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EMA workshop

How can scientific information needs of both HTAs and regulatory be accommodated in a common development track – Regulatory view

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Overview

- Role of the regulator
  - Marketing authorisation, Product labelling
- High level description of evidentiary requirements and good scientific and methodological practices
- Promoting efficient collection and processing of data without compromising roles and responsibilities

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Framework for marketing authorisations (MA)

- **Legislation** requires that marketing authorisation for a medicinal product shall be **refused** if:

(a) the **risk-benefit** balance is not considered to be favourable; or

(b) its **therapeutic efficacy** is insufficiently substantiated by the applicant; or

(c) its qualitative and quantitative composition is not as declared.

The risk-benefit balance is defined as an evaluation of the positive therapeutic effects of the medicinal product in relation to any risk relating to the **quality, safety or efficacy** of the medicinal product as regards patients' health or public health.

- Committee for Medicinal products for Human Use (CHMP)

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Framework for 'Scientific Advice'

- Legislation provides that *"The Agency shall provide the Member States and the institutions of the Community with the best possible scientific advice … advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products."*
- Given by CHMP, through Scientific Advice Working Party
- Hence Scientific Advice directly relevant to assessment, and is "morally binding" for the design of tests and trials in the development programme

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History of ‘Scientific Advice’

- Well established
- Increasing number
- Increasing range
  - Parallel FDA, Parallel HTA, Qualification of Biomarkers, Qualification of Novel Methodologies
- Adherence promotes chances of successful MA

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What are the regulators information needs? Pillars of drug licensing

- Quality
- Basic science to support development and to inform product labelling
  - Non-clinical
  - Clinical pharmacology
  - Understanding dose response

- **Confirmatory studies; clinical efficacy and safety**
- **Risk management plans and post-authorisation studies**

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What are the regulators information needs? Clinical efficacy and safety

- Randomised, controlled trials (RCT)
- Good Clinical Practice (GCP) / Database is available and can be verified and interrogated
- International Conference on Harmonisation (ICH)
  - Including E1, E9, E10
- EMA / CHMP guidelines
  - therapy area documents
  - methodological principles

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Studies to establish therapeutic efficacy and safety - general

- Balancing internal validity and external validity to understand the properties of the intervention under study in a relevant setting.
- Population
  - Homogenous for internal validity
  - Heterogeneous for external validity
- Endpoints
  - Clinical outcomes, surrogates, biomarkers
  - Short-term effects, longer-term effects, need for continued treatment, rebound effects etc.
  - Targeted PROs / QoL
- Choice of control
  - Placebo control where ethical and feasible “absolute effects”
  - (One) active control otherwise and always welcome for context

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Studies to establish therapeutic efficacy and safety – methodology

- Strive for unbiased estimates and ‘false-positive’ error control through direct comparisons
- Estimand = “efficacy” … benefits observed across a clinical trial population that are attributable to the intervention under study
- Frequentist* statistical methodology to support ‘pillars’
- Pooled analyses supportive for efficacy, more important for safety
- Dedicated evidence vs available evidence; modelling primarily for ‘interpolation’ not for ‘extrapolation’
- Considerable guidance, research and ‘case-law’ to set standards

* not mandated

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Post-authorisation

- Current:
  - RCTs to add another pillar for efficacy
  - Post-authorisation safety studies, registries, database studies, meta-analyses
- Future:
  - Integrating pre- and post- licensing safety data and risk-benefit decisions
  - Post-authorisation efficacy studies, pragmatic trials etc.
  - Maximising methodological rigour within bounds of feasibility

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For discussion - where to look for efficiency gains?

- Exploratory development. Too early?
- Promote that post-authorisation studies that meet everyone's needs. Too late?
- Start to build information for HTA into confirmatory trials?
  - More external validity to Phase III trials?
  - Additional assessments?
- Must not confuse roles and responsibilities, increasing hurdles, just because of a common development track

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For discussion - the single development track

- Which HTA need? Regulatory system more practiced in harmonising between EU member states.
- Longer studies, multiple active comparators, clinical outcome variables, broader populations etc.
  - Increase variability and decrease sensitivity to drug effects; neither necessary nor proportionate for the regulatory question
  - No compromise on bias or error control
  - Adaptation of studies after the ‘regulatory’ question is answered
- Harmonise certain standards in advance – therapy area guidelines

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For discussion - the single development track

- The role of the active control – why does one suffice?
- Assessment burden for the trial participants; opportunities in targeted data collection and monitoring
- The single analysis track
  - Format for data collection and storage
  - Key data for targeted trial monitoring
  - Analysis plans
  - Data presentations and summaries
- On the justification that ‘we need it for HTA’ and on compromise to agree a feasible development programme

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