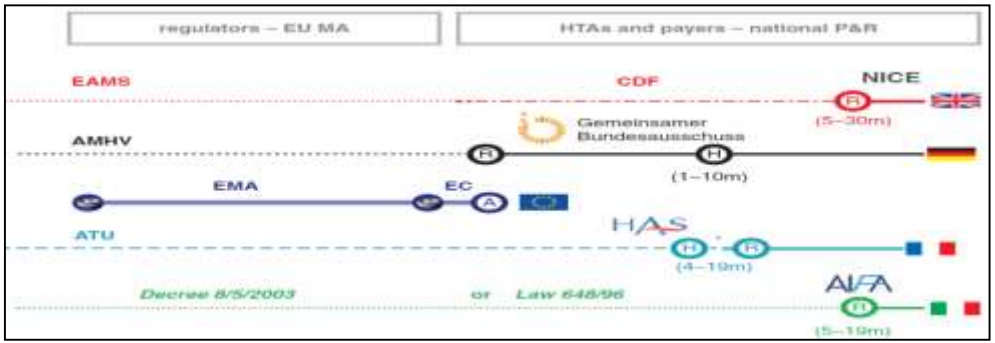
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Bridging the gap: Regulatory and HTA

Facing the Challenges: Equity, Sustainability and Access
30 November 2018

Presented by Michael Berntgen
Head of Product Development Scientific Support Department

Facing the challenge: from EU regulatory approval to national HTA/P&R decisions



A = authorisation; H = health technology assessment; R = reimbursement

Drug	Indication	EU MA Approval	Time for HTA/P&R after MA (month)			
bosutinib (Bosulif)	chronic myeloid leukaemia	03/2013	7	7	11	18
vismodegib (Erivedge)*	basal cell carcinoma	07/2013	n/a	7	5	20
cabozantinib (Cometriq)*	medullary thyroid cancer	03/2014	n/a	10	8	n/a

*first in class; MA = marketing authorisation; P&R = price and reimbursement cut-off: 15 September 2015

Martinalbo et al., Early access to cancer drugs in the EU. *Ann Oncol* 27: 96–105, 2016

Synergy through alignment of evidence generation plans

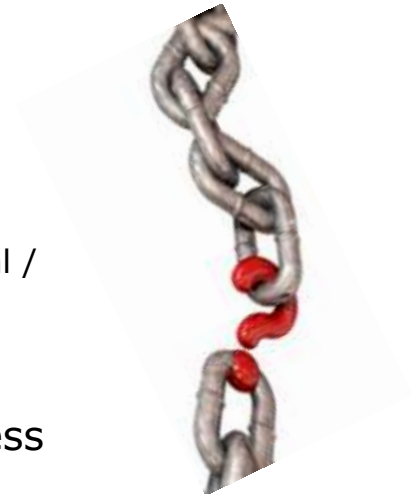
Starting point: Regulators and HTAs

- answer different questions
- have different requirements in terms of evidence

Aim: decision makers come together early to discuss

- the planned development including populations / comparators / design of trial / endpoints
- the requirements for post-licensing evidence generation

Expectation: Optimised evidence generation plan ➔ Improve access for patients



"Clinical benefit" is universal ➔ once established it can be contextualised

Early engagement on development: why (and how)?

EMA works with HTA bodies since 2010 and with payers since 2017

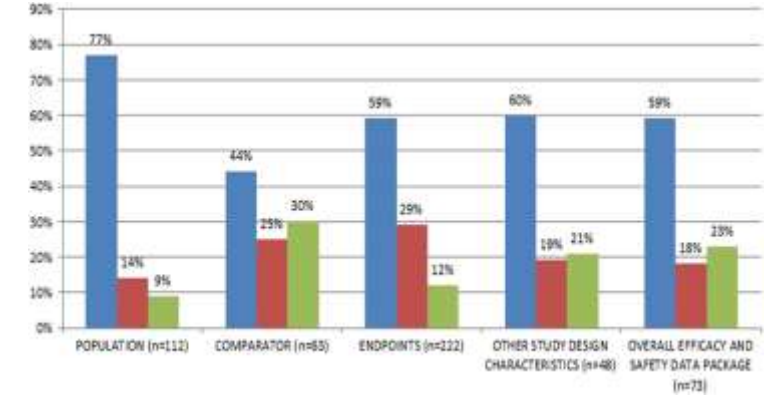
Parallel Consultation as central platform to discuss evidence generation

- Agree what evidence from clinical trials is needed to meet the needs of both regulators and HTAs
- Help to better understand the applicant's development plan and the basis for authorisation by CHMP
- Tripartite scientific advice (EMA-HTA-Payers) yet to start

Focus on facilitating the development of innovative medicines that serve patients' needs and are accessible for patients

The impact of cross-decision maker engagement in evidence generation planning - First analyses

Topic 1: Level of alignment

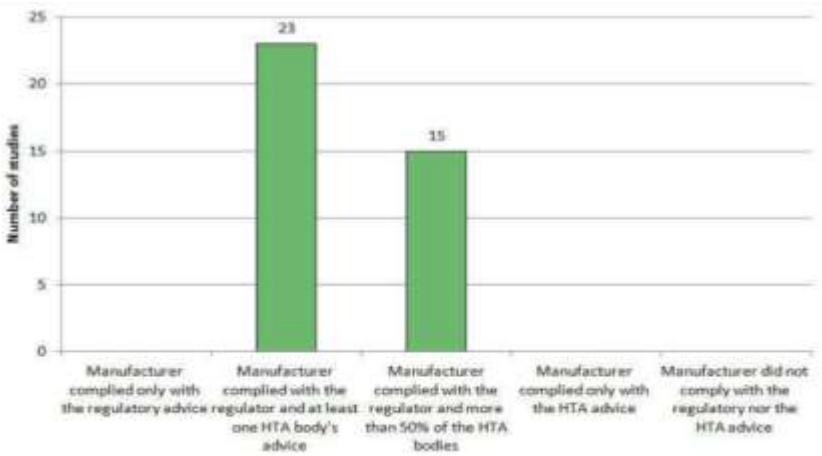


Level of agreement (position of HTA bodies *vs.* regulators; review of clinical trial features based on of 31 scientific advice procedures):

full agreement partial agreement disagreement.

Tafuri et al., British J Clin Pharm, Volume 82, Issue 4, 965-973

Topic 2: Uptake in development



Tafuri et al., British J Clin Pharm, doi: 10.1111/bcp.13524

Post-licensing evidence generation (PLEG) – the next domain of collaboration on evidence planning

Qualification of registries for post-licensing data generation:

- European Cystic Fibrosis Society Patient Registry (ECFSPR) ➔ parallel qualification with HTAs
- European Society for Blood & Marrow Transplantation (EBMT) Registry [relevant for CAR-T therapies] ➔ HTAs involved in the supporting workshop

Publicly available outputs!

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29 June 2018
EMA/CHMP/SAWP/423488/2018
Committee for Medicinal Products for Human Use (CHMP)

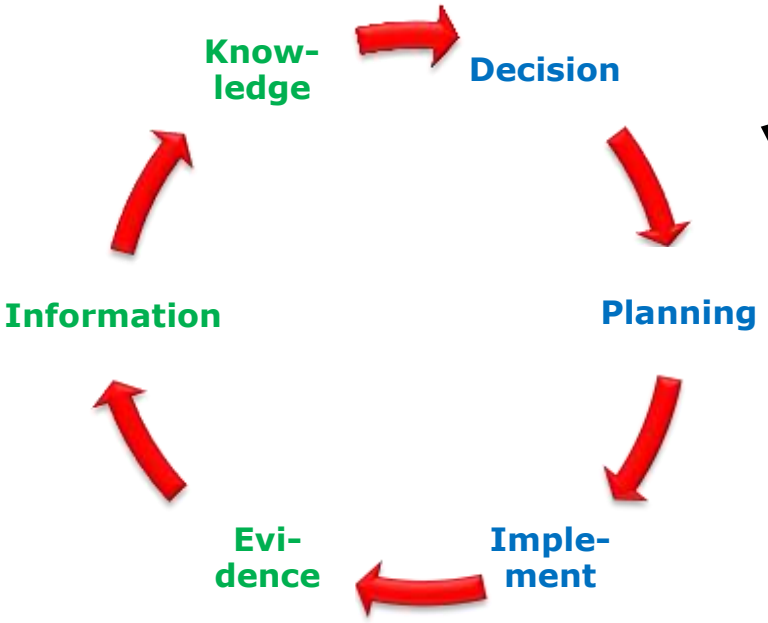
Draft qualification opinion on Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry

Agreed by Scientific Advice Working Party	17 May 2018
Adopted by CHMP for release for consultation	31 May 2018
Start of public consultation	29 June 2018
End of consultation (deadline for comments)	31 August 2018

Comments should be provided using this template. The completed comments form should be sent to anna.tavridou@ema.europa.eu

Keywords	Chimeric antigen receptor (CAR)-T cell therapy, haematological malignancies, European Society for Blood & Marrow Transplantation, registry, post-authorisation study, pharmacoepidemiology.

Guiding evidence generation to establish clinical benefit



Guidelines on development

New endpoints for drug development

Learnings from decision making

Guidelines make learnings and knowledge available

The revision of the Multiple Sclerosis guideline in 2015 considered

- Numerous product-specific scientific advices
- Two methodological advices
- Learnings from the review of several marketing authorisation applications
- Outcome of a public workshop in 2013
- Published position on regulatory and scientific challenges *

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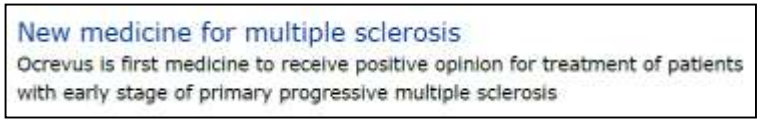
26 March 2015
EMA/CHMP/771815/2011, Rev. 2
Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis

Draft Agreed by Central Nervous System Working Party	May 2012
Adopted by CHMP for release for consultation	20 September 2012
Start of public consultation	01 October 2012
End of consultation (deadline for comments)	31 March 2013
Agreed by Central Nervous System Working Party	March 2015
Adopted by CHMP	26 March 2015
Date for coming into effect	01 October 2015

* Balabanov et al., MS Journal (20), 128201287 (2014)

The challenge in practice: Recent experience with ocrelizumab



Regulatory approval for treatment of adult patients with

- relapsing forms of multiple sclerosis (RMS) with active disease
- early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability

G-BA (DE)[1]	NICE (UK) [2]
• Active RMS ➔ minor added benefit compared to Interferon beta-1a/b or glatiramat • Highly active RMS ➔ added benefit not proven compared to alemtuzumab, fingolimod, natalizumab or baseline therapy • PPMS ➔ indication of minor added benefit compared to SoC	• RMS ➔ slows disease progression compared with some treatments but not others; uncertainty of slowing disease progression in highly active and rapidly evolving severe disease; recommended only after alemtuzumab (due to costs) • PPMS ➔ in progress (current position [Sep 18]: not cost-effective)

[1] G-BA decision of 2 August 2018 (AM-RL-XII_Ocrelizumab)
[2] NICE guidance TA533 (RMS) and ongoing NICE appraisal ID938 (PPMS)

Establishment of new endpoints for drug development

Qualification of Stride Velocity 95th Centile measured by a wearable device as outcome measurement in Duchenne muscular dystrophy (DMD) ➔ acceptability as secondary endpoint for regulatory decision making

- Patient-relevant ✓
- Use of digital data ✓

Draft guidance for public consultation (closed on 30 November 2018) ➔ input from all stakeholders incl. HTA/payers invited

Other examples: PUCA index; Dopamine transporter imaging to identify early PD patients

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20 September 2018
EMA/CHMP/SAWP/527447/2018
Product Development Scientific Support Department

Draft qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device*

Draft agreed by Scientific Advice Working Party	12 April 2018
Adopted by CHMP for release for consultation	26 April 2018
Start of public consultation	21 September 2018
End of consultation (deadline for comments)	30 November 2018

Comments should be provided using this template. The completed comments form should be sent to Qualification@ema.europa.eu

Keywords	Activity monitor, Duchenne Muscular Dystrophy (DMD), Real World Data, Stride Velocity, Ambulation

Learnings from sequential decision making

For Relative Effectiveness Assessment by EUnetHTA, EMA and EUnetHTA established a framework to share information (final regulatory output) and facilitate mutual understanding

- 3 products completed so far (4th in preparation)
- Learnings for optimising regulatory output to increase understanding of B/R assessment for use by HTAs

Regorafenib for hepatocellular carcinoma

EMA/CHMP EPAR[1]	**EUnetHTA REA**[2]
• RESORCE trail, OS gain (2.8 months) considered of clinical benefit • Uncertainties: sorafenib intolerant patients; patients with ECOG PS>1 and/or Child Pugh B ➔ addressed through SmPC changes	• RESORCE trail, OS gain (2.8 months) considered a modest gain • Insufficient evidence on impact on HRQoL ("regrettable" for end-stage patients) • Evidence gaps: sorafenib intolerant patients and patients with ECOG PS>1 and/or Child Pugh B ➔ further research data collection necessary

[1] EMA/CHMP EPAR EMEA/H/C/002573/II/0020
[2] EUnetHTA REA Project ID: PTJA02

Priority areas of the EMA/EUnetHTA work plan 2017-2020

- Early dialogue / scientific advice
- "Late dialogues" / peri-licensing advice
- Methodological approaches for study designs
- Unmet medical need and therapeutic innovation
- Significant benefit vs. added therapeutic value
- Identification of the treatment eligible population
- Information exchange regulators ↔ HTA bodies
- Patient and clinician engagement
- Population or intervention-specific areas

eunethta

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13 November 2017
EMA/661613/2017
Human Medicines Research and Development Support Division

EMA-EUnetHTA three-year work plan
2017–2020

Introduction

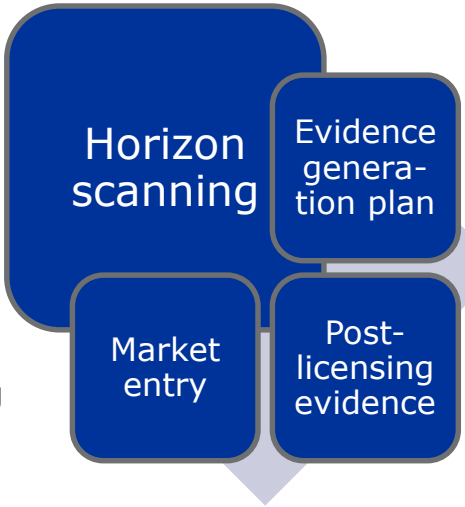
The EMA-EUnetHTA collaboration, which began in 2010 based on recommendations from the High-level Pharmaceutical Forum[1], aims to harness synergies between regulatory evaluation and health technology assessment (HTA) along the lifecycle of a medicine. Following initial work to improve the way data published by EU regulators as part of their benefit-risk assessment can contribute to relative effectiveness assessments by HTA organisations, additional topics of mutual interest were identified.

A first EMA-EUnetHTA work plan had been established for the years 2012-2015; a report on the outcomes of this joint work plan has been published in April 2016. Following up on the achievements and developments, a new joint work plan for the years 2017-2020 has been agreed. The overall goal of the collaboration is to improve efficiency and quality of processes, whilst respecting their respective remits and ensure mutual understanding and dialogue on evidence needs, to facilitate access to medicines for patients in the European Union.

EMA-EUnetHTA work plan 2017-2020

How can players along the technology lifecycle work together to support the introduction of innovative health technologies

- Collaboration on topic identification and prioritisation by various players
- Early flag of innovation that would benefit from closer engagement across decision makers



e.g. parallel consultation (scientific advice) involving various decision-makers to ensure evidence generation meets different needs

e.g. readiness for subsequent decision making in a timely manner, respecting different remits

e.g. preparedness of patient registries to collect relevant information in a robust manner

Collaboration between decision makers can enable better preparedness of the healthcare systems for development and introduction of innovation with true clinical benefit.

Thank you for your attention

Further information

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