SANOFI

14 November 2013

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

Dear

Re: Final Appraisal Determination - aflibercept for the treatment of metastatic colorectal cancer

Sanofi wishes 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, which we believe reflects both process failures by NICE, including an inadequate consultation process, and issues arising from the Committee's interpretation of key data. Had the appraisal been conducted fairly and the data been construed reasonably, it is Sanofi's position that the Committee would have reached alternative conclusions on the evidence with the consequence that aflibercept could have been approved by NICE, enabling clinicians and patients in England and Wales to access an effective treatment for metastatic colorectal cancer.

The Appendix provides an overview of aflibercept, and the history of the appraisal to date.

Executive Summary:

Ground one: The Institute has failed to act fairly

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.

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

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

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

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

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.

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

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.

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

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

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.

NICE's Supplementary Advice on end-of-life treatments

NICE's Supplementary Advice on end-of-life treatments is applicable to therapies which may be life extending for patients with short life expectancy and which are licensed for indications affecting small numbers of patients with incurable diseases. For the Appraisal Committee to issue a positive recommendation under the Supplementary Advice, involves a three stage process.

- Firstly, the criteria at Section 2.1 of the Supplementary Advice must be satisfied, including

  > "There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional three months, compared to current NHS treatment..." (Section 2.1.2).

- Where the Section 2.1 criteria are satisfied, the Appraisal Committee is then required to consider the technology as specified at Section 2.2, namely the impact of giving greater weight to QALYs achieved in the later stages of terminal diseases and the magnitude of the additional weight that would need to be assigned to the QALY benefits for the cost effectiveness of the treatment to fall within the current threshold range.

- Finally, in order to issue a positive recommendation, the Appraisal Committee needs to be satisfied of the matters set out at Section 2.3 of the Supplementary Advice, including

  > "The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials of which cross-over has occurred and been accounted for in the effectiveness review)..." (Section 2.3.1).

In other words, a technology may satisfy the section 2.1 criteria, for end-of-life therapies, as defined by NICE, with the result that the Appraisal Committee is required to consider the technology under the Supplementary Advice, but this does not mean that guidance will be issued under the Supplementary Advice unless the assessment under section 2.2 is also favourable and the section 2.3 requirement for robust data is met.

Application of the Supplementary Advice to aflibercept

At paragraphs 4.22 - 4.24 of the FAD, the Committee considered the application of the Supplementary Advice to the use of aflibercept. However the Committee did not apply the correct test as set out in the Supplementary Advice and set out above; the Committee therefore failed to consider that a technology may satisfy the end-of-life

criteria under section 2.1 of the Advice, but guidance may still be rejected because the evidence for extension to life is not robust as required by section 2.3.

Initially, the Committee concluded (paragraphs 4.22 and 4.23), that the criteria for short life expectancy and small patient populations had been met.

However, when the Committee considered the criterion that the treatment should offer an extension to life of normally at least an additional three months, the Committee inappropriately elided the test at Section 2.1.2 of the Supplementary Advice with the test at Section 2.3 (i.e. the Committee combined in a single stage the criterion for determining whether the Supplementary Advice should be applied, with the requirement that the estimates of extension to life should be robust, before Guidance based on such evidence should be issued). Accordingly, at paragraph 4.24 of the FAD, the Committee references the requirements of Section 2.3 of the Supplementary Advice (the requirement for robust evidence before Guidance may be issued under the Advice) as the basis for stating "the Committee therefore concluded that aflibercept did not meet the criteria for an end of life therapy as defined by NICE."

If the Appraisal Committee had applied the correct test, it would have found that aflibercept satisfies the section 2.1 criteria for an end-of-life therapy as defined by NICE

The correct test to apply when determining whether a product satisfies the extension to life criterion at Section 2.1.2 of the Supplementary Advice is that "there is sufficient evidence to indicate that the treatment offers..." such a benefit. It is only if all three criteria under section 2.1 are satisfied, that the Supplementary Advice "should be applied" by the Appraisal Committee and considered in light of the factors at Section 2.2 and, ultimately, at Section 2.3, with the requirement for "robust" estimates of the extension to life.

In considering aflibercept, the Appraisal Committee concluded that the analysis performed by the ERG, which assumed an equal risk of death for all patients beyond the trial period (hazard ratio equals 1.0) represented an acceptable compromise (paragraph 4.14 of the FAD); this assumption resulted in a mean overall survival benefit of between 3,4 and 3.7 months. In these circumstances, it is Sanofi's position that, had the Appraisal Committee applied the correct test of "sufficient evidence" at Section 2.1.2 of the Supplementary Advice, it would have concluded that aflibercept satisfied all three criteria under Section 2.1 and that, in those circumstances, the Supplementary Advice should be applied to the Appraisal.

For the avoidance of doubt, we do not suggest that, as a result of this error by the Appraisal Committee, the Committee was required to issue a positive recommendation for aflibercept following consideration of section 2.3 of the Supplementary Advice (we address the Appraisal Committee's conclusions with respect to the reliability of the evidence at Appeal Point 2.2 below), but simply that the error by the Appraisal Committee resulted in the incorrect conclusion that "aflibercept did not meet the criteria for an end of life therapy as defined by NICE".

The implications of the Committee's error

While Sanofi recognises that the Committee's application of the incorrect test to determine whether aflibercept met the criteria for an end-of-life therapy under the Supplementary Advice did not, by itself, alter the context of the substantive guidance in the FAD, the error by the Committee and the conclusion that "aflibercept did not meet the criteria for an end of life therapy as defined by NICE" is still of fundamental importance to this appraisal and to Sanofi.

Sanofi is entitled to understand why aflibercept has not been recommended for use in NHS patients and to be informed correctly of the target it has to meet in order to obtain a positive recommendation by NICE. The wording of the current FAD states simply that aflibercept does not meet the criteria for an end of life therapy as defined by NICE, when in fact, had the test been applied correctly, the Appraisal Committee would have concluded that aflibercept does meet the criteria set out in Section 2.1 of the Supplementary Advice - even though (subject to Sanofi's appeal at Appeal Point 2.2 below) the data are not viewed as sufficiently robust to support a positive recommendation, at least at the ICER values currently calculated by the Committee.

In order for Sanofi adequately to consider its position (including the possibility of proceeding under the rapid review procedure) it is therefore essential that the determination of the Committee with respect to the application of the Section 2.1 criteria is corrected.

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

While the Committee assumed no continuation of treatment benefit after the end of trial follow-up, the appropriate time horizon for considering the duration of survival in patients treated with aflibercept remains a key issue in this appraisal. However, despite recognising the fundamental importance of this aspect of the assessment, the Committee's conclusions are unclear, appear to change at different points of the FAD and disregard relevant evidence for the duration of overall survival of patients with metastatic colo-rectal carcinoma. This is unfair.

At paragraph 4.13 of the FAD, the Appraisal Committee recognises that "the time horizon should be sufficiently long to capture all the costs and health benefits in the full population (that is a lifetime horizon should be used)" and proceeds to conclude "a time horizon of 15 years was, in principle, appropriate because all patients are likely to have died by 15 years".

However, despite recognising at paragraph 4.13 that a 15 year time horizon was appropriate, at paragraph 4.7, the Committee states: "The Committee was aware that extrapolation periods should reflect the time in which all patients will have died, but that a longer than 5-year survival for patients with metastatic colorectal cancer is very unusual." The relevance of this statement is not explained, in circumstances where as recognised at paragraph 4.13, the time horizon should cover all patients, however unusual and Sanofi's modelling envisaged that only a small proportion of patients would survive beyond 5 years.

Furthermore, despite accepting a 15 year time horizon , at paragraph 4.24, the Appraisal Committee refers again to the substantial uncertainty resulting from the extrapolation of data in order "to capture the very small number of patients who might have very prolonged survival". The Committee therefore appeared to accept the validity of truncating the time horizon to 5 years, as suggested by the ERG, who concluded at paragraph 3.20 "the treatment benefit is unlikely to extend beyond 5 years", despite acknowledging patients might have very prolonged survival. (It should be noted that the ERG also suggest at paragraph 3.20 that a restricted mean based on actual data and disregarding all survival benefit after the end of the trial may be the "more valid" approach and, despite its apparent acceptance of the 15 year time horizon, there is no explicit statement by the Appraisal Committee rejecting this conclusion.)

Finally, while the Appraisal Committee expressed concern about the use of a 15 year time horizon and the "very small" numbers of patients who would survive beyond 5 years, the Committee apparently disregarded data confirming such survival and the reasonable inferences that through the use of various lines of therapy, individuals can survive for considerable periods. At paragraph 4.7 of the FAD, the Appraisal Committee considers certain additional data from the US Surveillance, Epidemiology and End Results (SEER) database relating to survival of patients with metastatic colo-rectal carcinoma, submitted by Sanofi, in response to a request by the ERG. While the SEER database showed that 6.9% of such patients survive for 5 years, the Committee did not consider this evidence reflected the population of patients who would receive aflibercept therapy in accordance with the product's marketing authorisation. However, in reaching this conclusion, the Committee failed to consider the other data submitted by Sanofi, which confirmed comparable survival periods, including:

- National Cancer Intelligence Network (NCIN) in the UK (6.6% 5 year survival for Dukes D stage cancer);

- Long-term follow-up data from the N9471 trial (Sanoff 2008) (5 year survival of 6.6%; the rate for patients treated with first-line FOLFOX was 9.8%.) and

- a paper by Kopetz et al (Kopetz et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009 1; 27(22): 3677-83.) which showed an continued improvement in survival associated with use of medical management (after resections had been censored from the analysis).

Sanofi also referred to the decision of the Appraisal Committee in NICE TA118, which quotes a value of 12% for the 5-year survival rate of mCRC, although this statement is unreferenced.

In summary, it is Sanofi's position (a) that the Appraisal Committee's conclusions regarding the appropriate time horizon are confused and unclear and that (b) that the Committee have not considered substantial consistent evidence demonstrating long term survival of a small but significant group of patients following "medical" treatment for metastatic colo-rectal carcinoma. Overall these failures by the Committee have unfairly contributed to its concerns regarding uncertainties surrounding the survival benefits associated with aflibercept therapy.

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

At paragraph 4.6 of the FAD, the Appraisal Committee refers to the difference between the overall survival benefit of 4.7 months estimated by Sanofi through extrapolation over a 15 year time horizon and the median value of 1.44 months. While the Committee has accepted that a 15 year time horizon is appropriate, they nevertheless concluded that, "given the data from the VELOUR trial, the true mean overall survival benefit is likely to be closer to the median estimate of 1.44 months than the manufacturer's mean estimate of 4.7 months".

The conclusion that the true mean is closer to the median is unexplained and unjustified, and appears inconsistent with the available clinical evidence and conclusions of the Committee, including:

- The Committee's acceptance of a 15 year time horizon;
- The median is clearly an underestimate of the true OS benefit associated with aflibercept. The restricted mean OS benefit (based on data available at the end of the trial with the clearly incorrect assumption, that all remaining patients die immediately at the end of the trial) is 33% higher than the median
- The fact that, at the conclusion of the VELOUR trial, 17.2% of patients randomised to receive aflibercept and 7.9% randomised to placebo were still alive and therefore any figure based on actual data at that point will be an underestimate;
- The consistent evidence (see Appeal Point 1.2 above) showing long term survival in a proportion of patients with metastatic colo-rectal carcinoma
- The emerging data showing increasing survival for patients with metastatic colo-rectal carcinoma as a result of improved medical management rather than resection of hepatic metastases (e.g. Kopetz et al (2009) see above)

Against this background, the Committee's failure to explain its conclusions with respect to the true mean overall survival value for aflibercept or why they have concluded that this value is likely to be closer to the median than the mean calculated by Sanofi, hampers proper response or consultation and is unfair.

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

The FAD appears to reflect an assumption by the Committee that survival improvement in patients with metastatic colo-rectal carcinoma, and long-term survivorship is driven solely by resection of metastases. This assumption is important both for determining the view of the Committee in relation to long-term survivorship and also their approach to

the supgroup of patients, identified by Sanofi, who have metastasatic disease limited to the liver.

Accordingly the Committee makes the following statements in the FAD:

- paragraph 4.3 :"The Committee understood that the proportion of patients with metastatic colorectal cancer who survive over 5 years has increased because of successful tumour resection";

- paragraph 4.7: "It was also aware that, with surgical resection of liver metastases, survival can increase, but that a very small proportion of patients in the VELOUR trial had surgical resection of liver metastases";

- paragraph 4.9: "The Committee also considered that resecting liver metastases to achieve a cure was more appropriate in the first-line setting than in the second-line setting".

However, in reaching these conclusions, the Committee has seemingly failed to consider data presented from Kopetz et al (2009), referenced at Appeal Point 1.2 above, which show that the increase in survivorship over time has been driven partly by improvements in resection but also latterly by improvements in medical management. Nor does the Committee take into account the comments made by Dr Adams at the first Committee meeting when we understood him to say that those patients surviving after first line treatment, and remaining fit enough to receive 2nd line treatment represent a 'self-selected' funnel of patients with greater chance for better survival outcomes.

These conclusions also ignore the rationale for the liver metastases subgroup which was based partly on the fact that this may represent a subset of patients with distinct disease characteristics who have a differential response to therapy and it is this aspect of their disease which results in an improved prognosis, rather than resection of liver metastases. For the avoidance of doubt, Sanofi at no time suggested that the rationale for the liver metastases sub group was linked to resection procedures. which appeared to be the Committee's own rationale, and not one presented in the Manufacturer's submission.

The failure to consider evidence suggesting that improved survival is linked to medical management rather than being limited to effects on resections, has the result that the Committee's consideration of (a) long-term survivorship and (b) the liver metastases subgroup are inadequate and therefore unfair.

2. **Ground 2 The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted**

   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.

At various points in the FAD, the Appraisal Committee, refers to the lack of follow up data from the VELOUR trial, after the cut-off date of 36 months, expressing the view or

otherwise inferring that such data were available but were not provided to NICE by Sanofi. By way of example:

- (paragraph 4.6 of the FAD): "The Committee was aware that the cut-off date for the trial was 07 February 2011, and that the manufacturer had continued to follow up patients for overall survival. The Committee met 18 months after this date, but the manufacturer did not present the Committee with follow up data to support its extrapolation…" .

- (paragraph 4.14 of the FAD) "…As the manufacturer had not provided the follow up data from the trial on which to validate its new approach…".

- (paragraph 4.24 of the FAD) "….in the absence of other evidence (including the lack of data on survival after 07 February 2011 from the VELOUR trial in support of the overall survival claims)…"

However, as indicated in the description of the VELOUR study at Table B3 of Sanofi's submission, "following documentation of progressive disease, patients were to be followed for survival status every two months until death or withdrawal of patient consent or until the cut-off date for final analysis of OS was reached, whichever came first". The cut-off date for final analysis of OS was 7 February 2011, 36 months after commencement of treatment in the first group of patients and, accordingly, there were no further survival follow up data generated after that time.

The Committee's repeated references to further follow-up data from VELOUR are therefore inconsistent with the available evidence and wholly incorrect and the inference that Sanofi has, in some way, concealed data from the Committee is unreasonable. It is unclear to what extent the Committee's belief that Sanofi had not provided all data obtained from the study, influenced the Committee's decision making. However, the wording of the FAD suggests that this was a factor affecting the Committee's conclusions regarding the overall survival benefit associated with aflibercept.

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.

At paragraph 4.24 of the FAD, the Committee concludes that the evidence for aflibercept is not sufficiently robust to confirm a survival benefit of at least 3 months. Sanofi strongly believes that this conclusion is not reasonable in the context of the evidence submitted.

The Committee's estimate of the most plausible ICER - £51,000/QALY gained (paragraph 4.26 of the FAD) is based on a method of extrapolating overall survival that assumes no treatment benefit after the end of trial follow-up (30/ 36 months), as described at paragraph 4.14. This assumption gives an estimate of mean overall survival of 3.4 – 3.7 months and is on any view a conservative approach.

- The Committee has not however made any allowance for the conservative nature of the assumption of no continuing treatment benefit even though their concern regarding any ongoing benefit beyond the trial was based on the fact that "most patients had died during the 3-year follow-up period of the trial", whereas in fact some 25% of patients continued to be alive at that stage and the assumption disregards the possibility of additional benefit in these individuals.

- The Committee relies on the conservative assumption of no treatment benefit beyond the trial (giving a mean OS benefit of 3.4-3.7 months) to generate their best estimate of the ICER, but still refuse to accept that the data for aflibercept are sufficiently robust to demonstrate a 3 month extension to life for the purposes of the Supplementary Advice on end-of life treatments.

- In analyses which do not conservatively assume a curtailment of the treatment effect (i.e. allow for a continuing benefit after the end of trial follow-up), all parametric functions evaluated provide a mean OS benefit in excess of 3 months at 5, 10 and 15 year time horizons (with the exception of the Weibull function, where the mean OS was 2.9 months with a 5 year time horizon).

- It is only when the Committee assumes no continuing treatment benefit beyond the end of the trial and also truncates the data at 5 years - despite accepting that a 15 year time horizon is appropriate and disregarding the substantial data confirming a small but significant proportion of patients surviving beyond 5 years, that a mean OS benefit below 3 years is produced.

In summary therefore, the conservative approach assuming no treatment benefit beyond the trial, clearly fails to take into account a proportion of the benefit associated with aflibercept therapy and the reliance on data truncated at 5 years is wholly inconsistent with the Committee's own conclusions on the appropriate time horizon and the available clinical data. In these circumstances the Committee's refusal to accept that aflibercept is associated with an OS benefit in excess of 3 months for the purposes of consideration of the Supplementary Advice on end-of-life treatments, contrary to the approach followed for the purpose of calculating the most plausible ICER and adopting the most extreme assumptions, does not reflect the available evidence and is unreasonable.

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.

At paragraph 4.24 of the FAD, the Appraisal Committee considers the application of the Supplementary Advice on end of life treatments to aflibercept, in the context of the extension to life benefit associated with use of the product. The Committee noted uncertainties regarding the duration of the survival benefit and the requirement at section 2.3 of the Supplementary Advice "that these estimates of life extension are robust...". In these circumstances, the Committee declined to recommend use of aflibercept, under the Supplementary Advice.

However, similar uncertainties in determining the duration of survival benefit were identified when what was essentially the same Appraisal Committee considered the MTA of cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer (TAG 242). In that appraisal, the Committee noted the difficulties interpreting the survival data for panitumumab in view of patient cross-over confounding the trial data, but concluded that the progression free survival benefit for panitumumab could be assumed to be similar to that for cetuximab, which produced an extension to life of over three months and therefore that "there was sufficient evidence to indicate that panitumumab offers an extension to life of approximately three months compared with best supportive care alone". However, while the progression free survival associated with aflibercept in an earlier line of therapy is numerically greater than that associated with cetuximab, the Committee declined to assume that a similar relationship between PFS and OS would be present. While the Appraisal Committee refers to its earlier consideration of panitumumab at paragraph 4.25 of the FAD, it provides no explanation for the difference in approach between the two appraisals, suggesting an arbitrary basis for decision making, which is unreasonable. For the avoidance of doubt, while paragraph 3.4.6 of NICE's Guide to the Appeal Process specifies that "two different Appraisal Committees could reach different conclusions based on the same evidence without acting unreasonably", in this case, different conclusions based on substantively similar factual evidence, have been reached by essentially the same Appraisal Committee.

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

At paragraph 4.16 of the FAD the Appraisal Committee considers the utility values used in the economic modelling for aflibercept. While the Committee accepted Sanofi's value of 0.78 for stable disease, obtained from an ongoing clinical study investigating mCRC patients, they rejected the value obtained by the company for progressed disease on the basis (a) that the figure represented early progressed disease only; (b) concerns expressed by the ERG in relation to the reliability of the mCRC utility study; and (c) the fact that the mCRC utility study had not yet been submitted to a peer reviewed publication. Instead they concluded that the appropriate value for early progressed disease would lie between the value proposed by Sanofi and that proposed by the ERG (used in TAG 118).

Sanofi considers the approach of the Committee to be unreasonable.

- The ERG's preferred utility figure of 0.6, in contrast to Sanofi's, is not based on relevant patient data but is described by the ERG itself as an arbitrary calculation by a previous Assessment Group in an earlier appraisal
- It is inapproriate to criticise Sanofi's data for because it has not yet been peer-reviewed, when the research has only recently been concluded (and now presented), and both the ERG and Appraisal Committee have received the study report and no alternative estimate is subject to peer reviewed supporting data
- The conclusion that the figure used in TAG 242 is inappropriate because "it was based on patients who had lived long enough to receive more lines of chemotherapy than patients in VELOUR" is not supported by evidence; it could equally be concluded (consistent with NICE's usual position) that such second and subsequent line patients would have a lower utility

In summary, the Committee's rejection of utility values proposed by Sanofi in favour of a compromise involving data which are not evidence based and were rejected by another Committee - with many of the same members - in an earlier related appraisal is arbitrary and unreasonable.

Request for an Oral Hearing

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

I look forwards to hearing from you shortly.

Yours Sincerely,

Head of Health Outcomes

Appendix

Introduction to the Technology

Aflibercept (ZALTRAP) was approved by the European Commission for use in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy for the treatment of adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen. As the first multiple anti-angiogenic agent of its kind, aflibercept has a novel mode of action that works in a different way to other available treatments licenced for use in the UK. Aflibercept works by preventing the formation of new blood vessels within and around a tumour thereby stopping or slowing the spread of cancer. It is important to note that the VELOUR trial is the only double-blind, randomised study to have demonstrated a statistically significant and clinically meaningful benefit in overall survival, progression free survival and response rate, in combination with FOLFIRI in this setting.

More detailed information is provided in Sanofi's original submission in this appraisal dated 14 February 2013. The Appeal Panel is invited to consider this material.

History of the Appraisal

Sanofi was invited to participate in the single technology appraisal for aflibercept (Zaltrap) for the treatment of metastatic colorectal cancer in late 2012. The concise history of the appraisal was as follows:

12 December 2012:	Invitation to participate received.
11 January 2013:	Decision Problem Meeting.
14 February 2013:	Sanofi provides submission to NICE.
25 February 2013:	Sanofi provided the utility study report (omitted from the Submission Appendices in error) following a request via NICE from the ERG
6 March 2013:	Sanofi received Evidence Review Group (ERG) requests for clarification.
14 March 2013:	Sanofi and NICE Secretariat discuss the ERG clarification request via teleconference and understand scope and priority of responses required
20 March 2013:	Sanofi responds to ERG request for clarification
23 April 2013:	Sanofi offered NICE access to a copy of the VELOUR CSR – but this was declined on the 24/4 by the NICE Secretariat
29 April 2013:	ERG issues report commenting on the Sanofi submission.
30 Apr. - 8 May:	Sanofi requests a copy of the aflibercept model (as adjusted by the ERG), for use reviewing the ERG report – Various email and telephone communications with the NICE Secretariat

9 May 2013:	Sanofi responds with Fact check on the ERG report, and raises concerns that the extensive additional analyses provided by the ERG in their report cannot be independently verified without a copy of the 'adjusted' model.
22 May 2013:	First meeting of the Appraisal Committee
14 June 2013:	Appraisal Consultation Document (ACD) issued to consultees.
28 June 2013:	Sanofi receives a copy of the aflibercept model – as adjusted by the ERG
15 July 2013:	Sanofi provides comments on the ACD.
23 July 2013:	Second meeting of the Appraisal Committee
5 August 2013:	Email to Stakeholders that FAD is expected for release w/c 2/9
5 September 2013:	Email to Stakeholders that FAD is expected for release w/c 16/9 – no explanation for delay is provided
19 September (17h):	NICE Secretariat informs Sanofi that the FAD has been embargoed by the Guidance Executive – and a call will be arranged in the following week to discuss which AiC information is required to be disclosed in the FAD before it can be released
20 September 2013:	Email to Stakeholders that FAD is delayed – because confidential information needs to be agreed with the Company
23 Sept. to 11 Oct.:	Sanofi seeks clarity on why the FAD has been embargoed and which data is being requested for disclosure – Various email and telephone communications with the NICE Secretariat
24 October 2013:	Final Appraisal Determination (FAD) issued to consultees.