Readying for the second wave: What, when and how must orphan medicine manufacturers prepare for EU HTAR?

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INTRODUCTION

As we approach the expansion of the EU Health Technology Assessment Regulation (HTAR) for orphan medicines in 2028, manufacturers must start considering how they adapt their organizations and ways of working to account for the new Joint Scientific Consultation (JSC) and Joint Clinical Assessment (JCA) procedures.

While many elements of the legislation were clarified when EU HTAR was launched for oncology medicines and advanced therapeutic medicinal products (ATMPs), some uncertainties remained regarding the assessment of orphan products under the new regulation. How will products with no clear comparator be scoped? How will methodological guidelines consider trial designs commonly employed for orphan products(e.g., single arm trials, natural history studies)?

Given the complexities of evidence generation for orphan products, there is an urgent need to provide clarity regarding preparations required to ensure all JCA requirements are met.

OBJECTIVES & METHODOLOGY

This research examines the scope of manufacturer's preparatory activities head of the January 2028 implementation, providing recommendations on when and how orphan medicine manufacturers should act to ensure their readiness.

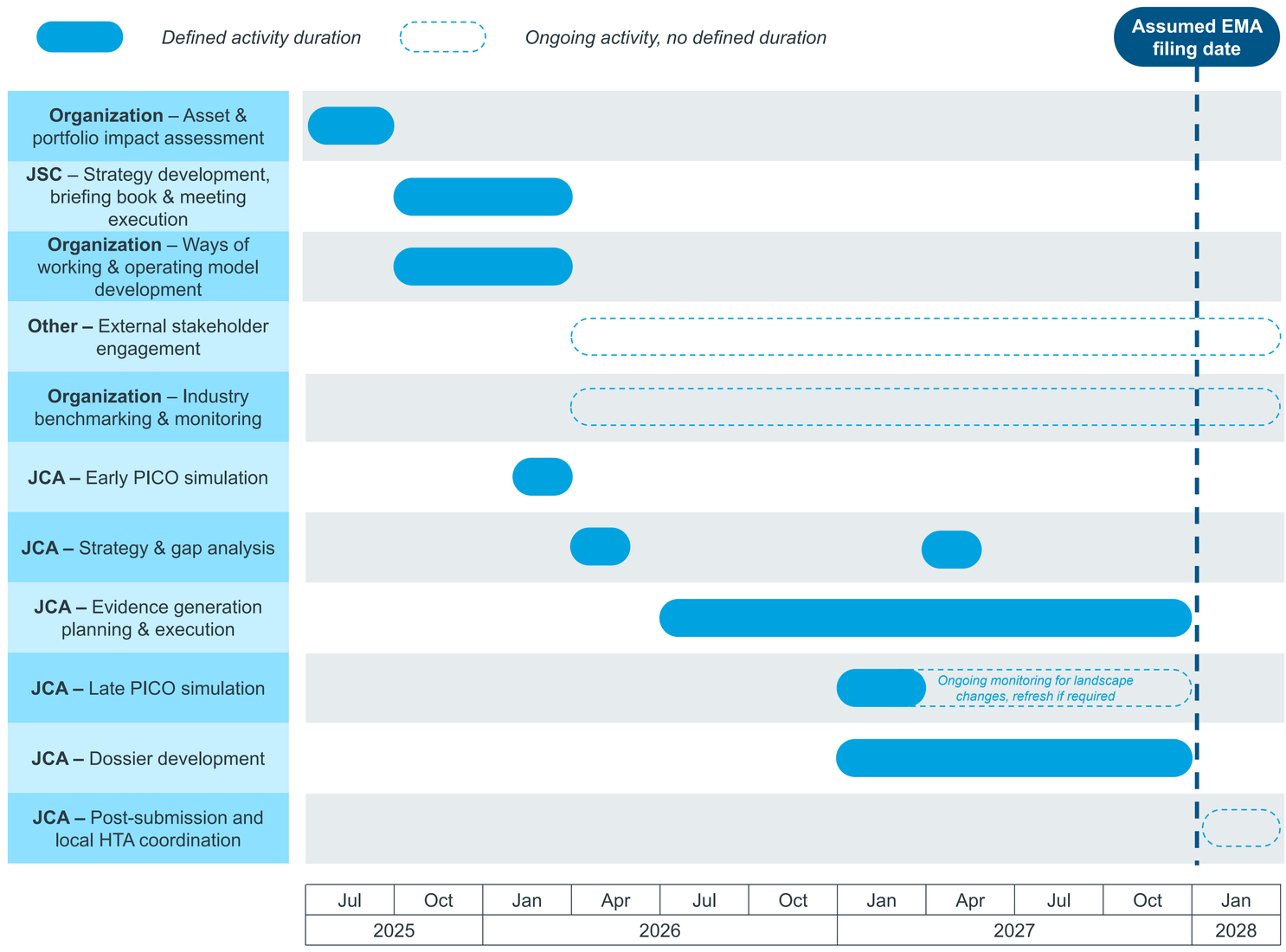
Engagements conducted by IQVIA for clients preparing for EU HTAR procedures of oncology and advanced therapy medicinal products (ATMPs) were collated across 2024 and 2025 and categorized into twelve categories: Asset and portfolio impact assessment; JSC strategy development, briefing book and meeting execution; Ways of working and operating model development; External stakeholder engagement; Industry benchmarking and monitoring; Business training delivery; Early PICO (population, intervention, comparator, outcome) simulation; JCA strategy and gap analysis; Evidence generation planning and execution; Late PICO simulation; Dossier development; In-depth project management; Post-submission and local health technology assessment (HTA) coordination.

Engagements were assessed based on typical start date relative to expected European Medicines Agency (EMA) filing date, and typical duration. For PICO simulations, average population, comparator and required ITC (indirect treatment comparison) counts were aggregated and compared between orphan and non-orphan oncology medicines (Figure 1). Overall findings were translated to a timeline, assuming an EMA filing date of January 2028 (Figure 2) for an organization's first orphan medicine.

Figure 1: *Comparison of PICO complexity between orphan and non-orphan oncology medicines, across average number of PICOs requested, average number of requested PICOs (including number expected to require an ITC, populations and comparators*

Measurement metric	Orphan oncology PICO simulations **Average** *(minimum - maximum)*	Non-orphan oncology PICO simulations **Average** *(minimum - maximum)*
Average number of requested PICOs	**6** *(6 - 6)*	**11** *(5 – 21)*
Average number of requested PICOs requiring an ITC	**4.5** *(3 - 6)*	**7.5** *(0 – 15)*
Average number of requested populations	**6** *(6 – 6)*	**6.5** *(1 – 16)*
Average number of requested comparators	**5.5** *(4 – 7)*	**9** *(4 – 18)*

Figure 2: *Hypothetical timeline of all asset, portfolio and organizational engagements to support JSC and JCA submission and support local HTA efforts post-submission, based on real-world experience with JSC, JCA and local HTA engagements. The timeline assumes an EMA filing date of January 2028 for an organization's first orphan medicine in scope*



RESULTS & DISCUSSION

Analysis of prior PICO simulation parameters showed that orphan oncology PICO simulations typically yielded similar results to non-oncology simulations, with oncology PICO parameters always sitting within the range of the non-oncology simulation results. Analysis of prior engagement timing to support EU HTAR readiness showed that earliest preparations focusing on asset-agnostic actions typically begin at ~2.5 years ahead of an HTD's first asset in scope for JCA. Asset specific work (e.g., PICO simulations, strategy & gap analysis, evidence generation, dossier development and project management) typically begins 30 months prior to EMA filing and continues until the filing date. External-facing efforts (e.g., external stakeholder engagement, industry benchmarking & monitoring) typically begin 27 months prior to filing and continue indefinitely as an ongoing source of information. Once all asset, portfolio and business efforts are completed, short-term efforts typically focus on business training, beginning at the time of EMA filing and lasting approximately 1 month.

Translating such insights into a timeline for orphan medicine preparation, with an assumed earliest possible EMA filing to be in scope for JCA in January 2028, showed that early asset-agnostic and JSC preparations should have begun in Q3 2025, while asset-specific preparations are expected to begin shortly in Q1 2026.

CONCLUSIONS

It is hoped that the ongoing JCAs of oncology products, which are also orphan medicines, will provide some clarity but it is very likely that uncertainties will remain. HTDs that have already started organizational readiness preparations and are not seeking JSC for their first orphan asset are on track, but for those who have not begun such work, analysis of the typical timeline for preparations highlights three key considerations for preparations for the January 2028 rollout:

1. **The best time to start is now –** Introduction of the JSC and JCA procedures to launch planning is highly disruptive and requires HEOR, regulatory, market access commercial and many other functions to adapt their methods of working and collaborate in ways previously never required. Such adaptation takes time to assess, formulate, execute and socialize across an organisation, and once the process starts there is minimal time to iron out any final details. While 2028 may seem in the distant future, the time to start preparations may have already passed
2. **Simulation of evidence needs is increasingly essential –** The evidence scope definition for the 27 EU member states is complex and can lead to a high volume of PICOs, requiring many ITCs with subgroups across all relevant populations. PICO simulations for orphan oncology drugs noted significantly more uncertainty in predictions of populations and comparators, typically due to uncertainties on guideline implementation across markets and the most appropriate treatment choice, respectively. Given such uncertainty, one of the safest approaches to ensure strong evidence planning is through robust, and repeated PICO simulations from prior to registrational trial lock through to EMA filing
3. **Preparations can be supported by understanding the external environment –** Understanding the optimal approach for your company to JCA and JSC, alongside key stakeholder perspectives, will be vital for efficient and effective preparations. Conducting industry monitoring (e.g., first JCA procedures in orphan oncology products) and stakeholder engagement activities 2-3 years from launch up until EMA filing will support in understanding the requirements and defining ways of working well in advance of EMA filing

Outside of this analysis, additional activities required for EU HTAR, such as evidence generation activities, run along similar timelines with an external comparator typically taking 24-30 months. Evidence planning for JCA in orphan medicines is more complex than specifically and integration of such work with EU HTAR readiness must consider elements such as: Length of time for setup and execution of comparative evidence generation via an external control study, with PICO simulation timings and JCA strategy setting accounting for these longer timelines; Increased complexity for indirect evidence generation, typically as a result of differences in endpoint collection frequency and follow-up length in orphan medicine trials; Earlier and higher priority engagement with clinical, patient and HTA experts to understand relevant comparators across European markets; Greater focus on leveraging the opportunity provided by JSC to provide clarity on evidence requirements and preferred format

1 Regulation (EU) 2021/2282 of the European parliament and of the council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU

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