5 April 2016

Pharmaceutical Benefits Advisory Committee Guidelines Review Committee
Department of Health
GPO Box 9848
Canberra ACT 2601

Dear PBAC Review Committee,

The review of the PBAC guidelines is timely and this examination is critical if Australia is to keep pace with world leaders in Health Technology Assessment (HTA). Accordingly, Sanofi welcomes the opportunity to provide a stakeholder submission at this stage of the review.

Sanofi, an integrated global healthcare leader, discovers, develops and distributes therapeutic solutions focused on patient and consumer needs. We are proud to be the most diversified healthcare company in Australia and New Zealand. Our business spans prescription pharmaceuticals, consumer and over-the-counter healthcare products, vaccines, medicines for rare diseases and animal health products. By working with patients and consumers we can find new ways of helping them feel better, live longer, keep healthy and stay stronger. As Australia's number 1 consumer healthcare business, we help people take a positive and proactive approach to their daily health and wellbeing. As the world's largest vaccine manufacturer, we have the broadest available range of vaccines to protect adults and children from infectious and childhood diseases. As one of Australia's largest pharmaceutical suppliers, we continue to develop innovative treatments for diseases such as diabetes, cancer and heart disease.

The draft guidelines include a number of areas of improvement which will assist in the development of submissions for PBAC consideration and ultimately support the decision-making process. There are however a number of key elements in the draft guidelines which are of significant concern. Sanofi believes these elements undermine the draft guidelines as a whole and if implemented as proposed, could have a negative impact on the availability of new medicines for patients. Additionally we believe the guidelines as proposed, would put Australia not in step with international HTA best practice.

Ultimately, the guidelines review is an opportunity for all stakeholders to work together in presenting a united vision for the future of HTA in Australia. Our expectation of the guidelines review is to bring forward changes to the current system with the sole purpose of improving the development of HTA submissions, and ultimately decision making, for the overall benefit of consumers, healthcare professionals, Government and industry in Australia. Unfortunately, the draft guidelines provide minimal guidance on recommended best practice and limited or nil information on critical areas for Australians, such as the evaluation of vaccines, rare disease therapies and biosimilars. This is inconsistent with the original term of reference for the review itself, as *"… the PBAC is seeking to develop a more concise, clear, focused and up-to-date methods Guidance..."*

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Further, the draft guidelines appear to have a disproportionate focus on cost, with the '*Key factors influencing decision making by the PBAC*' (p. 5) highlighting the number one factor as 'comparative cost-effectiveness' followed by 'comparative health gain'. In reality these factors are interlinked with the robustness and magnitude of the comparative health gain required before any consideration of cost-effectiveness. Further, this perceived theme of cost over clinical place could be most clearly misinterpreted in the discussion on the choice of main comparator. The main comparator is defined as *the therapy that prescribers would most likely replace with the proposed medicine in practice, should it be listed on the PBS* which is unchanged from current guidelines. However, the draft guidelines further state *where multiple alternative therapies could be used for the majority of patients, the PBAC cannot recommend a new medicine at a price that is substantially higher than the least expensive alternative medicine unless it is satisfied that the new medicine provides a significant improvement in efficacy and/or reduction in toxicity over that alternative medicine.* Such an approach could miss the opportunity to fully utilise HTA as a tool to bring better health outcomes to the Australian population particularly when the draft then appears to contradict this statement as: *In situations where the proposed medicine has more than one alternative therapy and there are distinct groups of patients in whom one alternative therapy, but not the other(s), is appropriate, and those alternative therapies have different prices, then the new medicine's price can reflect the proportions of the treated population in which the different alternative therapies are appropriate*.

In the last 10 years there has been a significant restructure of the PBS and the introduction of measures, such as price disclosure, which have been constructed to deliver savings from the commoditisation of the off-patent medicines market. However, the most recent savings package included a measure which also impacts on medicines which are still patent protected. In this context, the matter of comparator erosion with the potential to select the comparator on the basis of lowest cost, and in the environment where the price of a new medicine is benchmarked potentially to older medicines which have been subjected to multiple rounds of price disclosure is a significantly critical issue for consideration. The potential impact is the viability of bringing innovative medicines to Australia.

Ideally, the guidelines would include recommendations for reducing uncertainty via the most up to date modelling and statistical methodologies, similar to the approaches taken by HTA agencies around the world. Instead, the draft guidelines '*suggest'* sponsors provide a high volume of information on multiple, potentially unlimited scenarios, which will only serve to provide additional information without necessarily reducing uncertainty and therefore enhancing evidence for decision-making. For example, '*provide multiple listing scenarios* (p.30)', '*present individual pairwise comparisons when presenting a network meta-analysis* (p.70)', '*provide one/several cohort models when presenting individual-level models* (p.101)', '*present both epidemiological and market share approaches for predicted medicines use* (p.143)'. Not only does this substantially increase the complexity and resource requirements for sponsors presenting a submission, it increases the burden on evaluators without ever explicitly detailing what is acceptable or best practice.

The lack of clarity on a number of elements of the draft was best illustrated by the recent briefing session initiated by the Department of Health[1], which highlighted the variability in interpretation of certain elements of the guidelines even amongst the panel on the day. Indeed statements by the panel were at times contradictory to each other highlighting the subjective nature of some of the draft guidelines. Whilst guidelines are understandably not expressly prescriptive there needs to be a common understanding of the relative importance of each step and how this ultimately feeds into making the optimal decisions for the funding of medicines in Australia.

What follows are the key issues that, in our opinion, require immediate attention within the current draft guidelines and suggestions on how they can be addressed.

Choice of main comparator

There is insufficient clarity regarding main comparator selection in the revised guidelines. This lack of clarity is driven by a disproportionate emphasis on cost as a factor in the determination of the main comparator. The main comparator/s is ultimately determined by the place in clinical therapy and the therapy that will therefore be displaced. The clinical determination of the main comparator is a fundamental premise of HTA therefore inclusion of cost as a consideration for comparator selection undermines best practice.

Putting this aside, it is unclear with the revised wording how much weighting should be given to prescribing and how much to cost when selecting a comparator. The new guidelines state, "*Where multiple comparators with large disparities in cost are available, and these are equi-effective in the target population, sponsors should be prepared to provide both a comparison against the comparator with the greatest market share and a comparison against the most cost-effective comparator.*" (p. 18)

If a sponsor is required to present a comparator that is clearly cost-effective but has limited market share, generally as the particular therapy will not be replaced with the proposed therapy, this will result in an inaccurate reflection of the treatment practice should the new medicine be listed on the PBS. Further, where there are multiple comparators, *"the submission should present a comparison against each comparator, rather than a comparison against a weighted or mixed comparator."* (p. 18). There is no real guidance on when a comparator is relevant to include.

Further clarification around comparator selection was sought at the recent Department of Health briefing session. It was stated by the panel that where drugs have similar market share (i.e. drug X has 50% and drug Y has 45%), both should be included as comparators and greater weighting would be given to cost. However, where a drug has clear market share (i.e. drug X has 90%), then this should be the comparator regardless of cost. It is suggested that this guidance be included in the guidelines.

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[1] Presentation forum on the revised PBAC Guidelines and consultation process. Sydney, Australia. Tuesday 15 March 2016.

Ultimately, the choice of comparator should reflect the therapy that will most likely be replaced with the proposed therapy in terms of prescribing, regardless of cost. Cost should not be the criteria upon which the comparator is selected recognising that the cost of the true clinical comparator is a significant component of the final cost effectiveness assessment.

Appendices and additional information

There was an opportunity when revising the PBAC guidelines to include specific guidance on a number of therapeutic areas, such as vaccines, rare disease products and biosimilars, plus the inclusion of the consumer voice in the HTA process.

Vaccines, rare diseases and biosimilars

These specific areas are unique in terms of the value they offer society. Whilst many areas of the draft guidelines are common for vaccines it is unfortunate there are less than 10 pages of guidance for vaccines which due to the very nature of the intervention rely on complex clinical and economic modelling to sufficiently capture value to society. It is also important to note whilst these guidelines rightly focus on technical matters there are broader process improvements for vaccines, such as the ability to pursue parallel TGA and PBAC evaluation, which require consideration. Further, there is no guidance provided for rare disease therapies or biosimilars – arguably two of the critical areas requiring clear guidance to ensure Australian stakeholders are clear on the evidentiary requirements underpinning submissions for subsidy.

Vaccines are unique in terms of the value transfer to society, with health gains for the prevention of infectious diseases felt more broadly than simply to the individual vaccinated. Whilst the draft guidelines recognise the importance of dynamic models for vaccines: *Dynamic models allow herd immunity and age shift to be assessed, and should be considered when the force of infection is likely to change following immunisation (ie if the proposed vaccine blocks transmission of infection, and coverage is extensive), and when the risk or severity of the disease depends on age. (p.195)* there is a real limitation in the guidance offered. This lack of recognition of the guidance to capture the value of a vaccine remains with this guidelines review. This is further compounded with an essentially unchanged approach to discounting of costs and benefits. Agencies around the world, including the National Institute for Health and Clinical Excellence, recognise the need for discount rates not only specific to vaccines but specific to the different settings in which vaccines are used.

Rare disease therapies and the appropriate subsidy model are currently under review as part of the LSDP review. The next iteration of the draft guidelines must address the specific requirements for the valuation and evaluation of therapies for rare diseases. A response of 5 pages is not sufficient to provide feedback specific to rare disease therapies. However, Sanofi is working with other industry parties to provide specific feedback on this therapeutic area.

In addition, while there has been limited experience by the PBAC with the evaluation of biosimilars to date the need for guidance for sponsors of biosimilars and the associated originator biologic is clear. This would seem an opportune time to include such guidance in this substantive review of the PBAC guidelines.

Consumer voice in the HTA process

The consumer voice as part of the PBAC consideration process has become increasingly important. The opportunity to provide comment through the PBAC agenda process through to stakeholder meetings has brought the understanding from the consumer perspective to the forefront. The draft guidelines are a real opportunity to consider *"enhancing and formalising mechanisms for consumers and clinicians to play a more central and substantial role in the evaluation of new medicines and new indications for already listed medicines."*[2]

Appropriate attention to these specialised areas should be included in the final PBAC guidelines.

Modelling guidance and justification

The section of the draft guidelines to address economic modelling (Section 3) focusses heavily on the validation and justification of an economic model. Unfortunately this provides minimal guidance on the optimal approach to utilising the most appropriate methodology. While it is reasonable to expect sponsors to clearly articulate and justify the approach taken, the suggestions for validation within the draft guidelines are excessive without necessarily providing increased certainty. In current form, the draft guidelines request the sponsor present potentially unlimited amounts of information when an individual-level modelling technique is utilised to demonstrate cost-effectiveness.

This is illustrated for example in part C of Section 3.7 'Model Validation': *"External review: Has the computerised model been examined by modelling experts? (If yes, who are they? why are they expert? are they independent? what were the results of the review? If no, why not?)"* (p. 119)

Firstly, external validation is part of both the review process and the ESC evaluation process. Secondly, the process of identifying an additional and sufficiently qualified modelling expert could be challenging in terms of capacity and perceived conflict of interest not to mention the time and resource impacts. The proposal is not to remove the need for robust and validated models but to achieve this though a pragmatic approach which utilises best practice. Sponsors constantly strive to bring new therapies, and the resulting health outcomes, to patients as soon as possible. This extra burden of external validation could potentially delay access for Australian patients particularly if a suitable expert were not available.

Based on these concerns, it is recommended that the guidelines revise the section on validation. Similarly, explicit clarification of what is considered appropriate regarding methods of justification and how they have previously been implemented would be greatly beneficial to all stakeholders.

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[2] Senate Community Affairs References Committee's report on *"Availability of new, innovative and specialist cancer drugs in Australia. 2015.* http://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/Cancer_Drugs/Report

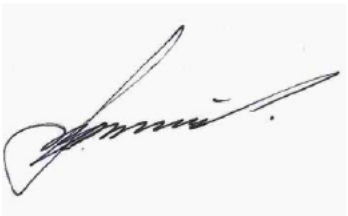
Conclusion

While this response has primarily focused on our concerns regarding the draft guidelines, Sanofi reiterates there are improvements proposed. Section 2 for example has been improved by the presentation of the literature search results aligning with recommended Cochrane best practice.

However, we firmly believe the guidelines should reflect best HTA practice to provide sponsors with the tools to present the most appropriate form of a submission or model that effectively presents the case for the proposed therapy. In its current form the draft guidelines do not facilitate this process as well as they could which is to the detriment of stakeholders, most importantly patients.

Whilst the draft guidelines are not necessarily the place to provide potential reference cases, or previously accepted best practice, for example with modelling assumptions, we note that there has been limited information on the next steps once all the feedback on the draft guidelines has been reviewed.

Yours sincerely,



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