Lessons Learned from EMA/HTA Scientific Advice

An Industry Regulatory Perspective

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Introduction

- Learnings from past experiences to inform implementation of the future regulation
- New HTA regulation includes patients associations and facilitates the dialogue between stakeholder organizations
- Aiming to accelerate Patient access to treatments across Europe by increasing transparency and reducing duplication of assessment efforts.
- How will patient experience and treatment journey be included and reflected in this JSC to help predict a JCA?

Regulatory and HTA framework have different remit, objectives and organization

Patient perspective?

EMA / Regulator

Does it work?

Central/ National

How well does it work?

National/ Regional/Local

Do we want to pay for it?

Access to Patients

HTA
Relative Effectiveness -PICO & Safety

Regulators
Benefits/Risks
Label of use

Payers
Economic value

Legal Decision -Making

Early Development

Product Life Cycle

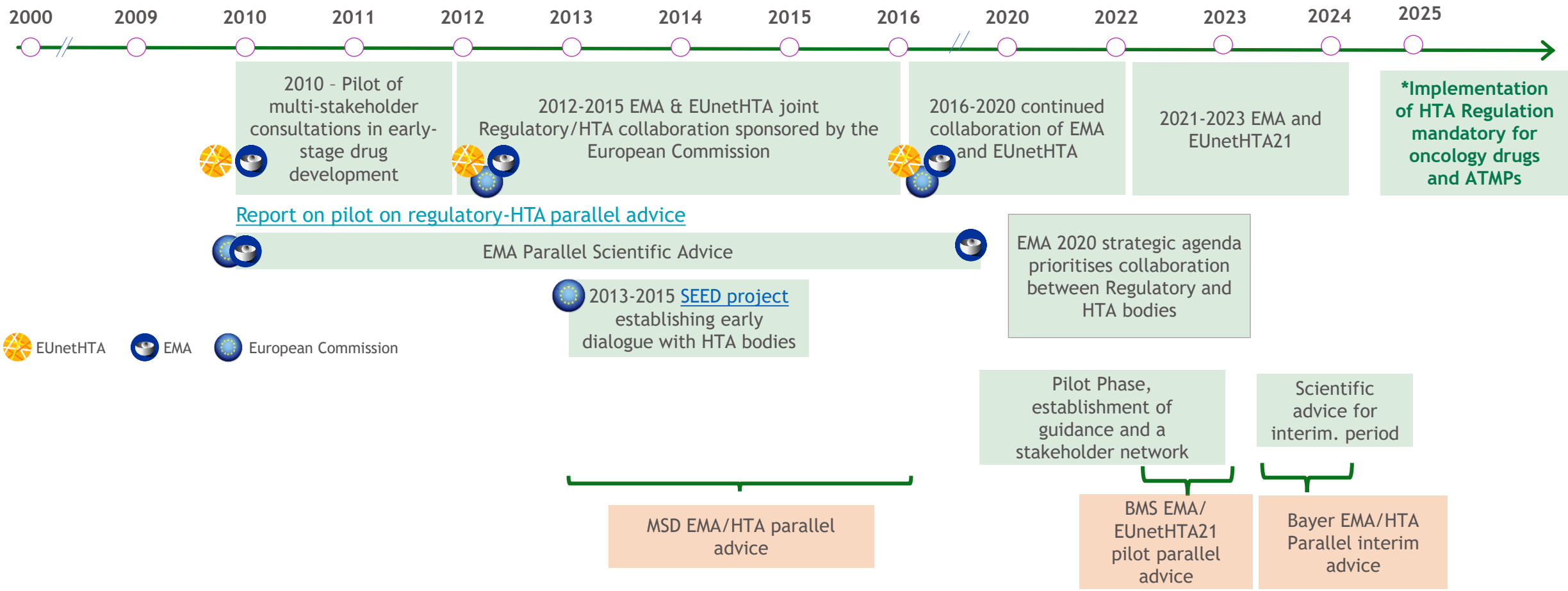
Generic Competition

EU ecosystem is a multilayer structure, what does this means?

Views on the evidence needs may differ, identifying early respective positions during SA dialogues

PICO *(Population, Intervention, Comparator, Outcomes)

Previous Pilots, synergies and collaborations prepared the future framework



* JSC under HTA regulation primarily for joint HTAb advice and EMA is parallel advice is optional

Key Highlights

- Experience from 3 industry cases
- High level feedback received
- JSC/EMA : Pros/Cons
- JSC: Challenges/opportunities

Our Industry experience: focus on 3 Cases in Oncology

- MSD experience from 2014 to 2016 (multiple meetings on several indications in Oncology)

Date	Indication	HTAb	Meeting	Comments
2014	Lung	HAS (FR), G-BA (DE), NICE (UK)	F2F	3 h meeting
2015	Gastric	G-BA, NICE, HAS	F2F	3 h meeting
2015	Rare tumors	NICE, G-BA, NoMa (NO), HAS	F2F	Adaptive Pathways pilot, 3 h meeting
2015	Breast	NICE, G-BA, TLV (SE)	F2F	Patient representative, 3 h meeting
2015	Heme	NICE, AEMPS (ES), NoMa, G-BA	F2F	Patient representative, 3 h meeting
2016	Head & Neck	NICE, G-BA, AEMPS, NoMA, KRIS (DK), Infarmed (PT)	F2F	Patient representative, 3 h meeting

- BMS experience on EMA/EUNETHA 21 pilot in 2022-2023 for and indication in DLBCL

Date	Indication	HTAb	Meeting	Comments
Sept 2022- Mar 2023	RR DLBCL	G-BA, NOMA, AIFA (IT), NCPE (IE), NIPN (HU), ZIN (NL)	Video conf	3 h meeting, EU/ national patient rep

- Bayer experience from 2023-2024 for an indication in Lung Cancer

Date	Indication	HTAb	Meeting	Comments
Dec 2023- Jun 2024	Lung	HAS (FR), G-BA (DE), RIZIV/INAMI (BE), NoMA (NO) – centralized recruitment Observers: DCM/DVSV (DK), AEMPS, AU, FIMEA, STM/HILA (FI), GR, CZ	Video conf	3 h meeting, no patient rep

JSC is part of multiple options for Scientific Dialogues in EU

Stepwise concept is highly important, contributing to build scientific knowledge from Global to central to national

Almost all are Voluntary! Assessment of the best Path is key

Which one for which purpose?

Regulatory Scientific advice only

National

- EU: Examples include Germany (BfArM), France (HAS), Italy (AIFA), Spain (AEMPS)
- US (FDA), UK (MHRA), Canada (CADTH)

Centralized/Regional

- EMA
- EMA / CTCG (NCAs)

Multi-National/International

- EMA/FDA parallel*
- Simultaneous National SA

HTA scientific advice only

Individual Country

Examples include Germany (G-BA), UK (NICE), Canada (CADTH), France (HAS)

Multi-Country

- EUnetHTA
- Multi-HTA early dialogues (e.g., NICE-CADTH)
- **JSC under HTA Regulation**

Joint Regulatory and HTA Scientific Advice

@ National level

- EU: Germany (BfArM and G-BA), Sweden (MPA and TLV)
- UK (MHRA and NICE), Canada (HC and CADTH)

@ EU level

- Parallel EMA/EunetHTA 21
- **Joint Scientific Consultation in parallel with EMA (HTACG in 2025)**

BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte; MHRA: Medicines and Healthcare products Regulatory Agency; NICE: The National Institute for Health and Care Excellence; EMA: European medicines agency; FDA: Food and Drug administration; G-BA: Gemeinsamer Bundesausschuss; HAS: Haute Autorité de santé; TLV: Tandvårds- och läkemedelsförmånsverket; MPA: Medical Products Agency; EUnetHTA: European network for Health Technology Assessment; CADTH: Canadian Agency for Drugs and Technologies in Health *May be binding

What is the value of a Joint Scientific advice between regulators and HTAs?

Building both perspectives into drug development/evidence generation

Understand Main point of divergence:

- Patient population
- Surrogate endpoints
- Data maturity
- Comparator

Identifying the point of convergence

Opportunity for receiving Patients input

Post licensing evidence generation is becoming the critical part of discussion

Eligibility criteria for the JSC are quite restrictive

JSC eligibility much more restrictive than other early dialogues

Limited slots

		New Medicine
Eligibility criteria for JSC according to EU HTA Regulation Art. 16(2)	1 A health technology is likely to be the **subject of JCA** pursuant to Article 7(1), **and**	✓
	2 The clinical studies and clinical investigations are **still in the planning stage.**	✓
Selection criteria for JSC according to EU HTA Regulation Art. 17(3)	1 Unmet medical needs (no treatment or only unsatisfactory treatment available);	✓
	2 First in class;	✓
	3 Potential impact on patients, public health, or healthcare systems;	✓
	4 Significant cross-border dimension;	✓
	5 Major Union-wide added value; **or**	✓
	6 Union clinical research priorities	✓

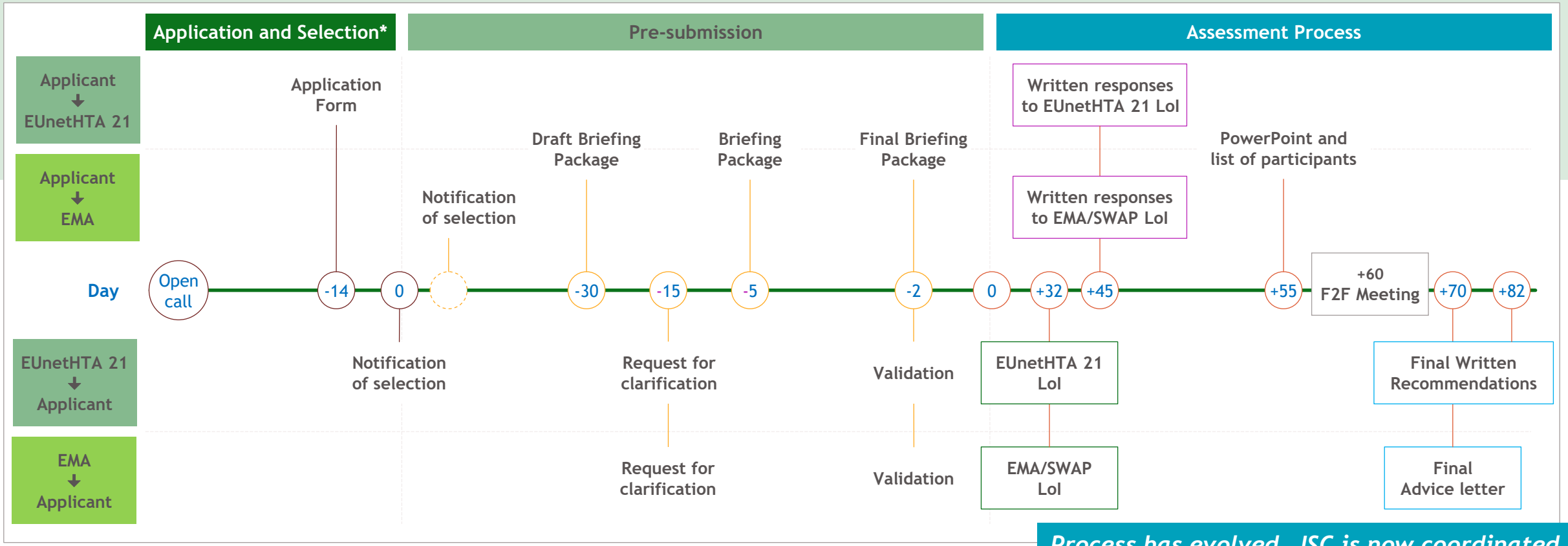
➢ ***Alternative dialogues process*** *to investigate for products not eligible to JSC or with no slot available*

Source: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32021R2282&from=EN

Key takeaways from past pilots: duration of parallel advice is long and require information exchange between EMA and HTAs, while outputs may be different

The Parallel JSC is a process which consists of three separate and distinct phases that involves the exchange of information between the EMA and EUnetHTA 21 and has a synchronized timing, while preserving the separation of respective remits, especially with regard to the LoI and final advice.

General overview of the process



Source: Abbreviations: F2F: Face-To-Face; JSC: Joint Scientific Consultation; LoI: List of Issues; SAWP: Scientific Advice Working Party

*The formal JSC process has 3 phases: Simultaneous notification, pre-submission and evaluation. In practice, however, the first phase can be considered as application

Process has evolved, JSC is now coordinated by HTACG that facilitates cooperation across stakeholders including patients

Applying for a Parallel advice EMA/HTA implies robust internal alignment

- Determining the full value of a JSC vs other pathways at time of the request
- Ensuring sufficient internal understanding of the JSC process
- Securing cross functional team alignment
- Identifying core team responsibilities and key decision makers
- Defining an internal process for the JSC
- Ensuring team alignment on the questions and that the questions clearly define the problem
- Navigating Tight Prep Timelines Post-LoI and Preparing Efficiently

From Key uncertainties in development to the list of issues from the regulators / HTA bodies at the JSC

Questions triggering the SA by the developer

- **Population**: Inclusion/exclusion criteria, line of therapy, ..
- **Trial characteristics** and feasibility : Proposed dose, proposed comparator, …
- **Statistical considerations:**
  - primary and secondary endpoints including PROs and their importance from reg/HTA perspective,
  - Estimands vs PICO

Issues raised during the discussion with EMA / HTA

- **Population:** to clearly define eligibility for newly registered therapies
- **Outcomes:** Different visions in terms of endpoints, e.g EMA agreed to PFS as primary endpoint with mature OS data when HTA bodies asked for OS as primary endpoint or mature OS as key secondary endpoint
- Acceptance of surrogate end-points/comparators
- **Health economics approach:** The discussion on the health economic aspects was inconclusive due to the heterogeneity of the HTAs represented and the lack of pronouncements on the economic aspects at this early stage of clinical development

Learnings from Assessment Process

- List of Issues and advices from HTAs (with divergence across agencies) and EMA are distinct and separated, with the only connection being the meeting.
- The issues raised by EMA and HTA, even if they are about the same aspects, can be significantly different in terms of the focus and the depth of the questions posed.
- The preparation of the written responses and the slide deck is particularly challenging in terms of resources and timing, requiring a high level of coordination and alignment.
- Most efforts are devoted to address the LoI from HTA, particularly in relation to clinical development, which is significantly thorough.
- Health economic aspects may be not relevant for products in early stages.
- Gain insights on providing strategic thinking to focus on key questions for future JSC and JCA.

Overall learnings on parallel EMA / HTAs Advice

Pros

- Understand HTA expectations in advance alongside with regulatory requirements and anticipate future JCA
- Contemporaneous evolution of development to satisfy all parties before the development plan is fixed
- Minimization of discrepancies and identification of trade-offs
- One collaborative discussion with simultaneous feedback – immediate clarifications
- Long duration meeting 3 hours that allow for open non-binding discussion, opinion expression

Cons

- No process for bridging divergences that could be identified between Reg vs HTA or between HTAs
- Complexity of parallel separate processes EMA / HTAs to maintain documentation coherence
- Resources and length of the process in a fast-paced development
- Being too prescriptive with a potential to increase evidentiary threshold
- Outcome of HTA advice could impact the time to regulatory submission (data maturity)
- No choice of HTAs involved
- Dynamic epidemiology – evolution of the SoC and Comparator

Joint Scientific Consultations should predict future JCA and support HTDs in preparing for submission

Future looking under thew HTA regulation

JSC Advice

- Non-binding, consolidated scientific advice whilst maintaining the positions of individual HTA bodies
- JSC with option to include EMA advice in parallel
- No requirement for reaching a consensus position

CHALLENGES

- **Voluntary cooperation by HTA bodies within the JSC** (not pre-defined)
- **Limited JSC slots available** with strict eligibility requirements
- **Views of individual HTA bodies may differ from the joint EU view**, which could require advisory consultations at both EU level and Member State level
- Time lag between early advice and national HTAs/payers negotiation

OPPORTUNITIES

- **Reduction of the time between regulatory approval and HTA outcome**
- Joint advice from the EMA and EU HTA bodies enables HTDs to adjust **their clinical development plans**
- **Potential to align on the PICO** and further alignment on methodological uncertainties
- Patients involvement although process of incorporation of patients input and perspective is still unclear

Given the possibility of lack of consensus between the participating HTA bodies and failure to reach compromise, this can lead to uncertainties in how to implement the advice and adapt the research question and trial design

Abbreviations: JSC: Joint scientific consultation; HTA: Health technology assessment; EU: European Union; PICO: Population, Intervention, Comparator and outcomes; HTD: Health technology developer; ATMP: Advanced Therapy Medicinal Products

Questions?