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Dear Mr. Powell:

RE: WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION (WMHTAC) ASSESSMENT REPORT ON ADALIMUMAB, ETANERCEPT, INFLIXIMAB, RITUXIMAB AND ABATACEPT FOR THE TREATMENT OF RHEUMATOID ARTHRITIS AFTER THE FAILURE OF A TNF INHIBITOR: A SYSTEMATIC REVIEW AND ECONOMIC EVALUATION – COMMENTS ON THE TECHNOLOGY ASSESSMENT REPORT (TAR)

Schering-Plough welcomes the opportunity to comment on this report and its technical content. Following a thorough review of the WMHTAC report, this letter sets out Schering-Plough's comments – firstly, a summary of what we perceive to be the critical issues and subsequently, more detailed information relating to these and other related issues.

1. Key Issues

1.1 Lack of transparency and rationale for assumptions and input parameters

The TAR does not provide an explanation for included and excluded parameters which are critical in determining the analysis results. Base case assumptions for rituximab dosing frequency and infliximab costs were applied without explanation or reference. Infliximab beta distributions for HAQ multipliers were arbitrarily assumed equivalent to etanercept and are inconsistent with observed HAQ multipliers from ASPIRE, ATTRACT and GO-AFTER clinical trials. The WMHTAC excluded the OPPOSITE trial in the clinical effectiveness assessment; nevertheless the TAR inconsistently references this trial for the probability of early quitting of biologic treatment. Validation of the modelling was complicated by the 2,000 lines of sparsely commented source code provided by the WMHTAC. These numerous inconsistencies and lack of explanation for key input parameters is a critical failing as these assumptions are the principle components in determining the final model results.

Following an appeal to TA130, the Appeal Panel suggested in 2008 that the Appraisal Committee (the Committee) should consider all available evidence which is relevant to the decision problem and provide clarity around chosen parameters. Given the present inconsistencies in the TAR, it may be difficult for the Committee to reach an appropriate conclusion for the use of biologics in sequential setting.

1.2 Exclusion of key evidence

Despite the decision of the Appeal Panel in 2008, comparators such as golimumab, tocilizumab and certolizumab pegol, which could provide robust evidence from randomised controlled trials (RCTs) for the specific population under consideration, appear to have been arbitrarily and inconsistently excluded. Individual patient level data from GO-AFTER which is the first RCT to assess efficacy and safety of a TNF inhibitor after exposure to a first TNF inhibitor was submitted by Schering-Plough to inform the decision problem. This data and published findings from RADIATE (a RCT for Tocilizumab after the failure of a TNF inhibitor) were not assessed within the WMHTAC report. The exclusion of this potentially important evidence appears to have contributed to the Assessment Group's own finding that there is a lack of good quality data to establish the clinical effectiveness of biologics in sequential therapy.

1.3 Use of unrealistic treatment framework

The treatment pathway represented in the BRAM model was determined based on a survey with a methodology that appears to be flawed, The survey was conducted in just one small area, consisted of a small sample size and had an even smaller response rate. Therefore it is not representative of the United Kingdom as a whole. Furthermore, the ultimate decision to restrict the economic evaluation to only a second biologic followed by DMARDs is at odds with the findings of this survey.

The survey was restricted to the West Midlands region and received a less than 50% response rate to a survey sample of only 27. Therefore, it would appear these findings should not underpin the treatment pathway decision. Based on this limited survey, the Assessment Group determined that it would be appropriate to restrict the economic evaluation to only a second biologic followed by DMARDs. However, the survey findings show that (despite the restricted survey sample) the overwhelming majority of rheumatologists who responded indicated they would use a third biologic (96% of respondents) and a fourth biologic (88% of respondents). If the WMHTAC commissioned survey is to form the basis for the treatment pathway, a larger sample size which is representative of United Kingdom rheumatologists should be undertaken – and then the conclusions applied towards the modelled pathway.

1.4. No assessment of manufacturer submissions. No attempt to significantly update BRAM model from previous appraisal.

Section 6.2 of the TAR, entitled, 'Critique of manufacturer submissions' has not, in Schering-Plough's opinion, critically appraised the manufacturers' submissions as is intended. This assertion is reflected by a strikingly brief summary in the TAR on page 205. The apparent 'non-assessment' of manufacturers' submissions will make the task of assessing them more difficult for the Committee. The BRAM model should have been updated based on the most appropriate evidence including that provided by the manufacturers. Instead, only a few minor adjustments have been made to the 'updated BRAM model'. This updated BRAM model still relies on the same treatment pathway that was being followed 5 years ago and uses identical utility mapping, without drawing upon the manufacturer submissions to inform a more robust model. Given the course of this appraisal since its inception within TA130 over 5 years ago, it is a matter of concern for Schering-Plough that the Assessment Group has paid such a token interest in alternative modelling approaches presented by manufacturer consultees.

Schering-Plough submitted a patient level simulation model which included baseline patient characteristics from the GO-AFTER clinical trial, more appropriate utility mapping from ACR to EULAR, and evidence to support vial optimisation for infliximab. Schering-Plough's assessment found RA patients can achieve a good response to a different TNF inhibitor having received an inadequate response to a previous TNF inhibitor. All TNF inhibitors were found not only to be a clinical and cost-effective treatment in the first line treatment of RA but were also shown to provide further benefit to English and Welsh patients when used sequentially. None of these components were taken into consideration within the WMHTAC report.

1.5 No consideration of vial optimisation

Vial optimisation with infliximab in RA has implications on the cost-effectiveness argument currently being appraised; however the WMHTAC report did not address any of the submitted evidence. Following the Appeal to TA130, the Committee was instructed to consider an appropriate range of doses for infliximab and to take account of vial wastage; it is therefore counterintuitive to ignore ICERs that take account of vial optimisation.

Schering-Plough thus recommends the following:

- Improvement in transparency and consistency throughout the TAR: Explanatory text and references for key input parameters and source code should be included. The WMHTAC assessment should draw upon clinical trials to inform appropriate HAQ multipliers. Data for probability of early quitting should not be taken from short term efficacy studies but rather from 'real world' registries (ie the BSR registry).
- Inclusion of all relevant data which could inform the decision problem: RCT findings from GO-AFTER and RADIATE should be assessed. Tocilizumab, golimumab and certolizumab pegol should be included as comparators.
- Commissioning of a national survey to inform the treatment pathway: Online tools (such as Survey Monkey) can be used to quickly assess the national perspective. The modeled pathway should be consistent with the findings. The included/excluded products should be

consistent with the rest of the TAR (ie tocilizumab was excluded as a comparator in the clinical and cost effectiveness sections; however it was included within the WMHTAC treatment pathway survey).

- A thorough and transparent critical assessment of the manufacturers' submissions to determine relevant information which could inform an updated BRAM model and to assist the Committee in evaluating all available evidence.
- Incorporation of vial optimisation when calculating the cost of infliximab.

2. Detailed response on limitations identified in the TAR

2.1 The WMHTAC review of the existing evidence (excluding the submissions by manufacturers)

2.1.1 Relevant safety information excluded within rituximab assessment

Schering-Plough is concerned that the recent Important Drug Warning issued by the United States Food and Drug Administration (FDA) has not been considered within the Assessment Group's safety summary of rituximab (TAR, Section 5.3.5.4, Page 114). In addition to two fatal cases of progressive multifocal leukoencephalopathy (PML) in RA patients treated with rituximab, a third case has recently been reported suggesting that patients with RA who receive rituximab have an increased risk of PML[1]. An analysis published in May 2009 found 57 cases of the rare disease following rituximab therapy, many of which were not previously reported, therefore suggesting that 57 cases is a 'gross underestimate of the incidence of this complication'[2,3]. Whilst the risk of PML is estimated to be as low as 2.5 per 100,000[1], these recent developments may have clinical implications as patients may be wary of treatment on rituximab. This, may also be relevant to the Committee because the TAR outlined that one of its primary objectives was to assess the safety of the five biologics in RA patients.

2.2 The WMHTAC review of the submission by Schering-Plough

Schering-Plough is disappointed by the critique of manufacturers' submissions. The WMHTAC did not conduct a thorough assessment of the submissions but rather a top-line overview with stringent parameters. Table 71 of the TAR (Page 191-194) generally outlines the submission parameters without any comment or assessment. The table includes 'HAQ→QoL' as one of the submission features and Schering-Plough is very concerned that this submission feature records 'NA' for Schering-Plough because the utility mapping undertaken in our submission was not in exact accordance with the previous BRAM model. The utility mapping used by Schering-Plough was only briefly alluded to in the WMHTAC (TAR, Section 6.2.3, Page 199). All other components were briefly described with no additional insight. Schering-Plough recommends a more robust critique of the manufacturer submissions so as to assist the Committee in their assessment.

2.2.1 Optimistic base case assumption for rituximab dosing frequency

The WMHTAC report does not provide explanatory text for the choice of 8.6 months rituximab dosing frequency in the base case. This may represent some early studies in Rituximab wherein the

average clinically defined treatment on relapse was approximately 9 months. However, most of the subsequent clinical trials of Rituximab have used a 6 months dosing schedule. A patient record retrospective audit and survey was submitted by Schering-Plough (S-P submission, Appendix 5, Figure 22 and Table 67) which found rituximab dosing frequency to be at least twice yearly in 76% and 63% of treated RA patients, respectively. These findings greatly impact the ICERs for rituximab as shown in the one way sensitivity analysis (TAR, Section 6.3.2.2, Page 220), leading to a ICER range of £32,700/QALY (6 month dosing frequency) to less than half £14,800/QALY (11.6 month dosing frequency).

2.2.2 No consideration of vial optimisation for infliximab

Schering-Plough submitted evidence from a survey of rheumatology specialists which makes clear that vial wastage can be avoided reasonably easily in hospitals where large numbers of patients are treated[4]. Vial optimisation with infliximab in RA has implications on the cost-effectiveness argument currently being appraised; however the WMHTAC report did not address any of the submitted evidence. Following the Appeal against the FAD for Technology Appraisal 130, the Committee was instructed to consider an appropriate range of doses for infliximab and to take account of vial wastage; it is therefore counterintuitive to ignore ICERs that take account of vial optimisation.

Schering-Plough notes that NICE has previously issued recommendations for an asthma medicine, omalizumab, following evidence from clinical specialists and patients that vial wastage could be avoided (Technology Appraisal 133)[5]. Paragraph 4.12 of TA 133 states:

> "The Committee considered the basis for estimating omalizumab drug costs in the manufacturer's model. It noted that this had been done on a per-mg basis (assuming no wastage and reuse of unused vial portions) and that in scenarios in which omalizumab drug costs were estimated on a per-vial basis, the ICERs for omalizumab were higher. It was mindful that vial sharing might not be feasible in primary care settings. However, the Committee heard from patient experts and clinical specialists that vial wastage could be avoided reasonably easily in regional specialist centres where larger numbers of patients are treated. The Committee therefore concluded that the ICERs for omalizumab in comparison with standard therapy may be lower when omalizumab is administered in a dedicated session in a specialist day care setting where vial wastage can be minimised."

As infliximab is administered within specialist centres, it may be reasonably assumed that vial optimisation may be applicable. Indeed, the ongoing NICE appraisal of infliximab for the treatment of Crohn's disease recently released an Appraisal Consultation Document which stated that local vial sharing arrangements should be taken into account in the consideration of which treatment should be administered[6].

Schering-Plough therefore strongly urges that evidence from clinical specialists regarding vial optimisation will be taken into account by NICE in this appraisal and that the Appraisal

Committee will take a similar and consistent approach to the issue of vial wastage as that in previous appraisals.

2.3 The WMHTAC independent assessment

Schering-Plough would like to highlight at the outset, that the information provided in the working prototype of the model and the accompanying TAR was limited. Therefore, it was not possible to verify all the assumptions included in the WMHTAC's economic analysis. The general methods, assumptions and approaches employed throughout were poorly described (if at all) and hence detailed validation of the results or identifying the specific causes of the problems becomes difficult. Some of these inconsistencies have already been highlighted in the 'Key Issues' on page 1 and 2 of this document.

Schering-Plough has identified the following issues which may undermine the credibility of the TAR and their approach.

2.3.1 Comparators excluded on arbitrary grounds

The WMHTAC report excluded certolizumab pegol, tocilizumab and golimumab because these products had not received EMEA market authorisation prior to protocol finalisation on 09 July 2009 (TAR, Section 4.4, Page 41). Schering-Plough's view is that this date was an arbitrary boundary which excluded critical RCTs (RADIATE[7] for tocilizumab and GO-AFTER[8] for golimumab) which could have greatly informed the decision problem. Both of these RCTs were published prior to the commencement of the clinical effectiveness systematic reviews in July 2009 (TAR, Section 5.1.1, Page 44) but were unfortunately not identified due to the stringent, product-focused search criteria (TAR, Section 10.2, Page 240). Schering-Plough submits that a broader approach should have been applied to identify all available data which may be relevant to the submission. This would also have shown that the Assessment Group correctly followed the advice of the Appeal Panel in its decision on 29th September 2008.

Most importantly, the WMHTAC report has erroneously excluded tocilizumab as a comparator despite the fact that it received European approval for market authorisation on 16 January 2009[9]. As of 1 October 2009, certolizumab pegol and golimumab also received EMEA market authorisation approval.

Based on the limited clinical effectiveness evidence identified within the WMHTAC report following the failure of a TNF inhibitor, and given the considerable attention that has been paid to identifying all potential sources of evidence for sequential therapy during the course of TA130, it would appear illogical and extremely unhelpful to assess biologic DMARDs without inclusion of all available evidence for potentially relevant comparators.

Previous appraisals have drawn heavily upon clinical trials of products which are not under assessment. This was the case when using abatacept RCTs as a proxy for the control/placebo arm during the appraisal of adalimumab, etanercept and infliximab after the failure of a TNF inhibitor

(Section 4.2.3 of Final Appraisal Documentation)[10]. In the current analysis individual patient level data from GO-AFTER, submitted by Schering-Plough could have informed baseline characteristics and efficacy responses for TNF inhibitors as a class but were not assessed within the WMHTAC report. Furthermore, published findings from RADIATE and GO-AFTER were also overlooked and thus were unable to additionally inform the decision problem. Instead, the Assessment Group concluded that there was lack of good quality data to compare the biologics.

2.3.2 Reliance on inappropriate methods to inform the treatment pathway

The WMHTAC report has restricted the treatment pathway to the results of a limited survey of rheumatologists, which is not representative of the UK in its' entirety (TAR, Section 10.11, P305). A considerable amount of variability was found within the small sample of 27 rheumatologists who responded (< 50% of those polled responded). Even in this limited assessment, 96% of respondents suggested they may use a third biologic agent and 88% of respondents suggested a fourth biologic agent could be used. We believe this survey was not of the quality required by NICE for its determinations. However, even considering these data we believe the WMHTAC report has unreasonably concluded that the 'most common approach' of a second TNF inhibitor or rituximab followed by non-biologic DMARDs would be the appropriate treatment pathway to assess. Contrary to these findings, the Assessment Group restricted the economic evaluation to only a second biologic agent followed by DMARDs.

The survey, which was restricted to the West Midlands region, introduces further bias by including a biologic DMARD (tocilizumab) whilst excluding other potential comparators (golimumab, certolizumab pegol). As the WMHTAC report concluded that the condition of market authorisation was not met by golimumab, certolizumab pegol or tocilizumab, these products were excluded as comparators (TAR, Section 4.4, Page 41). The TAR states that the NICE Tocilizumab Single Technology Appraisal could greatly inform the considered treatment pathways (Section 3.3.2.3). The most recent Tocilizumab Appraisal Consultation Document published on 16 December 2009 suggests that fundamentally optimistic assumptions underpin the evaluation and need to be addressed prior to the third Appraisal Committee meeting[11]. The inclusion of tocilizumab in the treatment pathway survey and allowing the unrelated Single Technology Appraisal of tocilizumab to inform the treatment pathways considered is inconsistent with the approach outlined in Section 4.4 (TAR, Page 41).

2.3.3 Inputs and parameters within model unclear and inappropriate

Numerous inconsistencies and lack of explanatory text for key input parameters is an important failing. The assumptions detailed below significantly affect the ICERs and therefore should be critically appraised for consistency.

- **Vial optimisation not taken into account**

Schering-Plough has already set out the logical reasoning behind incorporating vial optimisation into the WMHTAC economic evaluation at pages 4-5 above. Vial optimisation with infliximab can yield vial savings of up to 14% as described in Schering-Plough's submission (Appendix 6). These savings have large cost implications which greatly change the cost-utility analysis outputs.

Schering-Plough thus recommends incorporation of vial optimisation into the sensitivity analysis to reflect clinical practice.

- **Discrepancy between observed and simulated HAQ multipliers**

In the BRAM model the change in HAQ on starting a new DMARD is sampled on an individual basis and takes the form of a multiplier applied to the HAQ score on starting treatment, hereafter termed the 'HAQ multiplier'. This was sampled from a Beta distribution. To investigate the face validity of the model, a comparison was undertaken between the simulated HAQ multiplier used for infliximab from the BRAM model with the actual HAQ multipliers observed in a number of clinical trials: ASPIRE, ATTRACT and GO-AFTER.

The Observed HAQ Multipliers from ASPIRE, ATTRACT and GO-AFTER are shown on the figures below:

Figure 1

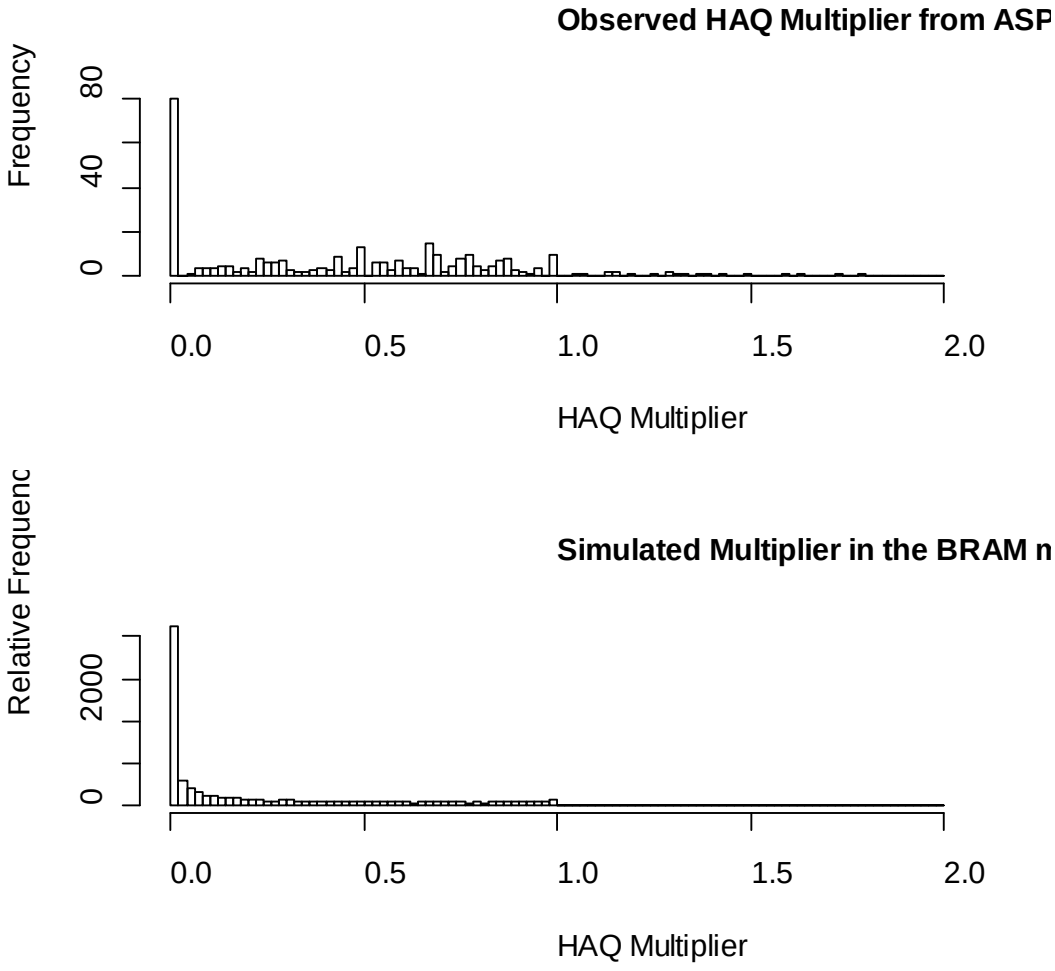


Figure 2

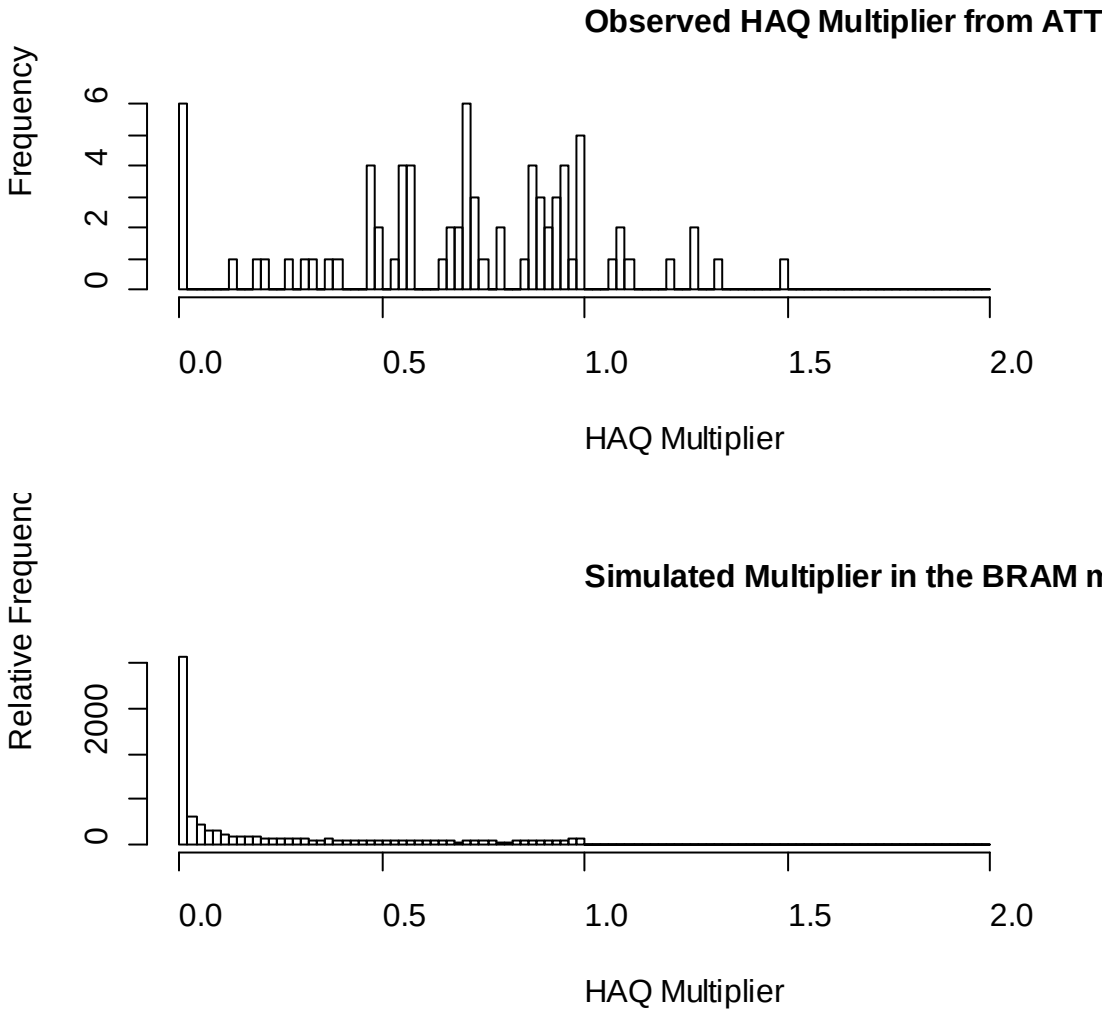
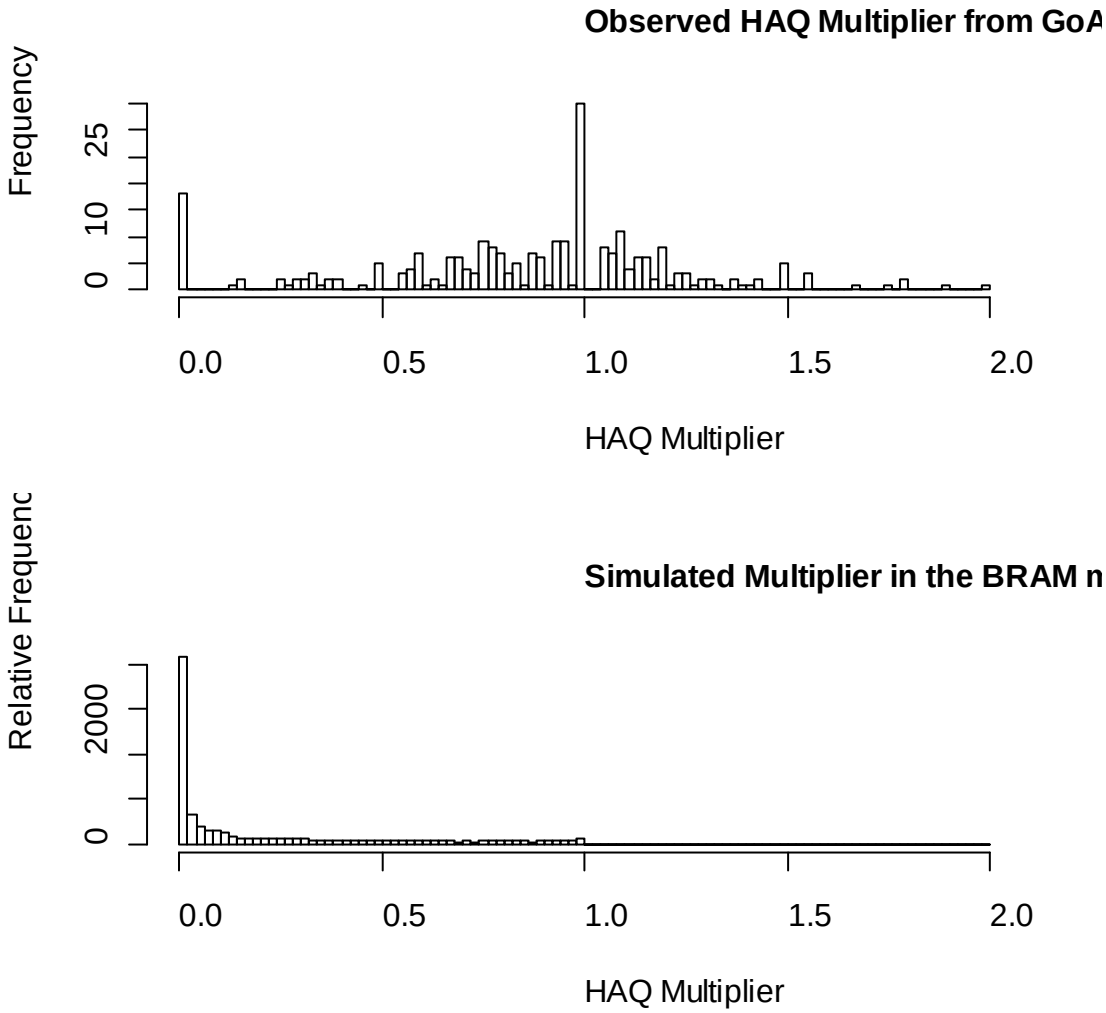

Observed HAQ Multiplier from ATT
Frequency
0
2
4
6
0.0
0.5
1.0
1.5
2.0
HAQ Multiplier
Relative Frequenc
Simulated Multiplier in the BRAM n
0
2000
0.0
0.5
1.0
1.5
2.0
HAQ Multiplier

Figure 3



In all cases the observed distribution is multimodal with a peak with a value of zero representing patients whose HAQ declined to zero and then a distribution with a peak between 0.5 and 1 representing those patients whose HAQ did not decline to zero. This is particularly noticeable in the GO-AFTER study.

As displayed in above figures, the simulated HAQ multiplier used in the BRAM model does not appear to provide a good approximation of the results observed in actual trials. The model does not appear to have face validity with respect to its most critical component, the HAQ multiplier.

The HAQ multiplier forms the backbone of the model and represents differential therapeutic effects between the various biologics. An artificially simulated HAQ multiplier, unrepresentative of the true effectiveness of biologics, can lead to erroneous conclusions about the treatment effects thus leading to unreliable ICERs. Schering-Plough therefore recommends that the HAQ be sampled from a real, clinical dataset rather than from a simulated HAQ multiplier.

- **Beta distributions for HAQ multipliers arbitrarily assigned**

Infliximab Beta distributions for HAQ multipliers were arbitrarily assumed equivalent to etanercept (TAR, Section 6.3.1.2, Page 210) with no explanation of the rationale as to why Bingham 2009 provides the most appropriate point estimates. As discussed in more detail above on Page 10, this input underpins the efficacy distinction between the assessed biologics.

- **Short term efficacy studies used to inform true 'survival'**

The WMHTAC report excludes the OPPOSITE trial (Open Pilot Protocol of patients with rheumatoid arthritis who Switch to Infliximab after an incomplete response to Etanercept) within the clinical effectiveness assessment (TAR, Section 2.4.1, Page 19) yet then inconsistently uses this study to inform the probability of early quitting of infliximab (TAR, Section 6.3.1.2, Page 211). The WMHTAC concluded that the OPPOSITE trial did not clearly define the population and the comparator was determined to be inappropriate. Therefore, this study should not inform a point estimate which has large implications on the resulting ICERs.

Furthermore, it does not appear valid to use short term efficacy studies to assess true "survival" or persistence of treatment as study patients may have treatment discontinued for non-clinical reasons. Data on persistence of treatment is best taken from retrospective 'real world' reports such as registries (eg, the BSR registry).

- **Conventional DMARD effectiveness overestimated**

The WMHTAC report inappropriately assumes that the change in HAQ for conventional DMARDs post-biologic in late RA is equivalent to half of the effectiveness in early RA (TAR, Section 6.3.1.2, Page 209). In reality however RA patients respond quite well to conventional DMARDs (55-56% ACR 20 and 30-33% ACR 50) as seen in the early RA DMARD trials,.[12] However, RADIATE tocilizumab data reported much lower response rates to conventional DMARDs in late RA patients following failure on a TNF inhibitor (10.5% ACR 20, 6.6% ACR 50, 2.6% ACR 70)[13]. Merely halving the early RA change in HAQ to determine the effectiveness for late RA overestimates the efficacy of salvage DMARDs. This reduces the relative cost-effectiveness of the comparators and skews the resulting ICERs. We believe the body of clinical opinion supports the contention that the further deployment of DMARDs in patients who have already failed DMARD and TNF inhibitors is not an effective intervention and does not lead to significant improvement in disability.

- **Difficulty in validating the model**

The NICE project team was aware of complications in transmitting the model to manufacturers. However, no attempt was made to ensure receipt of the economic model (ie send a confirmation email without the model to determine that it had been received). Schering-Plough made several requests for the economic model, with no received reply. Upon calling the project manager on 21 December 2009, the model was received to an external email address. At this time, Schering-Plough had been told that several manufacturers had experienced difficulty receiving the model. As a result, Schering-Plough has been unable to validate the code in the limited time available.

Furthermore, the 2,000 lines of source code are sparsely commented on and compounds an additional burden on the validation process. Schering-Plough requests additional details on the due diligence processes which NICE have undertaken to ensure the programme code is indeed valid.

The TAR in its current form does not assess all of the available evidence to inform this appraisal. Overall, inconsistencies in the model inputs and accompanying text seriously undermine the credibility of the assessment. Based on the concerns raised above Schering-Plough would like question the validity of the TAR and believes that significantly more work is needed before the TAR is presented to the committee.

Once again, we are grateful for the opportunity to comment on the TAR and look forward to continued dialogue with NICE regarding the issues raised in this response.

Sincerely,
Kind regards

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[redacted]
[redacted]
Schering-Plough

[1] Genentech Inc, Biogen Idec Inc, and FDA. Important Drug Warning Regarding Rituxan (Rituximab). October 2009.
[2] Carson, KR et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood* 113, 4834-4840:2009.
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[5] NICE Final Appraisal Determination (TA 133), Omalizumab for severe persistent allergic asthma, August 2007, available at http://www.nice.org.uk/nicemedia/pdf/FADOmalizumabAsthma.pdf.
[6] NICE. Crohn's Disease: Infliximab and adalimumab. Appraisal Committee Document. Section 4.3.11. Available from: http://www.nice.org.uk/guidance/index.jsp?action=folder&o=46233
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[8] Smolen JS, Kay J, Doyle MK et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor α inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase II trial. *Lancet* 2009.
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[11] Tocilizumab ACD 2, Available at: http://www.nice.org.uk/guidance/index.jsp?action=article&o=46642
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[13] Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008; 67:1516-1523.