specific genetic sub-types of each individual for a more common disease.

- Should the LSDP be extended to treatments that are specific to one or two individuals and/or to small subsets of individuals with a unique rare mutation which responds to a specific therapy (i.e. truly individualised therapy)?

- If so are the criteria of value and effectiveness currently used by the PBAC still relevant? If not what should be the criteria for each of the groups referred to in the question above?

- Should there be a distinction between the types of diseases with treatments on the LSDP for rarer sub-types of more common diseases and rare disease?

ToR 3. Conduct an international comparison of subsidisation of drugs for rare diseases and the definitions for a rare/ultra-rare disease.

3.1. Criteria for medicine special access programmes vary between countries and while most include rarity as one criterion, this criterion threshold ranges from 1 in 1500 (USA) to 1 in 500,000 (China). As noted above different rationales (discussed in the Evaluator's report, Chapter 6) underlie these different thresholds.

3.2. Even in Australia, there are different definitions of orphan drugs and rare diseases. Regulation 2 of the T*herapeutic Goods Regulations 1990* defines rare disease as a disease, or condition, likely to affect not more than 2,000 individuals in Australia at any time, representing an incidence at the time of about 1 in 10,000. This is much more frequent than any of the diseases currently treated through the LSDP.

3.3. The Reference Group considered that a reasonable definition of rarity would be a frequency in the general Australian population of 1 in 100,000. This is within the range currently used in national and international subsidy schemes.

3.4. The subsidy models used in other countries also vary in approach. Most include one or more of the following attributes:

- approaches designed to fast track new medications,
- managed entry schemes where continued funding depends on further evidence of effectiveness (and or cost-effectiveness),
- performance based risk sharing agreements,
- financial-based risk sharing arrangements,
- higher cost thresholds,
- explicit statement of lower levels of evidence of effectiveness, and,
- limited time period listings.

3.5. The Reference Group noted that Belgium, the Netherlands and Germany reportedly required no pharmacoeconomic evaluation, although this does not preclude risk-sharing arrangements (Denis et al. 2011; Garau & Mestre-Ferrandiz 2009; Vegter et al. 2010). The Netherlands allows dispensation from submitting cost effectiveness evidence when limited data is available but requires the manufacturer to submit a budget impact analysis. Hospital administered expensive drugs may be listed with the condition of collecting further evidence and having a re -appraisal by Dutch Health Care Reimbursement Board (College voor zorgverzekeringen - CVZ) within three years.

3.6. Garau et al (2009) reviewed a number of schemes to evaluate orphan drugs for reimbursement purposes. This review found there is no evidence that one scheme produces substantially different access outcomes than others. Predictably if the scheme has no requirement for pharmacoeconomic evaluations or has lower evidence requirements, then more drugs will be subsidised. Information about the price of these medicines available through international schemes cannot be verified from published information. Anecdotally the prices are reported to be lower than those published.

*Multi-criteria decision analysis aims to support decision makers faced with evaluating alternatives, and takes into account multiple, and often conflictive, criteria. Criteria may include the effectiveness and safety of the drug, the economic impact, and other considerations, such as severity of the disease, the equity / ethical and social implications of the drug, current health policy goals etc.

3.7. In the Evaluation Group report and in many of the comments received from consumer and industry groups, there is considerable discussion of the National Institute for Health and Care Excellence (NICE) approach using Multi-criteria Decision Analysis* and the formal adoption of broader societal perspectives in the decision framework. The Reference Group could see merit in the principles of the approach although it noted the practicalities of this prescriptive approach in decision making. While there were good arguments for moving away from a focus on the life extending benefits, the Reference Group is concerned that there are significant challenges in measuring broader benefits in a systematic and reproducible way.

3.8. Other than eculizumab for PNH, all other drugs subsidised on the LSDP are disease specific. The Reference Group considered that such exclusivity should be a criterion for consideration if the LSDP continues as a programme.

Issue 5:

There are a number of definitions for rare diseases. This ranges from 1 in 1500 to 1 in 500,000. Regulation 2 of the Therapeutic Goods Regulations (1990) defines rare disease as a disease, or condition, likely to affect not more than 2,000 individuals in Australia at any time, representing an incidence at the time of 1 in 10,000.

The definition of rare disease varies between countries and agencies. There are also other factors that may be relevant such as the impact of the disease and the availability of existing treatments.

- Should there be an explicit definition of what constitutes a rare disease for purposes of public funding and, if so, what should that be?

- What other criteria other than effectiveness should be taken into account in deciding the merits of public subsidy for a new drug under this category?

- What mechanism should be used to measure those criteria in a valid and reproducible way that could be applied generally to other drugs seeking subsidy for rare diseases?

ToR 4. Compare the subsidisation and equity principles of the Pharmaceutical Benefits Scheme and the LSDP.

4.1. The PBAC is required by legislation (*National Health Act, NHA (1953)* to consider the comparative effectiveness and cost of any new medication in making recommendations for listing on the PBS.

4.2. The PBAC assesses 'value-for-money' of proposed medicines using incremental cost-effectiveness ratios expressed as cost per QALY (quality adjusted life year).

4.3. The *NHA (1953)* and the guidelines for submissions to the PBAC do not specify a fixed cost-effectiveness threshold.

4.4. In addition to comparative effectiveness and cost, the PBAC also take into account other factors such as the availability of other effective therapies, severity of the medical condition, equity, unmet need and special need situations such as children and indigenous population

4.5. The PBAC also considers recommending medications under the 'rule of rescue'; that is agents of last resort. The 'rule of rescue' criteria are as follows:

- No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no non-pharmacological or pharmacological interventions for these patients;
- The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in the consideration by PBAC;
- The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the consideration by PBAC. However, PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances; and
- The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the consideration

by PBAC.

4.6. Many of the criteria for 'rule of rescue' are met by drugs subsidised through the LSDP where there are no other therapeutic options. However in applying this rule the PBAC will still examine the cost-effectiveness and financial impacts. The Reference Group considered that it is a reasonable option for government to consider having only one set of criteria covering both the LSDP and the 'rule of rescue'.

4.7. The PBAC may also make recommendations about special arrangements for the introduction of new medications where there is uncertainty about the likely use of the medication. The PBAC may require specific monitoring and reporting arrangements on the use of the medications. While not specifically the decision of the PBAC, risk sharing arrangements (such as capping the total costs of a specific medicine at a level based on the estimated use in the PBAC application) are also in place in Australia.

4.8. The Reference Group considered that the Highly Specialised Drugs (HSD) programme (a PBS section 100 programme) offers another model worth considering for any future subsidisation of drugs currently considered for the LSDP. The s100 HSD programme is for medicines for the treatment of chronic conditions which, because of their clinical use or other special features, are restricted to supply through public and private hospitals with access to appropriate specialist facilities. To prescribe these drugs as pharmaceutical benefit items, medical practitioners are required to be affiliated with these specialist hospital units. Benefits are available for the listed clinical indications only. There is no facility for individual patient approval for indications outside those listed. The nature of conditions on the LSDP and their treatment requirements means that most would mirror current PBS s100 HSD arrangements.

Issue 6:

The PBAC is required by law to consider the cost-effectiveness of any new medication. The PBAC also take into account other factors such as the affordability if not subsidised, availability of other effective therapies, severity of the medical condition, equity, unmet need and special need situations such as children and

indigenous population. Rule of rescue is applied when the drug is presented as an agent of last resort. 'Rule of rescue' has four main considerations; (i) no alternative treatment is available in Australia, (ii) the condition is severe, progressive and expected to lead to premature death, (iii) there are a small number of patients who would be treated, and (iv) a worthwhile clinical improvement is achieved.

For further information on the Rule of Rescue refer to http://www.pbac.pbs.gov.au/section-f/f3-other-relevant-factors.html

There currently exist a number of separate programmes that fund high cost and specific therapy drugs including the LSDP, and drugs approved by the PBAC under the Rule of Rescue and Section 100 Highly Specialised Drugs.

- Should the LSDP be continued as a separate programme? If so, why?

- Should there be one overarching subsidisation programme that applies to all high cost and/or specialised drugs (including those on the LSDP and those available through the PBS section 100 Highly Specialised Drugs)?

- What criteria would be applied to such a programme that would distinguish them from other drugs subsidised on the PBS, for relatively common conditions?

- Should a programme that subsidises high cost and/or specialised drugs have one set of decision rules that apply to all drugs meeting those criteria?

- Should there be one set of criteria to cover both high cost and/or specialised drugs?

ToR 5. Assess the value for money of the medicines subsidised on the LSDP by evaluating the benefit of each drug's treatment outcomes, including in terms of quality of life achieved through the programme, and their cost.

5.1. As summarized under TOR 1, there is inadequate evidence to address the value for money of medicines subsidised under the LSDP. Evidence of effectiveness for each medication is limited and is still based largely on changes in surrogate outcomes (biomarkers associated with disease outcomes), rather than measured health benefits (actual health outcomes).

5.2. Information on the relative costs of the listed drugs to the Australian Government compared to other countries is very limited. The review has identified a number of reports or ongoing inquiries from other countries

including Canada, Scotland and Wales that suggest similar concerns about managing the growing cost of medicine to treat these diseases and the poorly defined health benefits.

5.3. There are four areas where specific clinical research could assist in managing future costs and add information about health benefits, namely the evidence of dosing by body weight, evidence about the frequency of administration of treatment, the therapeutic equivalence where more than one medicine in the same class is available, and, clarification of when patients are not responding to treatment.

Issue 7:

There is inadequate evidence to address the value for money of medicines subsidised under the LSDP.

Clinicians could be encouraged to fill this gap by conducting research and providing evidence of dosing by body weight, where there is more than one medical agent in the same medicinal class, provide information of therapeutic equivalence, frequency of administration of treatment and provide information and clarification of when patients are not responding to treatment.

- What incentives are required to encourage clinicians and/or companies to undertake this type of research?

- To what extent should, continuance of public money for the purposes of subsidy, be linked to companies and/or clinicians undertaking such research?

ToR 6. Review the administration of the LSDP, including the Guidelines with which the programme is administered for each condition, and assess alternative administration systems.

6.1. The current administrative arrangements for access to the medicines approved on the LSDP across the country still relies heavily on the direct involvement of Canberra-based Commonwealth public servants who otherwise have no involvement in patient care. This does not seem consistent with good clinical care management and, given that the majority of these patients are seen in public sector services, is inconsistent with the division of responsibilities between the Commonwealth and the States and Territories for health service delivery.

6.2. As indicated in the summary of the public submissions there is support for the

re-establishment of the Disease Advisory Committees. These committees were convened on a national basis, and, while disease specific, membership substantially overlapped. Given the potential for a growing number of diseases and treatments seeking public funding, the Reference Group did not consider this approach would be sustainable.

6.3. The Reference Group believes there was merit in the establishment of a small number of centres of clinical expertise in rare diseases, incorporating state-based clinical advisory committees, with the larger states networking with smaller states or territories. Such an approach could also form the basis for more effective disease registries, where different centres might take responsibility for one or more different diseases.

6.4. Patient groups and sponsors supported establishing designated centres of treatment/expertise. Reduced travel times, parking costs, potential choice of doctor and more effective data collection were among the cited benefits of the centres.

6.5. The Reference Group noted the potential for involvement of designated pharmacies as a point of distribution and the convenience that this may offer patients. However, further clarification would be required on the implications of this on capacity to deliver medicines efficiently.

Issue 8:

The access and administration of drugs subsidised under the LSDP is managed by the Commonwealth Government but point of patient care is usually in public hospitals in the states and territories.

Access to drugs for patients should be efficient and support good health care.

- Would establishing a small number of State based Centres of for Rare Disease Expertise be more effective in delivering the best overall care? What are the benefits for patients, their carers' and clinical services?

- Would patients and their carers be disadvantaged by this arrangement? How could this be overcome?

- Is there a better way to improve clinical management of these patients, other than these state based centres?

Issue 9:

The PBS is a well-established framework that delivers appropriate drug subsidies to Australians. It has been in operation for over 60 years and has evolved from supplying drugs in the British Pharmacopeia to pensioners in 1948 to subsidising over 5100 drugs in 2014.

Under PBS the Commonwealth subsidises many high cost drugs which can only be supplied from hospitals to outpatients. These arrangements are known as Highly Specialised Drugs Programme or Section 100 drugs, after the relevant part of the National Health Act 1953. Section 100 allows alternative arrangements to be established where these are considered more appropriate. Other current Section 100 programmes include Efficient Funding of Chemotherapy and the Growth Hormone Programme.

One proposal under consideration is that instead of having a separate programme for rare diseases, a special Section 100 arrangement could be establish that takes into account the rarity of the patients' condition. A set of criteria would need to be established for each rare disease and the administration of the programme will be modelled on existing programmes like the Growth Hormone programme.

- What are the advantages of establishing a Section 100 special arrangement for rare conditions as oppose to having a separate LSDP? What are the disadvantages?

- Are there other approaches to access and drug delivery than via a special PBS programme that should be considered?

ToR 7. Establish a framework for data collection on rare diseases in Australia and assess how this could function internationally.

7.1. As indicated under several of the ToR, there is a need for better data on clinical management and clinical outcomes of people treated under the LSDP. There is likely to be longer-term public benefits in a more systematic collection of data.

7.2. However, as well described in the Evaluation Group report (Chapter 8), there are a number of challenges to doing this effectively as well as the cost.

7.3. The Reference Group considered that while the increased interest of different companies in the field of establishing registries and collecting data is laudable, disease registries based within individual companies will not produce the types of comprehensive data required to assess the long term value for money of these medicines.

Issue 10:

There is universal acknowledgement of the need for systematic collection of data and better data management in order to inform questions such as efficiency and ongoing benefit of subsidisation to patients and the Government. Many companies host their own patient registries. Additionally there are initiatives at the international level for rare disease data collection but these do not produce suitable information required to evaluate the drugs for the purposes of subsidy.

Establishing or adapting a data registry and maintaining the registry is expensive and consideration should be given to improving the data collected and ensuring that the data collected is 'fit for purpose'.

- Should the cost of maintaining a data registry be distributed across all the stakeholders (Government, drug companies and patients)? How might this be done?

- Drug companies' often maintain their rare disease registries in order to provide regulatory agencies with additional clinical data, generally on safety (pharmaco-vigilance), and sometimes effectiveness of the drug in the 'real world' setting. This data is not always adequate or 'fit for purpose' to answer questions raised about longer term patient benefits. Should the company's marketing these drugs be responsible for collection and maintenance of data that is 'fit for purpose'?

- If not the company who markets the drug, then what other effective and cost-efficient approaches are there for establishing and maintaining data registries?

8. General Issues

8.1. There remains a need for a funding mechanism for medications for rare conditions that are unlikely to meet the usual cost-effectiveness criteria applied within the Pharmaceutical Benefits Scheme due to the higher than average asking prices of these drugs.

8.2. Criteria for access to this funding mechanism need to remain tight and should include the rarity of the condition. However, genetically defined sub-sets of larger disease groups or conditions who overall are not rare are currently excluded from this funding source.

8.3. Providing the criteria are specified there appears to be no major practical reason as to why such a funding mechanism needs to be separate to the usual assessment processes of the PBAC. A parallel can be drawn with the process for decisions on the subsidisation of vaccines on the National Immunisation Schedule or listing on the PBS section 100 programmes.

8.4. While there is merit in the Multi-Criteria decision analysis, the Reference Group considered that the adoption of such an approach should not be exclusively for medicines such as those listed on the LSDP as this would create further inequities in the way medicines for different conditions are considered.

8.5. Given the costs of the medications, the inevitable increase in the numbers on these medications and the lack of clarity about many aspects of the clinical management, there is a substantial public interest in a more comprehensive, coordinated and ongoing collection of data on clinical outcomes, and targeted research on dosing regimens and therapeutic equivalence.

8.6. Pricing which includes a review price based on demonstration of effectiveness and reimbursement where effectiveness is not demonstrated should be considered.

8.7. The reference group sees the value of broader community consultation, for example establishing a UK NICE-style community panel to consider the broader issues of criteria that could be considered in decision-making, such as access, equity and affordability for all Australians with rare conditions. The committee recognised that implementation of a community panel could be complex and resource intensive. The likelihood of extending the time taken to consider eligibility of the drug for subsidy must also be considered.

Possible options for consideration

Option 1: LSDP continues in its current form	
Action	·No action required
Risks	·Administrative burden remains with the Commonwealth ·Sustainability of system, in coping with increased demand to list new medicines identified as part of the horizon scanning ·Cost could be unsustainable
Benefits	·Process and other pathways familiar to clinicians, patients and drug sponsors ·Access remains unchanged for current diseases and current patients
Option 2: LSDP ceases and becomes a S100 programme for rare diseases	
Action	·Drug may be listed through managed entry scheme with data collected through a registry ·An annual report generated and provided to the PBAC ·Opportunities to engage in risk sharing arrangements prior to listing and for maintaining subsidy ·Potential for online and fully automated applications and approvals through DHS in the future ·As an option PBS restriction could specify treatment at or in collaboration with/without accredited Centres of Expertise ·Entity to approve accredited centres or prescribers will need to be determined ·Option to incorporate current PBS rule of rescue and current LSDP criteria into one set of new decision rules ·Requires legislative and administrative change.
Risks	·If to be fully automated, would require objective set of guidelines and criteria ·Require IT systems to be built or modified by Department of Human Services ·If the operation of the PBS restriction require the establishment of Centres of Expertise the issues are: ·Time and resources required to establish Centres of Expertise ·Requires states and territories agreement and to determine Centres of disease Expertise ·Requires states and territories to take responsibility in providing services in area of disease expertise to regional areas or some smaller states and territories ·Approved prescriber and accredited centres would need to be identified ·Would require changes to legislation · If current PBS rule of rescue and LSDP criteria is combined the following issues arise: ·May be seen to disadvantage future LSDP recipients ·Decision making could be seen as more administratively complex ·Costs and resources required to make changes to the current system
Benefits	· Well established and long functioning mechanism ·S100 special arrangement programmes are already in operation and are familiar to stakeholders ·General oversight by the PBAC retained ·Specialised centres already exist eg. Fabry disease ·If more than one Centre of Expertise established in the larger cities,

	reduces travel time and costs ·Better clinical management for patients Improved data collection and building of expertise ·Allows standardization of assessments/testings in each state/territory ·States and territories have more ownership and able to ascertain and address need at point of care more quickly ·A fully automated system allows streamlining of process and will reduce/remove ongoing administrative burden ·Potential to improve cost-sharing arrangements ·If current rule of rescue and LSDP criteria is combined; the common rules and decision making process for high cost pharmaceutical would increase transparency and improve clarity to stakeholders.
Option 3: LSDP ceases and is subsumed into state public health system	
Action	·Transfer of funding to the States ·Decentralized administration ·Reduction in administrative cost to the Commonwealth ·Potential for better clinical management of patients ·States and territories able to tailor subsidy according to needs ·Requires AHMAC discussion in light of the Federation White Paper
Risks	·Agreement from states and territories required ·Clear criteria or agreement for balanced distribution of subsidies across the states/territories and across all diseases ·Upfront costs and resources to establish system ·Regulation changes required
Benefits	·PBAC retains responsibility to assess clinical and cost effectiveness, providing confidence in the health technology assessments and reduced regulation changes ·If the Commonwealth retains responsibility for setting price subsidy, states and territories undertake further purchasing actions to achieve lower prices ·States and territories have more ownership and able to ascertain and address need at point of care more quickly ·Administrative cost savings to Commonwealth
Option 4: Other Cap on total programme cost	
Action	·Government would allocate in advance a budget based on the present appropriation process applied to the LSDP ·Existing and new patients would be managed within that budget ·Clear criteria for allocation required.
Risks	·May be seen to disadvantage new drugs/patients ·Assumes there is capacity for significant efficiencies which could be difficult within a small programme ·Allocation of budget for each disease category may be difficult and if not clear may be perceived as not being transparent ·If the option is for an annual cap, this has potential to increase administrative burden for the Government and stakeholders as they prepare to bid for an allocation
Benefits	·Known cost to government ·Promotes more rigorous assessment ·Provide clarity to stakeholders if the criteria for allocation are clear and accepted by stakeholders

References

(Cited in the Life Saving Drugs Programme Review : Technical Assessment, April 2015)

Alberta Health and Wellness 2008, 'Alberta Rare Diseases Drug Program: Fact Sheet', p. 1, viewed 3 July 2014, <http://www.health.alberta.ca/documents/Pharma-Strategy-2008-rare-disease.pdf>.

Canadian Agency for Drugs and Technologies in Health 2013, 'Drugs for rare diseases: evolving trends in regulatory and health technology assessment perspectives', pp. 1-40, viewed 3 July 2014, <http://www.cadth.ca/products/environmental-scanning/environmental-scans/environmental-scan-42>.

Chien, YH, Lee, NC, Thurberg, BL, Chiang, SC, Zhang, XK, Keutzer, J, Huang, AC, Wu, MH, Huang, PH, Tsai, FJ, Chen, YT & Hwu, WL 2009, 'Pompe disease in infants: improving the prognosis by newborn screening and early treatment', *Pediatrics*, vol. 124, no. 6, Dec, pp. e1116-1125.

Elstein, D, Dweck, A, Attias, D, Hadas-Halpern, I, Zevin, S, Altarescu, G, Aerts, JF, van, W & Zimran, A 2007, 'Oral maintenance clinical trial with miglustat for type I Gaucher disease: switch from or combination with intravenous enzyme replacement', *Blood*, vol. 110, pp. 2296-2301.

Gao, JJ, Song, PP & Tang, W 2013, 'Rare disease patients in China anticipate the sunlight of legislation', *Drug Discov Ther*, vol. 7, no. 3, Jun, pp. 126-128.

Kishnani, PS, DiRocco, M, Kaplan, P, Mehta, A, Pastores, GM, Smith, SE, Puga, AC, Lemay, RM & Weinreb, NJ 2009, 'A randomized trial comparing the efficacy and safety of imiglucerase (Cerezyme) infusions every 4 weeks versus every 2 weeks in the maintenance therapy of adult patients with Gaucher disease type 1', Mol Genet Metab, vol. 96, pp. 164-170.

Ma, D, Li, D, Zhang, X & He, L 2011, 'Opportunities and challenges of rare diseases treatments in China', *Chin J Evid Based Pediatr*, vol. 6, no. 2, pp. 81-82.

Nicolino, M, Byrne, B, Wraith, JE, Leslie, N, Mandel, H, Freyer, DR, Arnold, GL, Pivnick, EK, Ottinger, CJ, Robinson, PH, Loo, JC, Smitka, M, Jardine, P, Tat•, L, Chabrol, B, McCandless, S, Kimura, S, Mehta, L, Bali, D, Skrinar, A, Morgan, C, Rangachari, L, Corzo, D & Kishnani, PS 2009, 'Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease', *Genet Med.*, vol. 11, no. 3, Mar, pp. 210-219. [Genetics in medicine : official journal of the American College of Medical Genetics].

Picavet, E, Cassiman, D & Simoens, S 2013, 'Do ultra-orphan medicinal products warrant ultra-high prices? A review', *Orphan Drugs: Research and Reviews*, vol. 3, pp. 23-31.

Song, P, Gao, J, Inagaki, Y, Kokudo, N & Tang, W 2012, 'Intractable and rare diseases research in Asia', *Biosci Trends*, vol. 6, no. 2, Apr, pp. 48-51.

Vedder, AC, Linthorst, GE, Houge, G, Groener, JEM, Ormel, EE, Bouma, BJ, Aerts, JMFG, Hirth, A & Hollak, CEM 2007, 'Treatment of fabry disease: Outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg', *PLoS ONE*, vol. 2, no. 7.

Visschers, RGJ, van Gemert, WG & Olde Damink, SWM 2011, 'Orphan diseases neglected: The faith of intestinal failure', *e-SPEN*, vol. 6, no. 5, pp. e232-e234.