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SCIENCE MEDICINES HEALTH

Regulatory point of view on clinical benefit assessment and parallel EMA/HTA advice

Ateliers de Giens Meeting - French Society of Pharmacology and Therapeutics - Paris, March 23rd 2016

Contents and Disclaimer

- Contents: B/R and parallel SA-HTA advice
- Personal views, not official EMA opinions

Benefit-Risk Balance

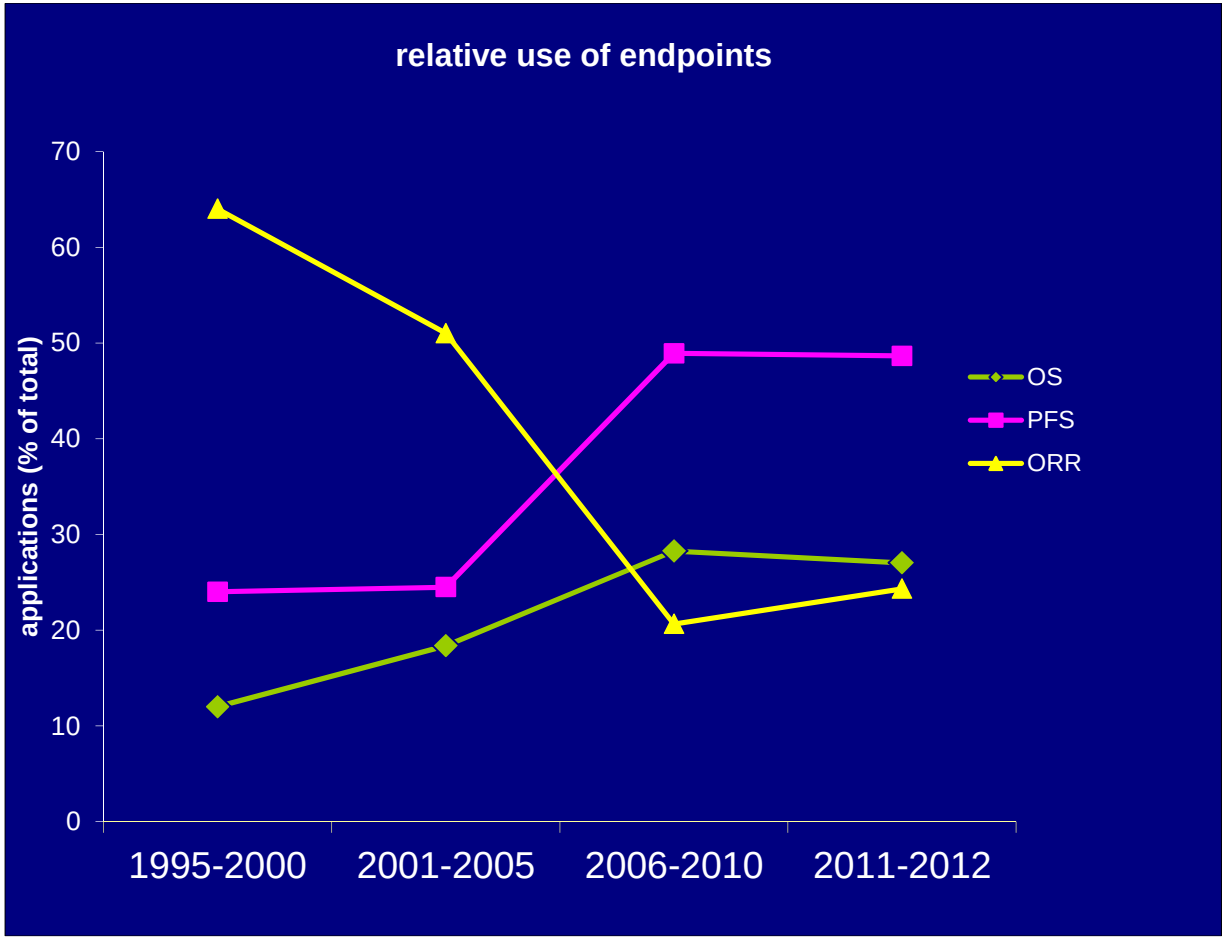
- The balance of benefits and risks occupies a central place in licensing and approval decisions
  - Defined as an evaluation of the positive therapeutic effects in relation to any risks as regards patients' health or public health, or any risks to the environment (EU)
  - Economic considerations are excluded
  - Similar requirements exist in U. S. Food, Drug and Cosmetic Act
- Need to strike a balance between early access versus having as complete information as possible on the benefits and risks

Choice of endpoints

- Assessment of benefit-risk balance is more complex than simply observing statistically significant effects.
  - Today this task is done mostly implicitly (holistically) based on expert judgment based on the totality of evidence (not just *P*-value).
- The primary endpoint should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial (ICH).
- "Clinical relevance" of endpoints lacks formal regulatory definition (generally OS>PFS).
- New intermediate endpoints such as MRD in CLL.

Pignatti, F. et al. Assessment of benefits and risks in development of targeted therapies for cancer - The view of regulatory authorities. [Review]. Mol Oncol. 2015 May;9(5):1034-41. doi: 10.1016/j.molonc.2014.10.003. Epub 2014 Oct 16

Primary endpoints over time (EMA experience)



* PFS includes all similar time-to-event endpoints

** ORR includes all response-related endpoints

Applications include initial MAAs and Extensions of Indication with positive or negative outcome for principal oncology products (no generics, biosimilars, antiemetics, epoetins, filgrastims etc).

Relevance and "value" in regulatory decisions

- What is the minimum effect size for an effect to be clinically significant for a patient?
  - In principle: "even one day improvement in OS worthwhile from a patient perspective, in the absence of any risks".
  - The clinical significance of observed effects is best discussed in relation to each other (benefit-risk balance).
  - Over-valuing of efficacy outcomes likely in view of the high unmet medical need (e.g cancer).
  - Conditional approvals frequent in oncology.

Whose values?

- Expected natural evolution of regulatory systems is towards more patient involvement in the decision-making process
  - Importance of the patient's point of view fully acknowledged
  - Interpretation of data about patients' values difficult due to methodological issues
- Reflection Paper on the use of patient reported outcome (PRO) measures in oncology studies

Pignatti, et al. *Mol Oncol*. doi: 10.1016/j.molonc.2014.10.003

Conditional MA and cancer drugs

Ann Oncol-2016-EMA early access (2).pdf - Adobe Acrobat Pro

Annals of Oncology 27: 96–105, 2016
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Early market access of cancer drugs in the EU

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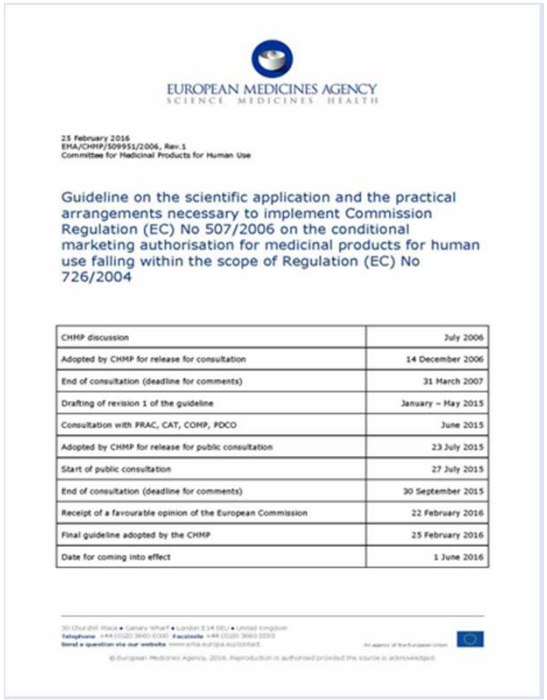
Patient access to new cancer drugs in the EU involves centralised licensing decisions by regulators as well as reimbursement recommendations in the context of national healthcare systems. Differences in assessment criteria and evidence requirements may result in divergent decisions at central and national levels, ultimately compromising effective access to patients. Early access decisions are particularly challenging due to the limited clinical evidence available to conclude on the benefit–risk and relative (cost-) effectiveness of new high-priced cancer drugs. We describe mechanisms to accelerate approval of promising anticancer drugs that fulfil an unmet medical need, review the experience from the European Medicines Agency, compare timelines and outcomes of reimbursement decisions in major EU markets, and discuss shortcomings of the current system, ongoing initiatives, and future steps to facilitate effective early access.

Key words: conditional approval, accelerated approval, HTA, adaptive pathways, early access

Conditional MA

- In the past, mixed bag of products with outstanding efficacy and products where the benefits need to be better understood.
- No major issues so far with company compliance with obligations.
- Wider use with prospective planning of CMAs in dialogue with regulators encouraged. Also possible in the course of a parallel EMA-HTA advice.
- GL updated



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25 February 2016
EMA/CHMP/509951/2006, Rev.1
Committee for Medicinal Products for Human Use

Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004

CHMP discussion	July 2006
Adopted by CHMP for release for consultation	14 December 2006
End of consultation (deadline for comments)	31 March 2007
Drafting of revision 1 of the guideline	January – May 2015
Consultation with PRAC, CAT, COMP, PDCO	June 2015
Adopted by CHMP for release for public consultation	23 July 2015
Start of public consultation	27 July 2015
End of consultation (deadline for comments)	30 September 2015
Receipt of a favourable opinion of the European Commission	22 February 2016
Final guideline adopted by the CHMP	25 February 2016
Date for coming into effect	1 June 2016

Different evidentiary standards

- Different evidentiary standards between regulators and payers call for good understanding and interaction between the two communities, e.g. in the format of iterative discussions and agreement during drug development.
- Parallel EMA/HTA advice in place since 2010.
- Optimised development plan - Improve access for patients.

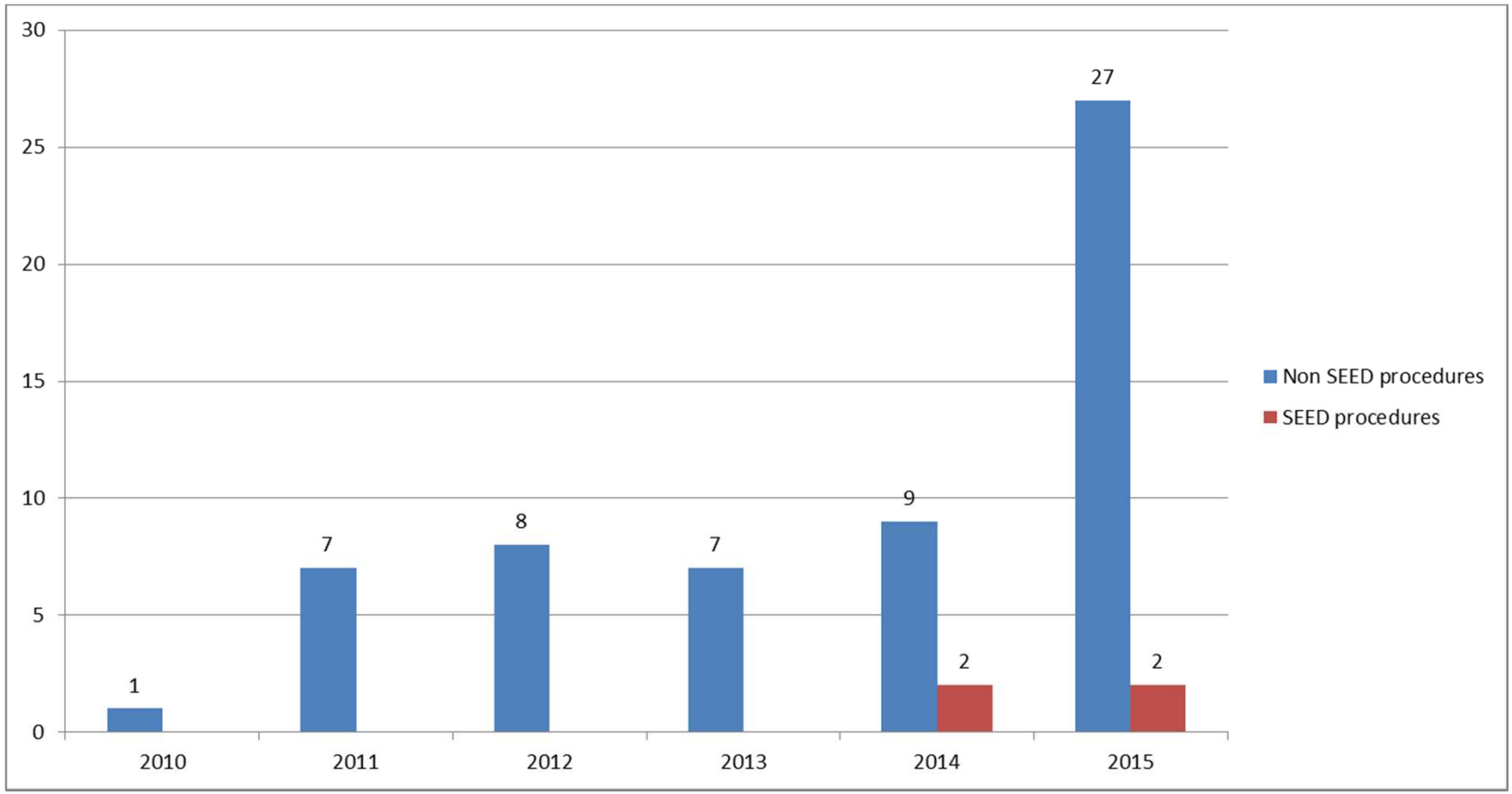
Parallel EMA HTA scientific advice- why

- Aim - generate data that meets needs of all stakeholders as efficiently as possible – preferably in one trial design/ one development plan. Avoiding excess burden on patients.
- Prevent avoidable/methodological reasons for failure later.
- Without layering on additional requirements.
- Understand views/needs of each others and the divergences.
- To find the solutions/third way.
- Not forcing agreement and adhere to remits.

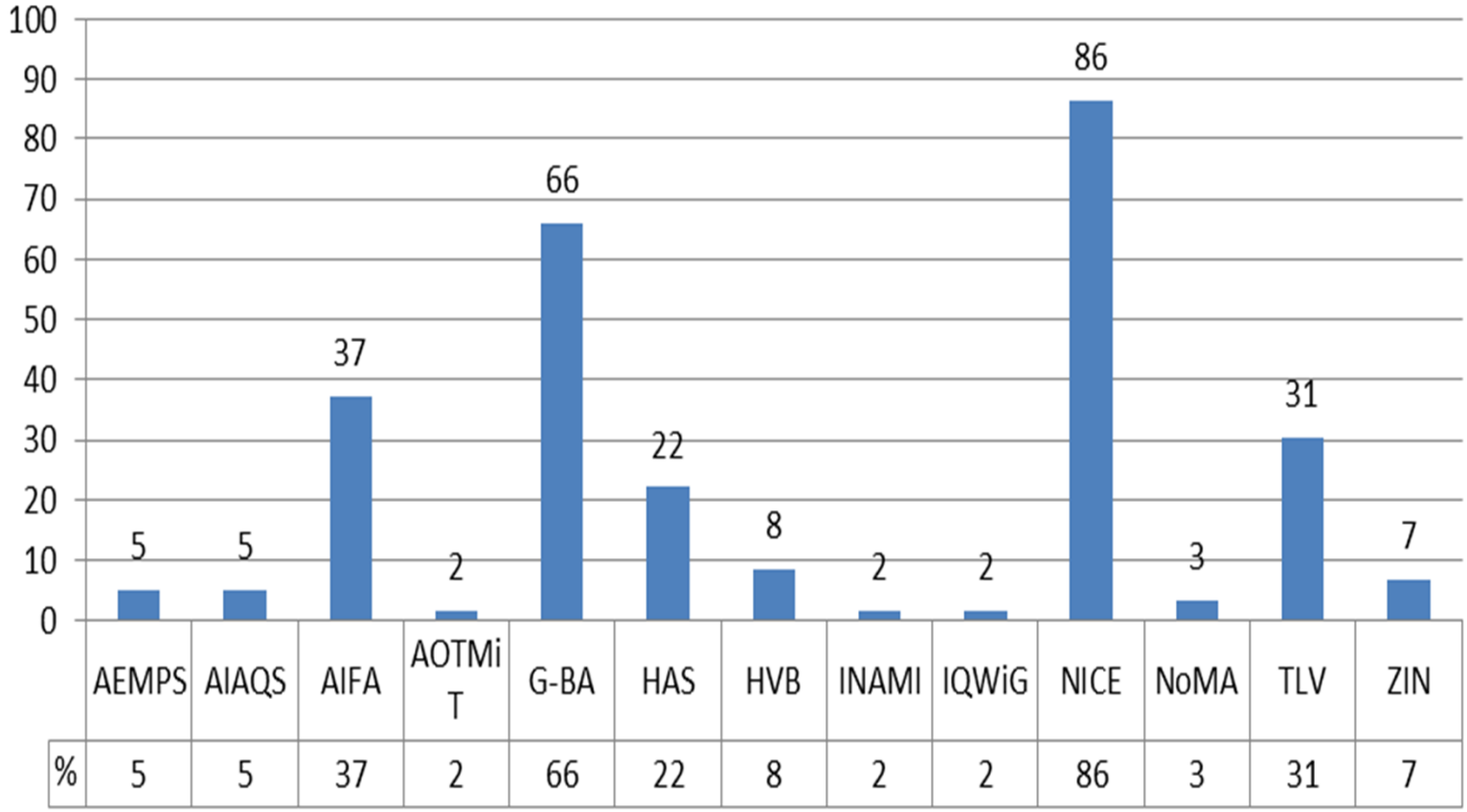
EMA HTA parallel advice: experience to date

- **63 completed parallel EMA – SA procedures** with EU HTA bodies variously from England, Italy, Germany, Sweden, France, Netherlands, Spain, Belgium
- **Broad range of indications**: Lung cancer, Breast cancer, Pancreas cancer, Melanoma, Asthma, COPD, Diabetes, Heart Failure, Depression, Alzheimer's, Migraine, Infections, Rare diseases, Myasthenia Gravis

Number of parallel advice procedures per year



Parallel Advice (nonSEED) closed to year end 2015 : HTAB participation rates in 59 procedures



	AEMPS	AIAQS	AIFA	AOTMiT	G-BA	HAS	HVB	INAMI	IQWiG	NICE	NoMA	TLV	ZIN
%	5	5	37	2	66	22	8	2	2	86	3	31	7

Level of agreement between HTAB vs Regulators and between HTABs

"HOW ALIGNED ARE THE PERSPECTIVES OF THE EU REGULATORS AND THE HTA BODIES? A COMPARATIVE ANALYSIS ON REGULATORY- HTA PARALLEL SCIENTIFIC ADVICE".

Giovanni Tafuri[1-2,*] et al.

Manuscript

Conclusions and future steps

- Increasing numbers early dialogue between different stakeholders seen.
- Best practice procedure guidance agreed and to be published.
- Long-term objective of parallel HTA/EMA advice -improved availability -not currently possible to evaluate as it takes time to compete development programs.
- Prospective use of conditional marketing authorisation, also aiming to incorporate the HTA needs.
- Increasing involvement of patients.
- PRIME –scheme for priority medicines launched.

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Thank you for your attention

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PRI*ority* ***ME****dicines (****PRIME****)*

Support to development of priority medicines for unmet medical needs.

An agency of the European Union

Drivers for change

Reinforcing ***PREDICTABILITY*** *of the EU regulatory system.*

Patients

- *Areas of unmet need*
- *Focus on accelerating regulatory approval of new medicines*

Research & Development

- *Scientific and regulatory challenges*
- *Importance of early dialogue with regulators and scientific advice*
- *Difficulty in access to capital investment for academia & SMEs*

EU Network Perspective

- *Optimising support to innovation*
- *Complementary approach to national initiatives*
- *Supporting global development*

Vision of the EU Medicines Regulatory Network

EU Medicines Agencies Network Strategy to 2020

- *Ensure timely access to new beneficial and safe medicines for patients*
  - *Better understanding of existing tools (conditional MA, accelerated assessment…) and prospective planning of their use*
- *Support for patient focused innovation and contribute to a vibrant life science sector in Europe*
  - *Facilitate innovation to ensure patient access to new medicines*
  - *Greater collaboration across network to support innovation*
  - *Consider further regulatory incentives for innovation, particularly in certain areas of public health need*

PRIME - Legal base

Regulation (EC) No 726/2004

According to Recital 33 and Article 14(9) of Regulation (EC) No 726/2004, the applicant may request an accelerated assessment procedure in order to meet, in particular the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, for medicinal products of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation.

Eligibility to PRIME scheme

For products under development which are yet to be placed on the EU market.

- *Entry to scheme at two different stages in development:*
  - *at the earlier stage of **proof of principle** (prior to phase II/exploratory clinical studies) focusing on SMEs.*
  - *at **proof of concept** (prior to phase III/confirmatory clinical studies).*
- *Must be based on adequate data to justify a potential major public health interest.*

Applicants not eligible to PRIME can still request accelerated assessment.
Guideline of the procedure for Accelerated Assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004.

Multiplicity and label claims

- ICH E9
- EMA points to consider on multiplicity issues in clinical trials- currently being revised into a guideline on multiplicity issues (to be published for public consultation in the next few months)
  - Wordings, dose finding, use of secondary endpoint,
  - alternative analysis methods / "modelling"
  - subgroup evaluation
  - composite endpoints
  - multiplicity in estimation
- SmPC guideline

Legal framework CMA

Scope (at least one):

- for **seriously debilitating diseases or life-threatening diseases**;
- to be used **in emergency situations**;
- **orphan** medicinal products.

Criteria (all):

- the **risk-benefit balance is positive**;
- it is likely that the applicant **will be in a position to provide comprehensive clinical data**;
- **unmet medical needs** will be fulfilled;
- the **benefit** to public health **of the immediate availability** on the market of the medicinal product concerned **outweighs the risk** inherent in the fact that additional data are still required.

'**unmet medical needs**' means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected

Regulation (EC) No 507/2006