Theme 1 regulatory comments

All views herein are those of Dr Filip Josephson and do not necessary represent European Regulatory policies

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How can industry get the required early regulatory feedback and agreement on the acceptability of M&S approaches to dose selection

- In early drug development
- For issues surrounding the design of the phase III program

The M&S approach to dose selection should preferably be discussed with the EMA/CHMP at the time of planning the phase Ib-II program

- **In an integrated approach to dose ranging and phase II development, not only do the trials support the M&S approach, but the M&S approach may determine the design of the clinical trials**

Relevant questions include:

- **How are M&S exercises specifically pre-planned to fill the empirical gaps in the phase I-II studies, likely including, e.g., underpowered comparisons, incomplete coverage of options and/or studies with only surrogate endpoints?**
- **How are the individual trials comprising the phase II program planned to complement or ”bridge” each other in providing a comprehensive PK/PD understanding, integrated by M&S?**

Relevant questions include:

- **How does prespecified M&S approaches cover gaps in the investigation of treatment strategies (e.g., different drug combinations, response guided treatment duration and dosing intensities, etc)**
- **How can the phase I/II program be maximally rationalised allowing for ”bridging” conclusions, maximising the relevant options covered?**

Some notes on phase III design: one or several doses? One or several pivotal studies? General observations

- If the dose/dosing strategy with optimal risk benefit in the relevant population(s) and clinical scenario has been sufficiently well identified, one dose/strategy in phase III may be justified
- Prerequisites for one pivotal study is covered by CPMP guidance (CPMP/EWP/2330/99). Need for more than one study depends on what is established for the product in earlier phases, and what is known about related products, as well as the need to demonstrate efficacy/tolerability in different subpopulations and clinical scenarios
- “The fundamental requirement of phase III documentation is that it consists of adequate and well controlled data of good quality from a sufficient number of patients, with a sufficient variety of symptoms and disease conditions, collected by a sufficient number of investigators, demonstrating a positive risk benefit at the intended dose and manner of use.”

Theme 3; M&S to characterize risk –benefit and support label claims

Regulatory comments

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The C.E.R.A case: Particulars of therapy with erythropoieting-stimulating agents

- **Hb is both a primary efficacy and safety parameter.**
- **Dosing is titrated to reach target Hb; Hb recommended to be monitored ”every two weeks until stabilised and periodically thereafter” (Mircera SmPc).**
- **Dose adjustments based on Hb are frequent when titrating; dosing is de facto individualised for each patient**

The relation of the dose of Mircera proposed based on M&S and that tested

- **The proposed initial dose of Mircera according to M&S was higher than that tested in phase III, but within the range of doses tested in phase II**
- **The magnitude of proposed Hb-based dose changes were smaller than those used in phase III**

Lessons from the hepatitis C case

- **The ribavirin dose used in the study of patients with normal ALT was lower than that shown to be more efficacious in patients with increased ALT**
- **”A priori there are no good reasons to suspect that patients with normal ALT should be administered a lower dose” (EMA assessment report)**
- **Furthermore, findings from the study of patients with normal ALT further indicated that this was not a pathogenetically different subpopulation; however, it did have a preponderance of women that are more prone to anemia when treated with ribavirin**

Preliminary reflections on the implications of these cases

- **Would in general the EMA accept the principle of relying on M&S approaches to label an unstudied dose or dosing regimen?**
- **What information and evidence are needed by the EMA to consider to label an unstudied dose or dosing regimen based on M&S approaches?**
- **In what circumstances would the EMA accept exposure in a sub-population outside the range of previously tested exposure in that subpopulation but within the range of previously tested exposure in an other sub-population?**

What information and evidence are needed by the EMA to consider to label an unstudied dose or dosing regimen based on M&S approaches? Lessons from the cases

- **The clinical and pharmacological assumptions of the model need to be adequately supported by empirical evidence**
- **resultant drug exposure should be within the empirically studied range**
- **the feasibility of adjusting the (modelled) dose based on clinical response (individualised dosing) may be helpful in accepting modeling based posologies**

Would in general the EMA accept the principle of relying on M&S approaches to label an unstudied dose or dosing regimen?

Particular circumstances made the M&S approaches under consideration acceptable

- **intensive clinical dose titration based on response, recommended doses within the empirically tested range**
- **implications that the subgroup did not substantially differ from the general population in which the more efficacious dose had been empirically tested**

In what circumstances would the EMA accept exposure in a sub-population outside the range of previously tested exposure in that subpopulation but within the range of previously tested exposure in an other sub-population?

If the assumption that PK/PD for efficacy and safety could be extrapolated from the one subpopulation to the other could be sufficiently justified