Consultee and commentator responses to the review proposal consultation of NICE Technology Appraisal Guidance No 75 & 106 Hepatitis C – peginterferon alpha and ribavirin (mild and moderate)

Consultee/commentator	Comment
NPHS Wales	NPHS Wales is not aware of any evidence which would suggest that an earlier review would be beneficial or of relevant research.
Royal College of Nursing	Nurses working in this area of health have reviewed proposals to review the above health technology guidance. There are no additional comments to add with regards to the proposal. Thank you for the opportunity to participate in this.
Department of Health	We note that one area (upon which several scientific papers have been published since the original guidelines were produced) concerns the duration of treatment. We feel that these have shown that treatment for genotypes 2 and 3 may be shortened to 14 to 16 weeks, without reducing the sustained virological response (SVR). In our view, duration of treatment for genotype 1 could also be reduced under certain circumstances, but paradoxically prolonging treatment to 72 weeks has shown increased SVR in "slow responders". We feel that this is something that should be considered,

	should NICE choose to proceed with this review. We are not aware of the proposed license extensions referred to, but two areas not covered in the original guidelines (and not covered by the original licenses) – about which more has been published in the meantime – concern the treatment of acute hepatitis C, a reasonably uncommon diagnosis, and the treatment of children. In the latter category, we understand that larger studies on children are still underway. In our opinion therefore, it may be premature to consider this, and we feel that a clinical view on where things stand would be more beneficial. Could you please consider newer evidence on the appropriate duration of treatment of patients with both genotypes 2 and 3, and genotype 1. Pending clarification of what the proposed license extensions are specifically for, we would be content to leave matters be. If the extensions are for treatment of acute hepatitis C then, in our view, that this should also be considered. In general, our view is that treatment in the acute phase tends to prevent chronic infection, and this would be useful following infections after occupational exposure in health care workers etc.
Roche	HEALTH TECHNOLOGY APPRAISAL – Review proposal of NICE guidance nos 75 and 106; Peginterferon alfa and ribavirin for the treatment of mild and moderate hepatitis C Roche welcomes the opportunity to comment on the proposed review of NICE guidance for peginterferon alfa and ribavirin for the treatment of mild and moderate hepatitis C. In light of forthcoming changes to the Pegasys licence and the evolving therapy area towards Response Guided Therapy we would like you to consider the timing around the following pending licence extensions prior to setting/confirming a date for a review of the currently available data:

	ACCELERATE: Shortening treatment duration in Genotype 2/3 patients Type II Variation 60 day (EMEA/H/C/395/II//33). Submitted 9 Nov 07 Approval expected Q2/2008 The ACCELERATE study investigated 16 weeks of therapy versus the standard 24 weeks of treatment in genotype 2/3 patients. It is anticipated that 16 weeks of treatment will be approved for use in a subset of patients with favourable baseline characteristics. REPEAT: Retreatment of previous Non-Responders (pegylated or non-pegylated) Type II Variation 90 day (EMEA/H/C/395/II/36). Submitted 22 February 2008. Approval expected Q3/4 2008 The REPEAT study investigated treating previous ViraferonPeg non-responders. It is anticipated that Pegasys will be approved for the treatment of previous pegylated and non-pegylated interferon non-responders. We believe that it would be beneficial for these data and the associated licence extensions to be included in any future review of the NICE guidance. We would therefore suggest that the review should not be scheduled to commence before Q3/4 2008.
Royal College of Physicians	Please accept this e-mail as confirmation that the Royal College of Physicians is supportive of the proposal to reconsider these guidelines. Key areas of advance since previous guidelines include the tailoring of treatment duration with monitoring of the viral load response to treatment, potentially leading to shorter courses of treatment in many instances, and the significance of weight-related dosing of ribavirin.
Schering-Plough	The trial descriptions below come directly from clinicaltrials.gov and use the U.S brand name for ViraferonPeg, namely PEG-Intron.

	New evidence around existing technologies Full results from a head-to-head trial of pegylated interferon α-2b plus ribavirin versus pegylated interferon α-2a plus ribavirin, titled IDEAL (PO3471), will shortly be released. The objective of IDEAL was to compare the safety and efficacy of the following three treatment regimens in previously untreated adult subjects with chronic hepatitis C infected with Genotype 1: (1) PEG-Intron 1.5 µg/kg/wk in combination with weight based REBETOL (800-1400 mg/day); (2) PEG-Intron 1µg/kg/wk in combination with weight based REBETOL (800-1400 mg/day); and (3) PEGASYS 180 µg/wk plus COPEGUS 1000-1200 mg/day. XXX Results from this trial may be useful in the proposed HTA review. A manuscript outlining the design of IDEAL is available in the March 2008 online issue of the Journal of Viral Hepatitis[i]. License extension for re-treatment (EMEA approval received November 2007, launched January 2008 Schering-Plough has filed for and received a license extension for this combination therapy which covers re-treatment in chronic hepatitis C patients who have previously failed antiviral therapy with an interferon-based therapy. EMEA issued marketing authorisation in November 2007. This license extension was supported by an open-label trial within the broader EPIC3 study program as follows: NCT00039871 PEG-Intron Plus Rebetol Treatment of Chronic Hepatitis C Subjects Who Failed Response to Alpha-Interferon Plus Ribavirin (Study PO2370AM2) The objective of this study was to determine the effectiveness of PEG-Intron 1.5 ug/kg/wk plus REBETOL 800-1400 mg/day in adults with chronic hepatitis C with moderate to

	severe liver fibrosis or cirrhosis who failed to respond to previous treatment with an alpha interferon in combination with ribavirin. Patients who do not respond to PEG-Intron plus REBETOL were enrolled in lon-term maintenance study to evaluate the effectiveness of PEG-Intron monotherapy versus no treatment for the prevention of disease progression (Protocols PO2569 and PO2570 shown in next section.) Preliminary results were published from this trial in 2005[ii]. A summary of final results has been published in a conference abstract[iii]. Schering-Plough expects to have access to the full clinical study report should a manufacturer submission be required for the proposed NICE review. Future evidence and potential license extensions - long-term prevention The EPIC3 programme includes a maintenance phase for subjects who failed re-treatment in P02370 described above. These subjects are randomised in an open-label manner and investigated in the following two randomised trials, which have the same protocol applied in two populations: i) severe disease and ii) moderate-to-severe disease. Results from these two long-term trials are expected in 2009. Consequently, an EMEA license and positive opinion are not likely to be issued before 2010, meaning that an early review of NICE guidance may have to exclude this potential new indication from its work programme. NCT00048724 Peg-Intron for Prevention of Disease Progress in Chronic Hepatitis C Patients With Cirrhosis (Study P02569AM2) The objective of the study is to evaluate the safety and efficacy of PEG-Intron vs. no treatment for the prevention of disease progression in adult subjects with compensated cirrhosis secondary to chronic hepatitis C, who failed to respond to therapy with an a interferon plus ribavirin.

	NCT00049842 Prevention of Disease Progress in Chronic Hepatitis C Patients With Liver Fibrosis (Study P02570AM2) The objective of the study is to evaluate the safety and efficacy of PEG-Intron vs. no treatment for the prevention of fibrosis progression in adult subjects with moderate to severe liver fibrosis secondary to chronic hepatitis, who failed PEG-Intron plus Rebetol treatment in protocol P02370. Summary In general, Schering-Plough supports the update of technology appraisals in the light of new evidence, especially when that evidence led to the licensing of a new indication for the technology. Schering-Plough is in a position to submit evidence to support all of its existing, licensed indications. A further license extension, namely long-term prevention of disease progression in uncured patients with moderate or severe liver disease, is possible within the next two years. The currently proposed NICE review would likely miss this extension if it is granted. It would be worth taking this matter into consideration during topic selection and scoping.

[i] J. McHutchison, M. Sulkowski (2008) Scientific rationale and study design of the individualized dosing efficacy vs flat dosing to assess optimal pegylated interferon therapy (IDEAL) trial: determining optimal dosing in patients with genotype 1 chronic hepatitis C. *Journal of Viral Hepatitis*. doi:10.1111/j.1365-2893.2008.00973.x

[ii] Poynard T, Schiff E, Terg R, Goncales F, Diago M, Reichen J, Moreno R, Bedossa P, Burroughs M, Albrecht J. Sustained Virologic Response (SVR) In the EPIC3 Trial: Week Twelve Virology Predicts SVR in Previous Interferon/Ribavirin Treatment Failures Receiving PegIntron/Rebetol (PR) Weight Based Dosing (WBD). Oral presentation. Sunday, April 17: 40th Annual Meeting of the European Association for the Study of Liver (EASL), Paris, France, April 14-17, 2005.

[iii] D. M. Jensen; B. Freilich; P. Andreone; A. DiBisceglie; C. E. Brandão-Mello; K. Reddy; A. Craxi; A. Martín; G. Teuber; D. Messinger; G. Hooper; M. Popescu; P. Marcellin. Pegylated interferon alfa-2a (40KD) plus ribavirin (RBV) in prior non-responders to pegylated interferon alfa-2b (12KD)/RBV: final efficacy and safety outcomes of the REPEAT study. Poster/Abstract #LB4 AASLD conference 2007.