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EFPIA-EMA Modelling and Simulation Workshop Report

EMA-EFPIA Modelling and Simulation Workshop, 30 Nov – 1 Dec 2011, London.

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Executive summary

Participants at a workshop held at the European Medicines Agency have agreed that modelling and simulation methodology provides an opportunity to improve the efficiency of medicine development, and could facilitate the regulatory assessment of medicines.

The workshop, jointly organised by the European Medicines Agency(EMA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) Clinical Development Committee (CDC), brought together key opinion leaders and regulatory and academia experts from Europe and beyond to discuss the role of modelling and simulation (M&S) in areas such as early medicine development, clinical pharmacology and dose finding studies, special populations, optimisation and analysis of pivotal clinical trials covered by different break out sessions (BOS). Approximately 190 participants joined the workshop, of which 50 were from Regulatory Agencies including the US FDA and the Japanese PMDA.

The workshop was co-chaired by Rob Hemmings (SAWP chair, CHMP member, MHRA) and Solange Rohou (AstraZeneca, EFPIA CDC chair). Industry, academia and regulatory experts worked together before, during and after the workshop with the common objectives to improve understanding between all involved parties, and ultimately optimise drug development and regulatory assessment by use of M&S approaches. The meeting had an open atmosphere with mutual willingness to share experiences, knowledge and learning as well as identifying areas of agreement/disagreements.

Great progress was achieved in streamlining the thinking between all involved parties. The attendees agreed that enhanced communication between the pharmaceutical industry, academia and regulators from the early stages of drug development, including sharing of data, models and qualification procedures, could overcome some of the current gaps in M&S methodology.

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It was also agreed that the workshop should set the scene for further dialogue, working towards greater integration of M&S in the development and regulatory assessment of medicines. European regulators have acknowledged their need to build expertise to be able to review M&S data provided by companies in their dossier. Regulators of the 3 regions and EFPIA have already agreed to publish the proceedings of this workshop and to keep the momentum identifying priority topics for future workshops.

Gaps Identified

- Misperception that exploratory development and dose finding is the company's risk and therefore that regulators have no interest in these critical aspects of development.
- Underreporting of M&S in regulatory submissions.
- Internal barriers in industry in deploying M&S and in supporting early regulatory interactions.
- Expectation that there is variable regulatory competence in assessing M&S across EU.
- Mechanistic, PD and safety models are currently lagging behind PK models.

Agreement reached

- M&S is a powerful tool that should be more integrated in drug development and regulatory assessment.
- Exploratory development and dose finding is of key importance for regulators.
- The current dose finding paradigm based on pair wise comparisons and significance testing is sub-optimal and needs revision.
- M&S is not limited in the exploratory setting.
- The regulatory scrutiny applied to a particular M&S exercise will depend on the impact of the exercise on the regulatory decision and product labelling.
- Regulators committed that the requirements for high impact M&S will not exceed the hurdles for standard statistical testing.
- Need for harmonization on good M&S practices.
- Share data, models and concepts in the precompetitive space is crucial.
- Mechanistic models/systems pharmacology are disciplines that will grow excessively in the near future and have a massive impact in drug development.
- All parties committed to keep the momentum and continue dialogue.

Action Points

- Bring together expertise within the European experts network and explore opportunities to build competence and capacity within the regulatory system.
- Explore the benefits of, and structures for, international collaboration between regulatory agencies.

- Consider updating regulatory guidance documents on dose finding.
- Consider developing M&S guidance document(s) / Reflection paper(s).
- Consider how to promote earlier and more frequent interaction with regulators on M&S to raise awareness and acceptability of these methods and to enable more productive and predictable regulatory review.
- Promote the availability of the 'Qualification Process' and Innovation Task Force as fora for early discussions on M&S.
- Organise further workshops to continue to share experiences and build a framework for increased use of M&S in different scenarios.

Day 1

Plenary session: Current position and expectations for use of M&S in drug development and regulatory decision making

On day 1, the plenary session was the opportunity to set the scene with EFPIA, EMA, FDA and PDMA representatives presenting their view and expectations of the use of M&S followed by a general discussion. Subsequently some selected examples that did or did not meet the regulators' expectations were presented and further debated.

Peter Milligan, the EFPIA representative, gave a brief overview of the reasons why companies have identified opportunities for greater utilization of quantitative approaches.

It was emphasized that MBDD (Model Based Drug Development) should start before a compound is selected for preclinical development by informing PK-PD and biomarker strategies, and the confidence in rationale for the proposed clinical target. Emerging data from each new experiment/clinical study must be integrated with relevant previous information to most effectively inform decision-making (e.g., design the next study or terminate the development of the new compound). Models especially those based on accepted scientific rationale allow integration of data from different studies in a logical manner based on our understanding of the drug and disease. Thus, drug development could be viewed as a model propagation and maintenance exercise during which our relevant information about a new compound is continuously updated and this knowledge is used to inform company decision-making and drug development strategy.

The pharmaceutical industry is facing considerable challenges as shown by the attrition rates for new drug development projects that have substantially grown across all R&D Phases from 1990 to 2004 (Pammolli et al, 2011). The low productivity and escalating costs of drug development have been well documented over the past several years. Less than 10% of new compounds that enter clinical trials ultimately make it to the market, and many more fail in the preclinical stages of development. The high rate of attrition in drug development and the need for efficiency becomes even more compelling when one considers where most of the attrition occurs in the pipeline. An examination of the root causes of why compounds undergo attrition in the clinic is very instructive and helps in the identification of strategies and tactics to reduce these rates and thereby improve the efficiency of drug development. The EFPIA speaker showed the reason why compounds undergo attrition and how this has changed over time. As an example in 1991, adverse pharmacokinetic and bioavailability results were the most significant cause of attrition, and accounted for ~40% of all attrition. By 2000, these factors had dramatically reduced as a cause of attrition in drug development, and contributed less than 10%.

These data provide further compelling evidence that the industry can identify and remedy the causes of attrition. Starting from a baseline value for the estimated capitalized cost of a single NCE of ~$1.78 billion, high failure rates in Phase 2 and 3 are nowadays the most important determinants of drug development cost. Failure rate in Phase 2 can be attributed to target selection; once target and compound are selected the benefit/risk in humans is largely pre-determined. This requires better understanding of human biology; pathophysiology which can be achieved via mechanistic models. Failure rate in Phase 3 can be attributed to inadequate "risk decisions" The systematic integration of compound specific (direct) and mechanism and disease area (indirect) relevant information is required in order to create a comprehensive, complete and contemporary body of evidence (meta-analysis). There is thus, an opportunity for greater utilisation of quantitative approaches to increase confidence in rationale for human efficacy. M&S can increase decision-making efficiency particularly when supported by the totality of relevant data and a "fit for purpose quantitative analyses thereby systematically identifying the right pathway, the right target, the right molecule and the right dose for the right patient. However, there is still a need to change the mindset in companies to help fostering appropriate use of M&S. An open question is how regulators envisage using this integrative knowledge and "body of evidence" of the product in their assessment and how model based drug development should be presented. The current eCTD does not lend itself to this purpose.

Terry Shepard (MHRA), expressed in her presentation harmonised views of experts across a number of European regulatory agencies. The EMA Benefit/Risk decision making process was described. A specific framework to illustrate how regulators weight the importance of models was presented. The degree of regulatory scrutiny, level of documentation and the need for early dialogue is proportional to the weight of the M&S exercise in regulatory decision making. In general EMA endorse and support growth of M&S applications to quantify information, inform decision making and design/analyse trials. For regulators, Benefit/Risk decisions are based on the totality of the data. Regulators, drug developers alike, are keen to have at hand the integrative knowledge and quantitative decision making that M&S offers, when they evaluate medicinal products. Proper use of M&S is an indicator of rational drug development and supports best informed outcome of risk benefit decisions. Lack of M&S/quantitative methodology misses opportunity to mitigate uncertainty in the B/R decision with potential impact on labelling and post approval burden.

Pravin Jadhav, the FDA representative, clearly mentioned that FDA is sharing the same views as EMA and EFPIA. While presenting the impact of Pharmacometric analysis on drug approvals and therapeutics, he detailed what FDA has put in place to improve use of pharmacometrics in drug development by industry, e.g. the End of Phase 2a meeting, the inclusion of M&S specific information in FDA guidance documents. Over the last 10 years FDA has seen a 10-fold increase in the demand and their experience is regularly published to further increase industry awareness. The scope of pharmacometrics in FDA includes mainly review but also research activities. The FDA pharmacometrics group also focuses on knowledge management and the use of information across products to improve decision making and drug development. How M&S can really change the way drug development is done was then illustrated through a few examples, eg. M&S had a pivotal role in the approval of topiramate to treat epilepsy in children. Also the example of Boceprevir was shown to demonstrate that pharmacometrics can play a pivotal role in approval and thus, in labelling.

Yuki Ando, the PMDA representative, emphasized in her presentation that global use of the clinical data while understanding ethnic differences, and appropriate use of innovative methods in the drug development will be key to providing effective drugs to the patients in the world, with sufficient information. To avoid M&S being considered as a 'black box', mostly because of its complexity and ambiguity of reason for selecting the method, she recommended to clearly identify the characteristics

of the selected method and its implementation. Active discussion of M&S between pharmaceutical industry and the PMDA was encouraged both in the clinical trial consultation meetings and during new drug review. As opposed to the FDA, PMDA may request sponsors to re-analyse the data. Since September 2011, PMDA has established a new project team to deal with innovative methods for drug development, which immediate objective is to assess the use of M&S in specific situations, such as the effects of ethnic factors on efficacy and safety or the selection of a pediatric dose based on PK/PD and M&S data; PMDA team members have specific skills in several areas such as clinical pharmacology, medical, and biostatistics. Additional topics are under consideration such as the natural course of a disease or the placebo effect as it is well known that placebo effect in some disease areas (neuro-psychiatry) can be higher in Japanese patients than in Western countries. PMDA is already expecting to gain experience via future consultations which are strongly encouraged.

Discussion

The regulators have not seen a lot of relevant M&S contributions in regulatory documents submitted by industry. Main and most known contributions are population PK modelling reports. There is overall a large willingness to learn and see more and industry is keen to share with regulators. However, M&S is not centric to the decision process and further integration of M&S in drug development and assessment will require a change in mindset. Regulators could help in this respect

There are obvious differences in M&S capacity within EU regulators (since the assessment is done at the national level) and between EMA, FDA and PMDA. M&S expertise is spread out in Europe within the member states. EMA and member states also rely on an academia expertise network. There is a need to grow and coordinate M&S capacity in the European regulatory system.

Plenary session: M&S examples that failed or succeeded to meet regulators' expectations

Valerie Cosson (Roche), presented two 'successful' examples, that were then further debated in break out session 4, on the successful approval of non-tested dosing scheme using M&S techniques without further dedicated prospective studies. In both examples, the knowledge of the exposure-response relationship was considered sufficient to rely on M&S approaches to investigate new doses. Clinical trial simulations were conducted to assess efficacy and safety clinical outcomes of non-tested dosing scheme (and dose adjustment) proposed in the SmPC (Summary of Products Characteristics). A general framework for accepting M&S as a basis for labelling an unstudied dose or dosing regimen was left open for discussion.

Monica Edholm (MPA), highlighted in her presentation that although there is no specific guideline on M&S, the Guideline on reporting population PK analyses contains useful information showing what regulators are expecting from the analysis plan and the report and the level of details. The report should provide a level of detail which will enable a secondary evaluation by a regulatory assessor. Every population PK model will depend on the data and decisions made by the model developer, and every model has therefore unique properties. It is therefore vital that every assumption and decision made during model development is made clear for the assessor. The analysis and report of the analysis need to be of sufficient quality so that the final model can be judged to be a good description of the data and that the results and conclusions ensuing from the population analysis can be considered valid. The analysis plan should be prospectively written and the report should contain justification for the model evaluation procedures and tools used for the specific evaluation.

In the case of substantial simulations based on the model, these should be described in detail, including description of the demographics (e.g. covariate distribution and variability) of the simulation data set.

There are indeed several reasons for failing regulators' expectations, e.g. deficiencies in quality of report, insufficient, irrelevant or missing information, or criticism of conclusions drawn, which were then illustrated by 4 different case studies. The issues raised by the regulators can often be solved with additional and appropriate information provided by the company. Guideline recommendations should be better taken into consideration since a better quality of analyses and reports would make the review process more efficient and would cause fewer burdens to both parties.

Oscar Della Pasqua (GSK), presented an example with fondaparinux, a Factor Xa inhibitor (anticoagulant) indicated for the prophylaxis of deep vein thrombosis (DVT) in patients undergoing fracture surgery and DVT or acute pulmonary embolism (PE) when administered in conjunction with warfarin. M&S analysis clearly showed that 0.1 mg/kg should be the recommended dose in children since this dose matched adult exposures. However, this failed meeting FDA expectations since FDA did not accepted the dose rationale based on the inferences from M&S results based on the argument that the anti-coagulant systems might not be the same in children as compared to adults. One cannot therefore assume that similar exposures will yield comparable efficacy and as a consequence, the FDA demanded prospective trial showing evidence of safety and efficacy in children taking into account dose titrations.

It is established that thrombin regulation in children differs from adults in presence or in the absence of heparin, but is this difference clinically relevant? A prospective dose-finding and PK open-label pilot study was conducted in children (between 1 and 18 years old of age) which showed that dosing of fondapirinux at 0.1 mg/kg once daily in children resulted in PK profiles comparable to those in adults receiving standard dosing. It was then concluded by the company that fondaparinux could be considered an attractive alternative to LMWH. However, this conclusion was also challenged by the CHMP that considered that no conclusion could be drawn with regard to clinical efficacy in children with DVT in this uncontrolled study. However, the CHMP was of the opinion that it could be of value to the prescriber to know what concentration could be expected with a dose that, when adjusted to body-weight, is similar to what is recommended for adults. Therefore the SPC was updated and study results are displayed in section 5.1.

This example was used to illustrate that the current paradigm for accepting extrapolation from adults to children might be incomplete. It is important to establish a framework to evaluate assumptions and propose measures to mitigate risks and uncertainty. The final data requirements should also consider these parameters.

Discussion

Key points arising from the examples presented were discussed in the plenary. The objective of the debate was to set the scene for more elaboration in the breakout sessions.

Initially the discussion was on **M&S as a basis to support unstudied doses in the SPC**. It was agreed that this is possible but certain conditions need to be fulfilled. The list which is neither exhaustive nor restrictive includes scientific plausibility of the modelling assumptions, availability of biomarkers, appropriate conduct and reporting of M&S, availability of at least some clinical data with the proposed dose, or the proposed dose being within the dose margins tested clinically, unmet

medical need, clinical context, understanding of the uncertainties and risks. Ultimately a benefit risk decision will be made.

The second topic discussed was the **regulatory standards for M&S**. It was agreed that different standards will apply depending on the impact of M&S. The current standards described in the CHMP POP PK guideline are indicative of what regulators will be looking at also when other types of M&S approaches are submitted. Some experts expressed the view that the mechanistic or PD models might require different approaches. Different standards might also be required for different objectives, e.g. when models are used for analysis, prediction or design optimisation. From a regulatory perspective it would be important not only to evaluate the capacity of the model to describe the data but most importantly to assess the model uncertainty and the risk from the prediction.

The third topic focused on the **reporting of M&S in regulatory submissions**. M&S is underreported with the perception that M&S is not relevant for regulatory decision making, or that additional hurdles might be imposed, or that regulators are not competent in assessing these data. Regulators are keen in seeing more M&S approaches because these can address questions in regulatory review and in any case provide a strong rational behind the proposed development and reduce uncertainty. The focus of regulators is indeed PhIII amongst others for practical reasons, but at the end the totality of the data is considered. If regulators bring earlier stages into spotlight, sponsors will be more committed to an efficient exploratory development.

The fourth topic discussed was **the modelling of toxicological data**. Mechanistic understanding of safety is not complete. However this should not preclude efforts to share data and develop toxicological mathematical models. Many of these data can be made available without sharing competitive information.

Finally the issue of **bias** was touched upon, bias in the selection of models to be reported, but also bias in the M&S exercise per se. This methodological problem is very difficult to resolve. Sometimes, however a trade-off should be accepted between minimising bias and improving precision for an experiment.

Day 2

Breakout sessions: Identifying advantages and challenges of using M&S to support decision making during drug development and in regulatory assessment, through case studies.

Full reports available separately.

Plenary Session: Debriefing from breakout sessions

BOS1

(Minutes of the plenary discussion. The discussion and the outcomes/conclusions of BOS1 are available in a separate full report).

Beatriz Silva Lima (Infarmed, CHMP) and Thomas Kerbusch (MSD/Merck) presented the outcomes from BOS1. Industry, regulators and academia were aligned in that M&S is a powerful tool for preclinical, FIM and early clinical development. There was a need identified for further development of mechanistic models focusing in pharmacodynamics and toxicity (whereas PK models are more established already).

Regulators felt that M&S is under-reported in the regulatory submissions and would like to get more exposed. Early discussion with regulators will help building confidence on the methods proposed and in the overall development. Even if at the stage of MAA the regulatory focus is in the clinical pivotal trials discussing early development with regulators will facilitate decisions at FIM, CTA, but also build to the level of evidence available at the MAA (coherency of development plan is a strong part of the evidence).

Industry would like to enhance dialog with the regulators at this early stage especially as they are using a wide range of model-based approaches and data sources nowadays with which the regulators have less experience. However there is some apprehension that regulators might put additional hurdles in this early exploratory development. Nonetheless the need for synergy was clearly acknowledged.

All parties agreed that this multi-way interaction would be beneficial for all stakeholders and predicted that M&S techniques will see an increased used in drug development and regulatory submissions. Also sharing data within industry in the pre-competitive space (non product specific) was considered important. All parties will be engaged in further discussions on how to implement M&S in drug development and regulatory assessment.

BOS2

(Minutes of the plenary discussion. The discussion and the outcomes/conclusions of BOS2 are available in a separate full report).

Leon Aarons (University of Manchester) presented the outcome from BOS2. BOS2 focused on two topics: 1) when and how M&S should be used and is accepted by the authorities for the dose regimen selection process and 2) when can the integration of data (e.g. across studies or clinical and in-vitro data) using M&S along with reasonable assumptions provide enough evidence for evaluation of efficacy/safety risks without the need for a separate study. There was common understanding that M&S is driven by and informs the underlying science. Therefore a requirement for the acceptance of modelling and simulation is consistency and evidence of the underlying science.

Regarding the first topic, there is a perception that scientific evidence is being restricted by the nature of the studies required by regulatory authorities. For example, in a dose ranging study which only involves pair wise comparisons, it may not be possible to elucidate the nature of the dose-response relationship. Modelling potentially can lead to greater precision in the detection of the signal from the background noise in clinical trials. Model bias and hypotheses are the main issues which have dissuaded some people from using a modelling approach.

On one hand the lack of predictable regulatory acceptance hinders the further implementation of M&S driven dose regimen selection approaches in the pharmaceutical industry. On the other hand, M&S scientists of companies might have to deal with scepticism regarding M&S approaches within their own organisation. Some decisions actually based on M&S may not end up in the Clinical Overview, a key document for regulatory assessment, thereby reducing the chance that the models are considered pivotal in the process of regulatory assessment.

With regard to the second topic, the participants were in general more comfortable using a modelling approach for interpolation rather than extrapolation. Confidence in extrapolation can be increased by the use of external data and prior information. An acknowledged advantage of M&S is the possibility to investigate situations that cannot be tested or should be avoided to be tested.

The approach to delay or replace TQT studies using the “totality of evidence” from preclinical and early clinical investigations was of high interest for all participants, however to convince the regulators completely a number of “totality of evidence” datasets need to be provided to them for thorough evaluation.

Key points for appropriate and efficient regulatory assessment of submitted M&S analyses are clear communication, and informing assessors adequately on the justification of the model, and on assumptions made by the modellers. Adequate validation, with an assessment of robustness and predictive performance of the model is a pre-requisite for regulatory acceptance.

There was agreement at three points that need to happen to advance the role of M&S in clinical pharmacology: a) Develop a guideline that endorses the use of M&S (but being not too restrictive to hinder this innovative field), or update relevant documents such as the dose regimen finding guideline b) To develop a framework for interaction between regulators and industry regarding M&S approaches (including how best data and the M&S analyses results can be shared) c) additional training for assessors to allow comprehensive evaluation of the approaches.

BOS3

(Minutes of the plenary discussion. The discussion and the outcomes/conclusions of BOS3 are available in a separate full report).

Lutz Harnisch (Pfizer) presented the outcome from BOS3. BOS3 attendees had reached a general agreement on the outcome presented.

The starting point for any extrapolation exercise was considered the feasibility of obtaining complete safety and efficacy data in the specific population. Very often (orphan drugs, paediatrics) complete evidence as generated from randomized controlled trials is not possible. It is then necessary to rely heavily on extrapolation and underlying assumptions.

It is important to objectively evaluate the assumptions/M&S, assess the likelihood and consequences of violation, and finally the weight of the assumption/M&S in the development program. Assumptions can be mitigated, violated or pertain as risk to the various stakeholders. Mechanistic models were pinpointed as a very useful tool in supporting extrapolation, since their inherent knowledge of the system reduces the likelihood of violation of their assumptions. A framework for linking extrapolation to the relaxation of significance levels in subgroup validation studies was proposed. This is based on the Skepticism Factor s, i.e. the “probability” that the treatment is not effective in the sub-population. In small populations we would have to accept that the evidence will be incomplete and risk mitigation measures such as adaptive designs and a progressive license pathway were discussed. In any case the models and assumptions supporting the extrapolation should be challenged with the new data. Data sharing is essential in order to fill in the knowledge gaps. The greatest gap currently exists in very young children.

BOS4

(Minutes of the plenary discussion. The discussion and the outcomes/conclusions of BOS4 are available in a separate full report).

Scott Marshall (Pfizer) presented the outcome from BOS4. The opinion that M&S was an important tool in improving R&D efficiency and decreasing late stage failure was shared by both groups. All parties agreed that the interaction between industry and EMA on M&S should be improved and take place ahead of the discussion of PhIII trials. Themes discussed were the use of M&S in optimising PhIII design (Theme1), the possibility of model based primary and key secondary analysis (Theme 2), the acceptability of using M&S to estimate risk benefit and finally the development of Regulatory guidance based on M&S analysis (Theme 3). There was a common understanding of how M&S could add value across the topics. The EMA supported these endeavors covered by Theme 1 and in general encouraged the integration of M&S activities into drug development plans, particularly where these approaches "fill gaps" between the planned studies and /or answer pertinent regulatory questions. The perception that dose finding is only the company's risk was agreed as being wrong; regulators have a clear role and responsibility in the selection of the best dose for PhIII. A longitudinal model-based test as primary inferential analysis (Theme 2) was recognised as having scientific merit and it was agreed that discussion on implementation should continue; including finding a way forward for simulation based type 1 error control, since this is crucial for bringing M&S innovation in confirmatory setting. All parties agreed that the hurdles required of model based PhIII data analysis should not exceed those for standard statistical testing. For pivotal trials aiming to demonstrate impact on disease progression, NLME modelling was considered to have an important role as key secondary analysis. It was agreed that M&S approaches can provide an important input into the Benefit-Risk assessment, providing data synthesis and "what if" scenario answers via simulation. The Theme 3 case-studies illustrated that this approach can lead to acceptance, by regulators, of an unstudied dose/ dose regimen. The circumstantial risk, underlying benefit, medical need and risk mitigation strategy were highlighted as being important in this decision. So it was considered difficult to give a general regulatory position on the acceptance of M&S as justification for an unstudied dose during or after the initial approval. The value of M&S in helping to add objectivity to design and optimization of the drug development path (particularly) for disease areas lacking previous pharmaceutical treatments was also highlighted.

In summary, this breakout session captured the current practice in the application of M&S in the confirmatory stage of development, through case studies which have either been submitted to European regulators or would be considered to be high impact within the new EMA regulatory framework. There was alignment on the need for clear technical requirements for application in this area, and agreement between the EMA and EFPIA on the action plan to address issues raised including the need for development of a common best practice for M&S.

Plenary Session: M&S good practices and next steps

Spiros Vamvakas (EMA), outlined the available procedures to early **approach the Agency** for regulatory feedback on drug development plans, also applicable to M&S. The Innovative Task Force, the Scientific Advice and the Qualification of Novel Methodologies were presented. The sponsors are welcome to contact directly the EMA staff, Spiros Vamvakas or Efthymios Manolis on how to best engage the Agency in discussions.

Don Stanski (Novartis), summarised the main points from the workshop. The openness of interaction and the focus to key regulatory and drug development issues were considered unprecedented and unique to this workshop. BOS topics were extremely relevant to the challenges that industry and regulators currently face and will need to be further discussed also in separate workshops.

Systems biology/pharmacology interface is expected to grow massively in the near future. Continuum of modelling throughout development is very important. Getting the dose right is fundamental and is an M&S exercise. There are great opportunities in extrapolation across populations, however further research and dialog is needed. The bottom line is that we must improve efficiency of drug development and cut failure rates and that M&S can help in this respect.

The major learning from FDA experience with pharmacometrics is that transparency and communication are essential. Transparency refers to the FDA indicating clearly the rational for agency modelling efforts on industry submissions which will impact regulatory decision making. Communication refers to the agency sharing modelling results with industry with adequate time to allow understanding of regulatory modelling efforts and the regulatory conclusions drawn from the agency modelling. Industry experience with the FDA has been that transparency is not always clear and the communication occurs late in the process. EMA could use the FDA experience to decide on the way forward regarding M&S. Different agencies follow different approaches when assessing M&S, however ideally assessment should be standardized across agencies.

The future of M&S looks positive. It might take long for M&S approaches to infiltrate the different groups in big regulatory organisations and pharma. The step forward should be to engage people outside the workshop, who might be more skeptical.

Rob Hemmings, focused on basic methodological issues that need to be addressed in M&S. The regulatory standards will depend on the impact of the M&S exercise but will not exceed the current regulatory standards for statistical testing. In any case high standards will help build acceptability of modelling. Fundamental to the M&S exercise is the development and challenging of assumptions, also issues like selection bias and conflict of interest bias require further reflection. Communication of M&S results and methods across different disciplines is crucial. The need to develop models based on sound scientific principles was stressed. A big question mark when assessing M&S methodology from a regulatory perspective is the degree and the necessity for pre-specification. Regulatory guidance on M&S would be useful but needs further discussion. Finally there is a need and opportunity to build experience/confidence in M&S and trust between involved parties along the way.

Tomas Salmonson (CHMP vice Chair, MPA), reiterated that this is a unique meeting. All stakeholders agreed on the value of M&S. It was stressed that rational dose development is not only risk to the industry but to the regulators, patients and payers. M&S has a greater role to play in this respect. It was noted that also within industry there are problems deploying M&S. The European regulatory system is very diverse regarding M&S competence. Also the experience of regulators is relatively limited. The most imminent challenge is how to move forward the outcomes of this workshop. Scientific advice (European and National) was considered a good forum for discussion on M&S. Also at the stage of MAA M&S could provide answers to specific questions and regulators should encourage such analysis. The need for new guidance and/or updating already existing guidance documents will be considered. A way forward is to establish a group of academic experts (Scientific Advisory Group) that can be consulted by CHMP on M&S issues. Another pragmatic approach would be to highlight the M&S exercises in the MAA submissions and to appoint rapporteurships to regulatory authorities with competence in M&S.

This would put pressure on the regulatory system to raise competence. International collaboration is important to address M&S issues. All the areas covered in the break out session were considered of major importance. In particular the extrapolation from non EU countries to EU setting was stressed out as a key issue.

Discussion

Following the presentations the discussion focused on the workshop deliverables. Both industry and regulators are keen to keep the momentum and wish to prioritise items for further discussion and implementation. Of major importance was considered updating the regulatory requirements for dose finding. Discussion on dose response and the role of M&S could be initiated in the context of a qualification procedure, ultimately, if positive, leading to updating the guidance documents. Also an additional workshop on dose finding was considered necessary.

Another action item discussed was the development of M&S good practices guideline. The companies have already their own internal documents and these could be shared to help drafting this guideline. Also PSI with EFSPI are currently working on M&S good practices and efforts could be streamlined across different disciplines. In any case when developing guidelines for M&S a multidisciplinary team of experts was considered necessary. It was agreed that the need and scope for a new guidance will need to get balanced against the risk of putting additional hurdles to drug development.

Sharing data and concepts was considered crucial in the precompetitive space where M&S resides. Also many consortia are currently working on M&S and participation of regulators in this work is important. Involvement of regulators, through e.g. scientific advice is strongly correlated with regulatory acceptance and industry is encouraged to follow this route.

The need for training both regulators but also drug developers, starting from University level was reiterated. So was the need to keep high standards and build trust.

Rob Hemmings, closed the workshop, with a summary of the discussions, focusing on the undisputable value and need for further integrating M&S in drug development and regulatory assessment. He expressed the commitment of all parties to keep the momentum and continue the dialogue leading to tangible deliverables.