1 July 2009

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Dear Rachel

Consultation on Revised Funding Application Guidelines

Thank you for the opportunity to comment on the proposed Revised Funding Application Guidelines.

The proposed Guidelines involve a substantial change from the existing edition, and the RMI's members have several major objections to the proposed changes. They are, in brief that the draft Guidelines:

- do not match PHARMAC's practices;
- do not mention information that PHARMAC has already agreed to publish;
- substantially weaken and bias the evidence base for assessing applications;
- request information that most sponsors will be unable to supply, such as patents and pipeline information, and that other Health Technology Assessment (HTA) agencies do not request;
- give PHARMAC the means to further delay listing of new medicines;
- permit unregistered uses of medicines to be listed on the Pharmaceutical Schedule;
- exempt generic medicine sponsors from providing crucial information – such as safety data;
- do not disclose cost-effectiveness criteria, even though the Guidelines make clear that this is a central issue in decision-making;
- make responding to the specific needs of Māori and Pacific people an optional extra;
- make unfair use of PBAC cost-utility analyses; and
- allow PHARMAC to generate significant commentary on submissions and seek external opinion, apparently without consulting or even informing sponsors.

The wording of the draft guidelines is also often ambiguous, and has the potential to create a great deal of unnecessary work for both sponsors and PHARMAC.

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We appreciate that some of the issues we have raised in this submission are complex. We would welcome the opportunity to discuss these with you in person. This, in particular, would allow each of us to explain to the other, the intentions behind our requests, as well as to identify where we may have misunderstood one another. We believe that a constructive dialogue is the best way to finalise these Guidelines, so they are fair and meet the needs of PHARMAC, industry and all New Zealanders.

1. The application process

1.1 Page 8 says "PHARMAC may, at its discretion, adopt a different process, or variations of the process." As a Government agency, PHARMAC is obliged to act consistently. If there are reasons for varying a published process, the criteria need to be spelt out – or, at the very least, a comprehensive list of past examples given, and the reasons for variations.

1.2 Furthermore, in many instances the diagram outlining the application process on page 8 does not match PHARMAC's actual process. There are also contradictions between the diagram and the text in the draft Guidelines. For example:

(a) The diagram suggests that PTAC receives a preliminary economic assessment, whereas sections 2.4 (ix) and 2.4.2 suggest (and would seem consistent with current practice) that cost-utility analyses (CUA) are generally not conducted until after PTAC has reviewed the application and assigned a priority. The RMI's view is that either (i) PTAC should not provide a final recommendation until it has seen the final price and CUA, or (ii) PTAC should not be allowed to base its recommendations on criterion (VIII) budgetary impact or (IX) cost-effectiveness.

(b) The diagram also suggests that applications are reviewed by PTAC and may be referred to a sub-committee. According to section 2.4, applications may first be considered by a sub-committee. The RMI considers that both these and PTAC's Guidelines should explain (i) the criteria used to decide the order in which applications are considered by PTAC and sub-committees, and (ii) whether the sub-committee will review the sponsor's full application or just a minute prepared by PHARMAC.

(c) The diagram inaccurately suggests that applications which receive a negative recommendation from PTAC will be presented to the PHARMAC Board. The reality is that this rarely, if ever, occurs. Most applications are stalled following the initial PTAC review, and no decision is made, either positive or negative. The current practice is a major change in PHARMAC's historical approach. PHARMAC's Annual Reports appear to show that, prior to 2004, PHARMAC reconciled the applications it received, processing most of those received in any one year to conclusion.

(d) While the diagram is accurate in reflecting PHARMAC's current practice of not consulting prior to declining applications, this would appear to inconsistent with Section 2.4.5 of the Guidelines which indicate that PHARMAC will

generally consult on matters that relate to the management of pharmaceutical expenditure.

1.3 The RMI considers that PHARMAC should be obliged to:

- complete its decision-making process for all applications; and
- consult before presenting any recommendation to the PHARMAC Board, including a recommendation to decline an application.

1.4 We consider that the recent High Court decision relating to Herceptin supports the case for an obligation on PHARMAC to consult before declining an application.

1.5 Our final point in relation to this section of the proposed Guidelines relates to section 2.2 – when the guidelines apply. While we are aware that the exclusion of non-oncology hospital treatments from this process was a conscious decision under the *National Hospital Strategy*, we suggest that it may be time to revisit this decision. Recent examples of cost-shifting between PHARMAC and DHB Hospitals indicate that greater equity of access could be achieved if all applications for pharmaceuticals, regardless of their point of use, were assessed using the same process. For example, some patients have had access via District Health Board (DHB) hospitals to Humira for indications not funded via the Pharmaceutical Schedule while an application for rituximab for an indication for which Humira is already funded has been stalled.

2. Application details published on the PHARMAC website

2.1 Section 2.4 outlines the information about submissions that PHARMAC proposes to place on its website. This list does not include the information that PHARMAC agreed in 2007 to provide to stakeholders, such as:

- the date PHARMAC received the application
- the date the product was listed on the Pharmaceutical Schedule
- the length of time between receipt and listing
- the status of the application at each point in the assessment process.

2.2 Furthermore, the most recent application listed was made in October 2008.

2.3 We ask that PHARMAC honor its previous commitments to the RMI and all other stakeholders, and provide this information on its website.

2.4 The RMI also requests that PHARMAC's process be altered so that all of PTAC's recommendations to PHARMAC are made public.

2.5 We also consider that PHARMAC should publish key performance indicators such as the time elapsed between the date of lodgment and the date PTAC makes recommendations to PHARMAC and/or date of listing on the Pharmaceutical Schedule.

2.6 Another type of information about applications the RMI feels that PHARMAC should publish is PTAC's prioritization of pharmaceuticals. Past listing decisions appear to suggest that there are differences between PTAC's and PHARMAC's priorities – although there is little published evidence that would allow sponsors, patients and clinicians to judge this. It is certainly the industry's experience, however, that PHARMAC frequently funds 'low' or 'moderate/medium' priority pharmaceuticals while other 'high' priority applications often remain unfunded. (Funding decisions by PHARMAC also show that the statement in Section 2.4.1 is untrue: "if a proposal … is given a high PTAC priority and … is relative cost-effective, it may be progressed sooner than an application that has been given a lower PTAC priority, or an application with a high PTAC priority that is not as cost effective.")

2.7 RMI requests that PHARMAC publish the PTAC and PHARMAC priority list, so that (a) it is clear where there are differences between the priorities assigned to applications by PTAC and PHARMAC, and (b) PTAC is as fully involved in priority setting as the draft Guidelines imply.

3. Effect on the evidence base

3.1 The Guidelines limit the types of data that sponsors may submit to "RCTs published as full articles in peer-reviewed journals in the English language that report … outcomes of intention-to-treat." This requirement excludes the large volume of high-quality research conducted and reported in, for example, Europe and francophone Canada, as well as the rapidly growing volume of material produced in Asia and South America. This is a substantial reduction of scope compared with HTA agencies internationally, and is quite inconsistent with HTA principles of systematic reviews, as detailed in the Cochrane Handbook.

3.2 Limiting evidence to just randomized controlled trials (RCTs) also significantly reduces the scope of evidence that HTA agencies normally consider, such as observational studies and post-marketing data.

3.3 Relying solely on published data may greatly delay the introduction of new medicines in New Zealand, as there is often a considerable delay between the completion of clinical trials and the publication of results in peer-reviewed journals.

3.4 Typically, published data only report top-line safety results – full safety information has to come from other sources. Relying on published data alone will significantly bias the assessment of safety.

3.5 In Section 5.8.2, the Draft Guidelines say that "if a trial remains unpublished and it is not registered on public trial register, then it is less likely that PHARMAC will consider the trial." The RMI supports the efforts of PHARMAC and other international HTA bodies to see clinical trials fully disclosed, and we feel that the criteria above in 5.8.2 is reasonable in the case of newer medicines. However, this requirement may create difficulties for sponsors comparing their products with older competitors or when making indirect comparisons. In such cases, HTA

agencies internationally (including PBAC and NICE) are prepared to accept unpublished studies, even though they too have a policy of preferring data from registered clinical trials. It is in no one's benefit to exclude this data – it may contain important safety and efficacy data, or caveats on use, or economic information.

3.6 We urge PHARMAC to use the same principles used by other HTA agencies internationally: sponsors should supply all relevant data they can identify, published or not. We feel that PHARMAC should be drawing on the same range of evidence as that considered by the PBAC in Australia and NICE in the United Kingdom, and that the draft Guidelines should be altered to reflect this.

4. Concerns about new information requirements

4.1 Unregistered uses

The Guidelines ask Sponsors to supply information about unregistered and unlisted uses in a number of places (Sections 2.2, 5.1 (viii), 5.2.vi, 5.2 (viii), and 5.3 (v)).

It is simply not possible or appropriate for sponsors to provided information on unlisted uses – sponsors are not permitted to promote off-label uses. In any case, most information about unregistered use is anecdotal – this is hardly a sound basis for managing the Pharmaceutical Schedule budget. Finally, sponsors do not control what uses doctors put medicines to, and therefore are not in a position to predict potential off-label uses in New Zealand.

It is a grave concern to the RMI that, although the Draft Guidelines say that "applications … should be for Medsafe-registered products and indications", PHARMAC last year declined to fund a registered use of Herceptin in favour of an unregistered one, and has proposed to list several companies' medicines for unregistered uses and for which there is no supporting clinical or safety evidence. Favouring unregistered uses over registered ones puts at risk the health of New Zealanders. PHARMAC was once prohibited from listing unregistered medicines, and RMI believe that this should be the rule once again – i.e. that PHARMAC should not be permitted to fund unregistered medicines unless the medicines has previously been registered in this country (i.e. is an orphan) and/or the costs of registering the product/indication would exceed the expected profit to be gained from sales of that product/indication in a specified period of time. Based on the Herceptin case, the RMI would also argue that PHARMAC should be prohibited from funding any unregistered use of a medicine that has registration for that same use or indication under another treatment regimen.

The RMI asks that all references to unregistered uses be deleted from the Guidelines.

4.2 Patents and pipelines

Section 5.6 asks sponsors to provide information about patents on products, and Section 5.1.x asks for information about all new formulations in the product pipeline. The RMI requests that these requirements be removed from the Guidelines.

It will usually not be possible for sponsors to supply this information on either patents or pipelines. Both are extremely sensitive information, and access to them is very tightly controlled – even within companies. New Zealand sponsors are rarely the patent-holders, and so they quite often will not have access to the information, in order to include it in their application. The PBAC in Australia does not request this data.

The draft guidelines do not make clear whether PHARMAC requires just company's own patent information, or all patents, including those of competitors. Obtaining information even on the sponsor's own drug is extremely difficult – obtaining information on all patents on plausible competitor's products would be virtually impossible.

Beyond the practicalities of supplying this information, RMI is – frankly – suspicious of PHARMAC's intentions in requesting this data. PHARMAC has a history of stalling applications until products lose their patent protection. It has both directly and indirectly opposed the granting of patents in New Zealand. The RMI believes that providing patent information in every funding application would give PHARMAC even greater opportunities to delay the listing of new pharmaceuticals on the Pharmaceutical Schedule.

We appreciate that PHARMAC has a legitimate goal in wanting to "assess… the budget impact associated with the Application." However, its past behaviour suggests that this is not the limit of how PHARMAC intends to use patent and formulation data. While there is no publicly available definitive list of products PHARMAC has listed on the Pharmaceutical Schedule, the RMI has compile information on some 63 listed since PHARMAC was established. The data show that the average length of time between the listing of a product on the Pharmaceutical Schedule and patent expiry has diminished steadily since 1994.

5. Generic products are not being treated thoroughly

5.1 The treatment of applications for generic medicines is unsafe. The information that the draft Guidelines require would be insufficient for a number of products, such as asthma devices where the performance characteristics of the device might , for example, change over time. The problems PHARMAC encountered with the introduction of Salamol (where despite "bio-equivalance" subtle differences in this regard gave rise to significant consumer concern) are an example of why more information is required than prescribed by these guidelines.

5.2 We ask that, at the very least, generic suppliers be required to provide the same information on safety as branded products.

5.3 Also, generic applications should not be processed before they have been registered.

6. Optional information required in mandatory decision-making

6.1 There is a considerable amount of information in Section 6 'Optional information' that is either mandatory elsewhere in the draft Guidelines, or else is normally required for HTA evaluation and decision-making in other agencies internationally.

6.2 For example, Table 4 (the PHARMAC decision criteria), asks the question "What is the disease's percent of population total DALY loss across all disease? Refer to Section 6 for further information." However, Section 6 consists of 'Optional Information'. We are particularly concerned that 'Health Need by Māori and Pacific Peoples' is also classified as merely 'Optional Information' (Section 6.6). Also misplaced are '6.3 Applicability of Evidence' and '6.4 Economic Analysis'.

6.3 We ask that PHARMAC clarify the draft Guidelines to clearly distinguish what information is actually essential for its decision-making process, from what is useful but not essential.

7. Cost effectiveness and cost effectiveness thresholds

7.1 We have concerns about the provisions of section 2.4.2. We object to the fact that suppliers do not routinely receive copies of PHARMAC's Cost Utility Analyses (CUA) nor have any input into them before they are presented to PTAC. We proposed more transparency around this subsequent to the PHARMAC workshop in Auckland in April 2009 and are disappointed that no change is proposed to this aspect of PHARMAC's procedures.

7.2 We also see large problems with this refusal to set and disclose cost-effectiveness thresholds. The end of Section 2.4.2 says:

> *… at PHARMAC, there is no threshold below which a proposed amendment the Pharmaceutical Schedule is considered 'cost effective'. The main reason for this is that cost effectiveness is only one decision criteria used by PHARMAC. One application may be more cost effective than another but rate poorly on other decision criteria and, therefore, may not be progressed… Another reason for not having a threshold value is that the spending on community pharmaceuticals is required to be kept within a fixed budget. Given the binding nature of this constraint … what is an is not considered 'cost effective' will vary with the amount of funding available (not just in terms of the total budget each year, but the available budget at any point in time). An application to fund a pharmaceutical can, therefore, only be considered 'cost effective' in comparison with other applications under consideration at any one particular time. (p14)*

7.3 First, this statement runs together two very different things: the cost effectiveness of a medicine (cost-to-treat) with the affordability of a medicine (how much money government has available to spend). Both are important and need to be kept separate. There is a large difference between saying "Product X would be cost-effective but Government cannot afford it at this point in the budget cycle – though it

may afford it next year" and saying "Product Y is not cost effective at any point in the budget cycle."

7.4 Second, saying "cost effectiveness is only one decision criteria used by PHARMAC" does not mean that there is no threshold, and that it cannot be published. The RMI accepts that cost effectiveness is only one factor for deciding whether to list. We also accept that this means that some medicines are more likely to be listed than others. While we accept that judgment will be required in some cases, the RMI is concerned that the statement on page 14 appears to imply that PHARMAC has no consistent or objective way of balancing different criteria.

7.5 To take an analogy: a government purchasing medicines is somewhat like a company purchasing a fleet of vehicles. For a company that must have a minimum number of cars, an important financing question is the on-going costs of fuel, parts and servicing – just as for government, the question is the on-going costs of providing medicines to a known patient group. For a company, there will be some options in vehicle models, and some one-off needs (for example, the CEO's car might be something special) – but it knows that there is a broad threshold of on-going costs per car that it cannot exceed, regardless of whatever the immediate status of the company's cash-flow. It is this broad threshold that the RMI wants to know for medicines in New Zealand. (Unlike a company purchasing vehicles, Government faces no major up-front cost; the costs are all on-going. This means that the threshold for on-going cost effectiveness is even more important for Government and suppliers to know.)

7.6 If PHARMAC does insist that cost effectiveness varies "in comparison with other applications under consideration at any one particular time", then RMI asks that it publishes league tables around the prioritization and cost effectiveness "at any point in time" when it is making listing decisions. At the very least, in could publish historical data of the cost cut-offs it has applied in the past, so sponsors have some general idea of what criteria their applications need to meet. The New Zealand Government acknowledges that medicines do have value – the corollary should be that PHARMAC should be prepared to say what the criteria for this value is, so that medicine suppliers can meet Government's goals.

8. Unfair use of PBAC cost-utility analysis

8.1 Section 6.4 allows sponsors to supply the cost-utility analysis (CUA) conducted by the Australian PBAC. There are problems with this:

- We are not clear that the PBAC and the Pharmaceutical Evaluation Branch actually permit CUA reviews to be used outside the PBAC process.
- The Australian Government has just introduced cost-recovery measures for PBAC evaluations. Companies are now charged $150,000 for major submissions. Using CUA Reviews prepared for the PBAC amounts to the New Zealand Government free-loading on the Australian Government and Australian pharmaceutical companies.

- Companies will have varying policies about whether they are prepared to disclose HTA commentaries from external jurisdictions. PHARMAC should not knowingly have major information requirements which only some companies will meet. As a Government agency, PHARMAC has responsibility to be equitable in its requests. Local NZ pharmaceutical companies are all subsidiaries of multinational companies, and it is not reasonable to expect these small offices to influence their headquarters' policies on such a significant issue. It is also unreasonable for New Zealand to expect to dictate the international industry's policy of disclosure, or expect a special case to be made for it.
- Any CUA model submitted to the PBAC will not address differences between indigenous and non-indigenous populations. The draft Guidelines do not make clear whether PHARMAC will look at these distributions, or whether the sponsor will be consulted in the process.

9. Confidentiality and public disclosure

9.1 Section 2.3.1 says that "PHARMAC is subject to the Official Information Act. PHARMAC will, at all times, act in good faith where it considers it necessary or appropriate to release information, including any consultation with affected parties."

9.2 Some of the information contained in submissions is amongst the most sensitive that sponsors hold. While we acknowledge PHARMAC's responsibilities under the Official Information Act, RMI members wish to see much greater clarity about how this information will be controlled and disclosed. However, we also recognize that HTA agencies internationally – such as NICE – now disclose large amounts of sponsors' submissions on their website, and that many of these companies also apply to PHARMAC.

9.3 For these reasons, RMI believes that the time has come for both industry and PHARMAC to discuss much greater levels of transparency – on both sides. This is far beyond the capacity of a letter like this to resolve, and we therefore request that PHARMAC and RMI hold discussions about ways of achieving greater disclosure and transparency.

9.4 Until that can be done, we suggest that PHARMAC retains the provisions of the current guidelines in relation to confidentiality which refer to section 4.3 of PHARMAC's Operating Policies and Procedures (OPPs). These at least provide some assurance that PHARMAC will not release applications under the OIA under the principle of "good faith." Ideally, the RMI would like to be assured that where PHARMAC receives a request for information under the Act, it would not to disclose (a) any material marked 'Commercial-in-confidence', or (b) any details of costing or pricing. Furthermore, we would hope that PHARMAC would contact sponsors [ten] working days before releasing information, and list all of the material that it intends to release, and consult with them about any commercially-sensitive material. In essence, RMI members seek assurance that PHARMAC will act with utmost good faith in its consultation and selection of material for release under the OIA, and will not release material that sponsors have told it would be commercially prejudicial.

9.5 Another difficulty around the requirement for public disclosure are cases where Sponsors use individual patient data (IPD) in their submissions. This naturally will not be in the public domain. If sponsors or their parent companies become concerned that IPD may be released into the public domain, they will quickly cease to provide it. The result would be to seriously limit sponsors' ability to provide appropriate data in support of their submissions.

10. Lack of consultation with sponsors

10.1 There are numerous places in the draft Guidelines where PHARMAC will generate information – by itself or from external parties – for consideration in the assessment process. However, the Guidelines do not make clear whether the sponsor will be told about this information or permitted to comment on it. For example:

(a) PHARMAC may "invite relevant medical groups or other interested parties to comment on the pharmaceutical that is subject of the application prior to the consideration of the application by PTAC or a Subcommittee" (p11). In the PBAC process, sponsors would be informed of this.

(b) "If an application is submitted for consideration at a particular PTAC or Subcommittee meeting, PHARMAC staff will usually draft a cover paper for the Application" (p11). Again, it is unclear whether the sponsor will be consulted, or whether the cover page will reflect the sponsor's position or PHARMAC's.

(i) "When PHARMAC receives a CUA from an applicant, it is reviewed, and amended if necessary, by PHARMAC analysts. … If amendments have been made to the analysis, PTAC will usually be supplied with a copy of the Pharmaceutical Supplier's CUA and PHARMAC's amended CUA, with the differences between them clearly explained" (p13). The Guidelines do not say whether the sponsor will be told that amendments have been made, or whether they have the opportunity to comment on the changes made by PHARMAC.

(ii) PHARMAC's [nine] decision criteria are … [9] any other criteria that PHARMAC thinks is relevant. PHARMAC will carry out the necessary consultation whenever it intends to take 'any other criteria' into account" (p15). This does not state whom PHARMAC will consult, or whether the Sponsor will be informed if there is consultation with external parties.

10.2 In all cases, it is a basic principle of procedural fairness and transparency that sponsors should be told where information about their proposal has been generated and will be considered by PHARMAC or PTAC. We request that consultation be written into the Guidelines at all of these steps.

11. Vagueness of language

11.1 The language in the Guidelines is frequently vague, and it is often unclear exactly what PHARMAC wants. For example:

- *details of countries where registration has been approved or declined*
- *details of countries where an application for funding has been approved or declined.*

11.2 It is not clear to RMI whether 'details' here refers just to the names of countries, or whether PHARMAC also requires details of the decisions, related documents in the public domain, or materials such as PBAC PEC commentaries.

11.3 Likewise, it is not clear whether 4.1(x), "summary of all relevant New Zealand patents", refers only to the sponsor's product or to all comparable products.

11.4 Lack of specificity has the potential to create a great deal of unnecessary for both sponsors and PHARMAC. For example, 5.8.4 says:

The primary and secondary outcome data should be obtained from the complete published reports of the trials.

11.5 A definition of 'outcomes' is important here. If PHARMAC wishes to see all clinically-relevant or patient relevant outcomes, then submissions will be considerably larger than they currently are, and resources intensive for sponsors to produce and PHARMAC to assess. RMI would like assurance from PHARMAC that all of this extra information will be genuinely needed and used by evaluators and decision-makers. Otherwise, we request that this sentence is made more specific.

11.6 Finally, section 5.8.7 appears to be asking for safety data from <u>all four</u> data sources: "observational longitudinal clinical studies (ii) RCTs (iii) case reports on adverse drug reactions and expected/unexpected side effects and (iv) post-marketing data." Providing all four types of information will require significant resources and skills for both sponsors and evaluators. The Guidelines need to make clear whether all four are required, or whether the list is a guide to the sources that would be useful for sponsors to provide. (A related question is: would a sponsor be penalized for not providing case reports for small patient groups, if they could provide sufficient data from RCTs or post-marketing data?).

12. General Concerns

12.1 Many of the new requirements represent significant additional workload and cost for members with no anticipated or apparent benefit to suppliers in terms of such as greater accountability and/or faster decision-making on PHARMAC's part.

12.2 The proposed requirements will also increase the complexity of PHARMAC's processes.

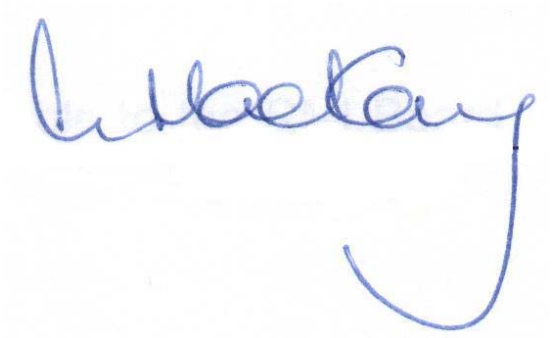
12.3 Furthermore, a great deal of what has been proposed by way of additional information does not appear to relate to PHARMAC's Decision Criteria. The RMI

considers that all of the information required to be provided in applications to PTAC should be directly relevant to these.

Thank you for considering our views.

We look forward to working with you in the future.

Yours sincerely,



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