26th January 2012

Dr Margaret Helliwell
Chair, Appeal Committee
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London WC1V 6NA

Dear Dr Helliwell

Re: Final Appraisal Determination - Cabazitaxel for the treatment of metastatic hormone-refractory prostate cancer

Sanofi would like to appeal against the Final Appraisal Determination (FAD) for the above mentioned technology appraisal on the following grounds:

- Ground one: The Institute has failed to act fairly.

- Ground two: The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted.

We are disappointed with the decision of the Appraisal Committee and in the way the FAD has been drafted. Our appeal reflects both process failures by NICE and issues with the Committee's interpretation of key data. Had these failures been avoided, we expect the FAD may have been written differently, and potentially the Committee would have reached an alternative conclusion on the evidence.

The Appendix summarises the disease background and need for cabazitaxel, and the history of the appraisal to date.

Executive Summary:

Ground one: The Institute has failed to act fairly

1.1: The failure to invite clinical or patient experts to the second Appraisal Committee meeting is contrary to NICE's processes and was unfair.

1.2: The Committee has failed to properly take account of various sources of evidence provided by the manufacturer through the consultation process; or has failed to explain why these have been disregarded.

1.3: The Committee failed to submit questions to Sanofi in relation to the evidence and prohibited Sanofi from commenting on matters of factual accuracy during the Appraisal Committee meeting; this is contrary to NICE's processes.

1.4: The basis for the Committee's conclusion that utility values for second-line metastatic prostate cancer process must be lower than demonstrated by EAP is unexplained

Ground two: The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted

2.1: The description of the EAP trial was misinterpreted, resulting in perverse conclusions in the FAD.

2.2: Data from the EAP trial, and additional contextual data from the literature, were incorrectly interpreted resulting in perverse conclusions in the FAD.

2.3: The Committee failed to understand the nature of interim data, resulting in perverse conclusions in the FAD.

1. Ground one: The Institute has failed to act fairly

1.1: The failure to invite clinical or patient experts to the second Appraisal Committee meeting is contrary to NICE's processes and was unfair.

No clinical experts were invited to attend the second Appraisal Committee meeting. The NICE Process Guide states that clinical experts should always attend the first meeting of the Appraisal Committee and that, in relation to the second meeting: "if clarification of issues raised during the consultation period is required, the Chair of the Appraisal Committee can, at their discretion, invite one or more of the clinical specialists, NHS commissioning experts or patient experts to attend" (Paragraph 3.5.39 of the STA Process Guide). The reason for this is emphasised in section 3.4.20: "It is important that sufficient expertise feeds into the technology appraisal."

In the ACD, the Appraisal Committee raised concerns related to how patients experience their disease and respond to treatment. This issue was, accordingly, addressed in detail in the response to consultation. In circumstances where the issue had been explicitly identified as an area of uncertainty by the Appraisal Committee, it was necessary for the clinical experts to be present at the second meeting of the Committee as without this expertise, the Committee clearly could not interpret, refute or confirm the nature of feedback received as part of the consultation. In these circumstances, the failure by the Chair of the Appraisal Committee to exercise their discretion to call the clinical experts to the meeting was unfair.

One area of debate that expert clinical opinion would have helped resolve for the Appraisal Committee was in relation to the interpretation of utility data collected during the cabazitaxel Early Access Programme (EAP) trial. The extent to which patients' experiences of their disease and their treatment were captured by the EQ-5D data, and the appropriate interpretation of this information in light of the knowledge of the clinical experts could not be thoroughly explored by the Committee in their absence or properly understood by the Committee. This is clear from the apparent misunderstanding of these data in paragraph 4.6 of the FAD.

1.2: The Committee has failed to properly take account of various sources of evidence provided by the manufacturer through the consultation process; or has failed to explain why these have been disregarded.

In our response to the ACD, updated utility data were provided from a second interim analysis of the EAP trial. This increased the information available to the Committee and lent further weight to the results of the first interim analysis, replicating the trends seen and increasing the patient numbers. We also provided several sources of evidence that support, with reasonable consistency, the utility values found through the EAP. These do not appear to have been appropriately and fully considered. This is contrary to NICE's principles and processes (section 3.5.38: "If an ACD is produced, the Appraisal Committee meets again, with members of the public and press observing, to consider the ACD in the light of the comments received").

The relationship between performance status and expected utility and the supporting evidence related to this provided through the consultation process does not appear to have been considered. This relationship was not discussed in the open part of the Appraisal Committee meeting and there is no reference to it in the FAD. The failure to adequately consider this relationship and the evidence supporting it or, alternatively, the failure to explain why they have been disregarded is unfair.

The Appraisal Committee appeared to express concern that the EAP utility values for stable disease were too high. The FAD notes that the Committee agreed that these were "implausible because people with metastatic prostate cancer refractory to docetaxel treatment would be expected to have a poorer quality of life". This disregards the important influence of patient performance status on expected utility. Sanofi provided evidence related to this during the ACD consultation. As highlighted within our ACD response, a simple examination of the definition of ECOG performance status (0 and 1) and responses that could reasonably be expected to correspond on the EQ-5D scale clearly indicates EQ-5D scores in the range of those found in the EAP would be expected.

As stated in our ACD response, "The ECOG classification system describes ECOG Grade 0 as "Fully active, able to carry on all pre-disease performance without restriction". ECOG Grade 1 is described as "Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work". Based on these descriptions, it is reasonable to expect a mixture of mainly level 1 and level 2 responses to the EQ-5D, which would be consistent with utility values in the range of 0.7 – 0.8."

In our response to the ACD we also referred to a study by Pickard et al (2007) which reported utilities in > 500 patients with advanced (Stage III/IV) cancer split by ECOG status. This study reported a mean utility values of 0.85 for ECOG 0 patients, and 0.73 for ECOG 1 patients.

However, the relationship between performance status and utility and the relevant evidence supporting this was not discussed at the second Committee meeting and is not discussed in the FAD.

We consider that the failure to give a proper and reasoned consideration to the various sources of information on utility, which taken together present a consistent view that utility scores in this population would be reasonably high, resulted in important information being disregarded and is fundamentally unfair.

1.3: The Committee failed to submit questions to Sanofi in relation to the evidence and prohibited Sanofi from commenting on matters of factual accuracy during the Appraisal Committee meeting; this is contrary to NICE's processes.

During the second Appraisal Committee meeting the Sanofi representatives became aware of a number of misunderstandings and/or misinterpretations of the EAP data, but were not permitted to clarify the position. This is a breach of NICE's processes – as outlined in section 3.4.21 – 22 of the Process guide ("The Chair will ask these representatives to respond to questions from the Appraisal Committee. The Chair will ask the representatives to comment on any matters of factual accuracy before concluding part 1 of the meeting.") and section 3.5.7 ("Clinical specialists, NHS commissioning experts, manufacturer representatives and patient experts respond to questions from the Appraisal Committee and provide clarification").

The areas where factual matters were misrepresented during the meeting included in particular:

- The incorrect interpretation of patient numbers at Cycles 2 and 4 of the second interim analysis as being indicative of high levels of drop-outs

- The relationship of estimated mean utility values for 'baseline' and 'stable disease'. The Sanofi representatives sought to clarify these misunderstandings during the meeting but were not given the opportunity, and were cut short during their opportunity to speak at the end of the meeting.

Immediately following the dissolution of Part 1 of the meeting the Sanofi representatives addressed these concerns to a member of the NICE secretariat who apparently appreciated the issues raised by Sanofi and agreed to relay them to the Chair and Committee during Part 2 of the meeting. While this would not provide a proper substitute for the required participation by Sanofi during the meeting, it would appear from the FAD that even the information we passed to the Committee via the Secretariat was not considered.

The failure of the Committee to permit Sanofi's representatives to provide clarification and correct matters of fact is contrary to NICE's processes and is fundamentally unfair. Furthermore, this defect in the process has resulted in inadequately supported conclusions being reached.

1.4: The basis for the Committee's conclusion that utility values for second-line metastatic prostate cancer process must be lower than demonstrated by EAP is unexplained

As highlighted above in section 1.2, the literature describing the influence of performance status on EQ-5D scores provides a strong rationale for believing that it is reasonable to expect utility values for patients with mHRPC in the range of 0.7 – 0.8 for patients with an ECOG performance status of 0 – 1. The Appraisal Committee did not present in the FAD the evidence supporting their contrary view that these patients would be expected to have worse scores and the basis for their position lacks transparency. This has prejudiced Sanofi in its ability to respond to consultation in this appraisal.

Ground two: The conclusions expressed in the FAD are not reasonable in light of the evidence submitted

2.1: The description of the EAP trial was misinterpreted, resulting in perverse conclusions in the FAD.

The EAP trial, which is the core source of utility data for cabazitaxel, appears to have been misinterpreted, and the disposition of patients eligible for cabazitaxel seriously misunderstood. This is despite clarification provided following the ACD both from Sanofi and from the EAP triallists (led by Professor Johann de Bono).

The FAD notes that "the manufacturer based the utility value for the stable disease state on a small selected sample of patients". The FAD goes on to note that: "The Committee also agreed that patients who participate in trials may be healthier than other patients for whom cabazitaxel might be appropriate, because to participate in studies involves time and travel to hospital." The Committee also noted that "open label designs such as in the early access programme bias results towards a beneficial effect as the outcomes are based on patient's self assessment."

We consider that these points represent serious misunderstandings of the EAP trial design and the patients for whom clinicians will seek to treat with cabazitaxel. Firstly, the "selected" sample of patients were in fact included in the EAP trial on the same basis as those included in the TROPIC trial, which was considered by the Committee as generalisable to the UK (FAD section 4.4). These patients can be characterised as fit enough, willing and able, to tolerate a further chemotherapy regimen; they are of a high performance status, namely ECOG 0, 1. The participants in the EAP trial are therefore fully representative of those patients who would be considered by clinicians to be suitable to receive cabazitaxel.

The Appraisal Committee's comment that participation in the EAP in some way selected healthier patients overlooks the fact that the majority of patients receiving cabazitaxel, or indeed any other intravenous chemotherapy delivered in a hospital setting, will similarly need to travel to receive their medication. It is therefore illogical to suggest on this basis that patients who travelled to hospital to receive cabazitaxel

through the EAP are necessarily healthier than those who are receiving it in current clinical practice.

Finally, the Committee expresses doubts about the usefulness of the EAP data as it is open-label, and based on patient self-assessment. However, the EQ-5D questionnaire, administered to patients, is in fact a requirement of the NICE reference case, and consequently, patient self-assessment cannot legitimately be considered a weakness. Further, the objective of the EAP was not to perform comparisons against a control, but was to collect descriptive data to allow assessment of the utility of patients receiving cabazitaxel – with this objective, we do not consider that the open-label nature introduces appreciable bias.

For these reasons we believe the interpretation of the EAP trial, as set out in the FAD is inconsistent with the available information and perverse.

2.2: Data from the EAP trial, and additional contextual data from the literature, were incorrectly interpreted resulting in perverse conclusions in the FAD.

We consider that the interpretation of data from the EAP does not take into account information from scientific literature and that the conclusions reached in the FAD are a perverse in light of the data as a whole.

The interpretation of the EAP relative to other utility data sources is flawed. For example, the FAD section 4.16 notes that "The Committee further noted that the PROTREAT [sic] study indicated lower utility values than the baseline utility values from the second interim analysis of the early access programme." This statement is factually correct, however, the actual difference is very small indeed – the baseline utility reported in PORTREAT was 0.696, while the baseline utility reported in the EAP was [redacted](second interim analysis; the value in the first interim analysis was [redacted]). This difference is not particularly notable, ranging between [redacted] and [redacted] ([redacted] and [redacted] respectively). It is therefore unreasonable to draw a conclusion that EAP values were higher than other sources based on this evidence.

As highlighted above in section 1.2, the literature describing the influence of performance status on EQ-5D scores provides a strong rationale for believing that it is reasonable to expect utility values in the range of 0.7 – 0.8 for patients with an ECOG performance status of 0 – 1. The Appraisal Committee appear to have disregarded this and have not provided at any point any evidence to support their view that these patients would be expected to have lower utility scores.

The Committee have also expressed concerns about the broader applicability of the evidence, which we believe to be unreasonable; point 4.15 of the FAD states: "Therefore, the Committee was concerned about the uncertainty around the utility value and whether the utility value as calculated from the early access programme could be applicable to the wider population with hormone-refractory metastatic prostate cancer refractory to docetaxel treatment." This statement demonstrates a misunderstanding of the patients who will receive cabazitaxel – as described above, and throughout our submission and additional documents, patients who are eligible for cabazitaxel are those patients with good performance status who are willing and able to tolerate further chemotherapy. What is important in this appraisal is that utility values are reflective of

the cabazitaxel-eligible patient population, rather than being reflective of the entire docetaxel-refractory mHRPC patient population.

Overall, it appears that there is a belief, unsubstantiated by evidence, that the utility values for second-line mHRPC patients suitable to receive cabazitaxel must be lower than those found by the EAP, the only trial that has collected EQ-5D data in this setting. The difference between baseline utility found in PORTREAT versus that found in the EAP appears to have been interpreted as greater than it actually is. The nature of the relationship between ECOG performance status and utility and the implications for interpretation of the EAP utility data has been disregarded. As such, we consider that the conclusions drawn on the EAP utility data in the FAD represent a perverse understanding of the available data.

2.3: The Committee failed to understand the nature of interim data, resulting in perverse conclusions in the FAD.

There is an apparent failure in the FAD to understand the nature of interim data, specifically, that from the EAP. The FAD section 4.15 notes that "There were markedly fewer patients assessed in cycle 4 of the second interim analysis than in cycle 2 of the first interim analysis. The Committee noted that the manufacturer had not explored the reason for this." This is incorrect. The reason for these differences is very simple; because trials do not recruit every patient on the same day, not all patients had sufficient time to reach each milestone measurement when the time the interim analysis was performed, consequently, there are fewer patients with cycle 4 measures and more patients with cycle 2 measurements. As noted in 1.3 above, we were not given the opportunity to clarify this at the Committee meeting, but did raise this immediately afterwards with the NICE secretariat.

Following on from this, there appears to be a considerable misunderstanding about the potential impact of our approach to pooling cycle 2 and cycle 4 data. FAD section 4.15 notes "The Committee was also concerned that the manufacturer had pooled values for patients who had participated in the early access programme from cycle 2 and cycle 4, and insofar as their disease had not progressed at cycle 4, their disease may have been milder and their utility values higher than that of typical patients with hormone-refractory metastatic prostate cancer." However, as can be seen from the actual point estimates provided in our response to the ACD, the values at cycle 2 and 4 were very similar ([redacted] and [redacted]). There is thus very little difference between the value for cycle 2 used alone ([redacted]) and that found when cycle 2 and cycle 4 are pooled ([redacted]). The impact of using pooled values as opposed to using cycle 2 alone is therefore negligible. To raise concerns over the pooling of values therefore represents a perverse understanding of the data we had provided.

Request for an Oral Hearing

Sanofi requests an oral hearing for the determination of this appeal.

We anticipate that when these appeal points are upheld the sections of the FAD related to the points described in this appeal document will be rewritten, and we offer the Institute our cooperation with any further clarifications on the evidence it may require.

I look forwards to hearing from you shortly.

Yours Sincerely

Charlie Nicholls
Head of Health Outcomes

Appendix

Introduction to the Technology

Metastatic hormone-refractory prostate cancer (mHRPC) is the most advanced stage of prostate cancer. The gold standard first-line treatment for mHRPC is docetaxel chemotherapy however disease progression following docetaxel is inevitable. Until recently, there were no available therapies which had demonstrated a survival benefit in patients who had progressed following docetaxel. Cabazitaxel is a novel taxane chemotherapy specifically developed to overcome docetaxel resistance and was the first therapy to be licensed in this setting. In the pivotal Phase III TROPIC trial, cabazitaxel was compared with mitoxantrone, the most commonly used second-line chemotherapy. Median survival was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group ($p<0.0001$), with a hazard ratio of 0.70 (95% CI, 0.59–0.83) in favour of cabazitaxel.

History of the Appraisal

Sanofi was notified of NICE's intention to carry out a single technology appraisal of cabazitaxel (Jevtana) for the treatment of metastatic hormone-refractory prostate cancer in 2010. The concise history of the appraisal was as follows:

23rd April 2010: Draft Scope issued.

25th June 2010: Scoping Workshop.

17 March 2011: Marketing authorisation for cabazitaxel received.

6 April 2011: Final Scope issued.

6 May 2011: Decision Problem Meeting.

8 June 2011: Sanofi provides submission to NICE. This included data from the first interim analysis of the cabazitaxel early access programme.

28 June 2011: Sanofi received Evidence Review Group (ERG) requests for clarification.

12 July 2011: Sanofi responds to ERG request for clarification

8 August 2011: ERG issues report commenting on the Sanofi submission.

6 September 2011: First meeting of the Appraisal Committee

23 September 2011: Appraisal Consultation Document (ACD) issued to consultees.

21 October 2011: Sanofi provides comments on the ACD. This included data from the second interim analysis of the cabazitaxel early access programme.

28 October 2011: Sanofi receives ERG critique of the additional data provided in the response to the ACD.

1 November 2011: Second meeting of the Appraisal Committee

4 January 2012: Final Appraisal Determination (FAD) issued to consultees.