NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (including reviews of technology appraisal guidance 91 and 222)

Introduction

1. An Appeal Panel was convened on 24 April 2015 to consider an appeal against the Institute's final appraisal determination in the multiple technology appraisal of topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (including reviews of technology appraisal guidance 91 and 222).

2. The Appeal Panel consisted of:

Dr Jon Fear	Chair
Linda Seymour	NICE Non-Executive Director
Colin Standfield	Lay Representative
Dr David Gillen	Industry Representative
Dr Anthony Emmerson	NHS Representative

3. None of the members of the Appeal Panel had any competing interest to declare.

4. The Appeal Panel considered the appeal submitted by Pharma Mar, Madrid, Spain (also "the Appellant").

5. The Appellant was represented by:

Mark Harries	Chief Executive Officer, MAP Biopharma
Beatriz Garcia	Senior Manager, Market Access
José Miguel	Health Economics Research Manager, Pharma Mar
Christian Hill	Director Market Access, MAP Biopharma
Paul Ranson	Legal Representative, Pinsent Masons LLP

6. In addition the following individuals involved in the appraisal were present and available from the Appraisal Committee ("the Committee") to answer questions from the Appeal Panel:

Dr Jane Adam	Technology Appraisal Committee Chair
Janet Robertson	Associate Director, Appraisals
Meindert Boysen	Programme Director, Appraisals
Professor Olivia Wu	Lead Team Member, Health Economics
Dr Steven Edwards	Assessment Group Member, BMJ Technology Assessment Group

7. The Appeal Panel's legal adviser, Eleanor Tunnicliffe, DAC Beachcroft LLP was also present.

8. Under the Institute's appeal procedure members of the public are admitted to appeal hearings and several members of the public were present at this appeal. In addition, several observers were present, but took no part in the proceedings.

9. There are two grounds under which an appeal can be lodged:

Ground 1 (a):	The Institute has failed to act fairly
1 (b):	The Institute has exceeded its powers
Ground 2:	The recommendation is unreasonable in the light of the evidence submitted

10. The Chair of the Appeals Committee (Dr Margaret Helliwell) in preliminary correspondence has confirmed that the appellants had potentially valid grounds of appeal under grounds 1(a) and 2.

11. Trabectedin (Yondelis, Pharma Mar) is a synthetic antineoplastic drug, the structure of which is derived from a natural product originally extracted from the marine Caribbean tunicate. Trabectedin binds to the minor groove of the DNA and bends the helix to the major groove, a process that triggers various events that affect multiple transcription factors, DNA binding proteins and DNA repair pathways, and which disrupts the cell cycle. It has a UK marketing authorisation, in combination with Pegylated Liposomal Doxorubicin Hydrochloride (PLDH), for the treatment of women with relapsed 'platinum-sensitive ovarian cancer'.

12. The appraisal that is subject to the current appeal process is to provide advice to the NHS on the use of multiple technologies including the use of trabectedin with PLDH for the treatment of women with relapsed ovarian cancer; the appraisal also reviewed the technology appraisal guidance 91 (2005) and 222 (2011).

13. Before the Appeal Panel enquired into the details of the appeal points the following made preliminary statements: Mark Harries for Pharma Mar and Dr Jane Adam for the Appraisal Committee.

Appeal by Pharma Mar, Madrid, Spain

Appeal ground 1(a): The Institute has failed to act fairly

Appeal Point 2.2

The Appraisal Committee failed to take into account key differences in baseline characteristics in trial design of relevant studies that have formed the clinical and cost-effectiveness results and subsequent recommendations for the FAD including that of trabectedin.

14. In the preliminary correspondence regarding the appeal, Dr Margaret Helliwell determined that the failure to take into account key differences in baseline characteristics was not a valid appeal point. However Pharma Mar had raised the issue about the conduct of sensitivity analyses in accordance with paragraph 5.2.14 of the Institute's Guide to the Methods of Technology Appraisal and this was deemed to be a valid Ground 1(a) point. The appeal was therefore heard on the basis of this latter point.

15. Mark Harries for the Appellant stated that there was a high degree of variability within the baseline characteristics of included trials in network meta-analysis 1 and highlighted examples from Table 20 from the BMJ Technology Assessment Group's report. He highlighted the variability in the dose of PLDH and differences in population groups and expressed the view that in the Appellant's opinion sensitivity analyses should have been performed to determine the impact of the variability on the outcome, which were not done.

16. Seven trials had reported CA 125 levels which were felt to influence outcome and it was felt that these examples highlighted the need for greater exploratory analysis prior to inclusion of the studies. The appellant was also concerned that written expert evidence which had highlighted concerns with the variability of studies included had not been taken into account and whilst acknowledging that clinicians had been consulted was concerned that the number was low.

17. Dr Jane Adam, for the Appraisal Committee, stated that the Appraisal Committee had considered the inclusion of all trials and felt that there was sufficient homogeneity to allow assessment. She expressed the view that the assessment group and Appraisal Committee had to be persuaded that if sensitivity analyses were undertaken they would provide a more accurate assessment or reduce uncertainty. The Appraisal Committee did not feel that further sensitivity analyses would have been justified in this case.

18. In response to the issue of effect of CA 125 levels it was stated that there was a publication which had shown that CA125 levels did not influence outcome.

19. Professor Olivia Wu highlighted the fact that there were very few studies included in the evidence synthesis and that there always would be heterogeneity and that there was a balance between excluding studies and losing evidence and getting more precise data. The Assessment Group had therefore set out to include all studies and had made an assessment on whether any should be excluded and had concluded that none should be.

20. Dr Stephen Edwards highlighted the fact that the Assessment Group had tried to identify elements of heterogeneity and particularly to identify things that would have an influence on outcome and had used consultation with clinical colleagues at the time to determine this. There were a number of methods including meta-regression analysis but this required a minimum of 10 studies so could not be undertaken in any event.

21. It was emphasised that the Appraisal Committee was aware of the section of the Methods Guidance and had discussed whether any form of sensitivity analysis should be undertaken but it was felt that all trials were relevant and that there was no suggestion that excluding trials would have made the results more accurate.

22. The Appeal Panel referred back to paragraph 5.2.14 Methods Guide. This states:

    "The principles of good practice for conducting systematic reviews and meta-analyses should be carefully followed when conducting mixed and indirect treatment comparisons. In brief, a clear description of the methods of synthesis and the rationale for how RCTs are identified, selected and excluded is needed. The methods and results of the individual trials included in the network meta-analysis and a table of baseline characteristics for each trial must be documented. If there is doubt about the relevance of a particular trial or set of trials, sensitivity analysis should be presented in which these trials are excluded (or if absent from the base-case analysis, included)."

23. The Appeal Panel considered the arguments put forward and acknowledged that there was inevitable heterogeneity between the studies. It noted that the Appellant's argument was about how heterogeneity should be dealt with and not about whether the trials were relevant to the appraisal. The Appraisal Committee had explained that all the trials identified were relevant to the appraisal and that there was no rationale for carrying out sensitivity analyses where some trials were excluded. The Appeal Panel concluded that the Appraisal Committee had not breached paragraph 5.2.14 by not carrying out the sensitivity analyses identified by the Appellant because there was no doubt about the relevancy of the trials.

24. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted

Appeal point 2.4

An incorrect adjustment by the Assessment Group of drug costs for trabectedin and PLDH has been applied resulting in an inaccurate ICER being calculated

25. Mark Harries for the Appellant told the Appeal Panel that the correction made by the Assessment Group was to increase the costs of PLDH to the dose within the marketing authorisation but it had not adjusted the trabectedin dose. The Appellant considered that the drug cost for trabectedin was too high as this had been based on the market authorisation dose and there should have been a reduction in the cost of trabectedin to the average cost of doses used in the OVA-301 trial. He acknowledged that any reduction would have been small but the Appellant was concerned that there were

inconsistencies in the way that the Assessment Group had applied calculations for different technologies and that this had disadvantaged the calculation of the ICER for trabectedin.

26. The Appeal Panel noted that the ICER for PLDH plus trabectedin compared with PLDH alone was £77k (see paragraph 4.3.14 of the FAD). It asked the Appellant if this figure had been recalculated based on the costs it argued for. The Appellant explained that it did not have such a figure but it considered that the adjustment would make a few thousand pounds difference to the QALY.

27. Dr Jane Adam informed the Appeal Panel that the principle outlined in the Methods Guidance 5.5.1 had been used. This states that costs should relate to resources that are under the control of the NHS and personal and social services. Table 144 of the Assessment Group report was highlighted to the Appeal Panel, which showed that the total discounted cost calculated by the Assessment Group had actually been lower than that calculated by the manufacturer and that the difference between the incremental costs calculated using the Assessment Group's scenario analysis and Pharma Mar's estimates was very small. The Assessment Group's value had been used because it was the figure that most closely represented actual clinical practice.

28. The Appeal Panel considered the appeal on this point. It noted that there was very little difference between the Pharma Mar and the Assessment Group figures for incremental costs. The Appraisal Committee had explained its reasoning and considered that it was reasonable that the Assessment Group's value was slightly different from that calculated by Pharma Mar. It could not be said that the Appraisal Committee's recommendations were perverse in the light of the evidence submitted.

29. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted

Appeal point 2.5

Recommendations within the FAD for the use of paclitaxel within its marketing authorisation were based on extrapolated off-label data and costs in the monotherapy platinum resistant/refractory patients

30. Mark Harries, for the Appellant, stated that the essence of this appeal point, as it was not about Pharma Mar's technology, was inconsistency in the assessment of different technologies. A Number of assumptions had been made over the use of paclitaxel in platinum resistant patients and analysis had been undertaken using a lower dose of 80 mg/m^2 weekly rather than the higher marketing authorisation dose of 175 mg/m^2 once every three weeks. There had been an assumption that this lower dose worked just as well as the higher dose and clinical effectiveness data had therefore been taken from studies reporting outcomes after the use of the higher dose. The appellant's view was that this was inconsistent and there should have been application of sensitivity analysis.

31. Mr Harries observed that sensitivity analyses had been done for PLDH at 30, 40 and 50 mg/m^2 per dose. The Assessment Group and Appraisal Committee appeared to be inconsistent in that they were prepared to make assumptions in some situations but not others.

32. Dr Jane Adam stated that the Appraisal Committee had been aware of the issue of the appropriate paclitaxel dose to use in the cost effectiveness analysis. There was some trial evidence (Rosenberg P et al. 2002[1]) which showed that there was no difference in efficacy between the use of paclitaxel at 175 mg/m^2 given once every three weeks and a dose of 80 mg/m^2 given weekly.

33. It had been noted by the Appraisal Committee that oncologists used three weekly paclitaxel at the licensed dose in some clinical circumstances but also chose to use weekly paclitaxel at the lower dose in platinum resistant ovarian cancer patients. Analysis had been undertaken using the 80 mg weekly dose of paclitaxel as this was considered to be the most relevant dose used in the NHS. The Appraisal Committee had felt that the combination of the Rosenberg trial showing no difference in efficacy, along with clinical opinion, that the two different dose regimes were just as efficacious justified using effectiveness values from trials using the once every three weeks dose.

34. From a cost perspective the Assessment Group had used the most likely cost for the NHS which was the weekly regime and the decision to use this approach had been accepted by the Appraisal Committee.

35. Dr Jane Adam for the Appraisal Committee accepted that for transparency it could have carried out cost effectiveness analysis for paclitaxel on the basis of both dose regimes and accepted that this had not been done. She told the Appeal Panel that no request had been made to do so and that if a request had been made this could have been carried out.

36. Mark Harries informed the Appeal Panel that in fact the Rosenberg trial looked at doses of 67 mg/m^2 -V- 200 mg/m^2 so again assumptions had been made in the use of this trial data and stated that the Appellant was concerned over these apparent inconsistencies. He noted that despite the calculation of costs of treatment for the use of paclitaxel at a weekly dose of 80 mg/m^2 the recommendation in the FAD had been to use this within its marketing authorisation i.e. at a dose of 175 mg/m^2 once every three weeks.

37. Dr Jane Adam stated that during the assessment process one company had brought issues to the Appraisal Committee and these were then addressed and comments made. She stated that the Appraisal Committee did not underestimate the difficulties in doing the assessment and that there was no clear guidance on the costs that should be used

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[1] **Rosenberg P, Andersson H, Boman K, Ridderheim M, Sorbe B, Puistola U, Parö G. Randomized trial of single agent paclitaxel given weekly versus every three weeks and with peroral versus intravenous steroid premedication to patients with ovarian cancer previously treated with platinum. Acta Oncol. 2002;41(5):418-24.**

other than the general statement to 'use what was relevant to the NHS'. She stated that she felt that the Assessment Group and Appraisal Committee had done their best.

38. The Appeal Panel were mindful of the difficulties that the Appraisal Committee had in making complex assessments of different technologies with different dosage regimes and the requirement to provide advice to the NHS that was relevant. The Appeal Panel noted paragraph 6.1.13 of the Methods Guide which states:

    "Evidence relating to use of the technology under appraisal outside the terms of its marketing authorisation may be considered during the assessment phase of the appraisal and may inform the Appraisal Committee's deliberations regarding the licensed use of the drug."

39. The use of data from off-label trials did not make the recommendation of the Appraisal Committee unreasonable. However, the Appeal Panel was concerned that the Appraisal Committee had used different methods for choosing the appropriate dose regimes for different treatments, and therefore for calculating the costs upon which recommendations were made. The difference in approach for different treatments had not been adequately explained.

40. The Appeal Panel upheld this appeal point on this ground.

Appeal ground 1 (a): The Institute has failed to act fairly

Appeal Point 2.6
Recommendations for use of off-label PLDH in combination with platinum are unlawful

41. In the final scrutiny letter the Appeals Committee Chair, Dr Margaret Helliwell, explained that the issues about whether the Department of Health acted lawfully when it asked NICE to appraise PLDH in combination with platinum (an off-label use) could not be dealt with by the NICE appeal process. She stated however that concerns about the process by which the extension was dealt with and how this impacted on consultees and commentators was a valid appeal point. The appeal was therefore taken forward on the basis of this issue.

42. Mark Harries, for the Appellant, stated that from the Appellant's perspective the scope for this appraisal had clearly stated that recommendations would be made within the licensing recommendations for the different technologies. When asked whether the Appellant had commented on the inclusion of PLDH plus carboplatin in the scope as an "intervention" to be appraised (page 3), he stated that the Appellant had focused on Network 2 Meta-Analysis within which trabectedin was being assessed and had not concentrated on the interventions being assessed within Network 1 Meta-Analysis in which the PLDH combination with platinum was being considered for platinum sensitive ovarian cancer.

43. It had been noted that in response to the Appraisal Consultation Document there was reference to the need for a recommendation for PLDH and carboplatin. The Appellant pointed out that in the Appraisal Consultation Document, issued in October 2013, the recommendation was only for PLDH in its licensed indication. The second Appraisal Committee meeting had considered the responses to the ACD yet no comment was then made about the possibility of recommending the combination of PLDH and platinum following which a year had passed before the FAD was published in December 2014. It was therefore a surprise to the Appellant when an off-label combination of PLDH and platinum was recommended for the first time within the FAD.

44. Mark Harries for the Appellant questioned why there was a need for a new Department of Health direction to appraise off-label PLDH plus platinum there was not a similar direction to appraise use of paclitaxel off-label.

45. Paul Ranson for the Appellant stated that there was no process to add new products to the scope at that late stage. The Appellant had made a Freedom of Information Act request regarding communication between the Institute and the Department of Health with respect to inclusion within the Final Appraisal Determination (FAD) of a recommendation of an unlicensed combination of PLDH and carboplatin for the treatment of recurrent ovarian cancer. The correspondence showed that during 2014 the Institute had been liaising with the Department of Health about the Ministerial direction. This was eventually issued under Regulation 5 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013.

46. The Institute's technology appraisals are usually carried out under Regulation 7. On questioning by the Appeal Panel's legal advisor, Mr Ranson confirmed that the Appellant expected the Institute's technology appraisal processes to apply to referrals made under Regulation 5 as they did to referrals under Regulation 7.

47. Dr Adam stated that the Appraisal Committee had looked at all treatments and that paragraph 6.1.3 of the Methods Guide gives the Appraisal Committee discretion to consider those treatments it believes are most appropriate to each appraisal. It was acknowledged that the licensing issues have proved to be very complex.

48. Janet Robertson informed the Appeal Panel that there had been some uncertainty about whether or not PLDH was licensed for use in combination with platinum. The Institute had clarified with the MHRA that the licence did not extend to this combination use. It was only once that clarification had been received that the Appraisal Committee appreciated that a recommendation for PLDH plus carboplatin would be beyond the existing licence. She commented that in the appraisal consultation document the Appraisal Committee had not made a recommendation for PLDH plus platinum due to uncertainty about licensing status but by the stage of the FAD the Appraisal Committee had felt that it was no longer acceptable not to recommend this combination treatment due to licensing issues. She commented that it was important to try to resolve the issue of the off label use of PLDH and carboplatin as without adding this treatment combination the new multiple technology assessment guidance would not have added

anything to the previous two guidances TA 91 and TA 222. She noted that it had taken a long time but deemed the matter was resolved and that the Appraisal Committee wanted to make a recommendation.

49. On the question of whether it would have been better, given the complexities, to have issued a second Appraisal Consultation Document (ACD) including this recommendation Janet Robertson responded that the Appraisal Committee felt that it had consulted and did not see that there was value in a further consultation. It was however accepted that it would have been possible to produce a second Appraisal Consultation Document.

50. Meindert Boysen commented that the Appraisal Committee had consulted with the NICE Guidance Executive and that there was no reason to believe that there would have been anything gained in a further consultation.

51. Dr Adam stated that there was a concern over the risk of decommissioning of treatments within the multiple technology assessment and that this would result in a reduction of options available to clinicians especially if there was Taxane sensitivity. She stated that two of the three treatments assessed including the PLDH/carboplatin combination showed overall improvements in survival and one treatment did not. Hence if the Appraisal Committee was not able to recommend this (off-label) combination it would have left just one option for the treatment of patients which was cost-effective. The Appraisal Committee's view was that it was important for patients to have more than one option available. It was acknowledged that this was a very complex issue.

52. Mark Harries for the appellant stated that a second ACD would have given an opportunity to raise concerns over the inconsistency of applying for off-label use for one combination product but not for others such as the altered dose of paclitaxel. The appellants remained unclear why and when the Institute had applied to the Department of Health for permission to include PLDH/carboplatin as a combination therapy and why they had not applied for permission for other drug combinations that were off-label.

53. There was concern from the appellants as to why the Appraisal Committee had gone away from the scope and in their view why they had deviated from the evidence. Mark Harries highlighted the fact that the manufacturer's trial was of a much higher standard than much of the evidence upon which the analysis was made and also highlighted the fact that overall survival very much influences the outcome of trials. The Appellant had great concerns over the use of unadjusted proportional hazards and felt that these did not stand up to scrutiny.

54. The Appellant highlighted the fact that they had allowed the Assessment Group to use individual patient data from their trial which was not available for many other trials and those data had been used in a variety of areas to improve the quality of assessment but that these data had not been used consistently. The Appellant had great concerns over transparency within the process.

55. Dr Adam when asked what disadvantage there would have been to submit a new ACD responded that this depended on whether it was possible to recommend PLDH/platinum

combination or not. It was the Appraisal Committee's view that if it was not possible to recommend the combination therapy then the Appraisal Committee would have to have been reconvened to discuss the way forward. However, it was felt that if the licence issues could be resolved and a recommendation for PLDH plus platinum made, that would not be contentious and that a second ACD was not required.

56. Dr Adam confirmed that the issue with regard to the complexity of the licensing arrangements had not been discussed at the Appraisal Committee meeting, only a decision about the cost effectiveness of the treatment combination. It was not felt to be within the Appraisal Committee's remit to consider the licensing.

57. Janet Robertson responded to the question as to why there had not been a request to the Department of Health to allow the off-licence use of paclitaxel. She explained that as the recommended use of paclitaxel in the FAD was within its licence there did not need to be a further referral from the Department of Health to cover it.

58. Janet Robertson informed the Appeal Panel that methods guide 6.1.13 states that the use of a technology under appraisal outside the terms of its marketing authorisation may be considered during the assessment phase of the appraisal. It was felt, having identified PLDH and platinum as a combination therapy, that this was outwith the licence hence the request to the Department of Health for approval to include within the FAD.

59. Meindert Boysen confirmed the view that the Appraisal Committee can consider relevant evidence but that the issue was in the wording of the formal recommendation within the FAD and that it was felt that PLDH and platinum were clearly outside the licence and hence required the authorisation from the Department of Health to include this combination.

60. It was highlighted that there are technical arguments as to whether an altered dose also makes a product off label. Dr Adam again stated that in her view there was not likely to be any difference between outcomes after dividing the dose of paclitaxel into a weekly dose compared with a once in three weeks dose.

61. Clarification was sought as to when the PLDH/platinum combination was added to the scope and Janet Robertson informed the Appeal Panel that at the scoping stage it was not clear whether PLDH/platinum was to be considered as a treatment or comparator. The Institute had subsequently checked with the MHRA that the combination was not licensed. A similar check was undertaken for paclitaxel and the Summary of Product Characteristics (SPC) confirmed that this was licensed for first time use but not for subsequent use but the dose was considered to be the same. It was confirmed that all the discussions occurred after the ACD was published.

62. Mark Harries again emphasised the Appellant's view that the key element of the scope was that products would be recommended only within their licensing authorisation. They expected trabectedin to be compared with PLDH and paclitaxel as monotherapies, not combined with other technologies.

63. Janet Robertson informed the Appeal Panel that if the recommendation for PLDH/ platinum was not made then the MTA advice would not be helpful so the Institute consulted with the Department of Health about providing guidance on the off-label use of PLDH plus platinum.

64. Paul Ranson, for the Appellant, advised the Appeal Panel that the European law clarified by the 'Poland case' applied to regulation 5 as well as regulation 7 recommendations. His view was that the law could reasonably be extrapolated to exclude 'encouragement' to use off-licence technologies.

65. Clarification was sought of the Appraisal Committee whether, at the scoping stage, inclusion or exclusion criteria for studies were set and whether the Appraisal Committee ever excluded studies of off-label treatments. Dr Jane Adam confirmed that this is not done by the Appraisal Committee as the scope goes straight to the Assessment Group. It was at the first Appraisal Committee meeting that the Appraisal Committee became aware of the complexity around licensing.

66. Janet Robertson stated that the evidence from off-label treatments is relevant to the overall use of the drug. It is frequently the case that data have to be inferred from other treatment regimes. This is made more complex in a Multiple Technology Appraisal as all drugs are under assessment as both treatments and comparators. The Appraisal Committee was satisfied that it had focused on clinical and cost effectiveness so as to give meaningful advice to the NHS.

67. Mark Harries stated that it was only Pharma Mar that made submissions to the appraisal process as all the other drugs under assessment were off patent. He noted that in the discrete Network 2 Meta-Analysis all comparisons were at licensed doses but that unadjusted hazard ratios had been used even though the Assessment Group had acknowledged that they did not hold up.

68. Christian Hill, for the Appellant, stated that he was not involved initially in this appraisal but if a second ACD had been produced with the PLDH/carboplatin recommendation this would have given Pharma Mar an opportunity to make comments.

69. He also stated that if there was a willingness to provide 'meaningful' information for the NHS then, referring back to appeal point 2.2, it was unfair that adjustments for baseline patient characteristics had not been made.

70. The Appeal Panel considered the appeal point. The Appeal Panel accepted the Appraisal Committee's view that the assessment of the data had produced an important and clinically relevant treatment combination that did not have market authorisation.

71. The Appeal Panel considered that the direction from the Department of Health asking it to appraise PLDH plus platinum effectively added an extra technology to this appraisal. It was unclear whether the Institute's appraisal process documents applied to a direction made under Regulation 5. The Appeal Panel noted that in any event the Institute's guidance permitted that the scope be refined (in this case by allowing the appraisal of off-label use) in response to a request from ministers.

72. It appears, from the information provided in response to the FOIA request, that The Guide to the Processes of Technology Appraisal was in place at the time the new direction was made in July 2014. The Guide to the Processes of Technology Appraisal (in place until 1 September 2014) stated at paragraph 2.5.4 and paragraph 2.5.5 that:

2.5.4 If there is a significant length of time between scoping and the start of the appraisal, NICE may need to update the scope to ensure it is still relevant. Depending on the extent of this update, NICE may undertake further consultation with consultees and commentators.

2.5.5 NICE may need to refine the scope further at the request of ministers.

The Guide to the Processes of Technology Appraisal, published on 2 September 2014, contains similar provisions:

2.5.21 If there is a significant length of time between scoping and the start of the appraisal, NICE may need to update the scope to ensure it is still relevant. Depending on the extent of this update, NICE may carry out further consultation with consultees and commentators. An additional scoping workshop is not routinely held.

2.5.22 NICE may need to refine the remit and scope further at the request of ministers.

The Appeal Panel did not agree that the addition of PLDH plus platinum to this appraisal was contrary to the Institute's procedures as it was required by Ministers and therefore falls within paragraphs 2.5.5 and 2.5.22.

The Appeal Panel understood that as a result of the analysis of the whole body of evidence it became apparent to the Appraisal Committee that the combination of PLDH/Platinum was a cost effective and widely accepted therapy within the NHS for the treatment of recurrent ovarian cancer. However this combination did not have a marketing authorisation. The Appraisal Committee had felt that this was an important combination and hence a request was made to the Department of Health for a Ministerial direction as to whether this combination could be included in the FAD.

73. As set out by the Chair of the Appeals Committee in initial correspondence, any arguments about whether it was appropriate for the Department of Health to issue the direction should be raised with the Department.

74. The Appeal Panel concluded that publishing a recommendation for the off-label use of PLDH plus platinum for the first time in the FAD was unfair to consultees and commentators. This was because the introduction of the recommendation was a significant change from the draft recommendations in the ACD and consultees and commentators did not have an opportunity to comment on the recommendation before it was made. It did not appear in the ACD. Moreover, consultees and commentators were not expecting any recommendation on PLDH plus platinum to be made as they had not been informed of the new direction from the Department of Health that the Institute issue guidance on this off-label combination treatment.

75. The Appeal Panel was also concerned over the lack of transparency with regard to the process by which PLDH plus platinum was added to this appraisal. This lack of transparency meant that the Appellant had to obtain information about the new direction through a Freedom of Information Act request. It considered that this lack of transparency also meant that the Institute had not acted fairly. While it may have been inevitable that there was a delay in issuing the FAD, due to the need for Ministerial direction from the Department of Health, it was regrettable that the reasons for the delay had not been explained to consultees and commentators at the time.

76. The Appeal Panel therefore upheld the appeal point on this ground.

77. At the end of the Appeal Hearing the Chair offered an opportunity for any comments to be made that had not been covered in the Appeal Hearing and the Appellants were content.

78. Professor Olivia Wu for the Appraisal Committee addressed an earlier point that had been made by the Appellant suggesting that the Appraisal Group and Appraisal Committee had been selective in their use of data. She expressed the view that this was odd as the Appellant had stated that there should have been much greater selectivity in the studies used within the analysis. She stated that the Assessment Group had looked at the full body of evidence.

Conclusion and effect of the Appeal Panel's Decision

79. The Appeal Panel therefore upheld the appeal point 2.6 on Ground 1(a) that it was unfair not to have communicated transparently and provided an opportunity for consultees and commentators to respond to the proposed recommendation for the use of off-label PLDH in combination with platinum.

80. The Appeal Panel also upheld appeal point 2.5 on Ground 2 that it was unreasonable to recommend within the FAD the use of paclitaxel within its marketing authorisation when data and costs had been extrapolated from off-label dose regimes and had not provided good reasons why this had not been done for all other technologies.

81. The Appeal Panel dismissed all other appeal points.

82. The Appeal Panel sees little benefit in this appraisal going back to the scoping stage, given that the Department of Health has already issued its direction that the Institute provide recommendations on PLDH plus platinum and the Institute must comply with this direction. The Appeal Panel suggests that this appraisal is remitted back to the Appraisal Committee for the issuing of an Appraisal Consultation Document including the Appraisal Committee's recommendation on PLDH plus platinum. The Appraisal Committee should also explain the background to the Department of Health's new direction. Should consultees and commentators wish to comment on the Institute's handling of the new direction they may do so in response to the ACD.

83. There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision and NICE's decision to issue the final guidance may be challenged

by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of publishing the final guidance.