[redacted]
Chair, Appeal Committee
National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU

6 December, 2013

Dear [redacted]

Appeal against the FAD for aflibercept for the treatment of metastatic colorectal cancer

Thank you for your letter dated 22 November 2013, setting out your preliminary views with respect to the admissibility of the points of appeal raised in our appeal letter of 14 November 2013. We now respond to these matters, providing additional clarification of our appeal, before you make your final decisions with respect to the admissibility of each of the matters which is the subject of our appeal. Our comments are set out below, by reference to the individual appeal point to which they relate.

1.1. In concluding that aflibercept "did not meet the criteria for an end of life therapy as defined by NICE" the Appraisal Committee has incorrectly applied the Supplementary Advice issued by the Institute.

You express the preliminary view that point 1.1 of our appeal should not proceed to a hearing on the basis that:

- You say that "*Section 2.3 of the Supplemental Advice seems to be very clearly to guide and inform the Section 2.1 consideration, rather than being a stand-alone criterion*";
- You express the view that a Committee should not "*be obliged as a matter of fairness to reach a conclusion on what would be a hypothetical question*".

However, the clear wording of the Supplemental Advice is inconsistent with the construction placed in your letter. In particular, Section 2.1 states that the advice should be applied when the criteria listed at 2.1.1-2.1.3 are satisfied. If those conditions are satisfied, a Section 2.2 consideration is required. Finally, and "*in addition*" the Appraisal Committee needs to be satisfied of the matters at Section 2.3. There is no suggestion that the criteria at Section 2.1 are dependent upon the matters in Section 2.3, to determine eligibility for consideration and the term "*in addition*" at Section 2.3 confirms that this is a further test after eligibility has been determined, but before guidance is issued.

In our appeal letter, we explained why the distinction is important; however we are concerned that our explanation in this respect may have been unclear. In brief, it is fundamentally important for stakeholders to understand whether a product falls within the scope of the end of life criteria, even if, ultimately, it is not thought appropriate to issue guidance as a result of Section 2.3 matters. As a matter of fairness, stakeholders should be satisfied that the reason why they have been unsuccessful represents a proper construction and application of procedures. In this case, Sanofi believes that the Appraisal Committee's conclusion that aflibercept does not satisfy the criteria for the Supplementary Advice is unfair and incorrect; the issue is not hypothetical, but has implications not only for the ultimate conclusions reached by the Appraisal Committee in the FAD, but for the potential options open to Sanofi, for example through the rapid review procedure. It is of course in the interests of all parties for Sanofi (and other manufacturers in other appraisals) to have the ability to consider their positions in the way suggested.

Finally, the proper construction and approach to the Supplemental Advice is clearly an important procedural point. So far as we are aware, the issue raised by us at Point 1.1 of our Appeal, has not previously been appealed and we therefore believe the matter should properly be permitted to proceed to an oral hearing.

1.2. The Appraisal Committee's conclusions with respect to the appropriate time horizon for this appraisal are unclear and relevant evidence appears to have been disregarded

In your letter you suggest that the Committee accepted a 15 year time horizon for modelling the effects of treatments for metastatic colorectal cancer and that the alternative time horizons reviewed by the Committee simply reflect a means to explore uncertainty. You say that you have seen no evidence in the FAD that the Committee disregarded data submitted by Sanofi.

However, the issue raised by Sanofi is the fact that, while the Committee did appear to accept that a 15 year time horizon was most appropriate, the Appraisal Committee repeatedly referred to uncertainty regarding the duration of survival (for example by stating that long term survival was "very unusual") and ultimately based decisions on a time horizon of 5 years.

In considering whether a 5 year time horizon is in any way plausible (including in the context of consideration of uncertainty), the Committee has referred to evidence from the US SEER database which confirmed long term survival in a proportion of patients (paragraph 4.7 of the FAD[1]) and rejected such information. However, the Committee has given no consideration to any of the other compelling evidence provided by Sanofi, including data from the UK[2], which suggests that long term survival in patients with metastatic colorectal cancer is becoming more common (including in the absence of resection of liver metastases) and supports the data from the SEER database (listed at Point 1.2 of our appeal). As you say in your letter, this is not referenced in the FAD, and there is no indication that the Committee has considered it or, if they did review it,

[1] SEER data show 6.9% of mCRC patients surviving beyond 5 years and 4.8% surviving beyond 10 years

[2] From NCIN, which quotes a 5-year survival rate of 6.6% for Dukes Stage D

why they have, nevertheless, taken the view that should be rejected. In this context, the reasons for rejecting SEER, which do not reflect all the other consistent evidence, are inadequate and, based on the totality of the evidence it is unclear why an analysis using a 5 year time horizon, can be the basis for any conclusions regarding the cost-effectiveness of aflibercept or end-of-life criteria - including in the context of investigation of uncertainty.

1.3. The Appraisal Committee's conclusion that the true mean overall survival benefit is likely to be closer to the median survival of 1.44 months, rather than Sanofi's extrapolation of 4.7 months is unexplained and the basis for the Committee's view is unclear

Your conclusions are noted

1.4. The Appraisal Committee has seemingly disregarded evidence indicating that improved survival in patients with metastatic colo-rectal carcinoma may be attributed to improved medical management as well as resection of metastases

You say, in your letter that, while the Committee has accepted that resection of liver metastases improves 5 year survival rates in patients with metastatic colorectal cancer, you are *"less clear what the basis is for the assertion that they have concluded this is the sole factor*". You also say that you do not "*see what the basis is for the Committee having ignored the evidence*" cited by Sanofi.

While, as you say, the Committee has accepted that resection of liver metastases may improve 5 year survival, the Committee referred to the data from the VELOUR trial and commented that only a very small proportion of patients in the trial underwent surgical resection of liver metastases. These data were relied upon by the Committee to suggest that long term survival associated with aflibercept treatment was unlikely.

The thrust of point 1.4 of our appeal is that advances in medical management of metastatic colorectal cancer are also associated with improved long term survival and to that extent we reference additional evidence, including the study by Kopetz et al (2009) and the information identified at appeal point 1.2 above[3]. However, there is no indication in the FAD, that this evidence was considered by the Committee and no indication at any point that they assessed the evidence supporting a view that medical management could be associated with long term survival benefits, consistent with the results of VELOUR and Sanofi's modelling in this appraisal.

2.1 The Appraisal Committee have incorrectly assumed that further follow up data from the VELOUR trial are available and this has influenced their conclusions in this appraisal.

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[3] The Kopetz study concluded "improvements in outcome in metastatic CRC seem to be associated with the sequential increase in the use of hepatic resection in selected patients (1998 to 2006) and advancements in medical therapy (2004 to 2006)."

Your conclusions are noted

2.2 The Committee's conclusion that the data relating to abflibercept were not sufficiently robust to accept that a three month life extension benefit was produced is inconsistent with the available evidence and therefore unreasonable.

Your conclusions are noted

2.3 The Appraisal Committee has provided no explanation for the inconsistencies in its approach to the assessment of the overall survival benefit associated with aflibercept in this appraisal and that for panitumumab in TAG 242: in the absence of an explanation, these inconsistencies suggest an arbitrary approach which is unreasonable.

In your letter of 22 November 2013, you suggest that point 2.4 of our appeal should not proceed to an oral hearing on the following basis:

- You say that neither the Appraisal Committee nor an Appeal Panel could reasonably be expected to be familiar in detail with the evidence and reasoning in other appraisals;
- You say that the fact that the same (or essentially the same) Committee considered an earlier appraisal is not relevant to any inconsistency;
- That consistency can only be desirable between cases which are relevantly alike and that this is rarely the case.

In this case, the Committee was aware of Sanofi's concerns regarding inconsistency between the evidence and consideration of products used for essentially the same indications in two separate appraisals as Sanofi drew it to the Committee's attention in our response to the Appraisal Consultation Document.

We do not agree that it is irrelevant that the Committee which considered an earlier appraisal is essentially the same as the Committee considering the current case. Each case must be considered on its own particular facts and while it is possible that inconsistent decisions will, nevertheless, not be unreasonable, where there are decisions that appear inconsistent, it is necessary for an explanation to be provided. The fact that it is essentially the same Committee that has reached apparently inconsistent decisions is a factor to be taken into account in considering whether or not the inconsistency of the decisions amounts to arbitrariness.

Finally, while we note your comments that appraisals may rarely be sufficiently alike to require consistency, again that will depend on the individual facts of the case. We have explained why the particular issues arising in TAG242[4] require a consistent approach with that followed in the current appraisal and no explanation has been given by the Appraisal Committee to justify an alternative view. In these circumstances, we believe it is appropriate for the matter to be considered at a full hearing, rather than for differences in the appraisals to be assumed against us at the initial scrutiny stage, without proper reasoning by the Committee.

[4] Outlined in sections 4.4.16, 4.4.22 and the summary table of TAG242

2.4 The Committee's rejection of utility data from the mCRC study in favour of an arbitrary estimate for progressed disease is unreasonable.

In your letter of 22 November, you refer to the differing views reached by Sanofi and the Appraisal Committee in relation to the appropriate utility values to be used for the purposes of this appraisal and express the view that both may be reasonable interpretations of the available evidence. While, for the reasons set out in our appeal letter, we do not agree that this is correct, Sanofi has decided not to pursue this point of appeal.

Yours sincerely

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