

Dr Mark Chakravarty

Lead non-executive director for appeals

National Institute for Health and Care Excellence 2nd Floor, 2 Redman Place

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**CONTAINS COMMERCIAL IN CONFIDENCE INFORMATION**

Dear Dr Chakravarty,

Thank you for your letter of 18 August 2023 responding to Pfizer’s appeal letter of 11 August 2023. The correspondence concerns the final draft guidance (**‘FDG’**) for ID 1403: voxelotor for treating haemolytic anaemia caused by sickle cell disease (**‘SCD’**)

Pfizer are pleased that you have provisionally determined that six of the points raised in the letter of 11 August 2023 are suitable to go forward to the Appeal Panel for their consideration. Pfizer are grateful for the opportunity to address further comments to you on the three issues which you are provisionally not minded to treat as valid appeal points to be put before the Panel.

This letter sets out Pfizer’s further submissions to you in relation to those three issues. It elaborates on those reasons already put forward in the 11 August letter in support of Pfizer’s appeal application and also responds to your provisional views on them. This letter is to be read in conjunction with the 11 August letter.

In summary, Pfizer urges you to reconsider your approach on these remaining issues and to refer each of them to the Appeal Panel for consideration along with the other grounds that you are minded to refer to them. Pfizer have addressed each of the three issues under separate headings below.

# Ground 1(a).3: In a situation where the Committee considered there still to be multiple sources of uncertainty by the time of the second Appraisal Committee meeting (‘ACM2’), it was unfair nevertheless to proceed directly to the publication of the FDG with no opportunity for a further ACM or to explore suggestions such as managed access.

* 1. As your letter notes, Pfizer considers that there are two aspects to the contention that proceeding directly to the publication of the FDG after ACM2 was procedurally unfair in the circumstances. They are that:
     + Pfizer were wrongly deprived of the opportunity to address the Committee’s concerns about remaining areas of uncertainty following ACM2 at a third ACM; and/or

uncertainty, such as engaging in a managed access agreement (**‘MAA’**).

* 1. Both issues are addressed below. Pfizer have addressed the second point first as it gives a concrete example of why NICE acted in a manner that was procedurally unfair in not giving further consideration to resolving the uncertainties it had identified or how to manage them through further discussions, recommendations and by holding a third ACM. Further, if Pfizer are successful in persuading you that your provisional approach to the MAA issue is incorrect, it follows, in the submission, that Pfizer should also have had the opportunity to proceed with a third ACM at which that and other issues could have been explored. Pfizer therefore invite you to examine both issues together and to reverse your provisional decision in relation to both of them.

The failure to allow exploration of other means of mitigating uncertainty such as engaging in a MAA.

* 1. There were a number of methods that could have mitigated uncertainty which, because of the way in which Committee ultimately proceeded, Pfizer were unable to explore with it after ACM2. Principal amongst these was the possibility of entering into a MAA.
  2. As noted in paragraph 17 of the 11 August letter, Pfizer expressed to NICE’s Associate Director of Technology Appraisals their willingness to still explore a MAA during the pre-meeting before ACM2 and also explained to the Committee at ACM2 that they were willing to explore a MAA after the meeting if the Committee felt that was appropriate. The Associate Director told Pfizer at the pre-meeting that since no MAA proposal had been received from Pfizer it was too late for a MAA solution to be considered.
  3. Your letter expresses the provisional view that there has been no procedural unfairness as a result these actions by NICE and that the contrary position taken by Pfizer is unarguable.
  4. This appears to be based on your views that: (a) the Manual and the guidance given to Pfizer in the slides for the first ACM on 7 December 2022 set out expectations clearly in regard to submitting a MAA proposal; (b) Pfizer was given adequate opportunity and reasonable notice to submit a MAA proposal; (c) the Manual makes clear that the onus is on the company not just to indicate its interest in exploring such a solution, but actually to make such a proposal;

(d) neither the Manual nor anything else creates a procedural obligation for the Committee to invite a company to make such a proposal after a second ACM and before the FDG is published; and (e) it was not unreasonable and unfair to expect Pfizer to submit a proposal at an earlier stage and/or before the second ACM.

* 1. Pfizer respectfully disagree with each of these points for the reasons set out below and invite you to reconsider your position on them.
  2. Taking first point (a) in the summary set out above, in Pfizer’s submission the Manual does not mandate a particular (and inflexible) approach as regards a company submitting a MAA proposal, such that one cannot be considered at a later date or following a departure from the initial course of events relating to the consideration of a routine commissioning proposal.
  3. The Manual is not prescriptive about how consideration of MAAs may arise. Paragraph 5.5.21, to which you refer in your letter, clearly demonstrates that flexibility is inherent in the system. That paragraph refers to:

1. “multiple touch points within the evaluation process which provide opportunities for NICE, the company and stakeholders to identify if a medicine may be suitable for managed access, and that a managed access proposal could be submitted, including…
2. [Third bullet] At technical engagement (if held) when significant uncertainties are highlighted and a managed access proposal could be submitted”.
   1. The fact that this sentence refers to: (I) multiple touch points including (and therefore presumably not limited to) those listed; (ii) opportunities not just for the company, but also for NICE and stakeholders, to identify the suitability of MAA, as well as to consider that proposal could be submitted; and (iii) the fact that this could occur at a technical engagement stage (i.e. after the evidence submission stage) shows clearly that no invariable or inflexible approach has been adopted. The wording does not suggest either that technical engagement is the final point at which a MAA proposal could be submitted.
   2. Pfizer agree that if a company wishes from the outset to submit a MAA proposal, that should be done at the evidence submission stage, as paragraph 5.5.22 states. However, that is quite different from saying that a MAA proposal can never be considered at a later stage in the process in appropriate cases, certainly where matters develop as the evaluation process continues. The passages from paragraph 5.5.21 appear to them to confirm Pfizer’s understanding that it can, rather than ruling that possibility out.
   3. Similarly, paragraph 6.2.31 in the Section “Structured Decision Making and Value for Money” and the Table 6.3 “Committee recommendations” in “Types of recommendation” Section 6.4 of the Manual indicate the circumstances where a Committee is able to make a recommendation to proceed with a MAA.
   4. Paragraph 6.2.31 states:

a. “The committee should consider the reliability and generalisability of the evidence presented when considering cost-effectiveness estimates. In its consideration, the

on both the evidence presented and the impact of the evidence on key decision uncertainties. When the evidence is highly uncertain and leads to a high degree of decision uncertainty, the committee may consider making recommendations that include managed access, data collection or research.” (emphasis added)

* 1. Table 6.3 states against the “recommended with managed access” box:

a. “The case is not currently supported but the technology has the plausible potential to be cost effective and has potential to provide significant patient or healthcare system benefits if the uncertainties in the clinical evidence are addressed.”

* 1. The only criteria mentioned in these passages and in paragraphs 6.4.6 to 6.4.11 is uncertainty. There is no reference to any bar for a recommendation with MAA if a company has not, for instance, included a proposal at the evidence submission stage and/or regardless of the fact that the relevance of a MAA proposal only becomes clear once the Committee has taken a particular view about the nature of uncertainties in respect of an application.
  2. Once a medicine has been identified as a suitable case for MAA (which as stated above can be done by NICE as well as by the company), there is no doubt every reason for the company then to be required to make a proposal in good time before the next ACM and to allow for the supporting feasibility assessment from NICE to be submitted as well as a commercial access proposal, in the manner explained in paragraphs 5.45,23 and 5.5.24. However, neither of these paragraphs, nor paragraph 5.5.22, prevents a company or NICE from discussing MAA as a possibility if no proposal was submitted at the evidence submission stage. Such a detailed proposal could be prepared before a third ACM.
  3. Pfizer understand and acknowledge the need in general terms for companies to submit their evidence and any new materials and approach as early as possible. It follows from this that where a good explanation for not doing so is lacking, NICE may very well be justified in saying that a company should have taken earlier opportunities that were given to them.
  4. However, in this case, Pfizer was told that it was too late to do so in circumstances where they had reasonably held, up until that point, the view that NICE would find that a routine commissioning approach was not too uncertain for approval. By the time that Pfizer raised the MAA proposal issue shortly before ACM2, they had only been told a matter of days before that NICE disagreed with Pfizer’s assessment. By telling Pfizer that it was then too late, NICE was failing to follow the approach set out in the Manual set out above and also treated Pfizer in a manner which was procedurally unfair.
  5. As regards the question concerning on whom the onus lies to propose a MAA solution in the

can be discussed or consider therefore appears to Pfizer to be incorrect.

* 1. As regards (d) above, the obligation on NICE, consistent with the terms of the Manual already referred to above, was to consider all reasonable suggestions for mitigating the uncertainties that NICE had concluded existed. Once it had rejected Pfizer’s position that its routine commissioning application should have been granted, it was obliged to consider whether or not any further mitigation would be possible to allow the use of the medicine, such as a MAA approach, where Pfizer were stating that they would like to pursue that idea. The procedural error that NICE made was to shut down any such consideration of an alternative approach by Pfizer practically as soon as NICE’s views on uncertainty were communicated to Pfizer, on the basis that it was then too late for Pfizer to explore alternatives.

The ACM1 Slides

* 1. In addition to the points that you make in relation to the Manual, your letter also states that the Slides provided to Pfizer before ACM1 held on 7 December 2022 made clear what NICE expected of Pfizer. The implication of your comments is that Pfizer had ignored an obvious requirement on it, if they wished to pursue a MAA approach to submit an earlier proposal, and therefore cannot now complain about the fact that they were told shortly before and at ACM2 that it was too late to proceed down that route.
  2. Again, Pfizer respectfully disagree with your provisional interpretation of the wording of the slides in question. On page 41 NICE states that to consider a recommendation with a MAA it needs “a managed access proposal (requested as part of the company submission) along with a feasibility assessment from NICE (normally expected approximately 4 weeks prior to the committee meeting)”.
  3. However, this Slide does not state clearly that unless the company has submitted a MAA proposal at the original evidence submission stage, such a proposal will not be considered by NICE. To suggest this would be contrary to the provisions of the Manual set out above. Such a cut off would therefore need to have been clearly stated.
  4. Further, the questions at the bottom of the slide suggest that NICE was asking, at the time the slides were sent to Pfizer and at the ACM1 stage, about whether or not a MAA proposal would be brought forward. This too is inconsistent with any suggestion that a cut off was already in operation, or that a MAA proposal would not be able to be submitted subsequently.

a. “Are the uncertainties potentially resolvable through a period of managed access? Does the company plan to submit a managed access proposal?”

1. The difficulty in the present case is that Pfizer were only told of the outcome of NICE’s preliminary deliberations and given the slides for ACM2 a matter of days before ACM2 was due to take place. To be told at that stage that it was too late to explore other options was contrary to the requirements of procedural fairness. Pfizer were not given adequate opportunity and reasonable notice to submit a MAA proposal in this case for the reasons set out above. Pfizer therefore disagree with the point summarized at (b) above.

The unfairness and unreasonableness of expecting Pfizer to submit a MAA proposal at an earlier stage.

1. Contrary to the point summarized at point (e) above it was both unfair and unreasonable for NICE to expect Pfizer to submit a MAA proposal at the initial evidence submission stage, or at an earlier stage than raising the possibility (as they did) practically as soon as NICE had made its views on continuing uncertainties leading to its rejection of the routine commissioning approach known to Pfizer.
2. This is because Pfizer reasonably expected (although its expectation was ultimately disappointed) that NICE would conclude that its routine commissioning case would be accepted and not rejected based on NICE’s views on uncertainties. This view was based on the fact that the primary uncertainty in almost all Cancer Drugs Fund medicines is efficacy which is resolved via long term trial data. No such data was expected for voxelotor, meaning only registry data would be available. Potential limitations of such data in respect of the key area of uncertainty, Regular Transfusion Therapy (‘**RTT**’), meant that it was reasonable for Pfizer to have expected that routine commissioning would be the more suitable route in the present case. Pfizer also believed that discussions that the previous manufacturer (Global Blood Therapeutics) had had with the managed access team at NICE at earlier stages had indicated that this was likely to be the case. Pfizer did not know what NICE’s provisional views were regarding routine commissioning until these were communicated to them shortly before ACM2.
3. Pfizer also point out that no medicine has entered the Innovative Medicines Fund (‘**IMF**’) to date, which indicates the very real challenges faced by companies when seeking to mitigate uncertainties via registry data. Pfizer could have been given assistance by NICE and a reasonable opportunity to consider and prepare a MAA proposal in view of these difficulties, but they were not. IMF medicines will require greater flexibility to be shown towards them and potentially greater involvement and appropriate direction from NICE, because formulating a MAA in circumstances where normal data points for such access are unlikely to be available is inherently less conventional and more challenging.

uncertainties that it has not been able to dismiss or resolve.

1. In Pfizer’s experience, a MAA proposal is something that NICE is often prepared to accept at a later stage in the proceedings. Pfizer had good reasons for believing that it would not be necessary for them to offer such a proposal earlier on in the process in the present case. Pfizer should not have been prevented from suggesting a MAA as an alternative approach, once they had been told that the initial proposal was unlikely to be successful.
2. Further, as explained in the letter of 11 August, Pfizer could not on any view have prepared the commercial case that would have been needed to support the MAA proposal, where NICE took the view that it was unable to tell it what the relevant incremental cost-effectiveness ratio (‘**ICER**’) would be.
3. In all of the circumstances, Pfizer has acted reasonably and NICE’s refusal to consider a MAA at the point that Pfizer raised it with them was unfair. Pfizer therefore invite you to reconsider your approach on this issue and to conclude that in the present circumstances the absence of a plausible ICER from the Committee did render its decision to proceed straight to publication of the draft FDG unfair.
4. Whatever the position in other cases, the unusual feature of the lack of an ICER compounded the other difficulties Pfizer have experienced in the present case, namely the short notice before ACM2 of the fact that, after consideration, NICE considered the matter too uncertain to permit routine commissioning and indeed even to decide upon an ICER. This situation is extremely unusual in Pfizer’s experience and should have led to the Committee giving greater time and consideration to Pfizer, not less, to allow for steps to mitigate the uncertainties to be identified. This is especially the case in the situation where considerable health inequalities and a lack of effective means to resolve them were expressly acknowledged by NICE. Pfizer contend that there are good reasons for these circumstances to be looked at as a whole by the Appeal Panel.

The failure to proceed with a third ACM

1. Pfizer referred (in paragraphs 19 and 20 of its 11 August letter) to the facts that it is reasonably common it its experience for NICE to proceed to a third ACM where there are found to be considerable uncertainties in relation to the routine commissioning application and also to the flexibility that there is in the Manual both in terms of timing and the willingness to engage in further consideration to see if difficulties can be resolved or at least mitigated. Pfizer has identified 20 appraisal topics, within the last two years alone, that have proceeded to a third ACM. Pfizer also referred to the fact that at that time there was still two months left in relation to the provisional schedule window and that this additional time could have been usefully
2. The essence of your provisional view as regards a third ACM appears to be that a company cannot expect that NICE will investigate uncertainties it has identified further with the company, instead of incorporating those uncertainties unto its decision making. You state that there is nothing in the Manual nor in the conduct of previous Committees that could arguably support that proposition.
3. In Pfizer’s view, whatever the position in general, in the circumstances of this case, where very little notice was given to Pfizer prior to ACM2 of the view that NICE was taking in response to the routine commissioning case and to the attempts to resolve and/or mitigate uncertainties and practically no time was therefore available for Pfizer to prepare to explore alternative mitigations, a further ACM was appropriate. To deny one in this case was procedurally unfair. Pfizer’s letter of 11 August refers to the need to treat similar cases in the same way. NICE’s duty of consistency should have led it to hold a third ACM in this case.
4. The references in the Manual to the various ways in which uncertainties can be mitigated, and to different recommendations that may be given, show that the purpose of the process is to give full consideration to the steps that can be taken to support the use of a medicine through one or other of the routes that are available. In Pfizer’s view this is all the more so, in the case where there is a clear need based on acknowledged health inequalities for further treatments to be made available.

# Ground 1(a): 5: The Committee should have explained more clearly, during the appraisal process, how it intended to take (or not take) the health inequalities in relation to SCD into account in its decision-making and why.

1. Pfizer welcome the fact that you have agreed that the question of whether the Committee made adequate adjustments for health can be raised with the Appeal Panel in Ground 1(b)1. However, there is a prior point which Pfizer have also invited you to permit the Panel to consider, namely whether Pfizer received a fair opportunity to influence the outcome of the Committee’s consideration of this issue in the first place, and that the failure to allow such an opportunity was procedurally unfair. This remains an important point as explained below.
2. In your letter you rely on the fact that the FDG shows that the Committee were aware of the issues relating to health inequalities and that it specifically took them into account by indicating that it could accept a higher cost effectiveness estimate than it would otherwise have been prepared to. You also refer to the NICE response to the specific comments referred to in Pfizer’s 11 August letter in the ACM2 slides and paragraphs 3.18 and 3.20 of FDG.

been prepared to accept because of those inequalities. The very small changes between the ACD and the FDG, in the shape of the addition of two words, has already been drawn to your attention in paragraph 36 of the letter of 11 August. The position has remained throughout that Pfizer are therefore unable to tell why other proposed modifications on the basis of health inequalities were rejected.

1. Further, and absolutely crucially, no such explanations were ever given by NICE to Pfizer or others during the process and certainly prior to ACM2, as to whether and how the Committee intended to modify its approach (or not) in light of the substantial comments it had received on the ACD on the health inequalities issues (as set out in paragraphs 37 and 38 of the 11 August letter). Pfizer have never been presented with the case that it has to meet on this issue.
2. Importantly, as Pfizer’s 11 August letter also stresses in paragraph 39, other stakeholders including clinical experts and patient group did not have the opportunity to make informed and highly focused representations to the Committee that may well have succeeded in influencing the Committee’s actions in regard to health inequalities. The fact that stakeholders were motivated to set out their position on this issue of considerable importance to them is demonstrated by their participation in the process (as highlighted by paragraph 37 of the 11 August letter). Pfizer may, with adequate notice, have been able to bring evidence to bear on the issue, which in the event was not made available to NICE because of this procedural shortcoming.
3. The fact that references were made to the one type of adjustment (i.e. acceptance of a higher ICER) that NICE was prepared to make in the FDG does not answer this point. Pfizer and other stakeholders should at the very least have been told well in advance of ACM2 and with sufficient time to prepare responses, what the Committee’s approach was to the detailed submissions made on this point following ACD. If the Committee did not agree with Pfizer’s submissions it should have set out the reasons why not, so that Pfizer had an adequate opportunity to address those concerns during the process.
4. By not being transparent about its concerns and simply repeating its position in the ACD at all stages, rather than explaining any of its objections to Pfizer, NICE has acted in a manner that was procedural unfair. It therefore urges you to reconsider your approach to this appeal point and to permit this issue to be considered by the Appeal Panel.

# Ground 2.1: The Committee’s conclusion that there was too much uncertainty, such that it could not assess the cost-effectiveness of voxelotor, was irrational.

1. Pfizer acknowledge and welcome your acceptance that specific arguments about how the data
2. Pfizer invite you to permit the Committee’s approach to uncertainty as a whole to be considered by the Appeal Panel. Your view that the Committee’s overall approach to uncertainty could not arguably be said to be irrational is, with respect, incorrect. You rely on the facts that the Committee identified the issues, explained that it would accept a higher ICER than usual and explained why it could not calculate a most plausible ICER and that this was a reasonable approach in the circumstances.
3. As stated in our 11 August letter, failing to indicate an ICER at all was a highly unusual step on the part of the Committee. It should have been justified specifically by reference to individual uncertainties and to the reasons why they had not, in the mind of the Committee, been adequately resolved.
4. Your response letter does not, with respect, meet this point. In Pfizer’s submission, the argument that the Committee has not behaved consistently with its approach in other cases, where similar uncertainties have existed, nor given any reasons as to why any departure from that approach was justified in the present case, do plainly give rise to a cogent case that the Committee acted irrationally. Without examining the evidence on this point, as the Panel would be able to do if the issue is allowed to be raised before it, it is effectively impossible to conclude that the degree of uncertainty here permitted the Committee to take the unusual steps of not formulating an ICER, nor taking other steps to mitigate or deal with the types of uncertainties that frequently arise in other cases too.
5. Neither Pfizer, nor the Appeal Panel, should be limited in the appeal process from evaluating the position as to uncertainties and their effects as a whole, and confined simply to looking at the position on the data raised in appeal points 2.2 and 2.3. The overall approach of the Committee is one which merits a further look by the Appeal Panel. Further, it would be unfortunate if Pfizer were to succeed in relation to either of those points but could be (although it obviously hopes it would not be) hampered in achieving an overall re-examination of the points on rationality and a different outcome from that of the Committee, because permission for the broad challenge to rationality had been refused. In these circumstances, Pfizer submit that the broad rationality challenge in point 2.1 should also be permitted to go forward to the Panel.

Conclusion

Pfizer are grateful for the careful consideration that you have already given to its appeal submissions and your provisional view that the majority of the appeal points that were raised should be looked at in an appeal. Pfizer invite you to give permission for the remaining issues three issues addressed further in this letter to be considered also by the Appeal Panel.

Yours sincerely,

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