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EXPERT INSIGHT

THE FIRST EU JCA COMPLETENESS REVIEWS

Early signals from Tacquell and Catequentinib — Lessons, Hypotheses and the Emerging JCA Defiance

ABOUT REPORT

This synthesis proposes five operational lessons derived from the Tacquell and Catequentinib completeness reviews, along with five hypotheses regarding their rationale and potential implications.

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Published by MAS

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Part I — Five lessons every health technology developer should learn

Early signals from Tacquell and Catequentinib

The first Joint Clinical Assessment (JCA) completeness reviews published under Regulation (EU) 2021/2282 are much more than procedural notices. They provide the first practical evidence of how the European Commission is interpreting Article 9 and, consequently, what will be expected from future JCA submissions.

Although the reviews concern two individual products, Tacquell and Catequentinib, their importance extends far beyond these dossiers. They reveal the emerging operational standards that are likely to shape future Joint Clinical Assessments.

For Health Technology Developers (HTDs), these documents should be considered required reading.

Lesson 1 — A JCA dossier is no longer a regulatory submission

Perhaps the most important message is that a JCA dossier is not simply a collection of clinical studies supporting a product.

The Commission increasingly evaluates **the entire evidence-generation process**, including:

- how evidence was identified;
- why studies were included or excluded;
- whether all relevant evidence was considered;
- whether analyses are reproducible;
- whether conclusions can be independently assessed.

In other words, the dossier itself becomes an auditable scientific process.

Take-home message Think like a systematic reviewer rather than a regulatory writer.

Lesson 2 — Transparency has become an assessment criterion

Historically, many submissions focused primarily on demonstrating favourable clinical outcomes. The first completeness reviews suggest a different philosophy.

The Commission repeatedly requests documentation explaining:

- search strategies;
- excluded studies;
- methodological choices;
- analytical assumptions;
- supporting appendices;
- feasibility assessments.

The quality of the evidence remains important. However, the transparency of how that evidence was generated is becoming equally important.

Take-home message Future submissions should assume that every methodological decision may need to be justified.

Lesson 3 — "No comparison possible" is no longer sufficient

One of the clearest messages emerging from the Catequentinib review concerns indirect treatment comparisons (ITCs). Simply stating that an ITC could not be performed may no longer satisfy assessors.

Instead, developers should be prepared to demonstrate:

- what evidence was searched;
- whether indirect comparisons were explored;
- why they were considered infeasible;
- what alternative approaches were evaluated.

The expectation appears to have shifted from **explaining the absence of analyses** to **demonstrating that all reasonable analytical options were systematically assessed**.

Take-home message *Document the feasibility assessment — not just the final decision.*

Lesson 4 — Reproducibility is becoming a regulatory expectation

The Tacquell review places considerable emphasis on reproducibility. Assessors requested information allowing them to understand how complex analyses had been performed, including supporting documentation and analytical details.

This reflects a broader change. Future JCAs may increasingly evaluate not only *what* the results are, but also *whether an independent assessor could understand, verify and critically evaluate how those results were produced*.

Take-home message *Analyses should be developed with independent scrutiny in mind.*

Lesson 5 — Completeness now extends from evidence identification to final conclusions

Taken together, the two reviews suggest that "completeness" has acquired a much broader meaning than originally anticipated. Completeness now appears to include:

- systematic evidence identification
- transparent study selection
- justification of exclusions
- reproducible analyses
- comprehensive documentation
- traceability from evidence source to final conclusion

The consequence is significant. A dossier may contain excellent clinical evidence and still be considered incomplete if the evidentiary process itself cannot be adequately demonstrated.

Preparing for the next generation of JCAs

The first completeness reviews suggest that successful JCA preparation should begin well before dossier submission. Developers should consider integrating JCA requirements into evidence-generation planning rather than treating them as a late regulatory exercise. This includes anticipating future needs for:

- systematic literature reviews;
- evidence traceability;
- feasibility assessments;
- documentation of methodological decisions;
- reproducibility of analyses;
- governance of evidence generation.

Organisations that establish these capabilities early are likely to reduce submission risk and improve readiness for future assessments.

Looking Beyond Tacquell and Catequentinib

These first reviews should not be interpreted as isolated procedural events. They represent the first observable signals of an evolving evidentiary culture within European HTA.

As additional Joint Clinical Assessments become available, expectations will undoubtedly continue to mature. However, one message is already clear: the future European JCA dossier is no longer simply a clinical evidence package. It is an auditable, transparent and reproducible evidence-synthesis system.

For Health Technology Developers, adapting to this shift may prove as important as the clinical evidence itself.

Part II — Five hypotheses and the emergence of a JCA defiance for orphan -designated products & ATMPs

Early signals from Tacquell and Catequentinib

The first Joint Clinical Assessment (JCA) completeness reviews published under Regulation (EU) 2021/2282 are much more than procedural notices. They provide the first practical evidence of how the European Commission is interpreting Article 9 and, consequently, what will be expected from future JCA submissions. However, they also inform how HTDs have decided deliberately to manage the JCA submission.

Although the reviews concern two individual products, Tacquell and Catequentinib, their importance extends far beyond these dossiers. They reveal an emerging weak signal of a potential attitude of HTDs of orphan-designated products and ATMPs to comply with submission, but to keep it at a level that could not be audited by assessors and to avoid the publication of a JCA report with a predetermined conclusion.

The completeness notices tell us **what the Commission asked for**.

They do **not** tell us **why the HTD decided not to provide it after a first request and a second request**. They don't report the response of HTDs lacking the required transparency for the public to understand what has happened.

We therefore have to distinguish:

- what can be observed;
- what can be reasonably inferred;
- what would be speculation.

The observable fact is that after a first request, and again after a second request, some information remained missing.

That is unusual because pharmaceutical companies normally have a very strong culture of complying with regulatory requests. However, in a situation where non-compliance does not prevent reaching the market through normal conditions, where the outcome of the assessment is not fit for purpose for orphan drugs/ATMPs, and where the outcome of the assessment is well known ahead of the assessment — why should HTDs comply?

So the question becomes: what would make a rational company accept a completeness dispute?

Hypothesis 1 — The company genuinely could not generate the evidence

This is the most benign explanation. The company may simply have been unable to produce the requested information. For example:

- no suitable comparator existed;
- no observational data existed;
- no registry existed;
- no feasible ITC could be performed;
- no external control could be justified.

In that situation the company cannot provide what does not exist. This explanation is particularly plausible for:

- orphan diseases;
- rare cancers;
- ATMPs.

In this interpretation the completeness review is exposing a genuine evidence gap rather than non-cooperation. This is probably the explanation most likely to be publicly defended by a company — but obviously without strong evidence of an exhaustive negative search.

Hypothesis 2 — The company believed the request was scientifically pointless

This is where the Evidence Generation Paradox becomes relevant. The reasoning might be: we know the evidence hierarchy; we know observational evidence will be judged very low certainty; we know an unanchored comparison will be judged highly uncertain; we know the final conclusion in advance.

Therefore: why invest substantial resources producing analyses that will not materially change the assessment?

This is a much more provocative interpretation. The company is not refusing because the evidence cannot be generated. The company is refusing because the expected value of generating it is close to zero. The logic would be:

- high cost;
- negligible impact on conclusions.

This is not irrational. It is a cost-benefit analysis and conclusion.

Hypothesis 3 — The company disagreed with the interpretation of Article 9

This is a legal-governance hypothesis. The company may have believed: Article 9 requires submission of available evidence; it does not require generation of new evidence. This distinction is critical.

The company might accept:

- providing studies;
- providing analyses already performed.

But reject:

- performing new analyses;
- generating new comparisons;
- conducting new methodological exercises.

Under this interpretation the dispute is not about science. It is about the legal scope of completeness. The company effectively says: we submitted the evidence; you are asking us to create additional evidence. This would be a very important dispute if it emerges repeatedly.

Hypothesis 4 — Strategic avoidance of reputational risk

This is uncomfortable but plausible. Imagine a company performs multiple ITCs, observational analyses and external controls. The result is predictable:

- major bias concerns;
- major uncertainty concerns;
- very low certainty.

These analyses then become incorporated into a public JCA report. The company may conclude: producing the analysis creates more negative material than positive material. In other words:

- the analysis will not improve certainty;
- the analysis will generate additional criticism.

From that perspective, not conducting the analysis may be viewed as the less damaging option. Whether that is a good strategy is another matter — but it is economically understandable.

Hypothesis 5 — The company was signalling a structural disagreement

This is an interesting possibility. The company may have intentionally accepted the completeness dispute because it wished to make a broader point. The implicit argument would be: the framework is requesting evidence that cannot realistically be generated in this disease area and within the requested timeframe.

The company is not fighting the specific request. It is exposing the limitations of the methodology and the feasibility itself. In effect: we cannot satisfy these requirements because no developer in this situation would, especially within 100 days. This becomes almost a stress test of the framework.

Which explanation is most likely?

For Ojemda, Catequentinib, Tacquell and similar orphan/ATMP settings, the suspected explanation is probably a combination of all hypotheses.

The really important point is that the completeness notices reveal only one side of the conversation. The Commission's interpretation is visible. The company's reasoning is invisible. This creates an imbalance in transparency, and the Commission should also publish the request to the HTD and the response of the HTD. This may be requested of the Commission, as the HTAR has a transparency duty.

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