

Solving the challenge of combination treatments: summary of key insights from engagement with key stakeholder groups

Introduction

In 2021 Takeda UK Ltd held four roundtables, each focusing on a different stakeholder group involved in the landscape of combination treatments: the patient, clinical, health economic, and competition law communities. These roundtables were organised to debate and critique Takeda's proposed solution to the combination treatments issue, as detailed in two [Whitepapers](#) published in 2021, and to discuss the potential role of each stakeholder in supporting and advocating for a solution to be found and ultimately implemented.

Following each roundtable, a report was developed that summarised the discussion and recommended areas for further exploration of Takeda's proposed solution. These individual reports can be found on the [Takeda UK website](#).

This document is a summary report of the insights from these four roundtables highlighting the common themes and differences.

Background

Since NICE's Decision Support Unit produced a report in 2014 describing the issue of treatments being 'not-cost effective at zero price', finding a solution had been placed in the 'too-hard to fix' box.

Takeda initiated exploring the challenges associated with combination treatments at a roundtable meeting in Parliament in 2017 and at a further Amyloidosis Research Consortium UK (ARC UK) meeting in July 2018.

At these discussions, the concepts of treatment value attribution and voluntary arbitration between manufacturers of combination treatment components emerged as the preferred potential solution. Takeda subsequently established a Combination Treatments Project Advisory Group – comprised of experts representing the patient, clinical, academic and competition law communities – tasked with clearly defining the issue and designing potential solutions to the problem of assessing combination treatments. Representatives from NICE and NHS England also provided feedback to the Advisory Group on key challenges.

In 2018, under the [Voluntary Scheme for Branded Medicines Pricing and Access](#) (VPAS), the Pharmaceutical Industry was given the remit to find a solution. This agreement resulted in the wider industry to begin discussing a solution and further motivated Takeda to design a workable solution. Takeda's work has culminated in the creation of two 'Frameworks', which are outlined below. The solutions are treatment and disease agnostic and could be applied to any combination treatment.

1. [An Attribution of Value Framework for Combination Treatments](#)
2. [Voluntary Arbitration Framework for Combination Treatments](#)

The Attribution of Value Framework proposes an economic methodology that aims to define a fair division of value across the treatments in a

The Voluntary Arbitration Framework proposes a standard operating procedure to support compliant dialogue and agreement between pharmaceutical

combination by assigning a relative value to each treatment based on the health benefit. It takes into consideration health-economics methods used by NICE in making decisions about access to new treatments.

companies on the value attributed to each treatment within a combination. It takes into consideration competition law and current NICE/NHSE methods and processes in making decisions on access to new treatments.

Takeda is not alone in exploring potential solutions to the challenge of approving combination treatments and is very supportive of broader industry and other stakeholder efforts and alternative approaches.

Takeda considers that the best outcome may lie in a tapestry of possible options that can be selected on a case-by-case basis dependent on the assessment of the competition law risk at the outset of the negotiation. Takeda encourages all proposals brought forward by others in the industry to be properly explored.

Takeda's Whitepapers and further background information on the combination treatment access challenges are on the [Takeda UK website](#).

Insights summary

How can uncertainties in the Attribution of Value Methodology be addressed?

Roundtable participants agreed that the Attribution of Value Methodology was sound, practical and implementable. Roundtable participants who had applied the Attribution of Value Methodology retrospectively to projects reported that it was simple to implement without additional time or resource requirements.

Whilst the robustness of the methodology was acknowledged, participants highlighted several areas for further exploration, including:

- Uncertainty in determining the incremental value of an add-on treatment when its value as monotherapy is unknown due to the lack of monotherapy clinical data.
- Without a method of assigning additive value, this situation might lead to add-on treatments being trialled as monotherapies to determine their value, posing ethical issues in conducting such a clinical trial, given that a product may have a low likelihood of being further developed for use as a monotherapy.
- The potential issues of fairness in synergistic scenarios where the monotherapy value of each component may not be an accurate representation of the contribution per component when used in combination.
- Due to evidence uncertainties, it is rare for a NICE evaluation committee to have preferred base-case assumptions. Instead, decision making is likely to be based on a range of plausible costs, QALYs, and incremental cost-effectiveness ratio (ICER) estimates. Due to this uncertainty, particularly when data are redacted as confidential, it may be challenging to find a starting point for the QALY gain for each treatment.

It was agreed that uncertainty will always be inherent in instances where there is imperfect information about a treatment, as is the case now. It was felt essential to continue the development of the methodology to address uncertainty where possible.

Nevertheless, the Health Economics roundtable participants agreed that the Framework sought to address a complex problem and recognised that the Attribution of Value Methodology would provide a starting point for potential complex negotiations. It was acknowledged that the existence of a framework is helpful, even if it only provides an initial basis for further discussion.

What is an acceptable level of burden in the Voluntary Arbitration Framework?

Questions were posed about the complexity of Takeda's Voluntary Arbitration Framework and whether it might be overly burdensome to implement for every combination treatment evaluation. It was discussed if there might be circumstances where a more straightforward process could be adopted to achieve the same outcome. For example, a negotiated settlement between two or more manufacturers leading to patient access to the combination whilst adhering to competition law.

Having discussed the importance of simplicity in-depth at the outset of the project, Takeda believes that the Framework strikes the right level of simplicity whilst remaining sufficiently robust and appropriate to mitigate the challenges and competition law risks, which must take precedence in the solution. However, Takeda remains open to the possibility of reducing the requirements of the Framework on a case-by-case basis following individual companies' assessment of the level of risk they are willing to accept.

It was also made clear that not every combination treatment would need or warrant inclusion in the solution. This is because it may prove cost-effective utilising the current process available, as is the case now, as some combination treatments are available in the UK today.

What are the entry criteria for the Voluntary Arbitration Framework?

Determining and approving entry into the Voluntary Arbitration Framework was highlighted as important. There was a concern raised about it being overwhelmed by applicants, resulting in capacity challenges and delays to patient access.

As mentioned above, Takeda does not believe that every combination treatment would be eligible for entry into the process. The process would be used for products where it is believed there would be a significant likelihood that the combination would not be cost-effective at the current willingness to pay threshold.

It was felt that it would be the responsibility of the add-on manufacturer to signal a candidate for the process as early as the horizon scanning phase, with potentially the Arbitrator responsible for taking a final decision as to whether it was a candidate. There could also be a role for the NIHR Innovation Observatory to flag potential candidates in their early assessment forms.

Where should different stakeholders be involved in the process?

It was discussed whether Takeda envisaged a role for system stakeholders, most notably NICE and NHSE, and external stakeholders, such as clinical and patient organisations.

It was suggested that there might be instances where health technology assessment (HTA) agencies are required to be present at meetings to assist with confidentiality issues, or NHSE may be tasked with trying to unlock negotiations that may have stalled.

Takeda noted that the proposed solution did not stipulate a role for system stakeholders, being mindful of capacity and resource constraints. However, Takeda did acknowledge that there may be times when this involvement was desirable. However, it would be for NICE and NHSE to comment on the appropriate level of their involvement.

For the patient organisations and clinical communities, it was queried what opportunities existed for their input into the process and the need for the process to be sufficiently transparent to enable this.

Takeda suggested that further input from patients and clinicians was needed to define their potential involvement and agreed that it would be important that the Arbitration Framework was suitably transparent to keep them apprised of progress, opportunities for engagement and the eventual outcome. Whilst the negotiations themselves will need to remain confidential, Takeda suggested that regular updates be provided to relevant external stakeholders.

Who's accountable for the operation of the Voluntary Arbitration process?

Ownership of the process was queried during the roundtables. The potential burden of overseeing the Voluntary Arbitration Framework was raised, and it was questioned whether it would be feasible for NICE, or another organisation, to take responsibility for the process.

Takeda believes that the potential burden placed on the system for managing the process would be minimal compared to the burden already faced in complex and lengthy appraisals of some combination treatments. The process has been designed to avoid interfering or creating additional burden for NICE or NHSE by aligning, albeit in parallel, with existing evaluation processes. The add-on manufacturer will continue to be responsible for interacting with the formal NICE evaluation process. All negotiations within the Voluntary Arbitration Framework would seek to avoid system burden as far as possible until an agreement is reached.

Who will fulfil the role of the Arbitrator?

A crucial part of the discussions was around who would fulfil the Arbitrator role. While the Voluntary Arbitration Framework Whitepaper does not detail who the Arbitrator should be, it envisages the appointment of an independent organisation with sufficient expertise in mediation. In effect, fulfilling a role not dissimilar to the Prescription Medicines Code of Practice Authority (PMCPA) which regulates the ABPI Code of Practice.

Takeda felt that this would instil confidence amongst manufacturers entering the process that the Arbitrator was neutral, devoid of any potential conflict of interest, and able to mediate any disagreements between manufacturers on the value attribution successfully.

The Voluntary Arbitration Framework Whitepaper noted that further discussions amongst all stakeholders were needed to define what capabilities this role would require, by whom they would be governed, and how they would be compensated. Takeda believes this should be agreed upon through consultation led by the ABPI and other industry associations, with NICE, NHSE, and the DHSC.

During the roundtables, participants offered suggestions and guidance as to who might be capable of fulfilling this role. This resulted in consensus that the Arbitrator, if required, would need to have basic knowledge of competition law and HTA processes and be seen as independent. It was suggested that the ABPI could undertake this remit. However, it was acknowledged that a full review of the ABPI's current capacity to do this would need to be undertaken.

What is the role of the Arbitrator?

The remit and functions held by the Arbitrator were also topics of discussion. The main elements of these are detailed below.

1. Could the Arbitrator impose a mandatory outcome?

Discussion centred around whether the Arbitrator would have powers to instruct all manufacturers involved to accept a certain outcome as determined by the Arbitrator (in instances where a negotiated settlement could not be achieved).

Takeda maintained that participation in the Voluntary Arbitration Framework should be mandatory (given the envisaged inclusion of the solution in the VPAS), whilst the outcome of the Voluntary Arbitration Framework should be voluntary and aligned with the approach taken by NICE in its standard evaluation process. Takeda proposes that mandatory arbitration could risk undermining manufacturer uptake of the solution and impact its long-term viability.

2. Could the Arbitrator set timelines for negotiations?

Concerns were raised about the Voluntary Arbitration Framework's potential to delay patient access. Questions were asked as to whether the Arbitrator should set a timeline for negotiations at the outset to avoid delays, potentially via a 'terms of engagement' agreement.

Takeda reminded participants that combination treatments are already experiencing longer timelines for those who decide to submit within the current system due to ongoing cost-effectiveness and competition law challenges. Rather than increasing the evaluation timeline for combination treatments, the proposed solution could decrease the timescale for approving combination treatments compared to the current state of play and increase the rate of combination treatments submitted. It was noted that the Voluntary Arbitration Framework process had been designed to align with NICE's standard timelines for technology evaluations, which should avoid introducing additional delays into the process.

The Whitepaper also proposes that, in the event of the NICE Committee issuing negative draft guidance, there is the opportunity to re-enter manufacturer negotiations with a four-week time limit (consistent with responding to draft guidance). This would ensure neither side unduly delays the negotiations nor impacts existing NICE timelines.

Whilst the objective of the Voluntary Arbitration Framework is to minimise delays to patient access, Takeda does advocate for a mechanism whereby manufacturers can request a short pause to the NICE process to reach a negotiated settlement, as can happen now for specific reasons. It would be for the Arbitrator to assess the merits of a pause and how long is reasonable to secure an outcome on a case-by-case basis. Suppose the Arbitrator does not believe sufficient progress is being made, they should retain the right to unilaterally notify all parties involved that the pause will be terminated and NICE will be able to resume their evaluation.

3. Does the Arbitrator have a role in NICE/NHSE commercial processes?

The role of the Arbitrator in facilitating commercial discussions between the manufacturers involved in the Voluntary Arbitration Framework and NICE and or NHSE was explored. It was

argued that this might help secure a positive outcome, although it could also lead to additional burdens on the Arbitrator.

Takeda advised that the Whitepaper envisaged no role for the Arbitrator in these discussions; instead, the add-on manufacturer should retain responsibility for navigating the NICE evaluation process and leading commercial negotiations with NHSE for its component of the combination, in line with current methods and processes.

4. Would the Arbitrator need to be present during the Voluntary Arbitration Framework?

Given time and capacity constraints, it was discussed whether the Arbitrator needed to be present during all manufacturer negotiations as part of the Voluntary Arbitration Framework. Others offered the perspective that, from a competition-specific lens, the presence of the Arbitrator might not always be necessary to ensure legal compliance.

Takeda noted several benefits of an arbitration process beyond simply ensuring compliance with competition law, such as helping to secure a successful outcome to combination treatment negotiations (for example, acting as a mediator during negotiations).

Takeda noted that a position on whether the Arbitrator should be present during all negotiations had not been reached and was open to unsupervised manufacturer negotiations, provided this could be considered compliant. However, a final decision on refining the role of the Arbitrator would need to be taken holistically by weighing up the wider benefits of mediation.

Who are the constituents of a clean team?

Consideration was given to the external clean teams concept included in the Voluntary Arbitration Framework Whitepaper, including who could participate within a clean team and the expertise needed by these individuals.

It was agreed that it would be vital that clean teams had sufficient expertise in HTA, health economics, and pricing to discharge their duties effectively. However, a question was raised about whether in-house clean teams would be more appropriate than an external clean team given a) their existing expertise and b) the resource burden associated with assembling an external team, particularly for small companies. The feasibility of a 'mixed' in-house and external clean team was also considered.

Takeda agreed that an in-house clean team could be appropriate in certain circumstances, although reiterated the need to identify individuals with the appropriate expertise to negotiate whilst still being removed from wider pricing decision-making. Takeda advised that external clean teams had been proposed to avoid a situation whereby a clean team participant was also involved in internal company pricing decision-making (a requirement to avoid undermining competition law). It was felt that external market access/health economic agencies, which have sufficient experience, could be used to negotiate on a company's behalf.

Takeda believes that it should be for individual manufacturers involved in the Voluntary Arbitration Framework to determine the makeup of their clean teams based on; their assessment of the risks, discussions with their in-house and external legal counsel, and to set out the possible conflicts of interests of each member of the clean team, prior to commencing negotiations.

Is the implementation of non-uniform pricing necessary?

There was broad consensus that enabling non-uniform pricing for combination treatments was necessary for any solution to be successful. This is to avoid the unintentional manipulation or fixing of treatment prices, which can undermine competition. It is also to remove a disincentive to launching an add-on therapy if there is risk of devaluing existing indications where the treatment is already available as a monotherapy, for example.

Under the terms on the current 2019 VPAS, NHSE does not routinely operate pricing by indication. However, it allows “other forms of commercial flexibility” in the circumstances “where uniform pricing would reduce total revenue for a medicine.”

Takeda recognises that the proposed solution will require NHSE to evolve its current position on non-uniform pricing and advocate that NHSE enables non-uniform pricing to be considered in the specific context of combination treatments not regarded as cost-effective at zero, or near zero, price.

How can you incentivise manufacturers to participate?

The roundtables covered the imbalance of market power and incentives in the system, such as the backbone manufacturer already being reimbursed and there being no requirement for them to re-negotiate. It was noted that this could dissuade the backbone manufacturer from meaningfully participating in the Voluntary Arbitration Framework.

Takeda noted that potential mechanisms could be designed to secure all parties' involvement in the solution. This could include including writing mandatory participation in the Voluntary Arbitration Framework into the VPAS and being transparent around manufacturer involvement and the success of negotiations. This could take the form of the Arbitrator publishing public statements at key milestones throughout the process and / or a final statement on the success (or not) of negotiations, just as NICE currently does on the outcomes of evaluations and at key points during that process.

It was noted that the long-term success of the solution would be dependent on how companies view the effectiveness of repeated engagement in negotiations: if it secured patient access to treatments and the reputational impact of withdrawing from the process.

Next steps

Takeda is continuing its engagement with all interested stakeholders to discuss further the proposals contained within its solution. Takeda continues to welcome comments on its proposed solution from all interested parties, and you can contact the team via: combinationmedicinesUK@takeda.com

Takeda remains open to other perspectives on solving the combination treatments challenge and will continue to explore alternatives with all stakeholders through planned ongoing one-to-one engagement as well as supporting others in the development of their proposed solutions.

We look forward to a solution being identified and implemented soon. To read more about Takeda's work on this critical topic, please visit <https://www.takeda.com/en-gb/what-we-do/combination-treatments/>.