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Product Development Scientific Support Department

Report from Dose Finding Workshop

European Medicines Agency, London, 04 – 05 December 2014

Executive summary

The dose finding workshop was held in the EMA headquarters in London 4-5 Dec 2014

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2014/06/event_detail_000993.jsp&mid=WC0b01ac058004d5c3) and was attended by 150 delegates from Industry, Academia and Regulatory bodies, representing different scientific disciplines, i.e. clinical pharmacology, modelling, statistics, clinical therapeutics.

The Workshop follows key challenges and actions that were identified in the 2011 EMA-EFPIA workshop on Modelling and Simulation (M&S)

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/07/event_detail_000440.jsp&mid=WC0b01ac058004d5c3). The misperception that dose-response (D-R) or dose/exposure/response (D-E-R) characterisation and the subsequent dose regimen selection are determined solely at the company's risk was identified as both a misconception and a bottleneck for MID3 (model informed drug discovery and development). An additional outcome was the need to debate an update on dose ranging/finding regulatory guidance.

Regulatory experience, both FDA and EMA, shows that phase 2 is often abbreviated and simplified in order to move as quickly as possible to pivotal trials (and also the hope to have the simplified phase 2 study serve as one of the pivotal studies), the selection of dose is frequently empirical and rarely scientifically sound, and the D-E-R is poorly characterised due to the limited dose range tested in phase 2. The reasons for reduced standards in phase 2 lies in the fact that drug development is costly/competitive and accelerated access to the market is a considerable incentive for sponsors. Although it is acknowledged that in some cases the need to provide rapid access to the patient outweighs the need to optimise the dose (i.e. breakthrough treatments for cancer), regulators and industry alike agree that this strategy at large could prove very risky and is short sighted. Poor dose selection will in turn often lead to failed phase 3 trials, delayed/denials of regulatory submissions and/or changes in doses post-approval (Sacks et al, JAMA. 2014;311:378-384, Cross et al Pharmacoepidemiology and Drug Safety 2002; 11: 439–446), additional post-marketing commitments and further requirements for development in other age, ethnic groups, all of which ultimately eliminate/invert any initial gains. Taking the above into account, poor dose selection is one of the main causes for the soaring cost of drug development. Patients and prescribers also share the risk of poor

dose selection, with public health risk, as shown in the relatively high percentage of post marketing dose changes (data available from both EMA and FDA and presented in the workshop).

Given this background, the workshop re-emphasised the importance of rigorous, scientific dose finding (relying on model-based estimation, rather than hypothesis testing via pairwise comparisons) and the characterisation of D-E-R relationship for successful drug development, approval, labelling and beyond i.e. lifecycle management of the medicinal products.

Regulators clearly identify dose selection as a “shared risk”. In the past dose selection was erroneously referred to as “the sponsor’s risk”. The notion was reinforced by the fact that scientifically rigorous and optimal dose selection is not a requirement by US or EU law. Nevertheless, the wording is unfortunate and should be taken to mean that a sub-standard approach to dose finding and understanding D-E-R represents a risk to the development programme.

During the workshop many different approaches to dose finding were debated and there was wide agreement that all have their merit depending of the particular clinical scenario. Mathematical, statistical and pharmacological methodologies to characterise dose/response are scientifically well developed and available for application. Modelling and simulation and adaptive designs can provide valuable solutions. The need to plan dose ranging studies with more doses over a wide range was emphasised, so was the importance to design these studies to estimate dose-response characteristics. Traditional statistical pairwise comparisons to support dose selection by testing for statistically significant differences between the groups are not a regulatory requirement (indeed, model-based dose estimation approaches are preferable, as discussed further in the text). Characterising dose-exposure response using longitudinal time vs. response and non-linear mixed effects model can be extremely powerful and is encouraged. The characterisation of dose-exposure response relationship is much more valued, not only as a means to select the dose(s) for phase 3, but also as a way to strengthen proof of concept and support licensure decisions and post approval requirements. Especially for children, elderly, different ethnic groups, characterising D-E-R across populations is the starting point for any discussions on the need for additional data at planning and licensure phase.

The ICH E4 acknowledges the importance of dose-response characterisation and provides still valid recommendations. However evidently it has not had the desired impact over the past 20 years probably due to insufficient specific guidance on dose-response requirements and methods. The need to update the ICH E4 or supplement with more specific guidance can be discussed as an important step forward.

The incentives for dose finding and D-E-R characterisation were also discussed. Industry proposed a single pivotal trial and confirmatory evidence from an appropriately designed/analysed dose-response trial as a basis for regulatory approval. This idea is not new (Carl C. Peck et al Hypothesis: A single clinical trial plus causal evidence of effectiveness is sufficient for drug approval, *Clinical Pharmacology & Therapeutics* Volume 73, Issue 6, pages 481–490, June 2003), does not contradict the EMA regulatory framework and will be plausible in some therapeutic scenarios. The assessment of benefit/risk by health authorities is based on the totality of data. In this respect proper dose finding and demonstration of dose-exposure-response (D-E-R) relationship can provide evidence of activity and indeed efficacy and can be used to mitigate uncertainties and could support approval based on one pivotal trial (EMA points to consider on one pivotal trial). Regardless of the decision to pursue the above approach, in which case early dialogue with regulators is recommended, important industry incentives for investing in D-E-R characterisation are, the resulting optimal pharmacotherapy, and the gains in drug development efficiency.

Table 1 and Table 2 below summarise the key learnings and next steps respectively from this workshop.

Table 1 Key learnings
Dose selection is a shared risk
D-E-R characterisation is a key component of the development and evaluation of medicinal products. Especially for children, elderly and ethnic groups this is the mainstay of drug development. Failure to reproduce this information at the stage of MAA, misses the opportunity to mitigate regulatory uncertainties and may result in denial, delays in approval, and additional regulatory requirements in terms of post approval commitments
Traditional statistical pairwise comparisons in phase 2 trials to support dose selection, by testing for statistically significant differences between the groups are not a regulatory requirement, and are suboptimal in terms of dose selection
Dose ranging studies should be designed for estimating dose response characteristics. As many as 4-7 active doses across a >10-fold range (e.g. 0.1 - 1.0 of the maximum tolerated dose-MTD) might be targeted adapting to the reality of the specific drug and disease state
Mathematical, statistical and pharmacological methodologies to characterise D-E-R and optimal dose selection are scientifically well developed, available for application and welcomed by regulators. These should be tailored to the specific development needs

Table 2 Next Steps
Establish a post-workshop expert group with representation from regulatory bodies, industry and academia to progress areas of discussions and actions identified. This group will work towards emphasising the importance and promoting good practices for dose selection and D-E-R characterisation. Two publications, one addressing methodologists and one addressing late phase decision makers, will be the first outcomes of this group.
In addition it is envisaged that discussions will continue at product level, i.e. scientific advice, PIP submissions, at MAA, or methodology level, i.e. qualification procedures.
Update of the CHMP assessment report templates to reinforce the importance and facilitate the evaluation of dose-exposure-response relationships at the stage of MAA, to support B/R decisions and to inform the Risk Management Plan (RMP).
Debate the need to create/update a regulatory guidance on dose finding.
Follow up discussions to involve late phase decision makers from industry.

Session 1

Efthymios Manolis and Rob Hemmings highlighted that the current European regulatory framework does not request pairwise comparisons, on the contrary ICH E4 demands dose response characterisation as integral part of drug development. In addition European regulators, in particular through SAWP and MSWG, are very much involved and interested in dose selection since this is a shared risk between companies, regulators, prescribers and patients. Regulators do not have the mandate to refuse a marketing authorisation solely on the grounds of poor dose selection or lack of understanding of D-E-R. However getting the dose right and characterising dose exposure response, maximise the chances for success in phase 3 and provide evidence of a good development programme. In addition sound D-E-R relationships can serve as a basis to address limitations and uncertainties at the stage of MAA, promote confidence during regulatory assessment of data, may result in more informative SmPC, and reduce the burden of post approval studies or of studies in other populations (e.g. paediatric, geriatric). Given the return on investment for “getting it right”, it is surprising that poor dose selection and partial understanding of dose exposure response are still abundant.

Richard Lalonde and Donald Stanski highlighted that poor dose selection is still a leading reason for delay and denial of FDA approval based on a recent review of NDA approvals between 2000-2012. The cost of failure due to inadequate dose selection strategy is reflected in the soaring costs of drug development. Beyond approval, changes in dosage postmarketing further point to the need to strengthen dose selection premarketing. Common problems with dose ranging studies are that they often test only few doses within a narrow range with the objective to power for pairwise comparisons. On the contrary these studies should be designed for estimating dose response characteristics with a wider dose number and range >10-fold range (e.g. 0.1 - 1.0 of the maximum tolerated dose-MTD). The dose finding strategy for the anticoagulants field was presented to exemplify the challenges but also the tools available. In this example clinical trial simulations (CTS) facilitated the evaluation of many possible designs for phase 2b. A 6-arm randomized, parallel group study with adaptive dose range based on interim dose decision analyses of VTE and MB was chosen resulting in gains in efficiency. The presentation concluded with a proposal to consider a properly designed phase 2b dose-response trial as confirmatory evidence along with 1 pivotal phase 3 trial for primary evidence of efficacy, and emphasised the need for a clear regulatory guidance/statement from EMA, FDA for phase 2b dose-ranging studies.

Vikram Sinha (co-contributors, Dionne Price and Yaning Wang) from the FDA stressed that identifying the “right” dose is and should be the key goal of every clinical development program as too high a dose can result in unacceptable toxicity and too low a dose decreases chance of showing efficacy. The overarching goal is integrated summaries of safety and effectiveness that provide evidence to support the dosing regimen and dose adjustments in specific subsets. In early development, in addition to proof-of-concept, dose selection for late stage development is an important objective. A brief outline of two guidance documents that shape current guidance was provided. The first, ICH E-4, strongly encourages assessment of DR in every stage of development and to know the shape and location of DR for favourable and unfavourable effects. The second, the FDA exposure response (E-R) guidance speaks to the importance of integrating E-R relationship assessment in all phases of drug development and the selection of appropriate exposure metric. In certain situations, the over-estimation of the steepness in C-R relationship is observed when disease severity is confounded with efficacy. A key goal is to strive towards efficient, informative trial designs and analysis approaches tailored for specific therapeutic areas. In many therapeutic areas, 2-3 doses are routinely studied and in some dose optimization is conducted post approval via post marketing studies.

Session 2

The body of science to establish dose vs. response and select a dose for phase 3 is well established and rich, many excellent examples and methodologies were presented. The presentations in the methodology session were not intended to provide a thorough comparison of different approaches, but rather to describe the methods individually and propose some general guiding principles which in no way are regulatory binding. A critical review of the methods available for the well informed drug developer and regulator is provided based largely on the presenters' view and the review presented by Dr Jose Pinheiro.

Key learnings from this session are that a single method does not fit all purposes and the dose finding strategy should be tailored to the specific development needs. Regulators see the merits of the different methods and are open to discuss.

Pairwise comparison

This method was criticised by the workshop participants, including regulators. Nevertheless, this is still the most widely used approach in phase 2 studies. It can be used with any type of endpoint (e.g., continuous, binary, etc.), typically focused on one time point (e.g., change from baseline at end of study). The main motivation comes from the simplicity in designing, analysis and communicating the results and the hope that could be used as one of the pivotal trials if successful resulting in saving resources. On the negative side there is a need to control multiplicity in pairwise comparisons to ensure "confirmatory grade" control of Type I error and little incentive to consider more than 2 or 3 active doses (increases price of multiplicity adjustment). Dose response (or exposure response) estimation is a secondary objective; the number and range of doses are typically inadequate for D-R estimation.

Pharmacometrics (PMX), Modelling and simulation (M&S) (cf. Mick Looby and Charles Benson presentations)

PMX are highly encouraged and widely used. Unfortunately phase 2 studies are usually not optimised for this kind of analysis. PMX methods help elucidate drug action and covariate effects and can leverage data/information across studies. PMX can be used to inform decisions on development strategy (e.g. study design) and therapeutic use (e.g. dose, regimen and population) through simulation of specific scenarios. PMX go beyond dose-response by investigating also the response signal within its pharmacological context (i.e. regimen, non-linearity and time dependency) and the individual patient as the unit of observation. Response is usually longitudinal, however D-R assessment is usually cross-sectional. Pharmacostatistical PMX model based methods can account for longitudinal response across a wide range of different doses and regimens. The price to pay for more informative phase 2 designs and analysis based on PMX is the need to consider more complex and expensive designs. In addition the reliance on model based analysis methods and heavy assumptions which may be difficult to verify could potentially limit the confirmatory evidence from phase 2. In any case PMX should be routinely considered in support of dose selection together with more traditional D-R analysis, already at planning phase.

The SARM I/Tadalafil example presented by Charles Benson highlights the efficiency gains achieved with PMX in a fixed dose combination scenario.

Regulators (cf. Terry Shepard and Sofia Friberg Hietala presentation) highlighted the importance of PMX methods. In particular to identify subpopulations at risk, anticipate the impact of changing formulations and regimen, in support to extrapolation to other populations (DDI, RI, HI, paediatric,

elderly) and finally to mitigate uncertainty in the B:R decisions. However the E-R analyses as presented in MAA are often scarce and not as informative.

MCP-Mod (cf. Bjoern Bornkamp presentation)

MCP-Mod was recently qualified by the EMA as an efficient statistical methodology for model-based design and analysis of phase 2 dose finding studies under model uncertainty. It combines multiple comparisons and modelling for model-based dose selection (and D-R estimation) under model uncertainty. It can be used to test D-R signal (MCP step) and D-R estimation (Mod step) via model selection or model averaging. MCP-Mod is mainly intended for phase 2, but extension is available for confirmatory studies (e.g., adaptive phase 2/3). The focus of the method is on population dose-response (cross-sectional), but can also leverage longitudinal data. MCP-Mod can handle most common types of responses: continuous, binary, count, time-to-event, etc. In terms of design requirements, at minimum there should be 2 active doses (for the MCP-step), 3 active doses (Mod step), however the recommendation is for 4-7 active doses, >10-fold dose range for phase 2. The adaptive version which was illustrated in the talk requires timely availability of endpoint relative to recruitment speed, to allow adaptations to have an impact.

Model Averaging (c.f. Andrew Hooker presentation)

Similarly to MCP-Mod, the method accounts for model uncertainty by using a set of candidate D-R model families. No model selection is used: all candidate models are utilized, with weights accounting for goodness of fit (AIC). The focus of the method is on model-based dose selection in Phase 2 compared to MCP-Mod there is not testing of D-R signal. In principle, it can be used with any type of endpoint and taking into account longitudinal data although the focus is on population D-R. Similarly to MCP-Mod 4-7 active doses and a dose range > 10 fold are needed to adequately estimate D-R.

From a regulatory perspective (cf. Norbert Benda presentation) both MCP-Mod and Model averaging methods have their merits. In planning phase the requirement for a wide range and number of doses is encouraged. Optimal designs and adaptations can be considered. At analysis phase, regression methods are favoured to characterise D-R and select a dose for phase 3. Multiplicity adjustment, and type I error control are not required for a phase 2 study.

Emax Dose Response Model (cf. Neal Thomas presentation)

Based on 2 meta-analyses of dose ranging studies, most of the dose response curves were well-represented by a 3-parameter hyperbolic dose response curve. A more general 4-parameter sigmoid Emax was sufficient to represent all of the observed dose response curves, except one which had a non-monotone shape. Narrow dosing ranges (e.g., <10) represented by 3 or fewer active doses were common. These designs were typically inadequate to determine dose response. Distributions for the sigmoidal 'Hill' parameter and normalized ED50 parameters were derived from the meta-analyses. Combined with compound-specific information about placebo and maximum drug response derived from historical studies, pre-clinical, and early-stage clinical studies, empirically-based prior distributions can be supplied for all model parameters at the beginning of clinical dose finding studies. The prior distributions can be used in both design and analysis of dose finding studies. The reliance on a single model family assumption, which most likely holds true but might not in some rare instances, should be considered at the planning and analysis stages and weighed against alternative strategies that can include multiple model families to account for model uncertainty (cf. David Wright presentation). When weighing the use of methods based on multiple model families that may perform better in rare instances, it is important to understand that these methods depending on the scenario

may also produce invalid inferences. As a safeguard it is always recommended to factor the understanding of the pharmacology and the disease in the dose finding strategy. In this respect PMX methods can play an important role.

Adaptive dose ranging

Adaptive dose-finding methods allow one to update the doses (and/or dose allocation) used in the trial at interim analysis time-points. This prevents situations where the initial doses used do not cover the range of interest on the dose-response curve. As a trade-off, depending on specifics of the studied endpoint and the disease, adaptive dose-finding studies can pose a larger logistical effort which needs to be balanced against the gains of an adaptive design.

Bayesian adaptive dose ranging (c.f. Scott Berry presentation)

The specific method was discussed in the context of a phase 2/3 seamless trial for vasopressor dependent septic shock. The phase 2 dose-finding stage of the trial uses a response-adaptively randomized allocation over 4 active arms and a placebo. The dose-finding stage is flexible with a minimum of 300 and a maximum of 800 patients. A prospectively designed algorithm has been created for employing response adaptive randomization to the best performing arm using a Bayesian inverted-U shaped dose-response model. The dose-response modelling also drives the predictive probability of success in the phase 3 stage of the trial to dictate the decision to graduate from the dose-finding to the confirmatory second stage of the trial.

The design allows appropriate sample size to adequately explore the dose-range, using as many as 800 patients and as few as 300, if the dose-finding stage is successful. The trial allows these dose-finding patients to be included in the final confirmatory analysis, thus allowing exploration of the dose-response, while also allowing these subjects to contribute to the confirmatory analysis. The primary analysis is frequentist, with pooled data from all stages.

A point of criticism of this method is that although the focus is on dose selection to maximize probability of trial success, less emphasis is given to D-R estimation. A prerequisite for applying this method is the quick availability of primary endpoint/biomarker to allow for frequent adaptations.

From a regulatory perspective (cf. Martin Posch presentation) the proposed adaptive 2/3 design can be efficient to demonstrate efficacy of the test drug if robust type I error control can be demonstrated. However, confirmatory evidence for the finally proposed dose regimen is an open issue. EMA reflection paper on adaptive designs recommends justifying the use of adaptive designs by comparison of the operating characteristics to alternative designs, (e.g., less interim analysis and adaptive features). Simulation studies are a very efficient tool to investigate different design options and understand their properties in various scenarios. Robust demonstration of type I error rate control via simulation remains controversial.

Systems Pharmacology (c.f. Piet Van de Graaf presentation)

This method was not discussed in this session but is provided here for completion of information. Quantitative Systems Pharmacology (QSP) has been positioned mainly to contribute to target selection, validation and authorisation. However, there is also a role in dose finding. Depending on uncertainty of dose prediction and the quantitative understanding of the mechanism of action, the use of QSP can provide valuable solutions in the dose selection problem. For example when there are sound/established methods for dose selection QSP is of little added value for the specific dose question, although one can agree that the scope of QSP goes beyond a specific drug development and

expands to a more thorough understanding of the drug action and the system. In this respect QSP should always be encouraged. In case that there is a high uncertainty in the prediction of therapeutic doses and there is a good understanding of the system, QSP can provide valuable solutions. So is the case when the need is high but little is known about the system, but arguably the challenge is much higher.

The downside is that QSP platforms are difficult to develop and are resource and data intensive i.e. need for systems data coming from in vitro, preclinical in vivo and clinical experiments usually across several developments. These models are not made for confirmatory testing. However the replication of evidence across different platforms and experiments, together with the mechanistic understanding of the drug action and the system in general enable a robust assessment of the underlying assumptions and can potentially be used to support regulatory submissions.

Session 3 – Gap analysis by therapeutic area

As with session 2, key learnings from this session are that a single method does not fit all purposes and the dose finding strategy should be tailored to the specific development needs. Regulators see the merits of the different methods and are open to discuss.

CNS

Prof Luca Pani chaired and opened the session. The strategy for development of a new second generation antipsychotic highlights the challenges with dose finding/selection in CNS. The ideal molecule should have optimal pharmacological properties in blocking the dopamine receptors (i.e. selective, less potent, partially agonist), block receptors other than those for dopamine and block receptors with a differential brain regional distribution. In addition it should have optimal PK properties and the local concentrations at the site of action should be fine-tuned to balance positive and negative pharmacological effects due to multiple receptors' binding. As a result of the complex PK/PD profile of these products individual dose adjustments are proposed which are based on the severity of the symptoms and the response. In addition real life doses differ substantially from labelled doses, i.e. Risperidone (original dosing of 16 mg reduced to 2-4 mg), Olanzapine (original dosing of 10 mg increased to >30 mg), Quetiapine (original dosing of 75-300 mg increased to > 800 mg), Ziprasidone (average dose still often < 80 mg; > 50% of use is below 120 mg; while dose needs to be 120/160 mg for optimal efficacy), Aripiprazole (therapeutic range 10-30 mg; may consider 5 mg as starting dose in co-administration with potent inhibitors of CYP3A4 & CYP2D6; in slow cross-titration with other antipsychotics and in sensitive population). This means that the B:R balance of the “real” doses has never been subject to regulatory scrutiny. Dosing remains a critical issue in optimizing each agent but it should be studied early in the course of development taking into account the pathophysiology and the pharmacology.

Dr Mona Alameddine presented on how M&S can help optimise the selection of doses for phase 2a. The approach is summarised in the following steps:

1. Population Pharmacokinetic model using phase 1 data
2. PK/PD model for target occupancy using PET data
3. Simulate Target Occupancy time profiles at steady-state by dose
4. Compute the % of measurements where Target Occupancy was within given ranges over the dosing interval

5. Determine the optimal number of doses that should be tested in phase 2a to characterize the TO – Efficacy relationship

This approach provides valuable support to decide on the number and range of doses for phase 2a and paves the way to characterising D-E-R and optimal dose selection.

Prof Piet Van Der Graaf focused on **systems pharmacology**. Clearly in CNS where receptor occupancy and complex pharmacological interactions through different receptors are key factors for balancing efficacy and safety, systems pharmacology, by leveraging in vitro, preclinical and clinical/literature data, can contribute to the understanding of the complex networks and propose doses with predicted optimal characteristics.

Infectious Diseases

Antibiotics

The dose selection of ceftazidime (CAZ)-avibactam (AVI) (β -lactam / β -lactamase inhibitor combination), developed for the treatment of serious Gram-negative bacterial infections was presented by Shampa Das. This example highlighted generally accepted principles for the selection of antibiotic doses. Furthermore, it presented the dose selection for a β -lactamase inhibitor, a subject that is presently not covered by European regulatory guidance and on which there is little modern regulatory experience.

In the case of CAZ, like for other beta-lactams, the PK/PD index found to be most predictive of efficacy in vitro and in preclinical models was $fT > MIC$. While the presence of relevant bacterial β -lactamases increases MIC for CAZ to the point where in vivo efficacy is abrogated, the PD aim for AVI is to convert infecting bacteria to a β -lactamase-negative phenotype; i.e. to restore the MIC of CAZ. Dynamic hollow fibre models, which control drug concentration over time, were used to define the lowest concentration (CT) of AVI needed to protect CAZ from hydrolysis by relevant target β -lactamases, as indicated by the absence of bacterial regrowth. Further in vitro and animal model evidence indicated that the time that AVI was required to be maintained above the thus identified CT was matched to time CAZ must be maintained above the MIC. It was concluded that the efficacy of CAZ-AVI is driven by simultaneously achieving 50% $fT > CAZ-AVI$ MIC for CAZ and 50% $fT > CT$ for AVI. Using probability of target attainment analysis (PTA) based on population PK modelling from phase 1 and 2 data, a dose was selected which was predicted to simultaneously achieve the CAZ and AVI exposure targets in greater than 90% of patients. The relevant model has been further updated as patients PK data become available to reflect the PK in the patient population and to adjust the dose/regimen.

In antibiotic drug development, where the targets are well known and the preclinical models are predictive of clinical outcome, dose ranging studies may not be needed. In a case like that of CAZ-AVI, confirmation of the doses and exposures associated with maximal or near-maximal efficacy may come from positive phase 3 data, provided that infections with relevant β -lactamase producing bacteria are appropriately represented.

The presentation by Lena Friberg challenged the traditional PK/PD indices for antibiotics and emphasised the importance of mechanism based PK/PD models for selection of dosing regimens. Typically it is assumed that there is one 'true' PK/PD index and target magnitude, but they are sensitive to: 1) PK in the population, 2) MIC value, 3) Resistance development, 4) Study Design used to suggest the 'best' PK/PD index. Mechanism-based PK/PD-models could be used to improve design of animal experiments and limit the use of animals, better understand the time course of drug effects, explore a range of dosing scenarios and combinations and predict the time course for new mutants with limited data. It was emphasised that the mechanism-based PK/PD models developed from in vitro

data can earlier accurately predict suggested PK/PD indices defined from in vivo information, and in addition, the models can be a supporting tool to better tailor the dosing regimens to patient populations with different half-lives. These models could provide added value when used together with the traditional PK/PD approach.

Antivirals

Filip Josephson presented some basic principles for dose finding in antivirals. A general scheme evolved within the field of antiretrovirals that has subsequently been successfully applied for hepatitis C virus (HCV). As a starting point the (protein binding adjusted) EC50 for wild-type virus and drug pressure emergent viral variants (escape mutants) is determined in relevant in vitro expression system (covering, e.g., viral genotype/subtype diversity). Contrary to the case for antibiotics, animal models have had no role for the determination of PK/PD relation in HIV and HCV therapeutics. However, they have been used to investigate target compartment exposure in relation to plasma exposure.

A PK target (generally C_{trough} defined as some multiple of EC50) is determined, taking EC50 of common escape mutants into account. The initial dose range has then been selected based on HV dose/exposure relation and the EC50-based PD target. These doses have subsequently been tested in short term monotherapy in patients with viremia. The selection of dose(s) for combination therapy studies has been based on efficacy against wild-type virus (dominant circulating strain), inhibition of treatment emergent resistant variants and prevention of on-treatment viral rebound. Subsequent dose ranging in patients, in combination with other agents, has aimed at finding dose regimens yielding maximal viral suppression in the relevant drug combination, as well as prevention of virological breakthrough at an acceptable safety profile. Usually, but not always, a single dose has been tested in phase 3 trials, which sometimes compare different treatment strategies with the same drug (e.g., combinations, regimens). PK/PD modelling, which benefits from very good surrogate markers (i.e. viral load), is generally used to support decision-making along the way. This general scheme for antiviral dose selection may be adapted as appropriate for other viral diseases, e.g., in case predictive animal models are available, or if viral load is better quantified in a different matrix than plasma.

Oncology

1. Identification of the maximum tolerated dose (MTD) is still the most commonly used method to identify the recommended phase II dose (RP2D) for oncology products. There is, however, a need to reconsider the assessment of MTD for some medicinal products where continuous dosing is the foreseen schedule. This is demonstrated in the example below (cf. Frans Opdam presentation).

Cabozantinib: This is a multi-targeted TKI and a conventional 3+3 design was used to identify MTD. No case of dose limiting toxicity on the highest dose tested was identified among 6 patients during cycle 1 (28 days), but during the study altogether 23 patients out of 35 underwent dose reductions due to events such as diarrhea, fatigue, rash etc. The need for dose reduction in a high percentage of patients was confirmed in the phase III trial (79%).

Despite absence of DLT conventionally defined by grade 3 and 4 events, there was a need to for dose reductions in a very high percentage of patients in phase III. This illustrates that also events of lower grade might become of importance and that need for dose reductions also after the first cycle should be taken into account.

Provided that dose escalation in the absence of tolerability concerns would be possible to implement in confirmatory studies and in clinical practice a lower starting dose might be more appropriate, but this has been shown to be problematic.

2. In cases where differential target sensitivity between normal tissue and tumour tissue is foreseen, it is of importance to optimize the dose and exposure so that high degree of tumour target

saturation is achieved with only minor target inhibition in normal tissue. This is demonstrated in the example below (cf. James Yates presentation).

AZD9291: EGFR inhibitor selective for sensitizing including T790M mutations. Aim is not to take MTD forward, rather the biologically effective dose with good safety profile. PK/PD modelling and translational research is important to define the optimal dose regimen in human.

3. For products developed for the targeting of e.g. normal cytokines and growth factors, adverse reactions related to target inhibition are unavoidable. Due to the selectivity of some products, e.g. MoAbs these are also the only side effects of interest besides infusion-related reactions. In principle the need is thus to identify a sufficiently high dose to achieve target saturation in a high enough proportion of patients. This is demonstrated in the example below (cf. Kevin Smart presentation).

MabCSF-1R: Mab against CSF-1R. Selective agent. Similar to the AZ compound, dose finding is not limited by tolerability/toxicity, therefore take biologically effective dose with good safety profile forward. PK/PD modelling is helpful in defining the optimal dose regimen in human.

Robust identification of MTD is important in oncology. Further consideration should be given to alternative methods such as Bayesian model based methods. This coupled with PK/PD modelling to identify biologically effective dose from pre-clinical and emerging clinical data would allow the therapeutic index to be optimised in early clinical development.

Cardiovascular

Development of novel oral anticoagulants is very challenging in terms of dose selection. The target dose should be based on a fine balance between the positive and negative effects of the principal pharmacological action of the drug. Clinical events of interest are relatively infrequent, 2-3%, so large studies are needed. Studies are active-controlled, so differences being sought are only a small part of overall effect (cf. Christophe Gaudin presentation). In addition, there is the confusion of different types of strokes; thromboembolic and haemorrhagic. These are usually counted together, but are affected differentially by anticoagulants. A higher dose of anticoagulant should lower TE strokes and might raise haemorrhagic stroke rate. Dose response may be very steep at low end of dosing for TE stroke (as it is for warfarin). Past developments examined only on one or two different doses, and focused on bleeding to select a dose, which is more common than strokes, but this approach may be insufficient to select the right dose for achieving optimal efficacy.

At the end of phase 2 there are still many uncertainties in terms of efficacy, i.e. insufficient data on MACE, stroke/SEE all-cause/CV mortality, thromboembolism, and safety i.e. bleeding and unexpected adverse events. Surrogate endpoints are not very well correlated with clinical outcome. Phase 2 studies are underpowered to collect clinical outcomes and there are no good surrogate markers for long term efficacy and safety. As a result the decision for dose selection in phase 3 is an informed guess based on the totality of PK/PD and clinical data, compliance with the explored dose regimes and probably sometimes also influenced by marketing considerations. Clearly the better the understanding of dose-exposure-response relationship both in terms of efficacy and safety the highest the chances to select an optimal dose regimen. Thereafter phase 2 studies should be designed with multiple dose arms and with a wide range of doses; selected based on sound PK/PD and modelling & simulation. In addition adaptive dose ranging designs could be utilized with efficiency gains (cf. Richard Lalonde opening presentation). Depending on the uncertainties, TDM could be introduced in phase 3 to balance Benefit and Risks (cf. Robert Temple presentation), or/and more than one dose in an adaptive (or not) design could be used.

Immunology

Cf. presentations by T Dumortier, M Looby, Yaning Wang Lisbeth Barkholt, Flora Musuamba Tshinanu

Immunomodulator drug development currently faces several challenges including: (1) large variability in the pharmacokinetic and pharmacodynamics of drugs (candidates); (2) narrow therapeutic indexes; (3) need for concentration-guided dosing; (4) need for combination therapy; (5) practical and/or ethical issues not permitting use of a placebo arm, etc. Traditional methods are therefore not always suitable to support dose finding and/or selection for this class of drugs. Quantitative pharmacology methods constitute an alternative and have been employed throughout the drug development stages of immunosuppressants, to select rational dosing and optimize therapy.

Use of pharmacometrics has allowed addressing different questions such as: (1) the choice of safe and effective dose for first-time-in-man clinical studies, (2) the selection of rational target therapeutic concentration and optimal initial dose for late-phase clinical trials, (3) the identification of the optimal therapeutic drug monitoring strategy for managing patients and (4) the establishment of add-value of new combination therapies. An interesting example of successful use of pharmacometric methods while traditional approaches have failed is the FDA approval of the combination of everolimus with low dose of tacrolimus to reduce the renal toxicity of standard tacrolimus for prevention of rejection in liver transplantation while maintaining the efficacy.

However, given the extensive research undertaken during the past decades aiming to understand the pathways and the determinants of immune response after transplantation, and given the availability of sensitive analytical methods allowing quantification of different biomarkers in patients' samples, there is a potential for pharmacometrics to be even more useful through predictive models allowing optimal dosing in special groups of patients.

Session 4 The importance of D-E-R characterisation in dose selection, labelling and B/R assessment

Children

Dose selection is instrumental to ensure the success of a paediatric development program. Considering the span from a premature neonate to a 17 year old adolescent the diversity within the paediatric population means there is a diversity of need and opportunities for conducting clinical studies.

Knowledge of developmental pharmacology and appropriate scaling is indispensable to justify the selection of first dose in children across the age range. Maximizing the knowledge of the D-E-R in adults, linked with an early stage plan for the paediatric development makes it possible to describe and potentially collect relevant system data to support the paediatric development. In the long run such an approach may influence and potentially decrease the burden of studies required for the paediatric developments. Caveats to this would be that the D-E-R might not be well understood at the time of designing the paediatric development and not at all known in cases of pediatric specific drugs.

Even so, a general strategy mandating the explicit use of all relevant system and drug data would ensure sound paediatric developments. M&S is the tool of choice to support analysis of these data sets and it is recommended that state of the art in silico methods are used, preferably combining methods. This would further ease the possibility for explicit generalized learning on the developmental pharmacology and aid in determining the impact of growth, maturation or any other characteristics needed to scale the D-E-R from adults to children. Innovative approaches such as adaptive design based on M&S, provided adequately justified, can thus help optimizing the pediatric clinical program,

the number of pediatric subjects to enroll and maximize the quality and informativeness of collected data, especially in a limited recruitment setting.

The following questions were posed at the work shop and should be addressed:

- How can we ensure that we don't miss the opportunity to make the adult development data also useful for paediatric development?
- How to ensure a state of the art paediatric development; in phase with recruitment reality?
- How do we best support the generation of system data?

Elderly

For many drugs, the elderly are the main users. Despite this, the age distribution within clinical trials and actual patient populations are often mismatched with older people underrepresented. The EMA's Geriatric Medicines Strategy ensures that the needs of the ageing population in the EU are appropriately considered in the development and evaluation of new medicines. Modelling and simulation approaches have potential to greatly improve data interpretation for dose selection, labelling and B/R assessment in the elderly, when used in conjunction with an understanding of the nuances of drug handling, PD effects and pragmatic considerations. Examples were provided for discussion.

Promising approaches are: inclusion of sufficient numbers of elderly in appropriate age ranges (particularly the very elderly) for PK as well as PK/PD analyses, use of an age-appropriate measure of renal function (e.g. creatinine clearance), awareness of and openness to testing covariates reflecting biological rather than chronological age by considering degree of frailty, co-morbidities, mechanistic approaches such as PBPK/PD to anticipate informative covariates, support study design and for interpolation/extrapolation to allow dose recommendations for unstudied drug combinations and identification of patient groups that may be at risk of over/under-exposure due to combinations of predictors (e.g. elderly woman of small build with multiple concomitant medications). The very elderly often exhibit increased PD sensitivity and thus exploration of the minimum effective dose is key to improving tolerability.

Development decisions on dosage strengths should be fully informed by all relevant factors to ensure safe and effective use in the elderly.

Session 5 Impact on licensing decisions, post-authorisation commitments and lifecycle management of medicinal products

Dose and schedule determination and amendments of EMA reviewed medicinal products (EMA, Falk Ehmann)

135 medicinal products containing new active substances (NAS) evaluated by the EMA from 2010 until present were analysed. Major objections related to dose-finding and schedule raised during the evaluation of these products have been extracted and scrutinised. (Ref: Ehmann et al. Changes and determination of dosing recommendations for medicinal products recently authorised in the European Union Expert Opinion on Pharmacotherapy 2015, 16:6 , 903-911)

These 135 products were further studied for post authorisation 'Variations' related to dose and schedule changes in the label.

For 10% of the considered medicinal products a dose and/or schedule related major objections (MO) had been raised during initial marketing evaluation. Dose- and schedule related MO associated to efficacy evaluation include: not established optimal dosing regimen, unexplored impact of (non)-fasted and ethnicity on dosing, not justified dose recommendations and inconsistency of extrapolation from PK dose finding evidence to final recommended dose.

Further, 10% of the medicinal products investigated had their dose and schedule SmPC (label) section amended after initial authorisation - 7 of these experiences dose changes, 4 safety restrictions and 2 dose/schedule changes for patients' convenience and compliance.

This analysis highlights the importance of efforts to derive an adequate understanding of dose–response, dose–concentration–response, and underlying pharmacokinetic–pharmacodynamic relationships prior to final selection, testing, and regulatory approval of the final marketed dose. The target population should be carefully considered, especially in renal-hepatic impaired populations and with regards to drug-drug-interactions.

Dose selection is a shared risk between industry, regulators and patients/prescribers. The European regulators welcome discussions at an early stage on dose selection and dose-exposure response characterisation i.e. through scientific advice, and are open to novel approaches (discussed in session 2). If at the stage of assessment the dose selection and understanding of dose-exposure response is deemed insufficient, the regulatory framework has the tools for further optimising dose selection post approval-provided that B:R is positive, i.e. Post-approval obligation for Post-Authorisation Safety Studies (PASS), Post-Authorisation Efficacy Studies (PAES), Specific Obligations in the framework of a MA under exceptional circumstances or of a conditional MA. This possibility should not encourage deferral of dose optimisation studies to post marketing. Unless there are very pertinent clinical reasons, dose optimisation and characterisation of D-E-R should be a key deliverable of drug development.

Impact of D-E-R Information on Regulatory Approval and Post Authorisation Commitments: FDA Perspective (Yaning Wang, FDA)

Through some recent FDA approvals it was concluded that it is not sufficient to support the safety and efficacy of one dose relative to placebo/control. It is important to search for dosing regimen with optimal safety/efficacy profile or even individualized dose(s). The dose-exposure-response information is weighted in the approval decision. If this is not sufficient, PMC/PMR studies may be proposed to further address the question of optimal dose and D-E-R relationship.

Regulatory Evaluation and Perspectives on Dose-Exposure-Response Information in New Drug Applications in Japan (PMDA, Naoyuki Yabana and Naomi Nagai)

To approve the dose/regimen with optimal B/R balance for Japanese patients, PMDA take into account potential intrinsic and extrinsic ethnic variables in the evaluation of dose-exposure-response relationship based on data from global clinical trials. PMDA have issued and continuously been updating the points to consider for the interethnic comparison of PK and D-E-R in global clinical trials since 2007. Although these efforts resulted in accumulated knowledge of D-E-R evaluation of global clinical trials, further innovative regulatory approach should be explored. As the review/consultation with submitted electronic data will launch in the near future in Japanese regulatory process, pilot projects of PK and D-E-R analyses of electronic submission data and discussion on related guideline

development have started in PMDA involving also industry and academia. The analysis of clinical trial data to estimate D-E-R is expected to enable the identification of the dose/regimen with optimal B/R balance not only for Japanese patients but also for patients all over the world.

Session 6 Conclusions and Directions for the future

Don Stanski and Tomas Salmonson summarised the EFPIA and EMA position respectively.

There is a wide consensus on the following points:

- Phase 3 dose selection is an estimation problem and should not be addressed via hypothesis testing.
- Model-based dose finding methods are more efficient than pairwise comparisons approaches. Wider dose/exposure ranges (> 10 fold) and larger number of doses/regimens (> 3) should be used in phase 2, adapting to the reality of the specific drug and disease state.
- Adaptive dose-ranging approaches, when feasible, can lead to substantial efficiency gains (time, number of patients, etc.).
- Longitudinal data analysis (time vs drug effect using mixed effects data analysis) is extremely powerful and should be used more.
- Driving improved and innovative dose vs. response into industry drug development programs will require the engagement and support of senior research and development industry leaders.
- Improved regulatory guidance documents from health authorities on the important role of improved dose vs. response can drive the senior industry leadership engagement referenced above.

The incentives to invest more in phase 2 were debated. EFPIA proposed dose vs. response as confirmatory evidence coupled with a single phase 3 clinical trial. This proposal does not contradict the EMA regulatory framework and will be plausible in some therapeutic scenarios. The assessment of benefit/risk by health authorities is based on the totality of data. In this respect proper dose finding and demonstration of dose-exposure-response (D-E-R) relationship can provide evidence of activity and indeed efficacy and can be used to mitigate uncertainties and could support approval based on one pivotal trial (EMA points to consider on one pivotal trial). Regardless of the decision to pursue the above approach, in which case early dialogue with regulators is recommended, important industry incentives for investing in D-E-R characterisation are, the resulting optimal pharmacotherapy and the gains in drug development efficiency, as extensively demonstrated in this workshop.

Next steps

1. Establish a post-workshop expert group with representation from regulatory bodies, industry and academia to progress areas of discussions and actions identified. This group will work towards emphasising the importance and promoting good practices for dose selection and D-E-R characterisation. Two publications, one addressing methodologists and one addressing late phase decision makers, will be the first outcomes of this group.
2. In addition it is envisaged that discussions will continue at product level, i.e. scientific advice, PIP submissions, at MAA, or methodology level, i.e. qualification procedures.

3. Update of the CHMP assessment report templates to reinforce the importance and facilitate the evaluation of dose-exposure-response relationships at the stage of MAA, to support B/R decisions and to inform the Risk Management Plan (RMP).
4. Debate the need to create/update a regulatory guidance on dose finding.
5. Follow up discussions to involve late phase decision makers from industry.