Panel discussion

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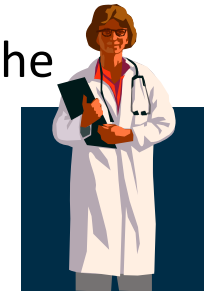
The views expressed are personal views and not necessarily the views of CBG-MEB or EMA.

Radboudumc

Perspectives from regulatory to patient

Perspective of treating physician and her patient

Evidence based decision for the (next) patient to treat, selecting from the available treatment options.



Perspective of market authorisation of a new drug

Evidence based decision of allowing physicians to add a new drug to their treatment options.

Provide information to guide the prescribing physician.

Provide information to guide the patient.

What do we/you believe?

- If there is a treatment effect, it is equal for all subjects (strong additivity).

- If there is a treatment effect, it will likely vary between subjects.

Despite all the caveats, exploring effects for clinically relevant subgroups is essential in assessment of benefit/risk.

Senn, Statist. Med. 2004; 23:3729–3753

Why subgroups analyses

Verify that the conclusions of therapeutic efficacy (and safety) apply consistently across subgroups of the clinical trial population.

Benefit-risk is borderline or unconvincing: identify post-hoc a subgroup, where efficacy and risk-benefit is convincing.

The clinical data fail to establish statistically persuasive evidence: identify a subgroup, where a relevant treatment effect and compelling evidence of a favourable benefit-risk profile can be assessed.

Guideline on the investigation of subgroups in confirmatory clinical trials

31 January 2019
EMA/CHMP/539146/2013
Committee for Medicinal Products for Human Use (CHMP)

Subgroup analyses & Regulatory assessment

Subgroup related Major Objections & Other Concerns

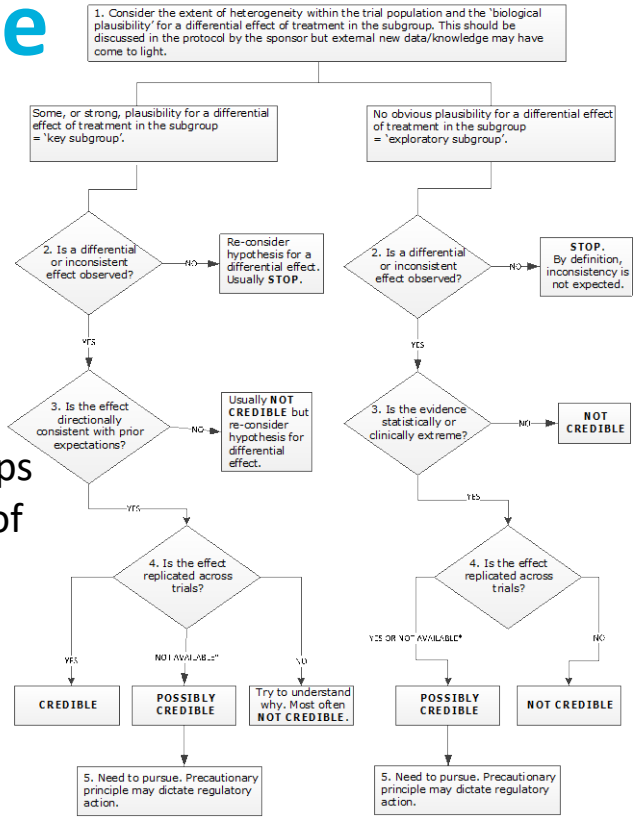
(across 162 products; 138 authorized)

	Authorized	Refused/withdrawn
At least one efficacy MO	25%	12%
At least one efficacy OC	59%	33%
At least one safety MO	9%	21%
At least one safety OC	22%	58%

" Subgroup analyses of PFS in subjects with an early stage disease at baseline did not show any benefit[….]. The clinical benefit of the treatment in this subpopulation is therefore debatable.

Although activity of treatment appears to be demonstrated, the magnitude of the effect observed appears to be clearly inferior to other standard treatment options currently available […]. The company should discuss and justify for which patients treatment could have a positive benefit/risk."

Key concepts in the guideline



Heterogeneity:

Differences within the target patient population in factors prognostic for outcome or predictive of treatment effects.

Consistency:

Extent to which estimated treatment effects in relevant subgroups assures that the overall treatment effect applies to the breadth of the trial population.

Credibility:

Depends on:

- The degree of well-founded, **a priori definition**
- The **biological plausibility** for a particular finding and
- **Replication.**

Reflections

(Kent)

- Important to explore clinically relevant subgroups, and focus on benefit-risk.
- ”Why most subgroup results are false or overestimated.”
  - *Especially a risk for small subgroups.*
  - *Shrinkage estimation of effects can be proven not to solve the problem universally.*
  - *“But a little replication goes a long way.”*

(Unger)

- Most subgroups analyses indeed exploratory: secondary assessment.
- Pre-definition:
  - Not so much list the subgroups in the protocol: *pre-definition of biological rationale for expecting differential efficacy is essential (but not common practice).*

Reflections

(Fleming)

- Significant interests of stakeholders not very statistical, but very relevant – research waste.
- Need to address the required standards to pursue new trials in subgroups, driven by previous findings (there is relevant work on this – replication).

(Shane)

- Triggers that we may need to extend our ideas about, and statistical armamentarium for, “subgroup analyses”:
  - Biological rationale, (statistical) properties of assays and variance components (subjects, over time, across tissues,..) become part of concept of “subgroup”.
  - Need to address appropriate modeling appropriate for the biology.