Passing a Camel Through the Eye of a Needle: How Flexible Will the EU Joint Clinical Assessment Process Need to be to Fit the Time Available?

HTA1

Griffin A[1,2], Vandorou C[1]

[1]Johnson & Johnson, Buckinghamshire, UK, [2]ISPOR Institutional Council

OBJECTIVES:

The EU-HTA Regulation requires the production of Joint Clinical Assessments (JCA) in parallel to the EMA Regulatory process that provides Marketing Authorisation for new medicines.

Whilst the EMA regulatory processes are well defined, some steps are of variable length. This study examines the impact of these variable EMA durations on the planned JCA timeline.

A key challenge in planning for JCAs is that the EMA uses a 'relative' timeline of 'EMA activity days', whilst the JCA process uses 'absolute' calendar days. The two therefore do not constantly align.

METHODS:

The process and procedure steps for developing a JCA report were reviewed in the following sources:

- EU-HTA Regulation (EU)2021/2282[1]
- Joint Clinical Assessment Implementing Act (EU)2024/1381 (IA)[2]
- EUnetHTA21 deliverable D5.4[3]

EMA procedural timelines were obtained from published sources.[4]

The relationship between the planned JCA durations and observed EMA timelines were compared.

RESULTS:

EMA Timelines

EMA Centralised Procedure

- EMA activity related to the Centralised Procedure is 210 days
- In addition, the EMA activity is interrupted by two scheduled clock stops (day 120 & 180), where HTDs respond to the CHMP List of Questions (LoQ). The average durations of these clock stops are 90 and 30 days respectively
- The European Commission then has 67 days to issue the Market Authorisation, resulting in a total duration of just under 400 calendar days Figure 1
- However, the clock-stop duration is variable: 10% of recent cancer drug approvals had a 1 month first clock-stop, and a further 20% had 2 months[4]

EMA Accelerated Approval Procedure

- For the accelerated procedure, the total duration is approximately 254 days (EMA 150 days, EC 67 days, clock-stops 30+7 days)
- 80% of cancer drugs going through the Accelerated procedure reported a 1st clock stop of 1-month duration[4]

JCA Timeline

- The HTA Regulation does not specify when the JCA process should start, so it can therefore be determined by the HTA-CG.
- Once initiated, the process contain 3 distinct steps:
  - **Step 1 - scoping**: The IA specifies that the JCA subgroup has up to 10 days after the CHMP adopts its list of questions (day 120), therefore up to 130 days (from start of EMA process) to finalise its scope and PICOs[2]
  - **Step 2 - Dossier**: Deadline for HTDs to submit the dossier is at latest 45 days before the envisaged date of CHMP positive opinion[1]
  - **Step 3 - Assessment**: The process from receipt of HTD dossier to final JCA report contains multiple steps[3], Table 1

Table 1: From Assessment to Final JCA Report

Assessment Phase	Included Activities	Duration (days)
1st Draft Report	• Completeness check • Request for additional content • Assessors prepare 1st draft	100
2nd Draft Report	• JCA-SG review 1st draft[2] • Assessors prepare 2nd draft	36
Final JCA Report	• Review by Experts (Pts, Clin. Etc)[2] • Fact check with HTD • Assessors prepare final JCA	26
Finalisation and Endorsement by HTA-CG	• Finalise report by JCA-SG - (by date of MA [2]) • Endorsement by HTA-CG[2]	25*
Durations from EUnetHTA21 D5.4, May 2023[3] *The deadline in the Regulation for the HTA-CG to endorse the final JCA report is a maximum 30 days following granting of Marketing Authorisation (MA)[1]		

- Combining the information above allows the estimation of a total end to end JCA process, alongside the EMA Centralised Procedure. Table 2, and Figure 1a
- The estimations were then repeated for scenarios where there is a short clock stop in the centralised procedure, and for the Accelerated Approval process. Figure 1b & 1c

Table 2: Key steps and default time allocation for JCA

JCA Step	Step Description	Output	Responsibility	Duration
1	Scoping: Identifying the question(s)	Final PICOs	Assessors / HTA-CG	130
2	Dossier: Compiling the Evidence	HTD Dossier	HTD	100
3	Assessment: of the Evidence	JCA Report	Assessors / HTA-CG	187
Total JCA duration, based on IA and EUnetHTA21 proposals				417

Figure 1: EMA Timeline Scenarios and Corresponding JCA Requirements

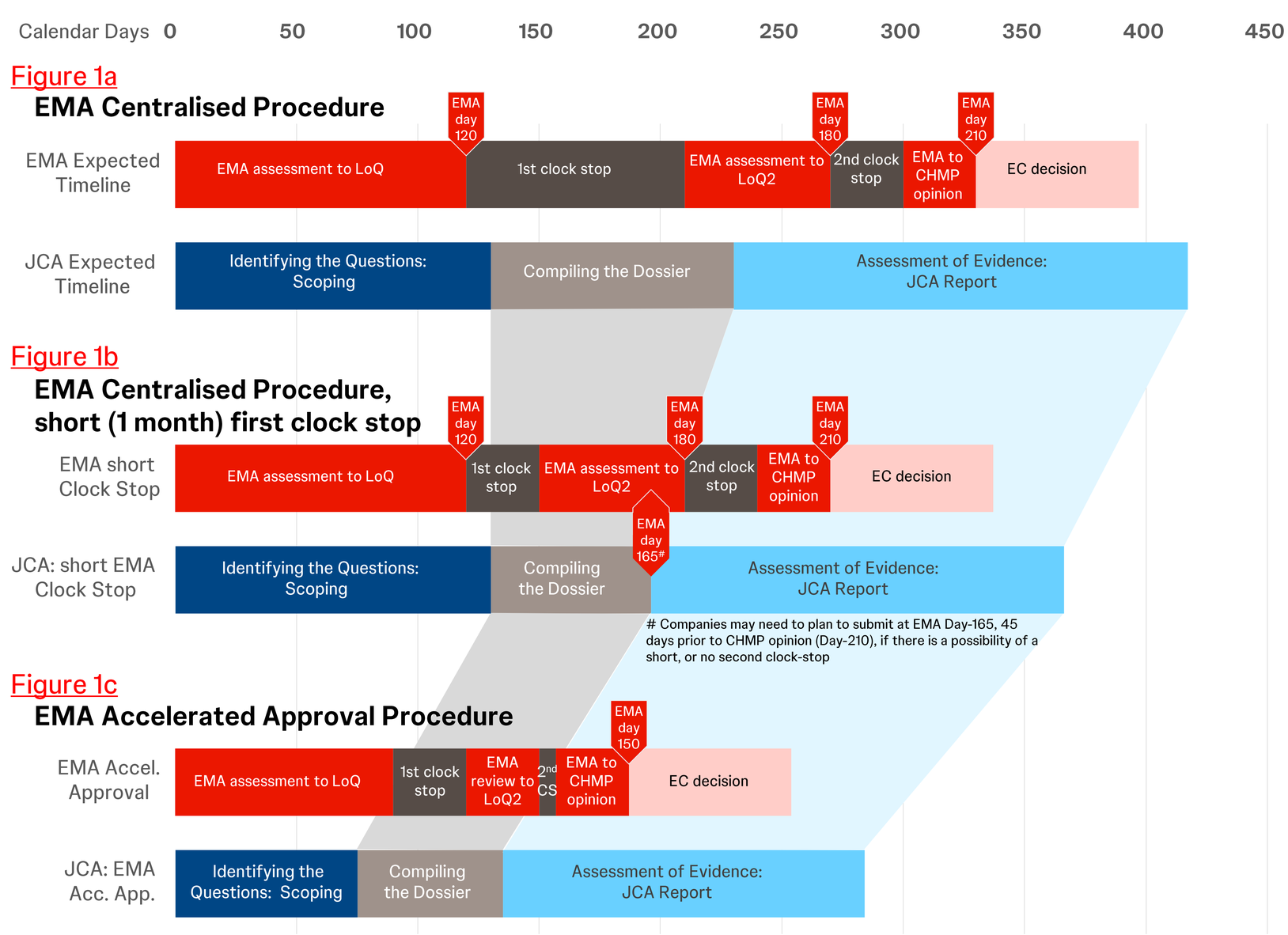

Table 3: Potential reductions in available time due to variations from expected EMA Centralised Procedure timeline

	Centralised Procedure (*default*)				Centralised Procedure, 1 mth C.S.				Accelerated Approval Process			
EMA Process Steps	EMA time allocation	JCA Time overlap with EMA			EMA time allocation	JCA Time overlap with EMA			EMA time allocation	JCA Time overlap with EMA		
		Scoping	Dossier	Assmt.		Scoping	Dossier	Assmt.		Scoping	Dossier	Assmt.
Assmt. to LoQ	120	120			120	120			90	75	15	
1st clock stop	90	10	80		30	10	20		30		30	
Assmt. to LoQ2	60		20	40	60		45	15	30		15	15
2nd clock stop	30			30	30			30	7			7
Assmt. to opinion	30			30	30			30	30			30
EC decision	*Up to* 67			*Up to* 67	*Up to* 67			*Up to* 67	*Up to* 67			*Up to* 67
HTA-CG adoption				25				25				22
Max. Available Days		130	100	*up to* 192		130	65	167		75	60	141
Planned JCA Assmt		130	100	187 [3]		130	100	187 [3]		75	60	184 [3]
Reduction in days from expectation:							35	20-40				35-56

DISCUSSION:

The proposed JCA timelines are designed to align with the EMA regulatory processes yet provide little flexibility for contingencies. This creates challenges, as EMA timelines are not fixed.

The duration of EMA clock-stops cannot be predicted, as the time required to respond to the CHMP LoQ cannot be determined until the questions are received.

EMA Centralised Procedure

- This study demonstrates that a short clock stop duration will impact the time both HTDs and Assessors have for their activities. Specifically:
  - Where the first clock-stop is 1 month:
    - The time available for HTDs to compile their dossier is reduced by around a third to approximately 65 days to meet the HTA Regulation requirement of HTD submission '45 days pre CHMP opinion' Figure 1b, Table 3
    - Assessors lose approximately 25 days, or a quarter of time allocated for producing the 1st draft of JCA, if subsequent steps are to remain unchanged Figure 1b, Table 3
- Furthermore, if there is no 2nd clock stop, the assessors will lose 30 days of their allocated assessment time. This can be in addition to any time lost due to a short 1st clock stop

Accelerated Procedure

- For Accelerated procedure, HTDs already have a shorter duration of 60 days between receiving PICOs and dossier submission
- Assessors have approximately 150 days to assess, draft, and complete all reviews. This appears to conflict with and be over 35 days short of the EUnetHTA21 suggested process of 184 days.[3] Figure 1c, Table 3

ABBREVIATIONS:

CHMP - Committee for Medicinal Products for Human Use; EMA - European Medicines Agency HTA-CG - Member State Coordination Group on HTA; HTD - Health Technology Developer; IA - Implementing Act; JCA - Joint Clinical Assessment; JCA-SG - JCA Sub-Group; MA - Market Authorisation; PICO - Population, Intervention, Comparator(s), Outcomes; C.S. - Clock Stop

CONCLUSIONS:

The JCA timelines are recognised as a challenge by stakeholders, with little scope for contingencies. In addition, the JCA process does not recognise that regulatory clock-stops are of varying duration.

For HTDs

- The planned 100 days between receiving final PICOs and dossier submission may make it challenging to perform new analyses to address unexpected PICOs. Furthermore, when the first EMA clock stop is short, or the accelerated procedure is followed, HTDs have even less time to address unexpected PICOs without falling foul of the Regulation timeline
- HTDs with efficient Regulatory practices should not be disadvantaged by the HTA Regulation

For Assessors

- Where clock-stops are short, the assessors will have significantly less time than expected to conduct their required activities
- Where products follow the Accelerated Approval process (an option taken by about a third of recent anticancer applications[4]), assessors will lose between 1 and 2 months
- Time constraints on reviewers will be exacerbated if higher numbers of PICOs are requested

It is noted that the timeline of activities during the assessment phase (step 3), has not yet been published. However, this study identifies that there are multiple activities to be delivered within a limited time, and that time may only get shorter.

One opportunity to reduce time constraints for HTD dossier development and Assessors' review activities would be to redistribute some of the time allocated to scoping, or start JCA scoping earlier.

REFERENCES:

1. **HTA Regulation**: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32021R2282
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4. **EMA timelines**: Garsen, M., Steenhof, M. & Zwiers, A. A Decade of Marketing Authorization Applications of Anticancer Drugs in the European Union: An Analysis of Procedural Timelines. *Ther Innov Regul Sci* **55**, 633–642 (2021). https://doi.org/10.1007/s43441-021-00260-5