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[redacted]

Initial Scrutiny Letter Dated 31 March 2010 ("Scrutiny Letter")

Thank you for sending us your initial views in the Scrutiny Letter. We are pleased that you have decided to allow our ground 2 points to proceed to the appeal. However, we would be grateful if you could review your initial position with respect to a number of our ground 1 and ground 3 arguments, particularly over the nature of Final Scope and ultra-orphan indications. We set out our reasons why below. We have also restructured our arguments so that they follow the format that you expect the Appeal Panel will adhere to on the day of the appeal.

1. FINAL SCOPE

The Scrutiny Letter states at 1.1.1 that "the committee is required to turn its mind to all of the issues within scope, but it is not required to base its final analysis on every issue referred to in the scope."

However, the importance of complying with the Final Scope document cannot be overstated, which is why it is consulted on with national groups representing patients and carers, organisations representing healthcare professionals, manufacturer(s) or sponsor(s) of the technology, the Department of Health, the Welsh Assembly Government, specialised commissioning groups, primary care trusts and local health boards. The resulting Final Scope document also forms the basis for the Secretary of State for Health's formal referral of the technology to NICE for appraisal.

The NICE Guide to the Methods for Technology Appraisal ("Methods Guide") reinforces the importance of the scope, indicating that it is "fundamental" to the assessment process:

> "*During the scoping process, the Institute determines the appropriateness of the remit and the specific questions that are to be addressed for each technology appraisal. The scope defines the issues of interest (for example, population, comparators and potential subgroups) as clearly as possible and the questions that should be addressed by the Appraisal Committee when considering the clinical and cost effectiveness of the technology. The questions to be addressed by the appraisal are fundamental to the assessment process and require an understanding of the context within which a technology is to be investigated, including currently available care and any alternative technologies for the specific indication. Consultees and commentators are*

consulted during the scoping process. The Institute revises the scope in response to comments received and develops a final scope that describes the boundaries of the appraisal and the issues that will be investigated." (Paragraph 1.3.1.)

The document also reflects the consensus view of all consultees on which evidence[1] and comparators[2] the Appraisal Committee should consider.

We accept that that Institute is not bound to base its final recommendations on all aspects of the final scope. However, the Appraisal Committee must give due consideration to the issues highlighted in the Final Scope and it did not do so in this appraisal.

Rather, it discarded the consensus view of numerous consultees during the scoping process in favour of the views of two individual clinicians who use best supportive care alone rather than chemotherapy in their clinical practice and, it seems from statements by the Chair of the Appraisal Committee during its meeting on 7 January 2010, second-hand hearsay evidence from an unnamed acquaintance of the Chair.

This amounted to an informal re-scoping of the appraisal, a process that is not envisaged by the Institute's procedures and one that has unfairly prejudiced Celgene and other stakeholders, since they were all unable to challenge the basis for those assumptions.

As stated in our appeal points under perversity ground 2, the Appraisal Committee's decision not to consider chemotherapy was also perverse based on the evidence before it and an abuse of NICE's power under Ground 3.

We have reformulated our Final Scope arguments to make our position clearer under Grounds 1 and 2. For the reasons above, we have retained our arguments relating to the departure from the Final Scope under Ground 3.

1.1 Guidelines (Paragraph 1.1.2 of the Scrutiny Letter) and Failure to Assess Fully Data From the Celgene Survey (Paragraph 1.1.3 of the Scrutiny Letter)

The Scrutiny Letter states that Celgene's argument that NICE ignored guidelines and failed to take account of data from the Celgene survey are not strictly issues of process. We can accept this on the basis that the issues are dealt with under ground 2. We have restructured our arguments to include a reference to the NICE cancer guidelines and the Celgene survey data under ground 2. We have restructured our arguments to include a reference to the NICE cancer guidelines and the Celgene survey data under ground 2. In that regard, we note your reference to the case of *Douglas Fraser and Kevin Short v the National Institute for Health*

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[1] The 'scoping' process examines the appropriateness of the proposed remit and defines in detail what the appraisal will and will not examine. Scoping is an important step because it determines the nature and content of the evidence included in the assessment phase of the appraisal. (Methods Guide, para 2.1.1)

[2] See Methods Guide, para. 2.1.2, which states that "The purpose of a scope is to provide a framework for the appraisal. The scope defines the issues of interest (for example, population and comparators) as clearly as possible and sets the boundaries for the work undertaken by those producing reports for the Appraisal Committee, including the independent assessment groups and the manufacturer(s) or sponsor(s) of the technology." and para. 2.2.4, which states that "The scoping process aims to specify the comparator technologies as precisely as the technology under appraisal."

and Clinical Excellence regarding the the failure to assess fully applicable data. However, we would refer you to a very recent Court of Appeal judgment that you may not have been aware of at the time of sending this letter that explores this issue further. In *Servier Laboratories Limited v National Institute for Health and Clinical Excellence* (the judgment was handed down on 31 March 2010),[3] the Court of Appeal considered that although the Appraisal Committee has discretion to decide how much weight to place on a piece of evidence, evidence cannot be rejected out of hand without properly explaining the reasons for doing so and explaining where the weaknesses lie, particularly where that evidence is central to a party's case. The Court of Appeal upheld Servier's argument that the rejection of data by NICE simply on the basis that the data were from a post-hoc analysis and therefore were not sufficiently robust was irrational. We feel that we have similar points to make here under perversity.

2. ULTRA-ORPHAN INDICATIONS

The Scrutiny Letter states at paragraph 3.1 that "I cannot quite understand how it is that you say the SVJ document makes it clear that ultra-orphan drugs must be appraised in a different way or to different thresholds? It seems to say that it is not expected they will be appraised at all, and is silent on what if anything should be done differently if they are?"

While the Institute would not normally expect to receive referrals for ultra-orphan drugs, it has done in this case. Under these circumstances, it seems that the Institute is obliged to either:

(i) suspend the appraisal of azacitidine, while the Department of Health conducts an appropriate review and considers specialist funding for this technology. We note that the Institute has previously ceased to appraise ultra-orphan drugs when the NHS has made alternative commissioning arrangements for them (see, for example, its removal of the multi-technology appraisal of drugs for the treatment of pulmonary arterial hypertension (PAH) from its programme.[4]

(ii) continue with its appraisal of azacitidine, but to do so fairly and in accordance with available guidance on ultra-orphan drugs, *i.e.,* taking into account the very small patient population and its implications for product cost. This is the option that NICE took in this case.

Given that NICE opted to continue with the appraisal under option (ii) above, it should have appraised azacitidine differently to other technologies and in accordance with available guidance. The SVJ implicitly makes clear that ultra-orphan drugs should be treated differently to orphan drugs. Otherwise, the SVJ would have stated that orphan drugs "and ultra-orphan drugs" will be appraised in the same way as any other treatment. It is for the Appeal Panel to decide whether the SVJ precludes NICE from appraising ultra-orphan drugs at all. If the Panel rule that the SVJ permits NICE to appraise ultra-orphan drugs, then it must also debate and decide whether the same methodology should be applied.

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[3] *Servier Laboratories Limited v National Institute for Health and Clinical Excellence* [2010] EWCA Civ 346. In particular, see paragraphs 44 to 46 of that judgment.

[4] See http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11708.

The Scrutiny Letter also suggests that the draft NICE guidance on appraising ultra-orphan drugs is not relevant. The Scrutiny Letter states: "I note the draft guidance to which you refer, but unless that has been adopted, I do not agree that a draft document from 2006 would be relevant to a decision taken in 2010." The Scrutiny Letter appears to suggest that the draft guidance is not current.

However, although the above NICE orphan guidance is marked as "Draft v3," the NICE website states that the document was submitted to the Department of Health as a "formal response". The content of this guidance is current and therefore well known to the Appraisal Committee and should have been taken into account when considering the appraisal of the product in general and particularly when applying the Life Extending Guidance. Further, to our knowledge, this guidance remains under consideration by NICE and the Department of Health. Similarly, the Department of Health has cross-referred to NICE's Citizen Council's guidance on ultra-orphan drugs in a recent consultation on specialist commissioning.

Regardless of whether the guidance is in draft form or otherwise, the guidance clearly states that ultra-orphan drugs are likely to be "cost ineffective" as a matter of default. From a procedural perspective, this amounts to institutional bias against ultra-orphan drugs such as azacitidine as NICE had predetermined its views on ultra-orphan drugs and conducted the appraisal with a closed mind.[5] Further, it is a concept of natural justice that the decision-maker, *i.e.,* NICE, should not have preconceived views as this can amount to an unlawful fettering of its discretion.

For this reason, we have maintained our ultra-orphan arguments under Grounds 1 and Grounds 3 and believe that it is a matter for the Appeal Panel to debate and decide after hearing oral arguments.

3. NEXT STEPS

We hope that you accept our reformulated arguments as set out above and in the enclosed appeal letter. We look forward to hearing from you and remain on hand to answer any questions you may have.

We would also like to take this opportunity to request that a stenographer be present during the appeal to transcribe the hearing. We would be happy to meet the cost of this service and share the transcript with the Appeal Panel and other appellants.

Yours sincerely,

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General Manager, Celgene UK

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[5] See *R (on the application of Fraser and another) v National Institute for Health and another* [2009] EWHC Admin (452), at paragraph 50. In deciding whether there has been bias, Simon J said that claimants "have to show (at least) predetermination: a closed mind at an early stage."