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Population, Intervention, Comparator, Outcomes (PICO) of ATMPs and Potential Impact on the Upcoming EU Regulation on HTA

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INTRODUCTION

The EU Regulation on Health Technology Assessment (HTA) entered into force in January 2022 and applies in 2025.

The new framework covers joint clinical assessments (JCA) across Member States (MS) to avoid duplicative effort. JCAs are non-binding, compilation of clinical evidence that must be given due consideration by MS and should be part of the documentation that supports national HTA activities.

JCAs will start with a small number of health technologies and will be progressively expanded:

- January 2025 – medicinal products with new active substances for the treatment of cancer, and those regulated as advanced therapy medicinal products (ATMP)
- January 2028 – orphan medicinal products
- January 2030 – all other medicinal products

As a starting point of JCAs, a scoping process will be conducted by a Coordination Group where it identifies population, intervention, comparator, outcomes (PICO) parameters reflecting MS needs ensuring that all PICOs relevant to all MS will be included. (Figure 1)

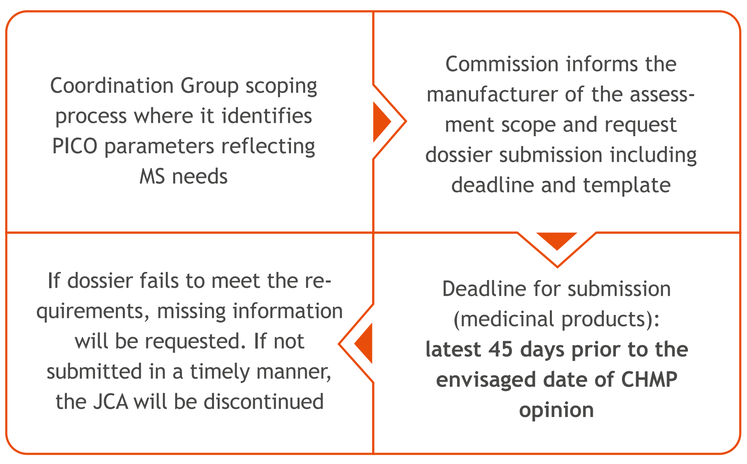

Figure 1. JCA Scoping Process

Based on this scoping exercise, the Commission will inform the manufacturer of the assessment scope which clarifies which data are needed from the manufacturer for the JCA dossier submission. The deadline for submission for medicinal products is at latest 45 days prior to the envisaged date of CHMP opinion.

Concerns were raised that a significant number of PICOs must be incorporated which may potentially complicate and lengthen the JCA process which may spillover to MS HTA processes, but the extent remains unclear.

OBJECTIVE

By example, this study aims to compare the extent of difference of PICOs of current ATMP HTAs in FR, DE, UK, and the potential impact on the upcoming regulation as ATMPs are one of the first technologies to be subjected to the JCA process.

METHODS

All ATMPs with marketing approval as of 2023 were identified from the EMA website.

From the identified ATMPs, all publicly available HTA reports were downloaded from the HAS, G-BA, and NICE websites.

For those ATMPs assessed in all three countries (FR, DE, UK), a comparative analysis of PICOs from the HTA reports was done and the potential impact on the upcoming implementation of the regulation was assessed.

RESULTS

Out of the 24 ATMPs with marketing approval (2023), 7 ATMPs covering 9 rare indications were assessed by HAS, G-BA, and NICE. Thus, 9 HTA reports were included in the PICO analysis.

The population(P) and intervention(I) are similar across countries.

There were differences in the comparators(C) in 7 out of 9 reports:

- **The rarity of the indications contributed to differences as they are mostly managed by non-standardized best supportive care (BSC) or salvage chemotherapies which differ per system. The comparators also include more than one intervention which contributed to the differences.**
- **In Germany, for an orphan drug with a sales volume < 30 M € in a 12-month period, no comparative analysis against a set appropriate comparator is required and additional benefit is considered proven based on the studies for marketing authorization approval. If the sales volume exceeds the 30 M € threshold, a full dossier must be submitted containing robust comparison vs. the appropriate comparator set out by G-BA.**

For the outcomes(O), endpoints have been similarly based on the clinical data and indirect comparisons submitted by the manufacturers.

Drug	Indication	Orphan	ATMP type MAA date	FR	DE	UK
				Comparator (C)		
Alofisel	Perianal fistulas in luminal Crohn's disease	Yes	CTMP 2018	Infliximab, adalimumab, surgical intervention	Orphan drug so no comparator required at assessment	Surgical intervention and seton placement
Yescarta	DLBCL and PMCL	Yes	GTMP 2018	Allograft, polychemotherapy with no specific recommended protocol, palliative care, Kymriah (DLBCL)		Salvage chemotherapy
Kymriah	B-cell ALL	Yes	GTMP 2018	Polychemotherapy, allogenic HSCT, anti-BCR-ABL TKIs in Ph+ ALL, inotuzumab ozogamicin in CD22+ B-ALL, blinatumomab for CD19+ B-ALL, palliative care		Blinatumomab, salvage chemotherapy
	DLBCL	Yes	GTMP 2018	Chemotherapy, autologous HSCT, allograft, palliative care, with no standardised therapeutic strategy		Salvage chemotherapy excluding pixantrone
Luxturna	Retinal dystrophy, biallelic RPE65 mutations	Yes	GTMP 2018	Best supportive care, lifestyle, dietary measures		Best supportive care
Zolgensma	SMA	Yes	GTMP 2020	Physiotherapy, occupational therapy respiratory assistance, non-invasive ventilation and gastrostomy, Spinraza (nusinersen)	Spinraza (nusinersen) or BSC (Exceeded 50M threshold for OD)	Best supportive care
	Presymptomatic SMA	Yes	GTMP 2020			Zolgensma for type 1 SMA, best supportive care for type 2/3 SMA
Tecartus	ALL	Yes	GTMP 2020	Revlimid (lenalidomide); Torisel (temsirolimus), chemotherapy, bortezomib, hematopoietic stem cell allograft	Orphan drug so no comparator required at assessment	Inotuzumab, blinatumomab and ponatinib
Upstaza	AADC deficiency	Yes	GTMP 2022	Best supportive care		Best supportive care

Different Similar GTMP: gene therapy medicinal product; CTMP: cell therapy medicinal product; MAA: Market Authorisation Approval

Table 1. Comparators across HTA

DISCUSSION

The extent of the difference in the comparators(C) is relevant. If true to the trend, the majority of the MS will have different appropriate comparators, the number of PICOs required for ATMPs across Europe will be high and the amount of evidence that must be compiled by the manufacturer to develop the JCA dossier will be extensive, which in addition must be submitted within tight timeframes.

Aside from the non-standardized polytherapy of these rare indications contributing to differences in comparators, treatment access differences across Europe may compound the reality of more PICOs:

- In the case of the HTA of Zolgensma in SMA (Table 1), Spinranza (nusinersen) was not available in the UK during NICE's assessment, unlike in DE and FR, hence best supportive care was used as the appropriate comparator leading to the dissimilarity.
- Disparities such as this may be wider across the 27 member states, each having its own health care system organization, pricing and reimbursement regulations, budget ceilings, and ability to pay.

CONCLUSIONS

ATMPs, the first to be assessed by JCA, may be subject to a complex process. Aside from the inherent complexity of the technology, a significant number of comparative therapies may need to be considered relative to the number of MS included.

To avoid challenges in the scoping process and delays in the assessment, an early coordination between the manufacturers and the HTA coordination group (HTACG) through the joint scientific consultations may provide an opportunity to validate PICO scope at an EU-level at an early clinical development stage. ATMP manufacturers must also ensure that they have the necessary resources to compile the required evidence in a short amount of time to comply with the timelines. Filling the JCA dossier template as much as possible even prior to the scoping process, e.g. disease and product-specific information, will save time. Adaptation and completion may follow through once PICO specifications are provided.

As operating procedures and further guidelines are still being developed by the HTACG, additional guidance may offer more clarity and support to ensure streamlined implementation of the regulation to avoid significant roadblocks. In addition, processes and guidelines will be subject to further refinement once the regulation is rolled out.

References

1) European Commission. Regulation on Health Technology Assessment. Accessed April 2023 Regulation on Health Technology Assessment (europa.eu) 2) EUnetHTA. D5.1 Submission Dossier Template – Medicinal Products. July 31 2023. D5.1 – EUnetHTA 3) EUnetHTA. D4.2 Scoping Process. Sept 30 2021. D4.2 – EUnetHTA 4) EUnetHTA. JCA timelines. March 15, 2023. EUnetHTA-21-D5.4-Timelines-JCA.pdf