Ongoing revision of the EMA Anticancer guideline

and thoughts on future evidence requirements

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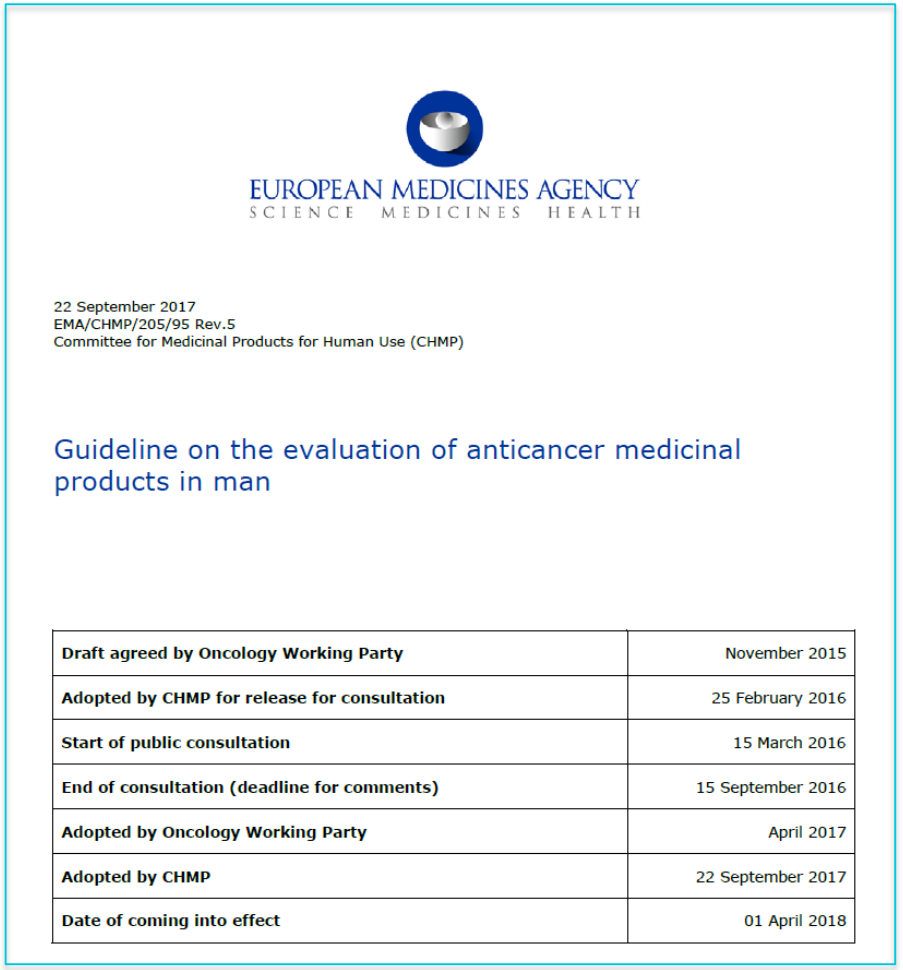
LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

The EMA
”Anticancer Guideline”

- Current version: 5th revision with a new safety section adopted in September 2017
- Concept paper on the need for an update of the guideline published in January 2019:
  - biomarkers
  - small populations
  - related new study designs



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 September 2017
EMA/CHMP/205/95 Rev.5
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the evaluation of anticancer medicinal products in man

Draft agreed by Oncology Working Party	November 2015
Adopted by CHMP for release for consultation	25 February 2016
Start of public consultation	15 March 2016
End of consultation (deadline for comments)	15 September 2016
Adopted by Oncology Working Party	April 2017
Adopted by CHMP	22 September 2017
Date of coming into effect	01 April 2018

Guideline on the evaluation of anticancer medicinal products in man

(Current version, Rev. 5, 2017)

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Changing regulatory landscape requiring updated guidance

For example (a cascade of developments):

- Rapidly developing techniques for genetic and other characterisation
- Biomarker-driven drug development
- Smaller patient populations
- Single-arm trials (SAT) as pivotal evidence for market approval
- Conditional market approvals (CMA)
- More focus on relative efficacy and safety (required for CMA in EU)

Ongoing revision 6, *draft*

1. Background
2. Scope
3. Legal basis
4. Pharmacokinetics
5. **Biomarkers – *major revision with new content***
6. Exploratory studies
7. **Phase III, confirmatory trials**

   Subsections updated:

   Endpoints

   Interim analyses

   Children – *mainly administrative update with references to other sources*
8. **Specific designs for special situations – *new section with new content***
9. Safety

Biomarkers

1 page → 3-4 pages
Subsections on:

- Sample collection
- Biomarker investigations in confirmatory studies
- Biomarker assays

Key messages concern:

- Quality and validation issues
- Ensuring a representative biomarker-evaluable population
- Pre-planning of subgroup analyses
- Biomarkers for patient selection in confirmatory studies (enrichment issues)
- New biomarkers with unknown prognostic effect requires controlled data
- Co-development of drug and diagnostic assay

Confirmatory phase 3 trials

Main changes in subsections on:

Endpoints

Interim analyses

Key messages concern:

- Regulatory thinking on PFS and OS (described in more detail)
- PROs as primary endpoints (general wording on added)
- Acceptability of early interruption for efficacy (situations specified)
- Terminology requirements with regard to “data maturity” (to be based on total N)

Specific designs for special situations

New section

Subsections:

- Studies in small study populations, very rare cancers
- Basket and Umbrella trials

Key messages concern:

- Under-powered studies usually preferred; optimisation possibilities
- Justification of single arm trials
- Real-world data and historical controls
- Different purposes of basket trials (exploratory vs pivotal, different requirements)
- Pooling of baskets, requirements for justification, acceptability of extrapolation

Disclaimer to the above-mentioned

- This is based on a **draft** (from the Oncology Working Party + Biostatistics WP)

- It has not yet been out on public consultation
- Further scrutiny by the EMA Guidance Consistency Group follows before:
- Final agreement and adoption by the CHMP (committee for approvals)

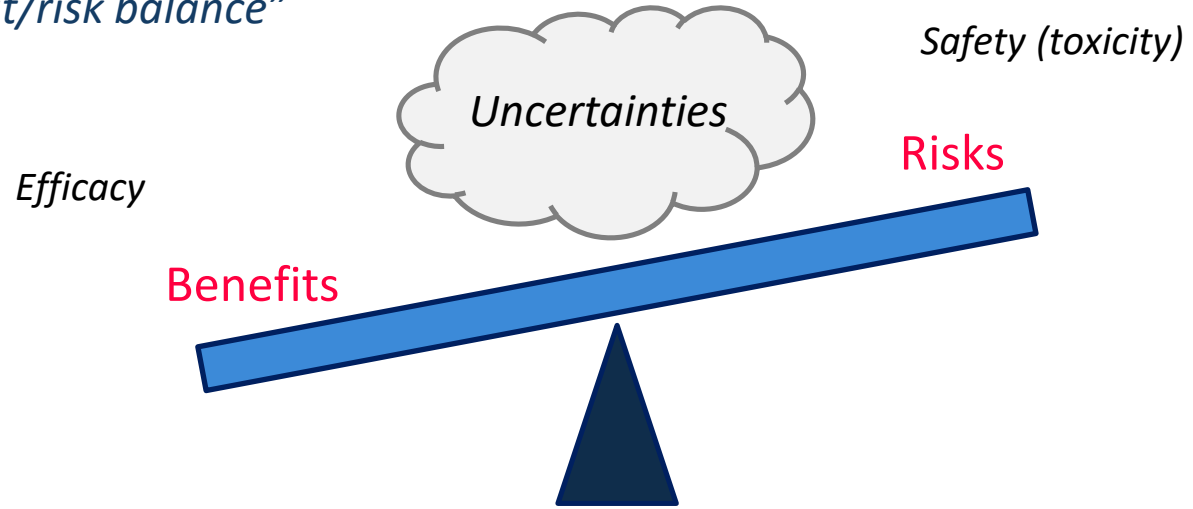
Future evidence requirements?

Disclaimer: personal reflections

First, the current principles!

Regulatory principle for approval

"The benefit/risk balance"



Positive B/R balance → Marketing authorisation

Image: Sigrid Klaar

Regulatory principles for approval

- An *absolute* benefit/risk assessment for market approval – in *essence*, *no comparison* with other drugs is made – if the positive effects of the drug on the disease outweighs the risks, mainly toxicity, then the benefit/risk balance is “positive” and approval is possible.

  However, in order to estimate and contextualise the treatment effect and risks, in *practice*, comparative data are often used (or even required).

- Increased number of **conditional approvals** (CMA): also relative efficacy and safety taken into account in order to address whether an unmet medical need is met

Future evidence requirements?

- New landscape: Biomarker-driven drug development, small populations, single arm trials…
- Increased number of conditional approvals (CMA), where also *relative* efficacy and safety is, by law, taken into account

➢ **A shift towards more relative efficacy and safety in regulatory assessments to be expected? (already seen…)**

– A need for new methods for relative assessments for regulators?

– A need for more detailed guidance to industry?

Future evidence requirements?

Type of evidence:

- In oncology, *to date*, treatment effects have mostly been in the form of some type of "objective" data such as imaging or hard events such as death
- Patient-reported ("subjective") data have rarely impacted the B/R balance
- Growing movement recognising the importance of the patient perspective

➢ **Could this change? More PRO-based approvals in the future?**

Appendix 2 to the EMA Anticancer guideline on the use of PROs, 2016

– Possibly in need of revision soon, due to emerging new methods?

Different stakeholders' evidence requirements

- Patient organisations and HTA/payers on different ends of a spectrum?

Patient organisations | *Regulatory* | *HTA / payers*

Activity | Absolute benefit/risk | Relative effectiveness

Anti-tumour activity
ORR, tumour shrinkage
But also: QoL, PROs

All types of efficacy endpoints and toxicity

Overall survival
QoL (e.g. EQ5D)

Image: Sigrid Klaar

Different stakeholders' evidence requirements

- Regulators criticised from both sides:

Patient organisations	*Regulatory*	*HTA / payers*
Activity	Absolute benefit/risk	Relative effectiveness
Anti-tumour activity ORR, tumour shrinkage But also: QoL, PROs	**Approval "too late" (patients)** **Approval "too early" (payers)**	Overall survival QoL (e.g. EQ5D)

Image: Sigrid Klaar

Different stakeholders' evidence requirements

Another spectrum? – Acceptance of real-world data (RWD):

Regulatory	*Patient organisations*	*HTA / payers*
Absolute benefit/risk	Activity / PROs	Relative effectiveness
Trial data	RWD?	RWD

Image: Sigrid Klaar

Different stakeholders' evidence requirements

Another spectrum? – Acceptance of real world data (RWD):

Regulatory	*Patient organisations*	*HTA / payers*
Absolute benefit/risk	Activity / PROs	Relative effectiveness
Trial data *- Possibility to refuse approval if evidence is not deemed sufficient*	RWD?	RWD *- Out of necessity and partly for other purposes (follow-up)*

Image: Sigrid Klaar

More alignment between stakeholders in future evidence requirements?

Potential developments:

- More relative efficacy / effectiveness in regulatory assessments?
- Patient-reported outcomes of increased importance?
- Real world data (RWD) ⟶ Real world evidence (RWE)?

➢ All with methodological hurdles!

More alignment between stakeholders in future evidence requirements?

Potential developments:

- More relative efficacy / effectiveness in regulatory assessments?
- Patient-reported outcomes of increased importance?
- Real world data (RWD) ⟶ Real world evidence (RWE)?

➢ All with methodological hurdles!

In addition, possible future alignment of evidence requirements for approvals based on SATs (e.g. basket trials) and RCTs?? Current discord in the requirements, e.g. statistical requirements, demonstration of clinical benefit…

Thank you for your attention!

Over to Ralf