EMA EFPIA workshop
Break-out session no. 4:

M&S to optimise the design of confirmatory trials, to analyse Ph3 data and to characterize risk-benefit & support label claims

BOS 4: Plenary Feedback

BOS 4 Aims :

- Improve how Companies and EMA interact with respect to the use of M&S in the design and interpretation of Phase 3 studies

- It is important for EMA to understand how EPFIA intends to apply M&S in the future including the confirmatory /risk benefit setting

- It is important for EFPIA to understand where application of M&S would be acceptable to the EMA in order to guide future activities in the following areas:
  - **Theme 1** :Phase 3 design (dose, comparator, selection, N etc)
  - **Theme 2 :**Model based primary or key secondary analysis
  - **Theme 3 :** Acceptability in estimating risk benefit **including** where this replaces the need for further studies
  - **Theme 3 :** In creation of development path guidance for novel or existing disease areas

BOS 4 : Pre WS EFPIA/EMA Agreements

- Shared view that M&S has an important role to play in the design, analysis and interpretation of Phase 3 data (including risk-benefit & labelling)
- Shared view that M&S has a key role in improving R&D efficiency and decreasing late stage failure
- Closer alignment between EFPIA and EMA with respect to the application of M&S approaches:
  - Shared expectation of good practice
  - ↑ understanding of scope of potential application and limitations
  - ↑ Drug development efficiency / better informed company positions
  - ↓Market Authorisation "failures" due to poor Phase 3 design or misaligned Evidence Synthesis
  - ↑ Learning with respect to future potential of M&S in later stages of R&D
- Jointly consider how to encourage use of M&S to facilitate creation of development path guidance for novel or existing disease areas

BOS 4: Pre WS Considerations for EFPIA

- Need for improved transparency in M&S Regulatory package, Documentation, standard practice, assumption setting & sensitivity testing:
  - EMA Expectations on levels on documentation will depend on the Impact level
  - Need for framework to identify and assess impact of both Statistical and Pharmacological assumptions
  - Need for clear prespecification of modelling being conducted in the confirmatory setting
  - Sharing of internal examples where M&S leads to project termination/ reduced risk-benefit
  - Need for industry to share standard practices and reach agreement on best practice

BOS 4: Pre WS Considerations for EMA

- Clarify meeting framework to facilitate discussion on M&S prior to and including project related Scientific Advice
  - Briefing meetings for M&S strategy / qualification meetings for technical issues?
- Guidance on circumstances when M&S can have High impact
  - Given appropriate assumptions & uncertainty
- Further consideration of the utility of NLME approaches in specific pivotal trials e.g. Assessment of Disease progression
  - Alignment of Clinical vs Statistical approaches to assessment of disease progression
  - Model based approaches lend themselves to simultaneous confirming and learning
- Provision on guidance on the use of model-based tests as primary analysis in a confirmatory setting
  - Acceptability in different circumstances, Type I error assessment etc
- Risk benefit
  - Role of M&S (predicted risk-benefit) in the on going EMA Risk-Benefit methodology project
  - Share understanding of the approach to trading off Risk-Benefit
  - How is the level of uncertainty balanced against the clinical assessment of Risk-Benefit ?

BOS 4: Common Goal

- **Goal:** Achieve greater EPFIA/EMA alignment leading to improved standardisation, transparency and consistency of M&S packages leading to more productive and predictable regulatory review

Theme 1: **M&S to optimize the design of confirmatory trials**

- **Question**
- *How can industry get the required **early regulatory feedback** and agreement on the **acceptability of M&S approaches**, **models**, **inferences** to minimise the probability of EOP3 discussion around the **Phase 3 study design**, choice of doses?*
- **Regulatory Viewpoint**
- *Impact assessment of Case study Low*
- *Need to ask right question at right times*
- *M&S to be integrated into Phase 2 plans*
- *Completeness of package – including safety and answering regulatory questions*
- *Used to fill gaps across Phase 2 studies - combinations /response guided therapy*
- **Outcome of the discussion**
- *Dose is not only sponsors risk*
- *Companies can seek adhoc advice prior to formal meetings?*
- *M&S done to reduce company risk ~not all relevant to EMA*
- *Simpler analyses may be more appropriate for discusssion with health authorities*

Theme 2: M&S to analyse & interpret Phase 3 data (High Impact) : Novartis 5

- **Question**
  - *Does the regulatory agencies agree that the **proposed longitudinal model-based test** is appropriate to be considered as primary analysis?*
- **Regulatory Viewpoint**
  - *High Impact*
  - *Statistical vs Clinical relevance*
    - *Numbers for safety, medical need, feasibility*
  - *Statistical assumption*
    - *Type 1 error controlled by simulations, handling dropouts, extreme sensitivity testing*
- **Outcome of the discussion**
  - For innovation need to find a way forward
    - re simulation based type 1 error control
  - Qualification procedures to address statistical issues
  - Clinical aspects would need to be DA /biosimilar guidance
  - No **new rules** for innovative approaches

Theme 2: : M&S to analyse & interpret Phase 3 data (High Impact): Disease Progression

- **Question**
- What is required to build greater acceptance of **NLME approaches** to analysis of **disease progression trials** within a **regulatory environment**?
- **Regulatory Viewpoint**
  - High impact
  - Questions around model validity
    - Difficult in pulling apart symptomatic and disease progression effects
    - Epidemiology evidence based: Are these assumption still valid with treatment
- **Outcome of the discussion**
  - It is only approach to make inference about disease progression: already in AD & PD
  - Acceptability facilitated by it being secondary to primary analysis
  - Labelling statements would need link between primary endpoint and underlying pathology e.g. Evidence via imaging
  - Designs for the future way forward already occuring :CAMD project

Theme 3: M&S to characterize risk –benefit and support label claims (High Impact): Roche 1/2

- **Question**
  - Would in general the **EMA accept** the principle of relying on **M&S approaches** to label an **unstudied dose or dosing regimen**?
- **Regulatory Viewpoint**
- 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
- The assumption that PK/PD for efficacy and safety could be extrapolated from the one subpopulation to the other could be sufficiently justified
- **Outcome of the discussion**
  - Strength of exposure response
  - Extent of risk (if highly unacceptable with high dose moving to intermediate dose would be more difficult)
  - Mitigation strategy :e.g. flexible dosing, readily managed safety issues
  - Regulatory role in proposing modelling (Epilepsy discussion) ?

Theme 3: AZ - Modelling to guide Regulatory Guidelines and decision making during development

- M&S is important, not only in individual drug projects, but also to understand a disease area and how the Regulatory requirements determines the feasibility for clinical development of a new compound. Agree
- At what stage of development is it suitable to have industry-Regulatory interactions? Any, including pre-Phase I
  - What should be the requirements of M&S work in such a situation?
  - Is there a potential for collaboration across companies? Yes
- M&S can help guide the development of future Regulatory Guidelines in terms of suitable endpoints in clinical trials (early & late stage) and requirements for registration and label claims. Agree in principle
- How to facilitate discussions, based on M&S, between industry and Regulatory agencies regarding new Guidelines? Good question

Theme 3: AZ - Modelling to guide Regulatory Guidelines and decision making during development

- Regulatory feedback
  - High impact re reg decision
  - ≠ controversy,

- "Design of PhIII to meet patient, regulatory and payer needs (incl claims) - population, endpoints, type of studies, comparator, sample size…"
  - Is there a 'conflict of interest here'? Display and critique of assumptions is critical
- Adds objectivity to predominately subjective exercise

- ITF (Innovation Task Force) meetings / Scientific advice – perhaps both

Back-up

Theme 1: M&S to optimize the design of confirmatory trials (Low to Medium Impact): Pfizer 4 /Roche 3

Position statement	Current key Template questions	Suggested additional Questions
Understanding the totality of data and how it relates to prior information from Phase 2 (for example, through evidence synthesis of literature data) provides quantitative evidence to support Phase 3 design and dose-selection	How can industry get the required early regulatory feedback and agreement on the acceptability of these approaches, models, inferences to minimise the probability of EOP3 discussion around the Phase 3 study design, choice of doses? Best timing for seeking this input, feedback? How to ask the right question(s) to get appropriate feedback?	Under what circumstances would using this supplementary information (internal or external) be considered acceptable: For dose selection ? For Phase 3 design (number of doses , numbers of subjects, comparator arms)? For Phase 3 programme design: 1 study vs 2 studies ? When should this approach not be considered?

Theme 2: M&S to analyse & interpret Phase 3 data (High Impact) : Novartis 5

Position statement

A Longitudinal model based test as primary analysis in phase III is appropriate provided it is pre-specified and has been appropriately evaluated

Current key Template questions

Does the regulatory agencies agree that the proposed longitudinal model-based test is appropriate to be considered as primary analysis?

If the answer is "no" at this point in time, what would it take to get acceptance for the proposed approach?

What do we need to do to address the type I error concern beyond simulating from extensive scenarios?

Is it really better to pre-specify just one model with minimal assumptions than use model averaging approach ?

Suggested additional Questions

What situations could this type of approach be applied ?
Range :
Biosimilars to new compound in new disease area
A number of other examples (see Novartis 5 slides)

Theme 2: M&S to analyse & interpret Phase 3 data (High Impact): Disease Progression

Position statement	Current key Template questions	Suggested additional Questions
"A parametric NLME approach offers a useful framework to design and analyse confirmatory trials that assess the impact of a new treatment on "disease progression"	What is required to build greater acceptance of NLME approaches to analysis of disease progression trials within a regulatory environment? What would be required for an NLME approach to become a key secondary or primary analysis for assessing disease progression?	

Theme 3: M&S to characterize risk –benefit and support label claims (High Impact): Roche 1/2

Position statement	Current key Template questions	Suggested additional Questions
Successful approval of non-tested dosing scheme using M&S techniques without further dedicated prospective studies	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 General Guidelines can be offered with respect to when such approaches would be accepted in other situations ?

Theme 3: M&S to facilitate creation of development path guidance for novel or existing disease areas (High Impact): AZ2

Position statement	Current key Template questions	Suggested additional Questions
M&S is important, not only in individual drug projects, but also to understand a disease area and how the Regulatory requirements determines the feasibility for clinical development of a new compound.	At what stage of development is it suitable to have industry-Regulatory interactions? What should be the requirements of M&S work in such a situation? Is there a potential for collaboration across companies?	
M&S can help guide the development of future Regulatory Guidelines in terms of suitable endpoints in clinical trials (early & late stage) and requirements for registration and label claims.	How to facilitate discussions, based on M&S, between industry and Regulatory agencies regarding new Guidelines? What should be the requirements of M&S work in such a situation?	

Framework for M&S in Regulatory Review

According to impact on regulatory decision

High impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +++

Medium impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } ++

Low impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +

Impact on regulatory decision

Framework for M&S in Regulatory Review

Low Impact

Describe

- General description of pharmacokinetic properties and exposure-response features in target population
- Interpret PK changes in important subpopulations
- Identify important covariates
- Internal decision making (hypothesis generation, learning)
- More efficient determination of dose regimen for phase III
- Verify conclusions drawn from preclinical observations and PK data in healthy volunteers
- Optimise clinical trial design for trials not pivotal to benefit-risk decision or labelling
- Descriptive content for SPC

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +

Framework for M&S in Regulatory Review

Medium Impact

Justify

- Identify PK parameters of importance for efficacy and safety leading to dose adjustment (C_{min}, AUC, C_{max}).
- Identify safe and efficacious exposure range (exposure-response in target population)
- Justify not doing a study (e.g. DDI based on PBPK and extrapolation from *in vitro* data)
- Intermediate dose levels not tested in phase II to be included in confirmatory trials
- Inferences to inform SPC content (e.g. posology when exposure is altered - elderly, impaired organ function, concomitant medications, pharmacogenetic subgroups)

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } ++

Framework for M&S in Regulatory Review

High Impact

Replace

- Provide evidence of comparability (biosimilarity, biowaivers for MR formulations using IVIVC and in vitro data)
- Provide evidence of sensitivity of study design to detect and support treatment differences.
- Extrapolation of efficacy and safety from limited data (e.g. term and preterm neonates, paediatrics, small populations)
- Model-based inference as evidence of efficacy/safety in lieu of pivotal clinical data
- Key model-derived M&S components which inform SPC content in at least a subpopulation (i.e. extrapolation of efficacy and safety from limited data)

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +++