31 January 2007

[redacted]

Dear [redacted]

Single Technology Appraisal – Varenicline for smoking cessation

The Evidence Review Group, ScHARR, and the technical team at NICE have now had an opportunity to take a first look at the industry submission document and economic model submitted by Pfizer. In general terms they felt the document and model were well presented and clear. However the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data at this early stage.

The comments and queries included in this letter are divided into two sections:

- **Clarification of the data and data sources – Clinical data**
- **Clarification of the data and data sources – Tables**

Both ScHARR and the technical team at NICE will be addressing these points in their reports. As there will not be any consultation on the evidence report prior to the Appraisal Committee meeting you may want to do this work and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by Wednesday 14th February. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

If you present data that is not already reference in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Yours sincerely,

Meindert Boysen, Pharmacist MScHPPF
Associate Director - STA
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarifications

A1. Please could you explain why Pfizer has not used the direct trial of varenicline versus NRT as the base case calculation for clinical and cost effectiveness of varenicline versus NRT? It is unclear what reasoning is behind your decision to prefer an indirect comparison over a 'head-to-head' RCT that directly compares the technology and the appropriate comparator. See also the NICE reference case in the Guide to the Methods of Technology Appraisals – sections 3.2.2.1 and 5.4.1.3 – and the preamble to section 5 of the 'specification for manufacturer/sponsor submission of evidence. Please also include in section 5.9 - 'interpretation of clinical efficacy' - your review of the earlier decision to exclude the direct comparison from the estimation of clinical efficacy and the impact this may have on the conclusions to be reached in 5.9.1.

A2. Please provide reasons why you have not considered using a 'multiple treatment comparison' approach to answering **all** the comparisons presented in your decision problem.

A3. Please could Pfizer request that Wu and colleagues make the event numbers available for all the analyses they present, in order that we can check this work? Rather than using existing Cochrane reviews which compare Bupropion and NRT to placebo, Pfizer has contracted a team from McMaster University, to produce a single systematic review of all three active interventions directly and indirectly compared. Some results presented by Wu and colleagues are different from those presented by Cochrane reviewers (Hughes for bupropion, Silagy for NRT and Cahill for varenicline) and validated by the ERG.

A4. Please quote in full the passages of the Wu review that were used, and the source of any other data used. Please can Pfizer also justify why treatment-specific efficacy rates were used instead of relative measures. Table 41 (p. 95) presents efficacy rates, the source of which is not transparent. There is no legitimate method in epidemiology for

pooling rates. Pooling, or 'meta-analysis', produces a weighted average of the relative measures of effect (in this case, odds ratios) from individual studies. The source given for the efficacy rate for NRT is the Wu systematic review (not in bibliography, but assumed to be *BMC Public Health* 2006, 6:300). The ERG notes that nowhere does Wu present rates, only odds ratios. Please make the full workings available that enabled Pfizer's analysts to convert pooled odds ratios presented in Wu to the efficacy rates presented in Table 41.

A5. The manufacturer's submission claims (p. 109) that the Pfizer analysts have used odds ratios to generate the probabilistic sensitivity analysis (PSA). The ERG has thus far been unable to find any odds ratios in the model. Please can Pfizer tell us where the odds ratios and 95% CIs are contained in the model? If this information is in fact not correct, please can they tell us how they have sampled from probability distributions for efficacy within the PSA without odds ratios and 95% CIs?

Section B: Tables

B1. Please make the correct event numbers available for tables 22 and 23 (p. 54). They probably present erroneous event numbers and rates for NRT (probably pasted without correction from tables 20 and 21).

B2. A minor query in Table 41, the submission suggests an efficacy rate of 15.7% for Buproprion, yet the model suggests this value is 15.5%. Which value is correct?