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The New Parallel Regulatory and HTA Processes in the EU

Opportunities and Challenges

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Agenda

- HTA Regulation in context - the Regulatory / Access interface
- Organisational challenges
- Opportunities & Outlook

Why is the EU HTAR relevant for RA professionals ?

- The HTA Regulation (HTAR) links to the Milestones of the Centralised procedure of the EU Marketing Authorisation Application (MAA) for products eligible to HTAR
- The RA manager is asked to share the **eligibility request and SmPC** with the HTA CG Secretariat and is **invited to the Scope Explanation meeting**
- The **JCA dossier** incorporates certain parts of the MA dossier
- The EMA communicates with the HTA secretariat during the procedure
- The RA manager will have to **communicate time shifts and major label changes** throughout the CP and those may impact PICOs
- Two EU public assessment reports for the same product: European Public Assessment Report and JCA report
- Shifting from sequential to parallel approach can be a **significant organizational challenge**

Regulatory Authorities and HTA Bodies – a longstanding interface

- Since 2010, collaboration between EMA and HTA Bodies (EUNetHTA21, HTA CG)
- Continuous **optimisation of regulatory outputs** as reference for down-stream decisions
  - Templates for preparing EPARs revised to better address the needs of HTABs
  - Template of the Orphan Maintenance Assessment Report (OMAR)
  - Guideline on indication wording and subgroup analysis [EMA/CHMP/483022/2019]
- Collaboration on establishing **value of Realworld Evidence** (from PASS to PAES to PLEG to DARWIN-EU)
- **Horizon scanning**: Increasing information exchange on early development products
- **Parallel Scientific Advices** HA and HTA Bodies in EU and on national basis (e.g. Germany)

EU HTA Bodies have aligned on an EU HTA guidance on hierarchy of evidence

HTA CG | MEMBER STATE COORDINATION GROUP ON HEALTH TECHNOLOGY ASSESSMENT

Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons

Adopted on 8 March 2024 by the HTA CG pursuant to Article 3(7), point (d), of Regulation (EU) 2021/2282 on Health Technology Assessment

https://health.ec.europa.eu/publications/methodological-guideline-quantitative-evidence-synthesis-direct-and-indirect-comparisons_en

Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons

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- **Gold-standard evidence:** adequate RCTs
  - **Indirect evidence:** comparison of two interventions A and B when there is direct RCT evidence comparing both A to C, and B to C
- **Non-randomized evidence:** single-arm trials, cohort studies, case-control studies, other observational studies and the use of historical controls
  - Non randomized **'un-anchored' indirect comparison:** compares absolute outcomes between treatments across different studies (rather than relative effects along a connecting path of RCTs).

HTA Bodies and Regulators have developed a common understanding on potential solutions for the evidence challenge

- Strong preference for **randomised evidence** - "guidance on… **complex clinical trial designs**… a priority"
- Post licensing **pragmatic RCTs / RCTs in registries**
- **Estimand framework as** shared language for aligning study design, multiple estimands in parallel if needed
- Improving quality of **non primary outcomes**
- Availability of **individual participant data (IPD**)
- **RWD** has unresolved challenges / substantial opportunities
- **Clinical importance** of favourable / unfavourable effects may be informed by **health utilities**

Case studies: Zolgensma / Rybrevant / Yescarta

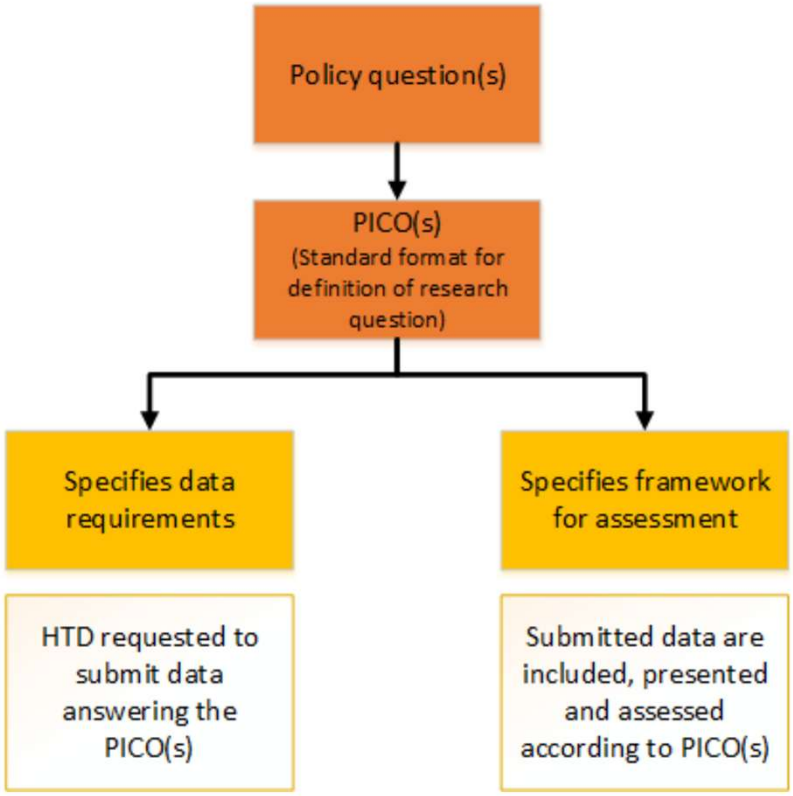
Conclusions

- Clear **research questions of clinical interest** need to be pre-specified, which together with **context-specific feasibility concerns** then drives the choice of what constitutes adequate evidence generation
- Regulatory and HTA body collaboration early on is key

Centralised procedure and JC Assessment scope differ considerably

	CHMP's Assessment	Joint Clinical Assessment
Decision informed	EU wide **legal decision** on approval / availability on the market for **any patient** with positive benefit / risk	**Informs national political decision** on **prioritising access** to new drugs relative to drugs serving the same population in an environment of limited resources
Criteria / Scope	Determines whether the medicine meets the necessary quality, safety and efficacy requirements and has a positive benefit – risk balance	An analysis of all available evidence to support the national relative clinical effectiveness conclusions
Assessment basis	MAA dossier	JCA dossier (structured by multiple PICOs)
Assessment focus	All Clinical Trials / Regulatory accepted endpoints	RCT, direct and indirect evidence, certainty of evidence, patient relevant endpoints
Economic considerations	No	No
Assessment public	Yes	Yes

HTA PICO scoping process serves policy needs



- Applicant provides input to the PICO survey (SmPC and eCTD Clinical Overview and further information)
- However, the **PICO Survey** is **not intended to reflect the data available**
- "PICO should **not be data driven** but inclusive and independent based on national policy needs national requirements" (Guidance)

- Potential risk that PICOs / assessment scope and available data do not match
- Co-Assessors consolidate and conclude on the PICOs / assessment scope
- Applicant has to provide data for every PICO in the JCA dossier

The Regulatory process has relevance for PICOs

Regulatory Dossier	**Intervention:** The Medicinal Product applied	**Comparison:** Is Phase III randomised controlled ?	**Comparison:** Do Phase III data cover the locally accepted comparative therapy ?	**Outcome:** Patient-relevant end-points with significant, clinically relevant results ?
Regulators B/R Assessment / EPAR	**Population:** Is there a subgroup that provides the highest value proposition?			
Regulatory Label / Indication	**Population:** Is the patient population included in the trial congruent with the regulatory label ?			

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Regulatory Dossier

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The Medicinal Product applied

Comparison:
Is Phase III randomised controlled ?

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Regulatory Label / Indication

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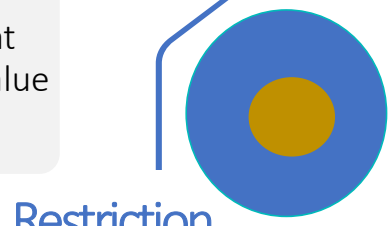
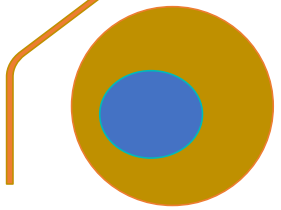


Restriction

Case 1: Indication focused on subpopulation with optimal B/R and highest value

HTA Bodies: high uncertainty - no added benefit ?

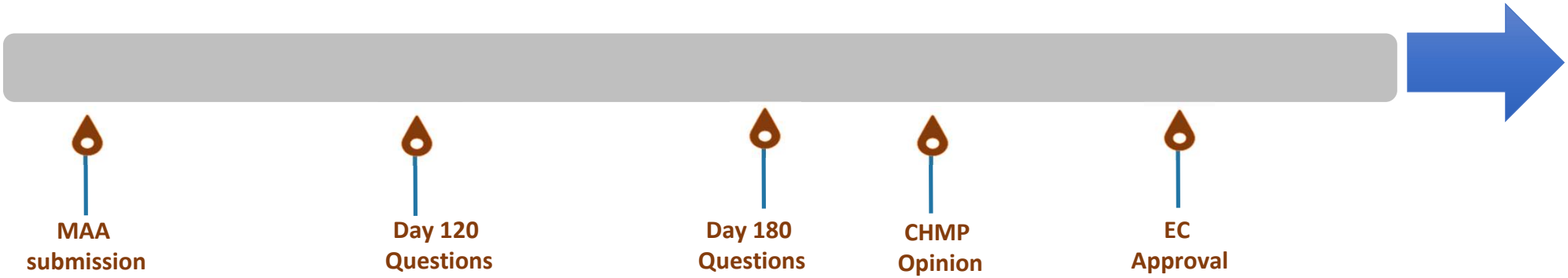


Broadening

Case 2: B/R considered positive for broader patient group

HTA Bodies: missing data, not covered by RCT – delay in access?

The parallel approach comes with organisational challenges



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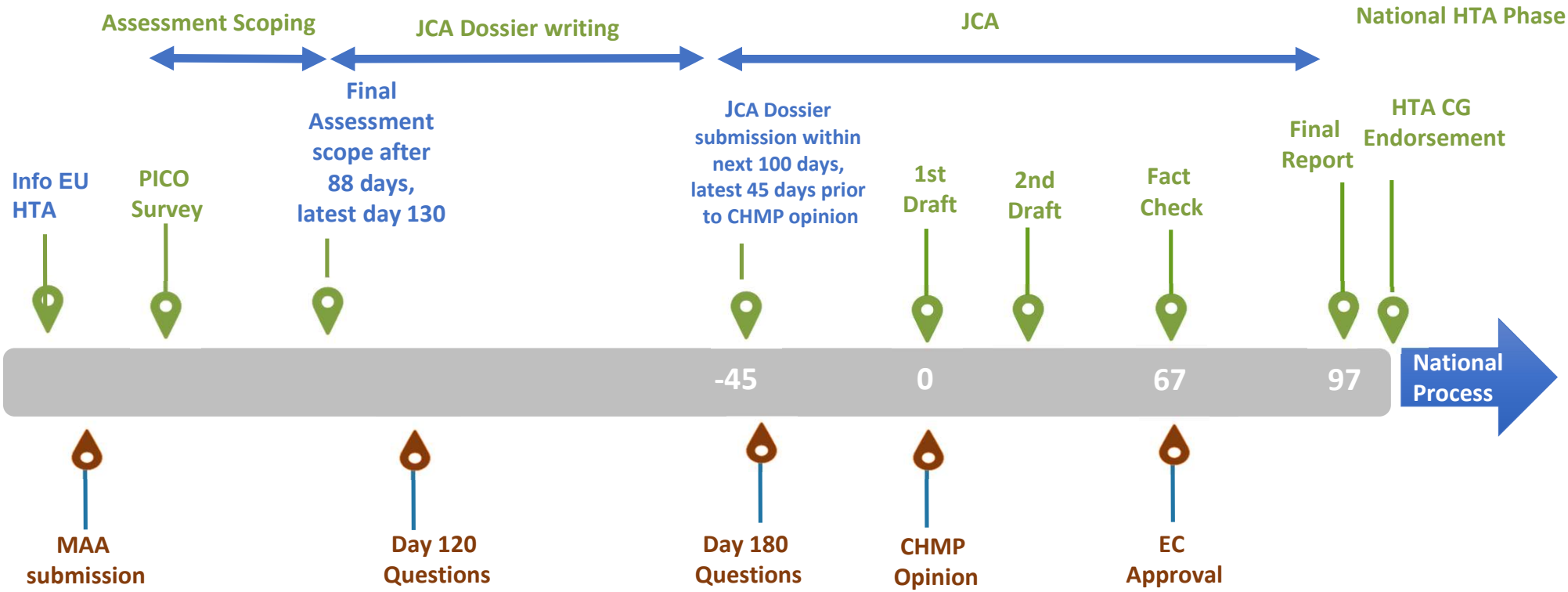
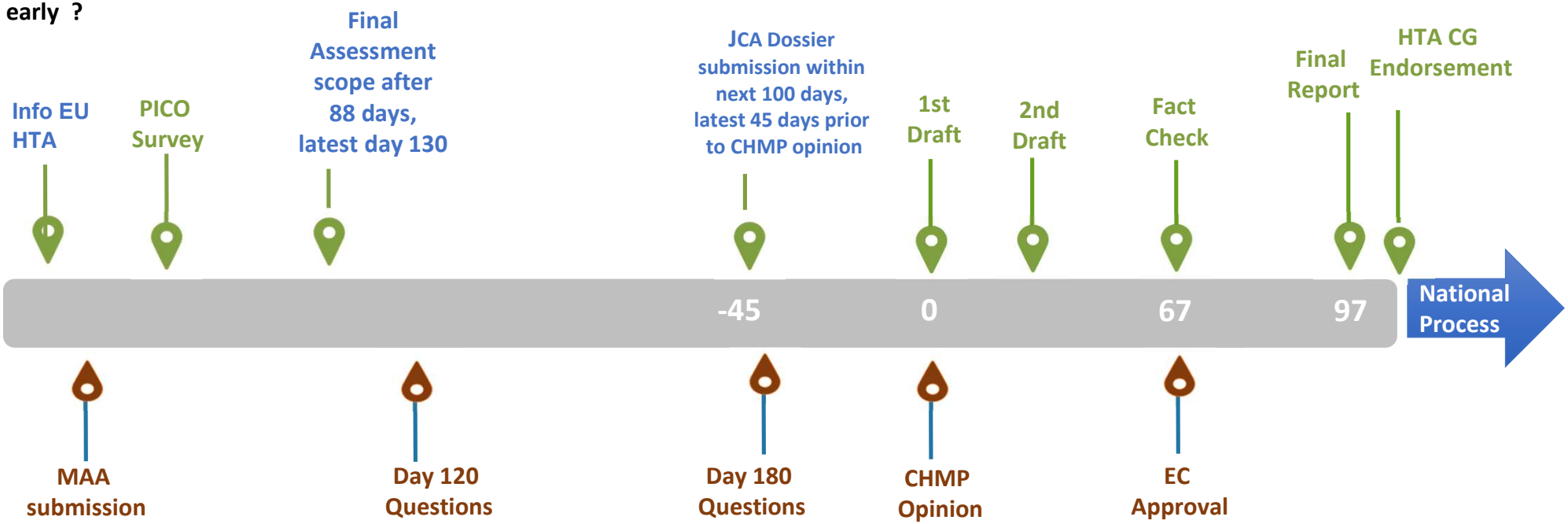


The parallel approach comes with organisational challenges

Short timeline for JCA dossier preparation: How to prepare early ?



Technical/Clinical experts available to address all PICOs in dossier?

How to manage the parallel review procedure and late label changes ?

Short timeline for JCA dossier preparation: How to prepare early ?

- Completing a comprehensive JCA dossier within the designated timeframe is a significant challenge
  - HTD has no direct involvement during scoping process, hence PICOs are only known late
  - High volume of data analysis and documentation required for each PICO

- Provide insights into global study / integrated evidence planning early on
  - Leverage the expertise of multiple country affiliates
  - National HTA Scientific Advice / EU Joint scientific consultation (JSC) with HTAb and EMA
- Establish internal PICO scoping process early on
- Prepare JCA dossier at risk with simulated PICOs
- Plan HTA and Regulatory dossier content strategically and aligned
- Submission deadline for JCA dossier can be expanded in exceptional cases

Are the Technical / Clinical experts available to address all PICOs in JCA dossier?

- At time of JCA dossier preparation, development teams are focused on clinical data base lock, analysis of data, alignment on key messages, writing global eCTD and communicating study results with key stakeholders
- Priority is often given to other key markets, focusing usually on first submission to FDA in U.S.

- Identify process and accountability for JCA dossier and timelines
- Decide / secure external agency for JCA dossier as needed early on
- Include JCA dossier into Global Project Plan, allocate resources and identify back ups
- Communicate timelines, opportunities, risks
- Keep submission plans on track

How to manage the parallel review procedure and late label changes ?

- **EMA** informs EU HTA at D120 on expected timelines, e.g. length of clock stop, and indicate questions or major objections to indication
- **Applicant** must inform HTA CG if relevant information is submitted in the procedure to the EMA
- **Label changes** may change multiple PICOs and, worst case, lead to a new scoping process (significant delay) and / or may impact national access scenarios
- **Additional requests** from JCA assessors any time during JCA during day 7 to day 30
- **No dialogue / meetings** with the JCA assessors foreseen during the JCA

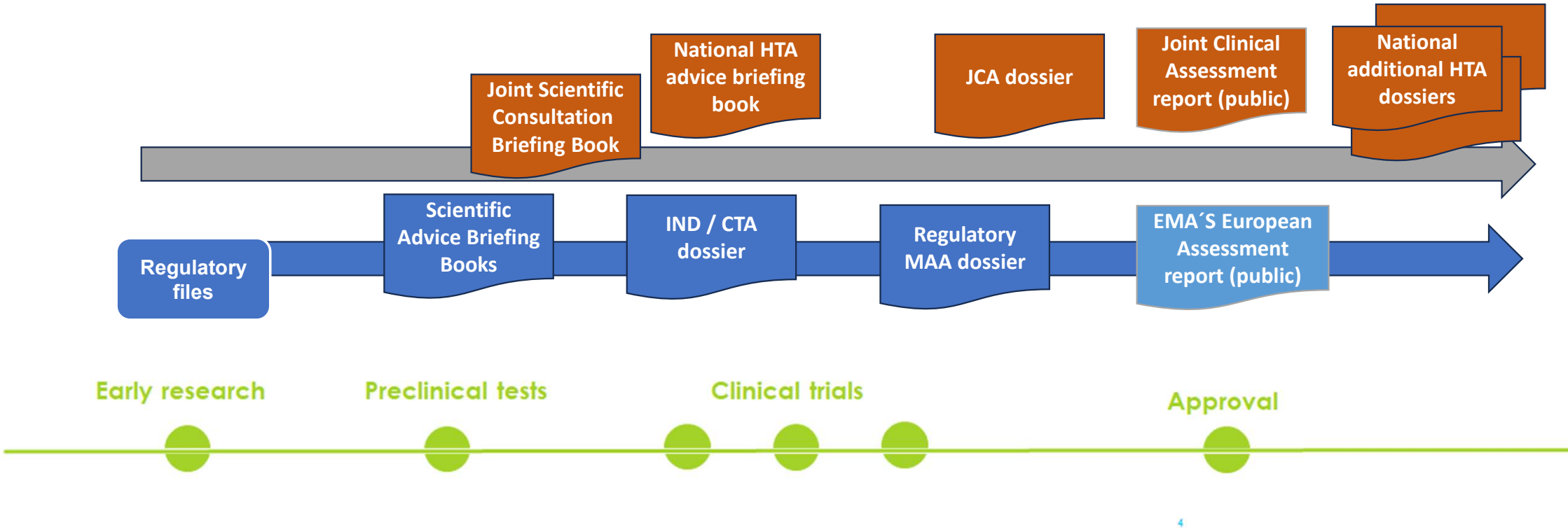
- Align all internal stakeholder early on labeling scenarios, probability of success, clear priorities
- Simulate impact of label scenarios on PICOs, on JCA dossier and down-stream access decisions
- Communicate, estimate and manage risk of delays with internal and external stakeholders
- Use all opportunities for dialogue: Information Meeting prior to PICO survey (on assessors' demand) and Assessment Scope Explanation meeting

Cancer medicines, ATMPs and orphan drugs may be particular sensitive to label changes

- Indication changes during the centralised procedure review generally restrict the population, the addition of a new population(s) is rare (Heikkinen et al.)
- Hence it can be expected that the broad initial PICO survey will cover most of the cases
- Cancer treatments are progressing rapidly (new indications, line of treatment, comparators)
- For Cancer medicines and ATMPs views on evidence across stakeholder can differ considerably:
  - Relevance of outcome (Patient relevant outcomes / PROs / PFS and RR vs OS)
  - Historical control / real-world evidence vs RCT
  - Challenges to retrieve data for indirect comparisons
  - Safety outcomes in the context of severity of disease

[I. Heikkinen et al. 2024 International Journal of Technology Assessment in Health Care, 40(1), e62, 1–7]

Coherent evidence generation & document development is needed



How to prepare as a company ?

01 Break Silos

- Close Alignment of **RA & MACS**
- A new role for a JCA manager
- Strengthen **EU Country Access Network**

02 Model the Job to be Done

- Build **Task Force**
- Monitor **Pipeline for first candidates for JCA**
- Design **Process** & Identify **Resource** Needs
- Train **First Affected** Teams

03 Align the Organisation

- On the **Job to be Done**
- On **Risk** and **Opportunities**
- On all levels

04 Continuous Dialogue

- National HTA body Scientific Advices
- Joint national HTA body HA Scientific Advices
- Plan Joint Scientific Consultation by default
- Learn from others through associations and public meetings

05 Design for Future Success

- From Target Product Profile to **Target Value Profile**
- From CTs to holistic **Integrated Evidence Development**
- **Plan early how to close evidence gaps**
- **From isolated documents to continuous storyboard**

06 Advocate for Europe

- Act on **Public Consultations**
- Identify **Challenges, Opportunities** and **Risks**
- Offer **Constructive** Solutions
- **Collaborate** with Stakeholders

[I.Stoeckert, E.Popa, I.Heikkinen, DIA Global Forum Aug 2024 https://globalforum.diaglobal.org/issue/august-2024/]

Will Europe‘s access to innovative healthcare gain or suffer?

Industry (Regulatory) view on HTA R implementation

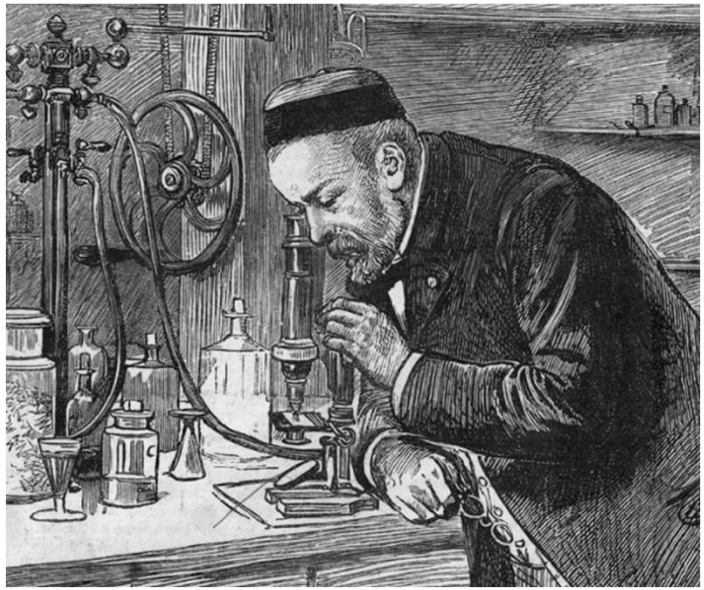
RISKS

- **Global (mis-)perception** of JCA results if out of context
- **Scientific integrity** of the EU Regulatory B/R Assessment impacted by HTA remit
- **Delays** to the **Marketing Authorisation** process in EU
- **Multiplying resource & time** for consultation & consensus
- **A new hurdle** on top, making EU less and **less attractive for developers** to introduce innovations rapidly

OPPORTUNITIES

- An **agile** and **modern** learning EU access system adapting to new evidentiary standards with **focus on true value for patients.**
- **Faster** and **more equitable** patient access if national processes are reshaped.
- **Efficient** and **effective** use of public resources at EU & national level.
- A **stronger voice for patients in EU**
- **Early identification** of promising health technologies, potentially accelerating their development and access for patients in EU.

Learning is key as…



…”chance only favours the prepared mind“
(Louis Pasteur 1854)