MHRA
Regulating Medicines and Medical Devices

Regulatory interface between “statistics” and “PK”

PKUK, Bath, 2014

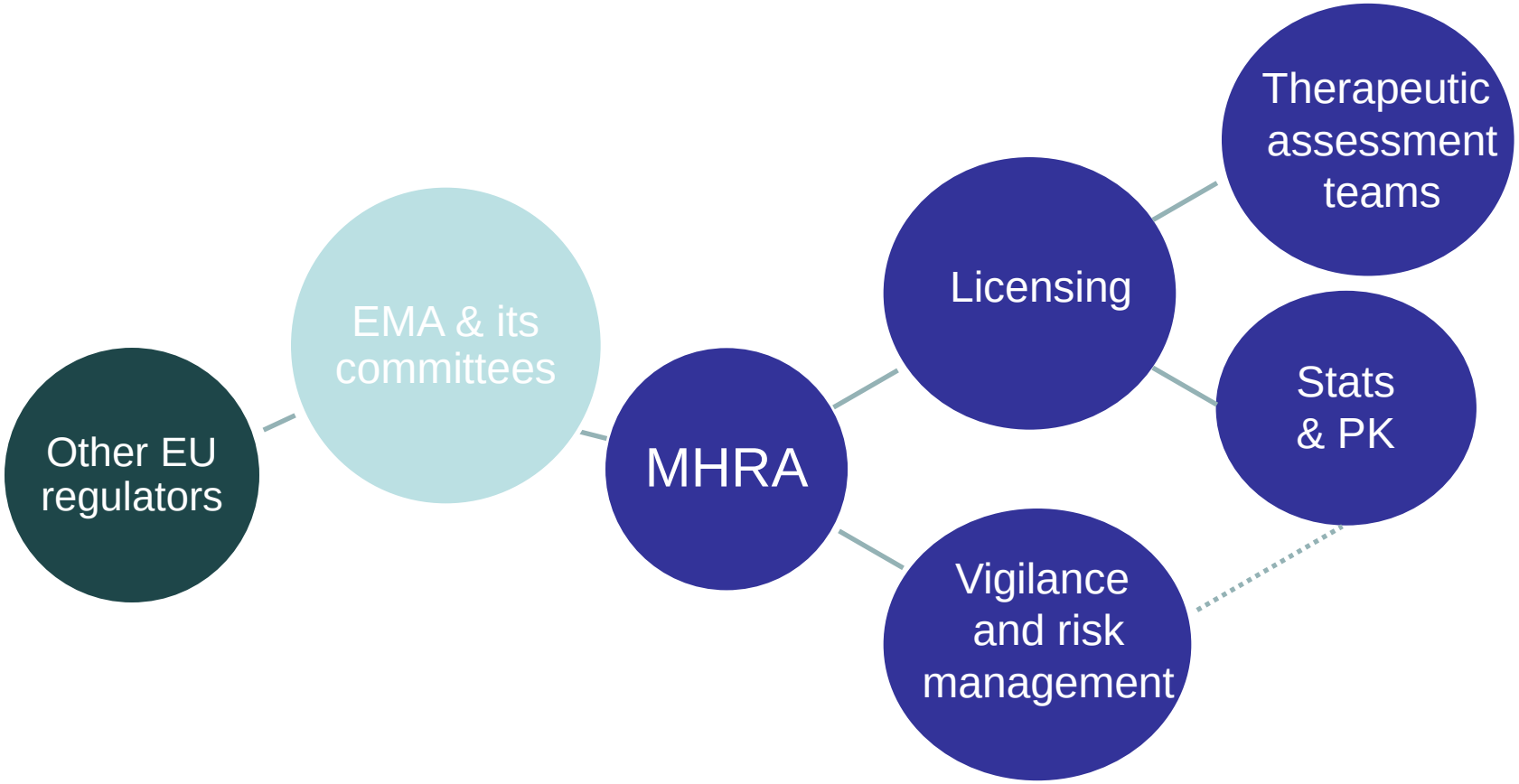
Julia Saperia, Statistical Assessor, MHRA

Medicines and Healthcare Products Regulatory Agency

Disclaimer

- The views expressed in this presentation are those of the speaker and not necessarily those of the MHRA.

The European regulatory network



EMA= European Medicines Agency

Stats & PK Unit at MHRA

- 6 statisticians
- 2 pharmacokineticists
  - Representation at EMA committees and working groups ➔ extensive input into Europe-wide regulatory decisions and guidelines
- What do we do?
  - assess marketing authorisation applications (MAAs)
  - give scientific advice on development programs

Statisticians

- Mainly assess efficacy studies (in Phase III)
  - Looking for appropriate study design and analysis methods
    - Does bias exist in the estimates of treatment effects?
    - Interested in missing data, type I error control (probability of reaching a false-positive conclusion), patient accountability etc

Pharmacokineticists

- Mainly look at clinical pharmacology package
  - Understanding dosing in different populations
    - Risks of over- and under-exposure
    - Potential impact on efficacy and safety

Phase III studies

- Statistical analyses rather simple
- Randomisation takes care of variability
- Want to generalise results to patients
  - cannot rely on assumptions

Getting to Phase III

- assume appropriate work has been done to identify correct dose(s)
- hope that dose(s) identified succeed
- Million dollar question: how do we find the right dose(s) to take to Phase III?

Approaches to dose-finding

- “What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects.”
- “It is important to choose as wide a range of doses as is compatible with practicality and patient safety to discern clinically meaningful differences.”

Approaches to dose-finding

- “It is all too common to discover, at the end of a parallel dose-response study, that all doses were too high (on the plateau of the dose-response curve), or that doses did not go high enough. A formally planned interim analysis (or other multi-stage design) might detect such a problem and allow study of the proper dose range.”

Approaches to dose-finding

- “Several dose levels are needed, at least two in addition to placebo, but in general, study of more than the minimum number of doses is desirable. A single dose level of drug versus placebo allows a test of the null hypothesis of no difference between drug and placebo, but cannot define the dose-response relationship. Similarly, although a linear relationship can be derived from the response to two active doses (without placebo), this approximation is usually not sufficiently informative. **Study designs usually should emphasize elucidation of the dose-response function, not individual pairwise comparisons.”**

Approaches to dose-finding

- “Agencies should also be open to the use of various statistical and pharmacometric techniques such as Bayesian and population methods, modeling, and pharmacokinetic-pharmacodynamic approaches.”

Approaches to dose-finding

- Pairwise comparisons in dose-finding studies are inefficient
- Regulators are open to innovative methods (since 1994!)
- So why do we still see pairwise comparisons of few doses in Phase II studies?
- …and what are the alternatives?

Regulatory view?

- ‘therapeutic efficacy’ and ‘benefit-risk’
  - If ‘benefit-risk’ is positive we will (must) license it regardless of dose
- ‘dose-selection is the sponsor’s risk’

Regulatory view?

- ‘therapeutic efficacy’ and ‘benefit-risk’
  - If ‘benefit-risk’ is positive we will (must) license it regardless of dose
- ~~‘dose-selection is the sponsor’s risk’~~
- choosing dose on weak foundations is risk for development
- regulators **are** interested in “various statistical and pharmacometric techniques”

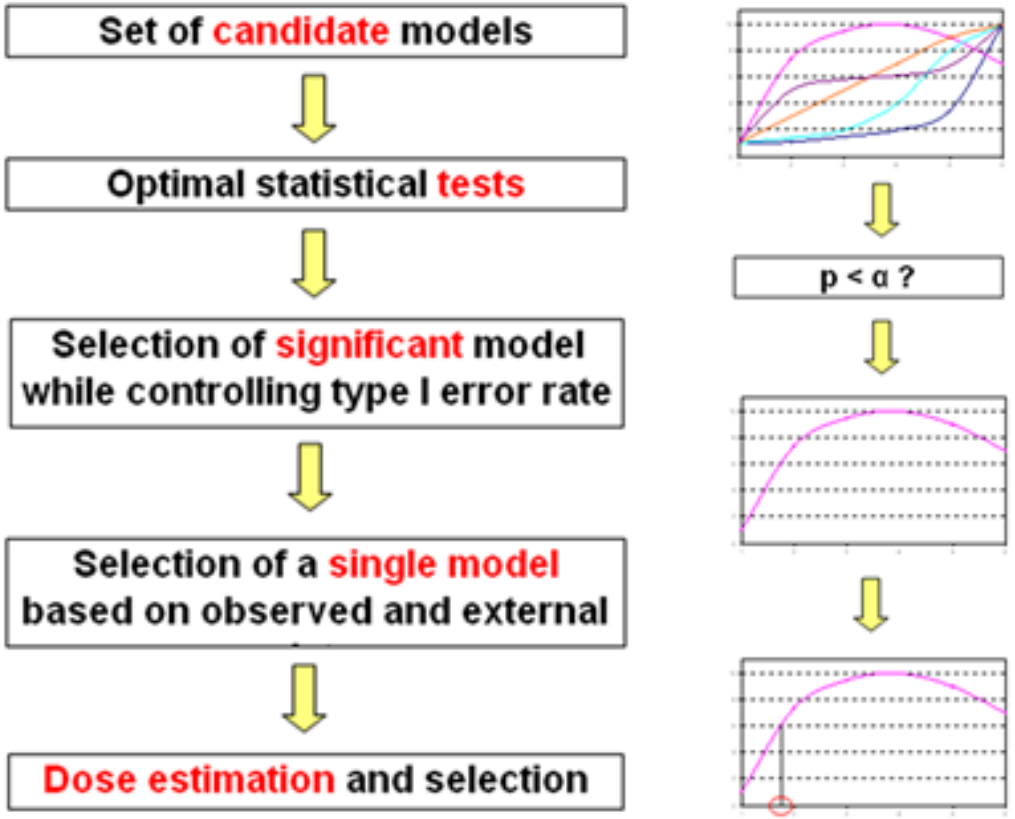
Example

- MCP-mod (Novartis)
- Multiple Comparisons and Modelling
- Approach “qualified” by the EMA
- **Endorsement does not preclude use of other approaches**

MCP-mod

- Combines testing and estimation
- Design stage
  - Pre-specification of candidate dose-response models
- Analysis stage: MCP-step
  - Statistical test for dose-response signal. Model-selection based on significant dose-response models
- Analysis stage: Mod-step
  - Dose-response and target dose estimation based on dose-response modelling

MCP-mod


Set of candidate models
Optimal statistical tests
Selection of significant model while controlling type I error rate
Selection of a single model based on observed and external
Dose estimation and selection
p < α ?

MCP-mod

- Controls type I error (probability of reaching a false-positive conclusion)
  - risk of taking wrong dose forward is controlled
- Efficient statistical methodology
- “MCP-mod qualification opinion"

Adaptive dose-finding studies

- Adaptive designs seen as efficient
  - Exploit resources
- Concerns in confirmatory adaptive trials are potential biases at each “look” at the data
  - (See CHMP reflection paper on the topic)
  - In dose-finding, be mindful of possible risks of reaching a false-positive conclusion

Thoughts on modelling

- Data sources are varied
- Assumptions are many
- Type I error may not be controlled
  - who cares?

Thoughts on modelling

- Data sources are varied
- Assumptions are many
- Type I error may not be controlled
  - who cares?
- **Your model is only as good as your worst assumption!**

Further regulatory thoughts

- Workshop, 4-5 December 2014
- European Medicines Agency (EMA)/European Federation of Pharmaceutical Industries and Associations (EFPIA) workshop on the importance of dose finding and dose selection for the successful development, licensing and lifecycle management of medicinal products