Wyeth

01st August 2008

Project Manager
National Institute for Health and Clinical Excellence
Midcity Place
71 High Holborn
London WC1V 6NA

30th July 2008

Dear

Re: Final Appraisal Determination – Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis after failure of a previous TNF-α inhibitor

Thank you for your letter dated 11th July 2008, enclosing the Final Appraisal Determination (FAD) for the above technology appraisal.

We hereby confirm that in accordance with the procedure set out in the letter and the "Guidance for Appellants", Wyeth wishes to appeal 9 aspects of the appraisal process and the resultant proposed guidance on 2 of the grounds of appeal, as set out below:

1. **Failure to adequately reassess the evidence for the cost-effectiveness of a second TNF-α inhibitor with an extended sensitivity analysis that considers a wider possible range of effectiveness for conventional disease-modifying drugs (DMARDs) when used after TNF-α inhibitor**

1.1. **Failure to utilize DMARD effectiveness data from the BSRBR**
In the conclusion of the Decision of the Appeal Panel regarding the previous appeal of this appraisal in April 2007, the Appeal Panel suggested that the Appraisal Committee should reassess the evidence for the cost-effectiveness of a second anti TNF-α inhibitor with an extended sensitivity analysis that considers a wider possible range of effectiveness for conventional DMARDs when used after a TNF-α inhibitor.

The subsequent review of the effectiveness of non biologic DMARDs after TNF-α inhibitor failure conducted by the DSU, whilst failing to identify any evidence that directly considers the effectiveness of non biologic DMARDs in the population of interest, did identify relevant evidence from two

sources; namely the abatacept and rituximab studies and the British Society for Rheumatology Biologics Registry (BSRBR).

Whilst, following consultation with the Institute, effectiveness data from the abatacept trial were included in the further cost-effectiveness analysis of sequential TNF-α inhibitors for rheumatoid arthritis patients performed by Pelham Barton, critically the effectiveness data from the BSRBR was not included. Wyeth acknowledges that the data from the BSRBR suitable for inclusion in the BRAM model was published after the further analysis of cost-effectiveness was performed. However given the paucity of available data and the significant impact of a decision not to recommend sequential use of TNF-α inhibitors on patients with RA who have failed one TNF-α inhibitor, Wyeth contend that in order to provide robust guidance to the NHS a cost effectiveness analysis utilizing the BSRBR data should have been performed.

Given that the above-mentioned review by the DSU acknowledged that 'the availability of registry data from the same source as estimates of the effectiveness of second TNF-α inhibitors does offer advantages in terms of consistency', Wyeth considers the failure to include effectiveness data from the BSRBR as a major omission.

Evidence from the BSRBR indicates a lower effectiveness of medical management in the absence of a TNF-α inhibitor than placebo treatment in the abatacept study which would be expected to translate into a lower incremental cost effectiveness ratio (ICER) for a second TNF-α inhibitor. As the existing analysis cites the ICER for a second TNF-α inhibitor in the event of secondary failure to a first as being between £31 - £34,000 it would be anticipated that the ICER based on the BSRBR data would be less than £30,000 and therefore within the range that the Appraisal Committee has previously considered to be an effective use of NHS resources.

In not recommending sequential TNF-α inhibitor treatment, based on an analysis which does not take the above-mentioned data into account, the Institute has prepared a FAD that is perverse in the light of the evidence submitted.

1.2. Inappropriate exclusion of the DMARD effectiveness data from the BSRBR

Section 4.3.7 of the FAD highlights that the Appraisal Committee uses the presence of a proportion of people in the BSRBR with a response to conventional DMARDs after the failure of a TNF-α inhibitor to conclude that an assumption of no positive effect was not supported by the evidence. Such an assumption would be valid in this sub-population of responders, but given that the mean HAQ change across the entire group was zero, the FAD fails to indicate or acknowledge that a proportion of the patients must also have suffered a deterioration in response to conventional DMARDs

and that the net effect in the entire population was indeed that of no benefit.

Given that the BRAM is designed to model a response with a variable distribution, to not include an assumption of net zero HAQ improvement on conventional DMARDs, on the grounds of a sub-population of responders, has led to the Institute preparing guidance which is perverse in the light of the evidence submitted.

1.3. **Inequitable use of effectiveness data from the BSRBR**

Section 4.3.15 of the FAD indicates that the Appraisal Committee considered that study enrolment could have affected the data for the effectiveness of TNF-α inhibitors taken from the ReACT trial, which would not have been observed in the BSRBR. This led the Appraisal Committee to conclude that it would not be appropriate to combine estimates of clinical effectiveness for TNF-α inhibitors from the ReACT trial with those for conventional DMARDs from the BSRBR. However, we note from Section 4.2.5 of the FAD that the converse was deemed acceptable i.e. using TNF-α inhibitor data from the BSRBR and data for conventional DMARDs as had been used in TA 130 (i.e. from clinical trials of early RA). Whilst it is not transparent as to how the Appraisal Committee thought study enrolment could have affected the data for the effectiveness of TNF-α inhibitors, combining the differing data sets in one scenario but not the other introduces an element of bias in favour of the conventional DMARDS. As efficacy estimates derived from trial data tend to be higher than estimates derived from registry data the most pessimistic estimate of cost effectiveness of the TNF-α inhibitors is presented in Section 4.2.5 of the FAD. However, for the reasons described in section 4.3.15 of the FAD the most optimistic estimates have not been modeled and discussed in the FAD.

Section 3.1.1 of the Guide to the Methods of Technology Appraisal states that consideration of a comprehensive and high quality evidence base is fundamental to the appraisal process and that to ensure that the guidance issued by the Institute is appropriate and robust, it is essential that the evidence and the analysis and their interpretation are of the highest standard and are transparent to scrutiny. Furthermore, Section 3.1.3 of the same Guide states that similarly the analysis and modeling should be methodologically sound and, in particular, minimise any bias. Wyeth considers that the Appraisal Committee did not follow these requirements of the appraisal process.

In utilizing TNF-α inhibitor but not conventional DMARD effectiveness data from the BSRBR, the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process, which incorporates the Guide to the Methods of Technology Appraisal.

2. Failure to undertake a more complete examination of the minimum effectiveness that would be required of a second TNF-α inhibitor treatment for it to be marginally cost-effective

In the conclusion of the Decision of the Appeal Panel regarding the previous appeal of this appraisal in April 2007, the Appeal Panel suggested that the Appraisal Committee reassess the evidence for the cost-effectiveness of a second TNF-α inhibitor with a more complete examination of the minimum effectiveness that would be required of a second TNF-α inhibitor treatment for it to be marginally cost-effective.

2.1. Failure to incorporate all relevant factors in the estimate of the cost effectiveness of sequential TNF-α inhibitor treatment

An examination of the minimum effectiveness that would be required for a second TNF-α inhibitor to be marginally cost effective should have been conducted in a transparent way that allows maximum understanding by consultees and stakeholders (Guide to the Technology Appraisal Process, Section 1.1.1). To achieve this, the impact of a number of factors on the estimation of cost effectiveness (e.g. effectiveness of conventional DMARDS, the inclusion of offset costs and the use of appropriate discount rates) would need to have been explicitly identified and included in the calculation of cost effectiveness.

As the magnitude of each of these factors has not been established and their cumulative impact on the cost effectiveness of a second TNF-α inhibitor has not been evaluated (as set out below and in sections 1.1 – 1.3 above) the Institute has failed to act fairly and in accordance with its published procedure as set out in the Institute's Guide to the Technology Appraisal Process.

2.2. Failure to incorporate offset costs

Section 4.2.2 of the FAD states that joint replacements and associated costs were not included in the analysis of the sequential use of TNF-α inhibitors, although they were included in the sensitivity analysis of the first use of TNF-α inhibitors (TA130). Such offset costs were also included in the economic evaluation of rituximab (TA126). As the incorporation of offset costs invariably reduces the ICER of the technology being appraised, failure to incorporate such costs in the analysis of the cost effectiveness of the sequential use of TNF-α inhibitors introduces bias disadvantaging the sequential use of TNF-α inhibitors relative to the initial use of TNF-α inhibitors and rituximab.

Section 3.1.1 of the Guide to Methods of Technology Appraisal states that consideration of a comprehensive and high-quality evidence base is fundamental to the appraisal process. Section 3.3.1 of this Guide states that for costs, evidence requirements include quantifying the effect of the technologies on resource use in terms of physical units and valuing those effects in monetary terms using appropriate prices and unit costs. Section

5.2.1.1 of this Guide states that in order to inform the Appraisal Committee's decision-making, all relevant evidence needs to be assembled systematically and synthesized in a transparent and reproducible manner.

Therefore, by not including these cost offsets in the current appraisal the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institutes Guide to the Technology Appraisal Process, which incorporates the Guide to the Methods of Technology Appraisal.

2.3. Failure to establish the impact of offset costs on the ICER for sequential use of TNF-α inhibitors

Section 4.3.11 of the FAD states that the Appraisal Committee noted that sensitivity analyses including offset costs had been explored in the first-use analyses of TNF-α inhibitors and that these had not demonstrated a significant impact on the incremental cost-effectiveness ratios. The Appraisal Committee concluded that consideration of offset costs was important, but that this had been explored by the Assessment Group in their original analyses and had been shown not to be a key driver of cost effectiveness.

The fact that the offset costs were not considered having a significant impact on the ICERS for the first use analyses of TNF-α inhibitors does not justify the failure to include them in the analysis of the sequential use of TNF-α inhibitors. As mentioned in Section 2.1 of this document, any cost offsets would need to be included in the cost effectiveness model, in order to establish the minimum effectiveness that would be required of a second TNF-α inhibitor for it to be marginally cost-effective. The magnitude of the impact of offsets costs on the ICER is dependent on the difference of HAQ response between TNF-α inhibitor and comparator. The difference in HAQ response and therefore the impact of offset costs may be greater in the case of the sequential use of TNF-α inhibitors compared with their initial use. As the existing analysis cites the ICER for a second TNF-α inhibitor in the event of secondary failure to a first as being between £31 - £34,000 it would be anticipated that the ICER which incorporates offset costs would be less than £30,000 and within the range that the Appraisal Committee has previously considered to be an effective use of NHS resources.

In not recommending sequential TNF-α inhibitor treatment, based on a cost effectiveness analysis which does not incorporate offset costs, the Institute has prepared a FAD that is perverse in the light of the evidence submitted.

2.4 Change in discount rate

The current FAD and TA130 are considered to be part of the same appraisal. As a consequence all the conditions and criteria used in the preparation of TA130 must apply to the preparation of guidance on the

sequential use of TNF-α inhibitors. However, the cost-effectiveness analyses carried out to compare the sequential use of anti TNF-α inhibitors with non-biologic DMARDs and rituximab used a discount rate of 3.5% for costs and benefits, instead of the discount rates of 1.5% and 6% which were used during the preparation of TA130.

As noted in section 4.3.16 of the FAD the different discount rates in the new sequential analysis would reduce the estimates of incremental cost-effectiveness.

In Section 4.3.16 of the FAD the Appraisal Committee notes that the use of different discount rates in the new sequential analyses would reduce the estimates of incremental cost-effectiveness. However, the Appraisal Committee still concluded that it did not alter their conclusions regarding the lack of robustness in the current evidence base for the clinical effectiveness of second use TNF-α inhibitors upon which the estimates of cost-effectiveness were based.

In reaching its decisions, the Appraisal Committee, according to sections 4.4.1.4, 4.5.1.8 of the Guide to the Technology Appraisal Process and sections 1.3.2.1, 3.3.1, 5.1, 5.3.1.1, 5.3.4, of the Guide to the Methods of Technology Appraisal, needs to consider both clinical effectiveness and cost-effectiveness evidence. Additionally, this is what was requested by the final scope and protocol of this technology appraisal, and the Appeal Panel for the first limb (TA130) suggested that the Appraisal Committee reassess the evidence for the cost-effectiveness of a second TNF-α inhibitor.

However, even though evidence on both clinical and cost-effectiveness was available to the Appraisal Committee in this technology appraisal, the Institute has given undue weight to the clinical opinion on clinical effectiveness to reach its conclusion presented in section 4.3.16 of the FAD.

In splitting the appraisal into 2 limbs, and changing the underlying decision criteria for TNF-α inhibitors (e.g. by applying a changed discount rate) the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process, which incorporates the Guide to the Methods of Technology Appraisal.

Wyeth asked for permission to submit updated evidence on the cost-effectiveness of the use of a second TNF-α inhibitor after the failure of a first one. It is Wyeth's view that these data are likely to materially affect the provisional recommendations in the ACD. This updated evidence demonstrates the impact of the changed discount rate on the cost-effectiveness results, demonstrating ICERs between £12,242 and £20,102/QALY in comparison with conventional DMARDs and £5,342 and £24,753/QALY in comparison with rituximab.

The request to submit this information was declined with the argument that the data submitted would not add information material to the decision-making and could not be accepted. Declining of our request will be discussed in more detail later in this document.

The ICERs demonstrated by Wyeth, fall within a range of £5,342 and £24,753, and therefore meet the criteria for acceptability of a technology as an effective use of NHS resources in line with section 6.2.6 of the Guide to the Methods of Technology Appraisal.

Therefore, in not recommending sequential use of TNF-α inhibitors despite demonstrating an ICER within the range typically considered acceptable, the Institute has prepared a FAD that is perverse in the light of the evidence submitted.

3. Failure to distinguish subgroups

The Final Scope of this technology appraisal states that if the evidence allows, the appraisal will attempt to identify criteria for selecting patients for whom these treatments are particularly appropriate.

Section 4.3.20 of the FAD notes that the Appraisal Committee was not persuaded that the current clinical evidence available supported a decision that TNF-α inhibitors when used after the failure of a previous one for the treatment of people who were intolerant of or had contraindications to rituximab or methotrexate, or because of the presence of seronegative disease, would be an appropriate use of NHS resources. In doing so, the Appraisal Committee has failed to identify criteria for selecting patients for whom these treatments are particularly appropriate. Instead it is applying a blanket decision to all patients.

In section 4.3.5 of the FAD the Appraisal Committee concluded that there was insufficient evidence to distinguish between the clinical effectiveness of the second TNF-α inhibitor when used in people whose condition did not show any response to their first TNF-α inhibitor (that is, primary failure) and people who, after an initial response to their first TNF-α inhibitor, had experienced a reduction in response (that is, secondary failure).

However, although the evidence is limited, what evidence there are shows consistently higher effectiveness in patients with secondary failures compared to those with primary failure. Therefore the Institute should have included this evidence in its decision making.

Wyeth considers that by omitting this evidence in its decision making the Institute was unreasonable and perverse; therefore the Institute has prepared a FAD which is perverse in the light of the evidence submitted.

In addition, by not taking into account differences between a primary lack of effectiveness and a secondary loss of effectiveness of a first TNF-α inhibitor the Institute has not followed section 6.2.5.4 of the Guide to the Methods of Technology Appraisal requiring the Appraisal Committee's judgments on clinical effectiveness to take into account the consideration of possible differential effectiveness in different subgroups of patients.

Therefore, in not distinguishing between primary and secondary failures the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institutes Guide to the Technology Appraisal Process, which incorporates the Guide to the Methods of Technology Appraisal.

4. Rituximab as new comparator

The Scope for this appraisal refers to comparator technologies as "current standard comparators", which are management strategies with of without anti TNF-α inhibitors, and other anti TNF-α inhibitors. Wyeth considers that "current" to mean as of the immediate present or the most recent or up-to-date and therefore, those competitive technologies, that were accepted as standard at the time of the scoping.

As rituximab received its license during the course of this appraisal, the Institute should have, following section 1.1.1 of the Guide to the Technology Appraisal Process, sought the views of consultees and requested updated submissions.

By including rituximab as a comparator in this appraisal the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process.

5. Failure to establish cost effectiveness vs. rituximab using different assumptions

Section 4.3.19 of the FAD states that the Appraisal Committee noted that if there were increased costs of rituximab treatment, and a deterioration in response to rituximab between infusions, then this reduces the estimate of incremental cost-effectiveness relative to a second TNF-α inhibitor. However, the FAD is not including the respective cost-effectiveness results for this scenario. Section 1.1.1 of the Guide to the Technology Appraisal Process states that all appraisals are conducted following a uniform, open and transparent process.

Section 3.1.1 of the Guide to the Methods of Technology Appraisal identifies that the consideration of a comprehensive and high quality evidence base is fundamental to the appraisal process and that to ensure that the guidance issued by the Institute is appropriate and robust, it is essential that the evidence and the analysis and their interpretation are of the highest standard and are transparent to scrutiny. However, this has not

been followed by the Institute in not consulting with and not requesting the submission of updated evidence from consultees and commentators in respect of the inclusion of rituximab.

In addition, Wyeth considers that in UK clinical practice the treatment interval for rituximab is more likely to be 7 months, rather than 9 months. This is also supported by data from clinical studies with rituximab, in order to maintain an adequate response with rituximab. Therefore, the cost per QALY of TNF-α inhibitors compared to rituximab would be lower and, we believe, within the range that the Institute has previously considered to be an acceptable use of NHS resources, in line with sections 6.2.6.10 and 6.2.6.11 of the Guide to the Methods of Technology Appraisal.

Consideration has not been given by the Appraisal Committee to UK clinical practice for re-treatment with rituximab. This requires loss of efficacy which leads to worsening of HAQ and reduction in utility. This has not been included in the modeling. Wyeth considers this a fundamentally flawed analysis of the evidence in breach of both section 1.1.1 of the Guide to the Technology Appraisal Process and section 3.1.1 of the Guide to the Methods of Technology Appraisal. Consequently, the Appraisal Committee has reached a perverse decision not to recommend the sequential use of these agents.

Therefore, by including results from the above mentioned flawed analysis in the FAD the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institutes Guide to the Technology Appraisal Process, which incorporates the Guide to the Methods of Technology Appraisal.

This in consequence has led to the Institute preparing a FAD which is perverse in the light of the evidence submitted.

6. Failure to accept additional data

NICE has chosen to add rituximab as a comparator into this appraisal even though this comparator, as discussed earlier in this document, is outside of the Scope for this appraisal. By not initiating a new appraisal in order to include this new comparator, commentators and comparators have not been given the opportunity to submit any further data relevant to this wider appraisal. Therefore, the Institute has not complied with section 1.1.1 of the Guide to the Technology Appraisal Process, which requires maximum input from consultees and stakeholders.

The original submission for this appraisal took place in 2005. Since then a considerable amount of new evidence on the sequential use of TNF-α inhibitors has become available. Therefore, Wyeth updated its literature review and cost-effectiveness analysis for the use of a second TNF-α inhibitor after the failure of a first one taking into account aspects which

have not been covered by the analysis during this appraisal either using the BRAM or by the DSU.

Section 4.5.2.10 of the Guide to the Technology Appraisal Process states that, at the ACD stage, new data will be accepted only if they are likely to materially affect the provisional recommendations in the ACD, and only by prior agreement with the Appraisal Programme Director. Therefore, Wyeth asked for agreement to submit our further evidence on the cost-effectiveness of the sequential use of TNF-α inhibitors, which includes a comparison with rituximab. Given that this further data on cost-effectiveness includes a direct comparison with rituximab as well as allowing for a comparison of the impact of different key parameters, such as the use of different discount rates, and effectiveness ranges for the different treatment options, Wyeth considers this information likely to materially affect the provisional recommendations in the ACD and therefore critical in the Appraisal Committees decision-making.

However, our request to submit this information was declined with the reasons given to reject our request, being that the Committee had already considered the points we made (namely no effect of conventional DMARDs and highest possible effect of TNF-α inhibitors) and found these assumptions to be implausible.

Wyeth considers that the Institute have not considered our data fairly, as the reasons given to reject our request, notably that the Committee had already considered the points we made, namely no effect of conventional DMARDs, and highest possible effect of TNF-α inhibitors, and found these assumptions to be implausible, are in breach of the Institutes published procedures (as above).

Therefore, by rejecting Wyeth's updated evidence on the cost-effectiveness of sequential use of TNF-α inhibitors in comparison with rituximab the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process.

7. Splitting of the appraisal

Following the appeal against the FAD for the first limb of this appraisal (leading to TA 130), the Institute, without consultation, has published a FAD that omits the matters referred back to the Appraisal Committee by the Appeal panel at that time in relation to the Appraisal Committee's consideration of sequential use of TNF-α inhibitors. There is no provision within the Institute's published procedures that permits such a splitting of an appraisal. In addition, Section 1.1.1 of the Guide to the Technology Appraisal Process states that the appraisal process is designed to achieve robust guidance for the NHS, developed in an open and transparent way that allows maximum understanding and input from consultees and stakeholders. This has not been followed in this case, as the appraisal was

split without seeking maximum input from consultees and stakeholders. In fact, no further input was sought from consultees and stakeholders at all, despite unilaterally changing the scope to the second limb of the appraisal.

Notwithstanding the above, this current FAD is part of the Scope of the appraisal that led to the publication of TA130 in October 2007. Therefore the same decision criteria and comparators should have been applied.

Therefore, in splitting the original appraisal of TNF-α inhibitors for the treatment of rheumatoid arthritis the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process.

This split of the appraisal has resulted in a change of the underlying decision-making criteria, such as the use of a changed discount rate (as described above in more detail) leading to a perverse decision not to recommend the sequential use of these agents. Therefore, in addition, the Institute has prepared a FAD that is perverse in the light of the evidence submitted.

8. Refusal to use DMARD efficacy from BSRBR in combination with ReAct data for TNF-α inhibitors

Section 4.3.7 of the FAD states that the Appraisal Committee examined registry data from the BSRBR that showed no change in HAQ score for people who had stopped treatment with TNF-α inhibitors. The Appraisal Committee heard from clinical specialists that there would be variation in response and accepted that an assumption that nobody would have a response was unlikely. Wyeth acknowledges this, and the fact that, as stated in section 4.1.14 of the FAD, the BSRBR data reported a variation of responses among the group, with 22% of people having an improvement in HAQ. However, if 22% have an improvement, and the group showed no change in mean HAQ score, then a substantial proportion would have had deterioration in HAQ score. Also, it is important to keep in mind the characteristics of this cohort of patients, who tend to suffer from more severe RA with longer disease duration, and therefore are less likely to have received early aggressive treatment. As the Appraisal Committee heard from clinical specialists, conventional DMARDs very limited in their effectiveness in people who receive appropriate clinical management early in the disease, including rapid escalation of conventional DMARDs. Therefore, Wyeth considers the data from the BSRBR as the upper part of potential effectiveness range of conventional DMARDs after TNF-α treatment. Notably, the Appraisal Committee has applied different standards to the evaluation of conventional DMARDs and TNF-α inhibitors, as described above.

Section 3.1.1 of the Guide to the Methods for Technology Appraisal states that consideration of a comprehensive and high quality evidence base is fundamental to the appraisal process, and that to ensure that the guidance

issued by the institute is appropriate and robust, it is essential that the evidence and the analysis and their interpretation are of the highest standard and are transparent to scrutiny. Wyeth considers that the Appraisal Committee did not follow this requirement of the appraisal process for the reasons above.

In section 3.2.1.2 of the Guide to the Methods of Technology Appraisal expert opinion is described as the lowest evidence grade (level 4). Therefore, the appraisal should have used the higher grade of data from the BSRBR (level 2) to inform the effectiveness of conventional DMARDs after TNF-α inhibitor treatment, especially as this is the only direct, real-life evidence on the effectiveness of conventional DMARDs post TNF-α inhibitors.

In this appraisal, the cost-effectiveness analysis uses efficacy data, in terms of HAQ improvement, for sequential TNF-α inhibitor from the BSRBR registry. However, rather than source the estimates of HAQ improvements for the comparator conventional DMARD sequence from the same registry database, values from rheumatoid arthritis clinical trial data (placebo arms) were used instead. These efficacy estimates show greater HAQ improvements, and lack face validity in light of the evidence available. This also means that the two cannot be compared.

The use of these inputs into the appraisal has resulted in bias. As a consequence the modeling cannot be considered methodologically sound and the analysis and interpretation of the evidence cannot be considered to be of the highest standard.

Therefore, by including results from the above mentioned flawed analysis in the FAD the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process, which incorporates the Guide to the Methods for Technology Appraisal.

Further, by accepting these flawed results and making recommendations based on them the Institute has prepared a FAD that is perverse in the light of the evidence submitted.

9. Some HAQ improvement values utilised in the further cost effectiveness analysis of sequential TNF-α inhibitors have been extrapolated from the ReAct study inappropriately

From its systematic review the West Midlands Health Technology Assessment Group identified a rank order for the effectiveness and cost effectiveness of the initial use of the available TNF-α inhibitors. Wyeth considers that it is reasonable to assume that differences in the effect on HAQ between the various TNF-α inhibitors observed during initial treatment would also be manifest in a second course of TNF-α inhibitors therapy following lack or loss of response to the first.

This interpretation is supported by the evidence identified in the update report by the DSU on the sequential use of TNF-α inhibitors dated January 2008. In particular, the large open label trial of the effectiveness of adalimumab in patients with a history of TNF-α inhibitor therapy (ReACT) clearly identifies that response to adalimumab is greater in patients failing infliximab than in patients failing on etanercept treatment. Whilst utilising HAQ improvements for sequential use of adalimumab after failure of either etanercept or infliximab from this study would seem entirely appropriate to assume the converse i.e. the same effect for etanercept and infliximab after failure of adalimumab is without foundation, would lead to an underestimation of the relative effectiveness of etanercept and therefore the cost-effectiveness of the TNF-α inhibitors.

The use of these inputs into the appraisal has resulted in bias. As a consequence the modeling cannot be considered methodologically sound and the analysis and interpretation of the evidence cannot be considered to be of the highest standard.

Section 3.1.1 of the Guide to the Methods for Technology Appraisal states that consideration of a comprehensive and high quality evidence base is fundamental to the appraisal process, and that to ensure that the guidance issued by the institute is appropriate and robust, it is essential that the evidence and the analysis and their interpretation are of the highest standard and are transparent to scrutiny. Wyeth considers that the Appraisal Committee did not follow this requirement of the appraisal process. The use of these inputs into the appraisal has resulted in bias. As a consequence the modeling cannot be considered methodologically sound and the analysis and interpretation of the evidence cannot be considered to be of the highest standard.

Therefore, by including results from the above mentioned flawed analysis in the FAD the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process, which incorporates the Guide to the Methods for Technology Appraisal.

Further, by accepting these flawed results and making recommendations based on them the Institute has prepared a FAD that is perverse in the light of the evidence submitted.

Had the Institute taken into account the data referred to in this document and included it in its analysis and decision-making, Wyeth believes the result of the economic modeling would have been very different, with lower ICERs. It is highly likely that the result of the economic evaluation carried out using the BRAM would have been below the threshold to be considered an acceptable use of NHS resources which is likely to have led to a recommendation for sequential use of TNF-α inhibitors for sequential use, following recommendations made in previous appraisals by the

Institute. As the combined impact has not been considered the Committee have failed in its duty. Consequently, Wyeth wishes to make an appeal based on the above appeal points.

Yours sincerely