Dolon Institute
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Joint Clinical Assessment: The finger on the scale for orphan sustainability in Europe?

January 2025

Introduction

Over the past few years, many concerns have been shared about the EU Health Technology Assessment (HTA) Regulation generally, and Joint Clinical Assessment (JCA) specifically. Key objections have centred on the loss of sovereignty of Member States; the potential for duplication and increased complexity; the difficulty of operationalising the scheme; and the risk of delays to patient access. At the same time, there is hope that JCA can help streamline HTA processes in a fragmented Europe, thus improving patient access and efficiency.

Whether the homogenisation of European clinical assessments will be beneficial to rare diseases is not straightforward – not least because it cannot be considered in a vacuum. The European policy and payer environment for orphan medicines has been rapidly shifting across the past two decades, on aggregate making Europe a more constrained market. Accordingly, this piece tackles two key questions:

- What might JCA look like for orphan medicines?
- What might the introduction of JCA mean for the sustainability of orphan innovation and access in Europe?

1. JCA implementation for orphans: a patchwork of knowns and unknowns

Because JCA is upon us, discussion is currently focused on practical questions on three main themes:

- EU-level implementation (e.g., What is the JCA process? What will the JCA report cover vs. not cover? How will stakeholders be involved?)
- Country-level implementation (e.g., How might countries adapt their national HTA/P&R processes in the short/medium term? What systems will be established to monitor the implementation of JCA recommendations at country level?)
- Evidence and PICOs (e.g., What type of evidence does the JCA require and favour? What is the process for PICO selection?).

At Dolon, we have mapped dozens of questions, from the most elemental to the most specific, and we have established a Task Force dedicated to tracking answers. These have been trickling through in the past few months, thanks to the publication of various Implementing Acts and guidance documents. Below is a summary of what we have learnt, and what remains to be clarified.

EU-level implementation Quite a lot has been settled with regards to EU-level implementation. The JCA process and timelines, in relation to EMA timelines, have been established. Requirements for the JCA dossier and format for the report are well characterised, plus experience from EUnetHTA helps grasp what the report might look like. High-level governance and stakeholder interactions have been mapped out relatively clearly.

Nonetheless, some gaps remain. For example, it remains unclear how confidential information will be handled within the Member State Coordination Group on HTA (HTACG), and the disincentives to maintain confidentiality appear to be negligible. Exactly how much tangible impact patients and clinical experts might have remains to be seen, as the guidance captures potential interactions but does not specify the extent to which the expert voice will be listened to. This is particularly relevant for rare diseases, where clinician and patient expertise is critical to interpret sparse evidence in poorly understood conditions. Beyond uncertainties, there are concerns. A key concern is about the feasibility for developers to comply with the timeline for submission. Meeting the compressed JCA timelines might be especially difficult for orphans. That is because less data is often available for rare indications, requiring indirect comparisons or extrapolation. Orphan medicines are also often developed by smaller biotechs, with less capacity for extensive statistical analysis.

Another relates to the management of conflicts of interest. The guidance sparked criticism from rare disease advocates, who worry that rules are overly restrictive to be workable. Indeed, the number of patient experts in rare diseases is small, and these advocates are often involved with developers, to help ensure that the clinical programme aligns with patient needs. Similarly, in many rare diseases there is only one expert centre per country, which will inevitably be involved in trials and other research with the manufacturer. By constraining the involvement of clinical professionals with the most experience of managing patients, conflict of interest rules will further hamper the interpretation of complex and sparse data.
Country-level implementation

We know even less about country-level implementation and the extent to which countries might modify their processes to comply with JCA. The HTA Regulation mandates countries to give "due consideration" to the JCA report and not to request evidence that is already captured in the report – which is a rather flexible mandate.

It is probable that the first year or two of implementation will see some confusion, complications, and delays across countries as stakeholders get accustomed to new processes. If we look beyond, to the three-to-five year mark, we can hypothesise how countries might adapt to JCA.

- Smaller markets, which currently face HTA capacity constraints, may change and benefit the most. Streamlined processes supported by the JCA report could help expedite market access for some medicines, although current delays to orphan access in lower income markets are often due to challenges in price negotiations rather than delays in clinical benefit assessment.
- Spain has indicated a clear intent to incorporate JCA into their processes, and to leverage the JCA report to accelerate local HTA timelines.
- Italy is in the midst of restructuring AIFA, which is not linked to JCA per se but could provide a platform to adapt current procedures to JCA.
- France and Germany are actively getting ready for the implementation of JCA, for example by preparing decrees of ministerial orders dictating adjustments to existing processes. Some changes to requirements for the national HTA dossiers are expected[1]. Nonetheless, because HTA processes and outcomes are very established in these countries, JCA seems unlikely to have a significant impact on timelines or requirements, at least in the short to medium term. What is critical for orphans in these markets is that existing adjustments to HTA processes that make the system workable for rare disease medicines, are not lost, most importantly the 'non-quantifiable benefit' floor for orphans in Germany.

Looking beyond Europe, the US, Japan and Canada might consider the JCA report, but at this stage it is improbable that JCA will trigger much change. The UK has not communicated on how it might integrate JCA within NICE. It is unlikely that a profound change is on the horizon: NICE methods are clearly established, plus using EU outputs in a post-Brexit Britain would be politically contentious.

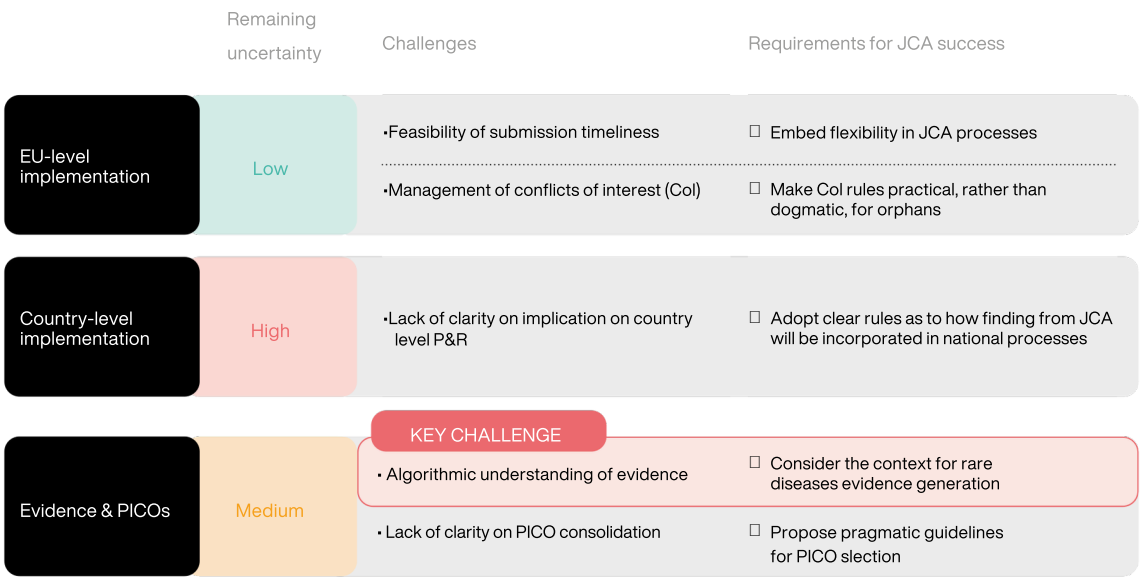
[1] APM News (2024). France and Germany preparing updates to national rules, '10/10' readiness for EU HTA. Available here

Evidence & PICOs

Perhaps the biggest present concerns relate to evidence requirements and PICOs. Guidance documents on outcomes, on evidence synthesis and on the validity of clinical studies shed light on the evidence requirements. Of critical importance for rare diseases is the strict evidence hierarchy, whereby evidence from randomised controlled trials is considered gold standard and evidence from single arm trials and real world data is discounted. Guidance documents include no mention of adaptations to the specific context of rare diseases or ATMPs, even though they face inherent challenges to meeting standard requirements. Whether there might be some deviations for orphans and ATMPs, for example at the discretion of assessors or in future revisions to the guidance, is an essential point to clarify. On PICOs (Population, Intervention, Comparator, Outcome), the general process for assessment scoping has been defined. A significant challenge lies in the lack of developer involvement in the scoping process, which means that the extensive manufacturer knowledge of the disease might not be reflected in the PICOs requested. This is a significant concern for rare diseases, for which disease knowledge is often limited. Moreover, the definition of 'Comparator' is unlikely to be straightforward in many rare diseases, given that the standard of care is often a varied mix of off-label medicines and non-pharmacological interventions.

In addition, guidance on PICO consolidation has been eagerly awaited and was only released one month before implementation. However, it remains to be seen how effectively member states' requirements will be harmonised, as there is significant potential for PICO proliferation. A recent study illustrated the importance of PICO consolidation. It showed that for a hypothetical product indicated for third line multiple myeloma (a rare disease), up to 16 products and 720 analyses could be requested – and this is the most conservative scenario. The study further highlighted that the number of analyses increases exponentially with each request. It showcases that pragmatism with regards to the number of PICOs will be essential to the feasibility of the JCA in rare diseases2.

Figure 1: Key challenges with current JCA guidelines and requirements for success for orphans



[2] Beate Wieseler, chair of the subgroup for methodological and procedural guidance, has indicated a shared inclination for pragmatism. While she excluded a cap on the number of PICOs, she stated (in early November 2024) "What we are trying hard to do is to minimise the number of PICOs so that we can answer as many requests per Member State as possible with the lowest number of PICOs as possible".

2.The bigger picture: implications for orphan sustainability

So far, most discussions have been focused on the aforementioned practical points. Relatively less attention has been devoted to the broader implications of JCA for orphan medicines in Europe. Yet it is critical to explore the potential impact of JCA on orphan innovation (i.e., orphans being developed for and approved in the European market), on access (i.e., orphans achieving reimbursement in Europe) and on the broader European ecosystem (i.e., whether investment in orphan R&D is viable in Europe). A rapidly shifting European environment Innovation, access and the broader ecosystem are impacted by the holistic 'incentives framework' for orphans that encompasses intellectual property rules, the regulatory framework, HTA and pricing and funding.

So far, Europe has benefited from a robust regulatory framework and strong market protections for orphans (thanks to the advent of orphan market exclusivity in the 2000 Orphan Regulation). However, HTA, pricing and funding challenges have limited the attractiveness of Europe for rare diseases. P&R outcomes for orphans have worsened over the past twenty years. In 2023, orphan drugs availability was only 35% according to the EFPIA WAIT indicator (8 percentage points lower than all medicines). Average time to availability was 542 days (ranging from 3 months in Germany to 2.5 years in Lithuania), compared to 493 days in 20183.
Orphans face ever tougher downward price pressure, through mandatory rebates and discounts, product-level caps, contracting agreements, use of low-cost comparators as benchmarks, lack of adjustment of willingness-to-pay for inflation and some pushback on the need to adjust price to prevalence. All in all, this means that the business case for developing orphans in Europe is marginal, considering the low revenue (€48 million on average), long time to patient access, high risk of research and significant costs of development and commercialisation. In a 2023 analysis, we showed that the average risk-adjusted net present value, an important measure of the attractiveness of investment propositions, was barely breaking even4. The picture has likely deteriorated since.
At the European level, the revision of the General Pharmaceutical Legislation, which was largely motivated by payer and policymaker alarm over 'over-incentivisation', is expected to decrease the overall amount of market protection and make their obtention more conditional.

At the Member State level, P&R continues to become more challenging for orphans. For example, Germany recently lowered the revenue threshold that triggers a full assessment of orphan medicines from €50 million to €30 million, something that has already led to orphans being removed from Germany5. The million (billion) dollar question therefore becomes: will JCA be the finger on the scale towards a more or less sustainable environment for orphans?

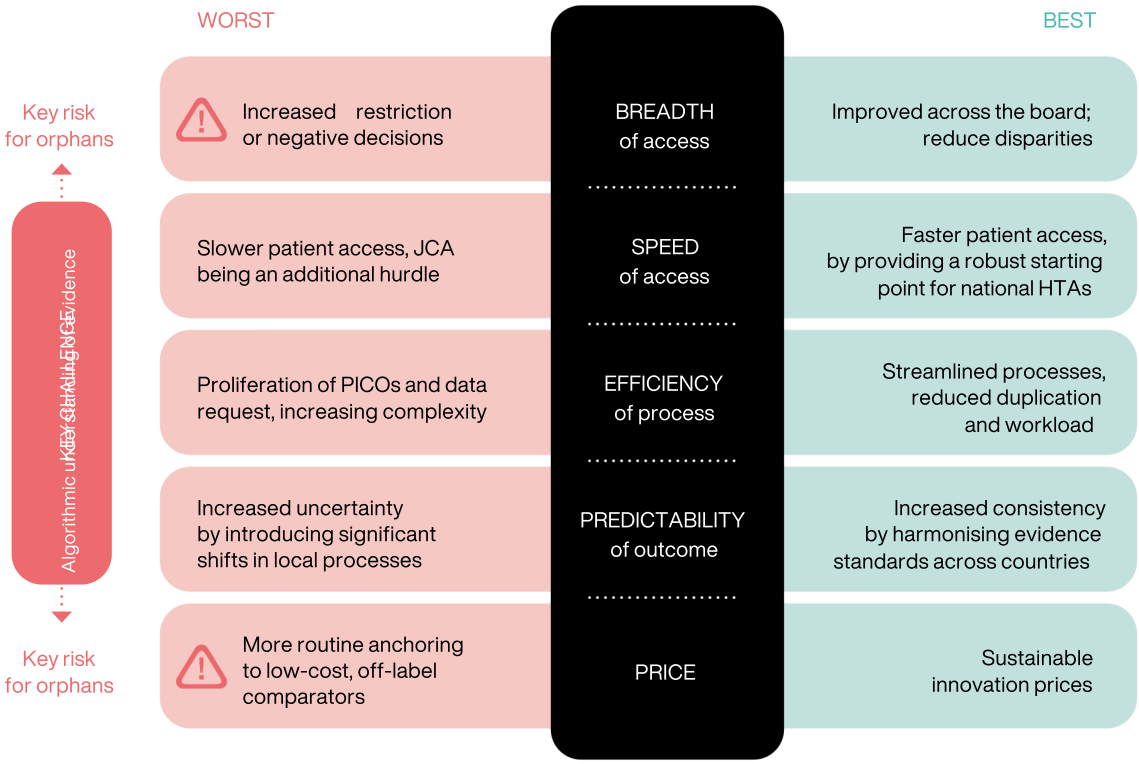
[3] Note that the country scope of the EFPIA WAIT indicator was slightly different in 2018 vs. 2023.

[4] Dolon (2023). Revision of the Orphan Regulation: Estimated impact on incentives for innovation of changes proposed by the European Commission. Available here

[5] For example, Abecma, a CAR-T cell therapy indicated in Multiple Myeloma, was withdrawn from the German market following an assessment of "no added benefit". Reference here

A case for optimism and a case for concern JCA has the potential to impact five dimensions of orphan sustainability (see visual): breadth of access, speed, efficiency, predictability and price. These are key factors in investment and launch decisions for developers.

Figure 2: Spectrum of potential impact of JCA for orphans across five dimensions relevant to orphan sustainability



It is currently unclear where JCA might take Europe, across these five dimensions, for orphan medicines.

Some see a case for optimism. Mario Draghi, in his report on European competitiveness, highlighted the importance of European coordination to restore competitiveness6. He appears to see JCA as a stepping stone towards a fully integrated European-level P&R process. (It should be noted that it took us 30 years to get from the EMA to JCA, so we might have another three decades before it becomes a reality.) Other stakeholders share his vision. EURORDIS, the European rare disease patient association, has in the past advocated for joint HTA and joint procurement as a way to reduce complexity and expand access to treatments for very rare conditions.

[6] European Commission (2024). The future of European competitiveness. Part B | In-depth analysis and recommendations. Available here. Relevant proposals are: "Expedite access to markets through coordinated action by medicines agencies, HTA authorities and public payers on guidance to industry, pricing and reimbursement as well as procurement" and "Rapidly and fully implement the HTA regulation and ensure the required resources are allocated to ensure the delivery of joint clinical assessments as of 2025, with the aim of establishing an EU agency in the long term".

A 'best case' future in which JCA improves access and investment in rare diseases is still a possibility, but only if two key requirements are met:

- evidence requirements within JCA are correctly calibrated for all medicines and particularly for orphans and ATMPs
- Member States' willingness to pay for orphan medicines is sufficient to make them economically viable.

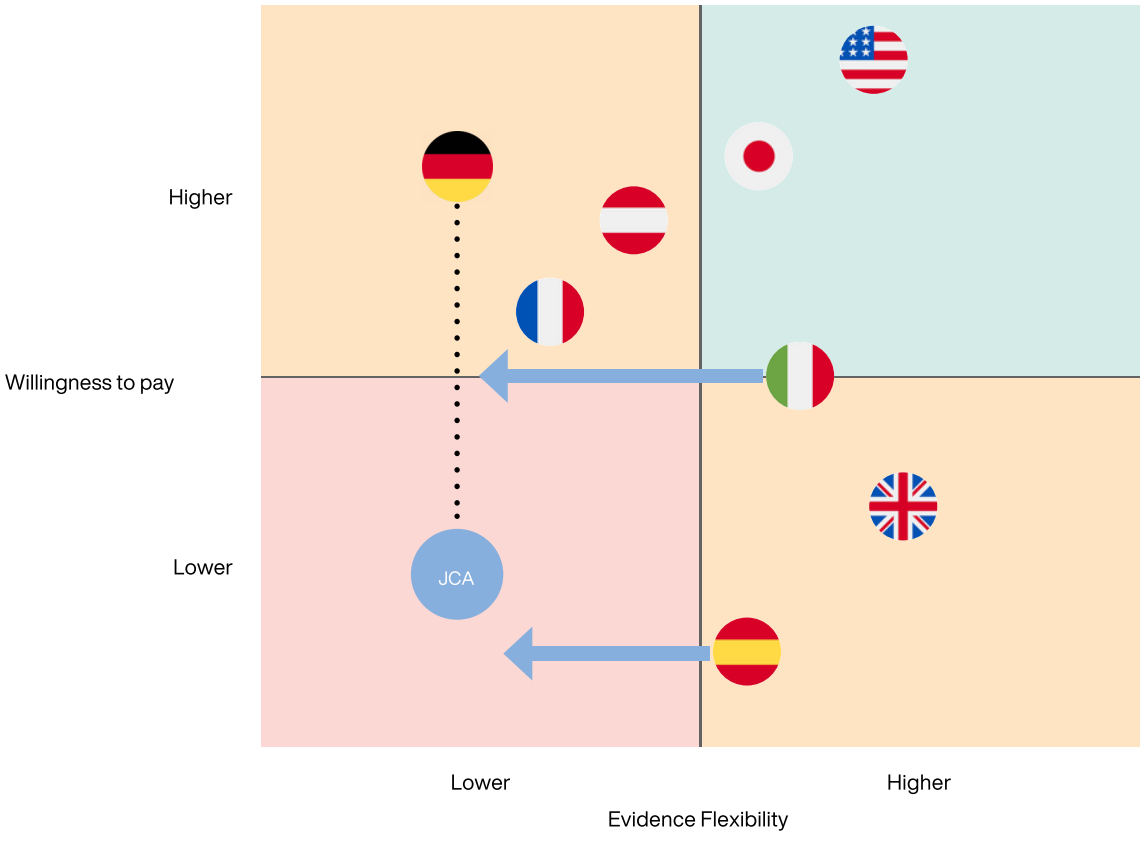
On both these points there is cause for concern.

To date, European countries have shown variable levels of flexibility in their acceptance of evidence for orphan medicines, and varying willingness to pay (see illustrative figure below).

In Germany, there are some challenges with these evidence requirements, but the existence of a "get out jail free" card, in the form of the automatic recognition of added benefit for orphans, and a generally appropriate willingness-to-pay, make the system largely workable for patients and manufacturers. (Of course, this may change, if the orphan exemption is revoked. The advent of JCA has given momentum to key proponents of repealing the exemptions to renew their advocacy.)

In some other countries, like Italy, the willingness to pay is lower, but flexibility in evidence interpretation has supported patient access to orphan medicines.

Currently, JCA evidence standards appear to be as stringent as Germany's with regards to the evidence preferred (around comparator, endpoints, study design). The difficulty is that other EU countries, which are poised to base their recommendations on the same strict evidence requirements, do not have the same pricing flexibilities for orphans. Therefore, there is a salient risk of negative impact on rate of availability and price, with potentially dramatic consequences.



The outlook

As much remains in balance, orphan developers can consider action across three levels.

- Prepare to work within JCA. Developers expecting to undergo JCA in the near term should actively anticipate JCA requirements, including PICO requests, so that they are equipped to submit the dossier within 100 days. This might entail rethinking pre-launch activities, to ensure planning reflects JCA timelines and processes. Enhanced communication across the Global Access, local Access and Regulatory teams might be necessary to prepare a JCA dossier that is aligned with the regulatory application and country-level strategy. Building capacity in statistics and HEOR teams might also be needed, to oversee the many indirect treatment comparisons that will be required.

- Advocate for the necessary flexibility for rare diseases. JCA evidence requirements must be tailored to the specificities of rare diseases, rather than uniformly applying the same 'gold standard'. In particular, they should reflect that uncertainty is sometimes unavoidable – and offer the possibility of experimenting with new HTA methodologies when that is the case. This could leverage the work done by the Rare Disease Interest Group within HTAi, of which Dolon's Elena Nicod is a member7. If nuanced requirements cannot be embedded within JCA itself, countries should take the lead on interpreting evidence flexibly. Orphan developers must continue pushing on adaptation of value frameworks to rare diseases, ideally within JCA and pragmatically within countries.

- Engage stakeholders on orphan sustainability. There is a need for policymakers to consider the collective impact of all changes in the environment (at European and country level; including changes to intellectual property rules and P&R systems). As multiple substantial reforms break on rare diseases at the same time, their effect cannot be considered in isolation from each other, nor from the broader trend of declining European attractiveness. Considering these trends and their effect is at the heart of our policy work. Orphan developers should educate stakeholders on how the legislative and P&R frameworks create (dis)incentives for innovation and access, and the requirements for sustained European competitiveness.

[7] The Interest Group has an ongoing project on "characterizing the issues about rare diseases that make HTA difficult and defining a roadmap on ways forward" and another on "New paradigms for evidence generation and interpretation of rare diseases, including relevant value assessment frameworks". Additional information available here