Chapter 2
Contribution of Modeling and Simulation Studies in the Regulatory Review: A European Regulatory Perspective

Siv Jönsson, Anja Henningsson, Monica Edholm, and Tomas Salmonson

Abstract Modeling and simulation of pharmacokinetic and pharmacodynamic/response data has been increasingly advocated during drug development, to allow more efficient utilization of collected clinical data and to support informed decision making, e.g., regarding future study designs and dosing strategies in subpopulations. This chapter reflects the view of the Swedish Medical Products Agency, one of the European regulatory bodies, on how M&S studies contribute in the regulatory review. The availability of European guidelines related to modeling and simulation is discussed and some insight is provided into the types of recommendations given, together with a few examples.

2.1 Introduction

Modeling and simulation (M&S) of pharmacokinetic (PK) and pharmacodynamic (PD)/response data has been increasingly advocated during drug development, to allow more efficient utilization of collected clinical data and to support informed decision making regarding future studies and study designs including dose selection (Sheiner 1997; Breimer and Danhof 1997; Minto and Schnider 1998; Derendorf and Meibohm 1999; Balant and Gex-Fabry 2000; Holford et al. 2000; Bonate 2000; Sheiner and Steimer 2000; Aarons et al. 2001; Meibohm and Derendorf 2002; Stanski et al. 2005). The application of M&S has been found beneficial in clinical drug development in terms of time and cost savings as well as being influential on the direction of the development program (Chaikin et al. 2000; Reigner et al. 1997; Gieschke and Steimer 2000; Olson et al. 2000; Blesch et al. 2003; Veyrat-Follet et al. 2000; Lockwood et al. 2006). From the regulatory side, several European

1This chapter reflects the view of the Swedish Medical Products Agency and may not be the view of the European Medicines Agency or any other European regulatory agency.

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guidelines recommend M&S as a useful tool to support dose selection and establish dose recommendations in special populations and some specific proposals have been described (Edholm et al. 2008; Manolis and Pons 2009). Moreover, the US Food and Drug Administration (FDA) has emphasized this technology in its discussion of the critical path from laboratory concept to commercial product (Food and Drug Administration 2004, 2006; Lesko 2007) and proposed that computer-based predictive modeling is one opportunity to improve predictability and efficiency during drug development. Recent publications describe the implementation of model-based drug development in large pharmaceutical companies (e.g., Miller et al. 2005; Chien et al. 2005; Zhang et al. 2006; Lalonde et al. 2007; Grasela et al. 2007) and the FDA has been active in reporting the use of M&S in regulatory decision making (Gobburu and Marroum 2001; Gobburu and Sekar 2002; Bhattaram et al. 2005, 2007; Powell and Gobburu 2007; Wang et al. 2008; JadHAV et al. 2009). FDA’s views on this technology are described as a separate chapter within this book (Chap. 3). As a consequence of the increased usage, applications submitted to regulatory agencies increasingly contain reports where M&S has been employed. Thus, regulatory agencies must be resourced with capabilities to assess and understand this type of documentation.

The European regulatory system is based on collaboration between the national regulatory agencies allocated in the 30 member states of the European Union (EU) and EEA-EFTA (European Economic Area–European Free Trade Association). In general, the marketing authorization of a new medicinal product requires the cooperation between member states through various regulated procedures according to Directive 2001/83/EC (EU Legislation – Eudralex 2001), i.e., the Centralised, Decentralised and Mutual Recognition Procedures (EU Legislation – Eudralex, Volume 2A). These procedures have their foundation via Rapporteurs or Reference Member States who are appointed with the main responsibility to thoroughly review submitted applications. Their initial review is subjected to secondary assessment by the other member states, eventually leading to a common decision for each marketing authorization application. European regulatory guidance is developed in various areas through joint efforts by Working Parties composed of delegates from several member states. The websites of the European commission and the European Medicines Agency provide further reading on European pharmaceutical legislation (European Commission; European Medicines Agency).

The experience with use and application of M&S documentation in regulatory decision making is limited among European regulators. Accordingly, common European views are currently not settled but are under development. However, generally, the use of M&S during drug development is accepted and encouraged, for the reasons stated above. This chapter will focus on how M&S studies contribute to the regulatory review process from the perspective of one European regulatory agency, the Swedish Medical Product Agency. Thus, the views given here may not reflect the European community overall. It should also be noted that the focus of this chapter is not on clinical trial simulation specifics but rather on how models and their simulation results can be useful in making regulatory decisions.
2.2 Regulatory Guidance

2.2.1 Available Guidelines

At present, there is one European guideline that specifically deals with population pharmacokinetic modeling, namely the Guideline on reporting the results of population pharmacokinetic analyses (CHMP 2007). This guideline does not explicitly state views on when and how M&S should be used from a regulatory perspective but describes what is expected to be reported by the applicant when submitting a population pharmacokinetic analysis. These expectations should be considered applicable to other types of modeling, e.g., exposure-response modeling. The contents of this guideline describe what the regulatory assessor needs to know to be able to make an assessment of the developed model. Thus, the aim of the model, the assumptions and methodology used during model development, and the qualification of the model are main topics discussed in the guideline. Using the guideline, drug developers can understand what is expected and how the model is assessed by the regulators. Apart from this document, there are several other European guidance texts that refer to M&S or exposure-response modeling as summarized in Table 2.1.

One guideline that advocates the use of modeling in more general terms is the internationally adopted guideline ICH Topic E 4: Note for guidance on dose response information to support drug registration (CPMP/ICH/378/95). The ICH guideline states that regulators, as well as developers, should be open to new approaches and statistical/pharmacometric techniques, e.g., Bayesian and population methods and pharmacokinetic-pharmacodynamic modeling, which may increase information extraction and interpretability of the data.

Guidelines with encouraging wording concerning the use of modeling and/or the evaluation of exposure-response relationships include the Clinical investigation of pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/04) and the development of medicinal products in pediatric patients (CHMP/EWP/147013/04 and EMEA/536810/08). The pediatric guidelines emphasize the importance of taking into account organ maturation and physiology, as well as body size, to predict systemic exposure in pediatric patients and suggest the use of physiologically-based pharmacokinetic models to predict characteristics in the pediatric population. Furthermore, it is also pointed out that pharmacokinetic data alone may be of limited value for the extrapolation of efficacy and safety from other age patient groups. In general, there is also a need for PD data to elucidate whether the exposure-response relationship is different in children compared with other subpopulations (e.g., older children and adults).

The usefulness of simulation is specifically mentioned in the guidance documents on evaluation of pharmacokinetics in organ impairment (CHMP/EWP/225/02 and CPMP/EWP/2339/02) and in pediatric patients (CHMP/EWP/147013/04) as a valuable mean to establish adequate dosing recommendations.

Finally, a therapeutic area where the modeling approach has clearly won acceptance is anti-infectives (CPMP/EWP/2655/99, CHMP/EWP/4713/03, CHMP/
<table>
<thead>
<tr>
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<tr>
<td>Clinical Pharmacology and Pharmacokinetics</td>
<td><strong>5.2. Population studies</strong>&lt;br&gt;It is often valuable to include a population approach in Phase II/III clinical trials to screen for pharmacokinetic drug interactions. Valuable additional information is then obtained from studies that are performed for other reasons.....</td>
</tr>
<tr>
<td>Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products. CPMP/EWP/2655/99 (July 2000)</td>
<td><strong>I Introduction</strong>&lt;br&gt;..... Based on the current status of scientific investigations in this field, the CPMP is of the opinion that there seems to be sufficient evidence to support a recommendation that the PK/PD relationship for an antibacterial medicinal product should be investigated during the drug development programme. Although, the CPMP currently takes the position that data on the PK/PD relationship cannot replace confirmatory clinical trials of efficacy, but rather complement them to arrive more quickly at better dose recommendations, there may be areas in which detailed study of the PK/PD relationship might potentially impact on the content of the clinical programme (e.g. with reference to certain types of infections, patients, and medicinal products, see below). At present there is a lack of published studies that have sought to prospectively validate the correlation between the PK/PD relationship and clinical and bacteriological outcomes. In principle, the CPMP encourages attempts to validate and confirm the PK/PD concept during the clinical development programme. .....</td>
</tr>
<tr>
<td>Note for guidance on the investigation of drug interactions. CPMP/EWP/560/95 (December 1997)</td>
<td><strong>III Aspects of characterising PK/PD relationships</strong>&lt;br&gt;..... PK and PD data from preclinical, early Phase I and Phase II studies could be used to build models that can then be used to help design Phase III trials. Through simulation, the influence of certain aspects of the planned Phase III trial can be assessed, and, the design (for example, with respect to dose or dosing interval) subsequently modified if needed.</td>
</tr>
<tr>
<td>Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products. CPMP/EWP/2655/99 (July 2000)</td>
<td><strong>IV.2 Presentation of data</strong>&lt;br&gt;..... Mathematical models may be constructed to evaluate the relationship between renal function and pharmacokinetic parameters. The intended result is a model that can successfully predict the pharmacokinetics behaviour, given information about renal function. .....</td>
</tr>
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| Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function. CHMP/EWP/225/02 (June 2004) | **IV.3 Development of dosing recommendations**<br>..... Study results including the graphical description and the model for the relationships between renal function and relevant pharmacokinetic parameters should be used to construct specific dosing recommendations ..... Simulations can be used to identify doses and dosing intervals that achieve that goal for patients with different degrees of renal
function impairment ..... Another approach is to estimate appropriate cut-offs and doses given the information on pharmacokinetic parameters and distribution of renal function in the population. ..... 

3.6 Physiological based pharmacokinetic models
The use of Physiological based pharmacokinetic models, may be used as a tool. ..... 

4.2 Presentation of data
..... Modelling of the relationship (linear or nonlinear) between measures of hepatic function and pharmacokinetic parameters should be considered if a relevant marker is found. ..... 

4.3 Evaluation of Results and Development of Dosing Recommendations
..... Study results including the graphical description and a potential model for the relationships between hepatic function and relevant pharmacokinetic parameters should be used to construct specific dosing recommendations. ..... Simulations can be used as a tool to identify doses and dosing intervals that achieve the target criteria for patients with different degrees of hepatic impairment. Simulations of the steady state exposure at the resulting recommended dose(s) could also be provided. The simulations may include graphical description of (total and, when relevant, unbound) concentration over time, also showing the predicted variability in the population. Graphical description of relevant steady state pharmacokinetic parameters versus hepatic function including appropriate measures for variability could also be supplied. ..... 

4.2.6 Population pharmacokinetics
Population pharmacokinetic analysis, using nonlinear mixed effects models, is an appropriate methodology for obtaining pharmacokinetic information in paediatric trials both from a practical and ethical point of view. ..... Simulations or theoretical optimal design approaches, based on prior knowledge (see Sect 2.2), should be considered as tools for the selection of sampling times and number of subjects ..... Adult data may be used as prior information and may be included in the analysis as long as the predictions in children are satisfactory. 

4.2.7 Interactions
..... Such studies may be of conventional design but may also be model-based using sparse sampling. ..... 

4.3.1 Parameter Estimation
..... The parameters can be estimated using either noncompartmental analysis or a model-dependent approach, for example nonlinear mixed effects models. 

4.3.2 Presentation of results
..... If population pharmacokinetic analysis has been undertaken, a prospectively defined analysis plan, a detailed description of the data, the methodology used, the model selection criteria and an overview of the main model development steps (run record) should be included. Proper graphical diagnostics (goodness of fit, parameter
distributions, etc.) should be included wherein any stratification by age/maturity, relevant descriptors of size, etc., should be visible. Proper model validation should be undertaken.

Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins, CHMP/EWP/89249/04 (January 2007)

3.2.7. Data analysis

Population pharmacokinetic analysis of Phase II/III using a sparse sample approach is recommended for characterising the pharmacokinetics and possible covariate relationships.

3.3 PK/PD relationships

It is recommended that the relationship between drug concentration and pharmacodynamic response (PK/PD) is evaluated. If feasible, markers for both efficacy and safety should be measured, preferably in the same study. Given that the pharmacodynamic response as well as the pharmacokinetics may be altered because of modifications of the molecule or the expression system for its production, binding to blood components, or formation of antidrug antibodies, evaluation of the exposure-response relationship is considered an important tool in the drug development. PK/PD models may allow extrapolation from volunteers to target population given that suitable assumptions have been made, e.g. regarding pathological factors. These models may provide guidance for dose selection and are helpful when interpreting changes in the pharmacokinetics in important subpopulations (Section 3.2.6) or when evaluating comparability (Section 2.2).

Reflection paper on the use of pharmacogenetics in the pharmacokinetic evaluation of medicinal products EMEA/128517/06 (May 2007)

5 STUDY DESIGN AND METHODOLOGY

The investigation of the effect of PG on the PK of a drug substance may be performed using a population PK approach in genotyped subjects and patients, or in a conventional PK study.

Clinical in various therapeutic areas

Appendix to the Committee for Proprietary Medicinal Products (CPMP) Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia, on the Methodology of Clinical

III. Pharmacokinetics

Data on release rate over time, residues in the injection site and accumulation may be estimated by using adequate pharmacokinetic modelling with the use of pharmacokinetic data after oral administration and data after single dose with the depot formulation.
4.2.1 Pharmacodynamics

It is desirable that the PK/PD relationship should be further explored during both the early and confirmatory clinical studies in infected patients to verify the conclusions drawn from the preclinical observations and pharmacokinetic data in healthy volunteers. (As suggested in CHMP/EWP/2655/99, these investigations may constitute sub-studies within larger trials or may be the studies that are specifically designed to address PK/PD relationships.) It is recommended that the relationship between drug exposure and safety and efficacy is explored also in confirmatory studies e.g. by means of population pharmacokinetics/pharmacodynamics.

4.2.3 Exploratory studies

…… Data derived from these studies may also provide important bridging pharmacokinetics/pharmacodynamics (PK/PD) documentation. Monotherapy studies are needed to characterise the relationship between anti-HBV activity and dose/concentration. In the dose ranging studies, a treatment arm with established anti-HBV agents could be included to assist selection of an optimal dose. Appropriate modelling might also provide information on pharmacokinetic markers of importance for efficacy in relation to virus with different degrees of reduced susceptibility in vitro.…… Early and repeated determinations of viral load and drug concentrations are recommended and PK/PD modelling may be a useful tool for dose selection. Dose selection for the phase III confirmatory trials of efficacy should be based on the considerations outlined above and should be preceded by well-planned dose ranging comparative studies.……

3.1 Efficacy criteria in exploratory studies

…… Population PK/PD modelling is encouraged.……

3.2.2. Secondary efficacy endpoints

…… Population PK/PD modelling may provide additional insight as regards, e.g. the temporal dynamics of the underlying condition and the activity of the experimental compound.……

4.1.2 Pharmacokinetics

…… The relationship between drug exposure and efficacy as well as safety should also be explored in confirmatory studies, e.g. by means of population pharmacokinetics. An understanding of these relations is a prerequisite for assessing the relevance of alterations in drug exposure, e.g. because of impaired hepatic function or drug-drug interactions.……
Table 2.1 (continued)

<table>
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<tr>
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| 633/02 Revision 2 (November 2008)           | 4.1.3 Exploratory studies in HIV-infected individuals  
Monotherapy studies  
..... Early and repeated determinations of viral load and drug concentrations are recommended, and PK/PD modelling may be a useful tool for dose selection. Appropriate modelling might also provide information on pharmacokinetic markers of importance for efficacy, in relation to virus with different degrees of in vitro susceptibility. ..... |
..... During the conduct of clinical studies of efficacy it is expected that: ..... Clinical and mycological outcomes should be analysed in the light of in-vitro susceptibility and patient pharmacokinetic data to further assess the PK/PD relationship. ..... |
| Multidisciplinary Guideline on clinical trials in small populations. CHMP/EWP/83561/05 (July 2006) | 3. PHARMACOLOGICAL CONSIDERATIONS  
..... The credibility of study results may be enhanced if a dose-response relationship is seen or in cases where a chain of events can be identified (for example, drug exposure to target occupancy, to pharmacodynamic measures, to clinical outcome). Cases where no such clear chain of events exists are much less convincing and will increase the data requirements regarding robustness and persuasiveness of study results. In very rare disorders, it is important that every patient participating in a study contributes as much information as possible to make a benefit-risk assessment possible. Therefore, the well-planned use of the best available techniques to obtain and analyse information is crucial. This applies throughout the study process from pharmacokinetic and pharmacodynamic modelling to handling and analyses of biopsy material. ..... |
| Guideline on the investigation of medicinal products in the term and preterm neonate. | 7 DOSE-FINDING  
..... PK/PD modelling techniques, using age appropriate and validated biomarkers, need to be considered to find the optimal dose. For a new medicinal product, the optimal dose has to be clinically verified. Existing physiologically based pharmacokinetic models to predict pharmacokinetic characteristics in the neonatal population may be |
considered if appropriate. .... The modelling of the influence of maturation on PK and on the PK / PD relationship may be considered to predict the changes in dosing as a function of age. Applicability of these models would need to be justified and new models might need to be developed. .... Allometric scaling should be considered for drug clearance when it is predicted from sparse data in neonates or extrapolated from data in older infants.

**8 PHARMACOKINETIC STUDIES AND PK/PD STUDIES**

.... However, pharmacokinetics alone is of limited value for extrapolating efficacy and safety from other patient groups, and extrapolation of efficacy will in general need pharmacodynamic data and PK/PD monitoring. A population PK approach is preferable because of the importance of finding covariates related to dose-individualisation between individuals and over time in the maturating individual. The analysis can be made on rich and/or sparse data depending on the number of patients available and the possibility of developing highly sensitive analytical methods where very small sample volumes could be used. The initial model could be based on rich data of a limited number of individuals and/or on data available in older children, as well as on other prior information, followed preferably by a population PK approach. It should be noted that population PK and modelling of oral administration require extra cautious consideration in the neonatal population as there may be marked absorption differences in neonates as compared to other age groups as well as very prolonged absorption in a subgroup of individuals....

**ICH guidelines**

ICH Topic E 4. Note for guidance on dose response information to support drug registration.

CPMP/ICH/378/95
(May 1994)

**3. STUDY DESIGNS FOR ASSESSING DOSE-RESPONSE**

.... Placebo-controlled individual subject titration designs typical of many early drug development studies, for example, properly conducted and analyzed (quantitative analysis that models and estimates the population and individual dose-response relationships), can give guidance for more definitive parallel, fixed dose, dose-response studies or may be definitive on their own. ....

**4.1. GUIDANCE AND ADVICE**

.... 4.6 Regulatory agencies and drug developers should be open to new approaches and to the concept of reasoned and well documented exploratory data analysis of existing or future databases in search of dose-response data. Agencies should also be open to the use of various statistical and pharmacometric techniques such as Bayesian and population methods, modeling, and pharmacokinetic-pharmacodynamic approaches. However, these approaches should not subvert the requirement for dose-response data from prospective, randomized, multi-dose-level clinical trials. Posthoc explanatory data analysis in search of dose-response information from databases generated to meet other objectives will often generate new hypotheses, but will only occasionally provide definitive assessment of dose-response relationships. A variety of data analytical techniques, including increased use of retrospective population-type analyses, and novel designs (e.g., sequential designs) may help define the dose-response relationship. For example, fixed dose designs can be reanalyzed as a continuum of dose levels if doses are refigured on a mg/kg basis,
or adjusted for renal function, lean body mass, etc. Similarly, blood levels taken during a dose-response study may allow estimates of concentration-response relationships. Adjustment of drug exposure levels might be made on the basis of reliable information on drug-taking compliance. In all of these cases, one should always be conscious of confounding, i.e., the presence of a factor that alters both the regurgited dose and response or that alters both blood level and response, compliance and response, etc. ....

ICH Topic E 7. Note for guidance on studies in support of special populations: geriatrics. CPMP/ICH/379/95 (September 1993)

B: Pharmacokinetic Screening Approach

.... Sponsors may opt, instead of conducting a separate PK evaluation of the elderly, to utilize a Pharmacokinetic Screen in conjunction with the main Phase 3 (and Phase 2, if the sponsor wishes) clinical trials program. This screening procedure involves obtaining, under steady-state conditions, a small number (one or two) of drug blood level determinations at "trough" (i.e., just prior to the next dose) or other defined times from sufficient numbers of Phase 2/3 clinical trials patients, geriatric and younger, to detect age-associated differences in pharmacokinetic behaviour, if they are present. ....


2.4.1 Pharmacokinetics

.... Several approaches can be used to minimize the amount of blood drawn and/or the number of venipunctures: .... use of population pharmacokinetics and sparse sampling based on optimal sampling theory to minimize the number of samples obtained from each patient. Techniques include: • sparse sampling approaches where each patient contributes as few as 2 to 4 observations at predetermined times to an overall "population area-under-the-curve" • population pharmacokinetic analysis using the most useful sampling time points derived from modeling of adult data. ....


3.2.3 Analysis of Relationship Between Drug Exposure and QT/QTc Interval Changes

Establishing the relationship of drug concentrations to changes in QT/QTc interval may provide additional information to assist the planning and interpretation of studies assessing cardiac repolarization. This area is under active investigation.

*aAll guidelines mentioned in the table can be found at the website of the European Medicines Agency (European Medicines Agency. Scientific guidelines for human medicinal products. Clinical efficacy and safety guidelines; European Medicines Agency. Scientific guidelines for human medicinal products. Multidisciplinary guidelines)

CPMP and CHMP = Committee for medicinal products for human use
EWP/6172/03, EMEA/CPMP/EWP/633/02, CPMP/EWP/1343/01). Here, the use of pharmacodynamic measurements is highly encouraged and exploration of exposure-response by means of modeling is recommended, both in dose-response and confirmatory studies to support dose selection.

Thus, it can be concluded from the available guidance documents that there is impetus and encouragement from the European regulatory agencies for an increased use of M&S methodologies, to better understand and interpret the collected data, to improve study designs and to move toward adequate dosing recommendations resulting in safe and efficacious treatment in all subpopulations.

2.2.2 Would a Specific European Guideline on M&S Be of Value?

As stated in the previous section, there is currently only one specific guideline concerning modeling, i.e., the Guideline on reporting the results of population pharmacokinetic analyses. There are several reasons for the limited availability of more specific guidance in this area. One major reason is that the methodology used for M&S involves advanced and rapidly evolving techniques. Consequently, there is a risk that the guideline, when adopted, is already outdated. Accordingly, in order not to constrain science and innovation, any guidance will have to be very general, and may therefore not provide specialized assistance, but merely provide a confirmation of the regulatory agencies’ acceptance of M&S in drug development.

So, can such a document still be of value? We think that the answer to this question is “Yes” and that it is time to reconsider the development of a new guidance. The production and adoption of such a guidance document would, in addition to extensive discussions, lead to training sessions for regulators, thereby increasing the awareness among regulators of the potential for using this type of information. Eventually, the guidance would describe the common European view and serve as a support for regulatory assessors as well as encouragement for drug developers.

2.3 Regulatory Decisions: When and Impact

In Europe, regulatory assessors may encounter M&S documentation at several time points during drug development. For example, a decision or view based on this type of documentation can be made early during drug development in the assessment of Pediatric Investigation Plans and Clinical Trial Applications or when giving Scientific Advice. Hence, regulators may influence the choices made and approaches taken during the drug development path. However, so far, the main focus of the regulatory assessment has been during the approval phase of the
marketing authorization application of new medicinal products. Here, M&S reports are a basis for efficient utilization and interpretation of the collected data and eventually the knowledge/information may be translated into dosing recommendations. Some insights into the type of recommendations given are outlined below.

2.3.1 Pediatric Investigation Plan

The Pediatric Investigation Plan is a newly required document based on the recently enacted European Pediatric Regulation 1901/2006 (EU Legislation – Eudralex 2006). According to this regulation, a Pediatric Investigation Plan must be generated for new drugs under development. This plan should describe in detail how and when the new medicinal product will be developed for use in the pediatric population. The Pediatric Investigation Plan is reviewed and adopted by the Pediatric Committee (PDCO), one of the Scientific Committees at the European Medicines Agency, and drug developers need to justify any deviations from the approved plan.

For new active substances, the Pediatric Investigation Plan should be submitted for regulatory review during early drug development, i.e., at the initiation of Phase 2, but may be updated when more knowledge is gained. The proposed selection of dose or approach to establish the dose to be investigated in pediatric patients is commonly based on modeling principles and the regulatory assessor has the opportunity to provide a regulatory view on this issue at an early stage. Because limited data are available at this time, the Pediatric Investigation Plan should preferably include a general description of the future modeling strategy and any regulatory comments given should not pose a hindrance to the further development. Thus, the regulatory assessment is, and should be, broad and provides a general opinion concerning concepts and suitability of using M&S in pediatric drug development. Regulatory experience in this area is growing, and general recommendations on how to use prior information concerning the relation between ontogeny and pharmacokinetic characteristics are often provided. Furthermore, the drug developer is usually advised to carefully consider the similarity of pharmacodynamics in children compared with adults, i.e., whether it is scientifically justified to aim for similar systemic exposure as in adults, and that exposure-response relationships in the pediatric population should be elucidated as much as possible. Because of the typical nature of pediatric data, i.e., sparse sampling, the general advice is to employ a population modeling approach. Even deterministic simulations, in combination with known distributions of body size for given ages, are considered valuable tools to predict the average systemic exposure in children.

2.3.2 Clinical Trial Application

M&S documentation is regularly available as part of the background documentation in clinical trial applications. In early clinical trials, predictions of exposure
levels for the doses proposed to be studied can be made on the basis of modeling using previous preclinical or clinical data. This is helpful information in the regulatory assessment of safety for the planned study. At later clinical stages, e.g., dose-response studies, the choice of dose level may be justified by clinical trial simulations originated from exposure-response models. This type of M&S approach is highly encouraged, because such exploration offers an efficient use of already collected data resulting in well-founded decisions for the drug developer. This also facilitates the regulatory understanding of the dose selection from both efficacy and safety perspectives. By the use of simulations, the drug developer also has the opportunity to evaluate alternative study designs. Eventually this may lead to fewer failed studies.

2.3.3 Scientific Advice

The drug developers can at any stage of drug development request scientific advice from the regulatory agencies. The companies have the option to seek scientific advice: (1) at the national level through each national agency or (2) at the community level via the European Medicines Agency. The national advice is often provided in an informal discussion setting, in comparison to the more formal community advice, which is mainly provided in written format. Drug developers often choose a combination of the two types of scientific advice.

The ultimate goal of scientific advice is to ensure that appropriate investigations are performed, so that no major objections regarding the used methodology are likely to be raised during evaluation of the marketing authorization application. Thus, scientific advice is prospective in nature and focuses on development strategies rather than pre-evaluation of data to support a marketing authorization application. The responsibility of the agencies is to provide the advice by answering the prespecified questions posed by the company on the basis of the provided documentation and considering the current regulatory framework and scientific knowledge. Thus, the role of the regulators is not to substitute the industry’s responsibility for the development of their products.

A scientific advice may be particularly useful when there appears to be no or insufficient applicable regulatory guidance available or where the company chooses to deviate from the available guidance in its development plan. For example, answers to many questions pertaining to what is and what is not regarded adequate in M&S activities cannot be found in a guideline at present, and the number of such questions is steadily increasing. Questions related to the suitability of using population modeling for identification of important covariates or for the estimation of drug interactions are often posed. Furthermore, M&S of exposure-response data is frequently used as a basis for justifying the choice of dose for use in Phase 3. Then, developers usually wish to obtain the regulators’ view on the strategy used for dose selection. As for Pediatric Investigational Plans, the advice is usually a general recommendation concerning M&S concepts and suitability of these methods.
In some cases, the advice may be quite detailed and, although not legally binding for either party, the applicant is recommended to justify deviations from the advice in a future application.

### 2.3.4 Approval for Marketing Authorization

The main review of the M&S documentation takes place during the drug approval procedure. Nowadays, M&S analyses are increasingly performed as an integrated part of the drug development by many companies and accordingly, applications for new medicinal products typically contain at least one modeling report. The reports usually concern pharmacokinetic data but there is a trend of an increasing number of exposure-response analyses of both clinical endpoints and adverse effects in recent applications. Exposure-response analyses put systemic exposure into a clinical utility perspective and help answer the following key questions:

1. Within which range of exposure will the drug treatment result in sufficient efficacy and with tolerable side effects?
2. What deviations in exposure can be allowed but still result in a positive benefit/risk balance for the drug treatment?

Currently, the regulatory assessors in Europe do not redevelop models or build new models based on raw data but rather evaluate and interpret the analyses submitted in the application. Based on the assessment of the models and the “whole picture” of the drug under evaluation, an overall judgment of the relevance of the information gained by the modeling is made. If the M&S documentation is critical for drawing conclusions on dosing recommendations or the overall benefit/risk assessment, then this material is very thoroughly assessed and the applicant is frequently requested to provide supplementary information. On the other hand, if the model is considered of little value as basis for dosing recommendations or for labeling purposes, then the analyses (which may be of poor quality) are not given any weight in the overall assessment. The requests to the applicant may vary in detail as exemplified below:

- Clarification on how models were developed, *e.g.*, procedures for model building
- Supplementary analyses, *e.g.*, additional evaluation of alternative structural models
- Additional information on the model’s capability to describe and predict the observed data, *e.g.*, additional goodness-of-fit plots or predictive checks
- Model predictions of studied and nonstudied situations, *e.g. *,
  - Drug–drug interactions
  - Subpopulations
  - Effect of concomitant food intake
  - Worst-case scenarios

At present, the models are rarely used as a main basis for assessment of overall benefit–risk from a regulatory perspective but rather for the following:
(a) As a general description of pharmacokinetic and exposure-response (pharmacokinetic–pharmacodynamic relationship) in the target population
(b) As an aid in judging the clinical relevance of changes in pharmacokinetics and for evaluation of
- Dose recommendations in special populations
- Dose adjustments with concomitant medications

2.4 Examples of Contribution of M&S Documentation in the Regulatory Review

In the following sections, a few examples are given on how modeling documentation was accepted and used during the approval phase. The product-related information is publicly available in European Public Assessment Reports (EPAR) for these products (European Medicines Agency 2007, 2008, 2009). Other examples where M&S and/or PKPD information has been considered useful can be found in EPARs of Baraclude, Inovelon, Invega, Ivemend and in the assessment of compassionate use of IV zanamivir (European Medicines Agency).

2.4.1 Keppra (levetiracetam)

Keppra contains the antiepileptic agent levetiracetam. Levetiracetam has been shown to have uncomplicated pharmacokinetic features: rapid and almost complete absorption after oral administration, formulations studied demonstrated to be bioequivalent, no relevant food interaction, eliminated mainly by renal excretion (2/3), and dose proportional pharmacokinetic properties.

In 2008, the marketing authorization holder (MAH) for Keppra applied to extend the indication to include children from 1 month to 4 years old in the indication of adjunctive treatment of partial onset seizures with or without secondary generalization. The main concern with this application from a regulatory perspective was the limited information in very young children. For the age group 1 month to 4 years, one pivotal efficacy study was performed and longer term open-label follow up data were also submitted. Overall, 226 children between 1 month and 4 years were exposed to Keppra, but the actual numbers in the youngest age groups were relatively small, with only 8 children aged <6 months (the youngest subject being 2.3 months old) and 15 children aged from 6 to 12 months. Short-term efficacy was convincingly shown in the pivotal study and the open long-term study indicated maintained effect over time. However, there was limited safety information gathered for patients <1 year old and a lack of long-term safety data in this new population.

For this application, a population pharmacokinetic model was developed using data from several clinical studies in 197 children aged from 0.19 to 17 years, weighing 5.5–93 kg of which 112 and 85 were male and female, respectively.
The data was described with a one-compartment model with first-order absorption and first-order elimination and the final model included body weight, concomitant antiepileptic drugs and age through a maturation factor on oral clearance, and age on apparent volume of distribution. This model was considered to describe the observed data sufficiently well and a visual predictive check stratified for body weight and age demonstrated adequate predictive properties of the model with respect to both central tendency and variability.

The dose recommendation suggested by the MAH aimed at obtaining similar systemic exposure in children younger than 4 years as that obtained in a 4-year-old patient when given a dose of 10 mg/kg.

<table>
<thead>
<tr>
<th>Suggested dose recommendation by MAH, including dose titration levels</th>
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<tr>
<td>Age range (months)</td>
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<tr>
<td>Recommended starting dose (mg/kg b.i.d.)</td>
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<tr>
<td>Recommended dose titration level 2 (mg/kg b.i.d.)</td>
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<tr>
<td>Recommended dose titration level 3 (mg/kg b.i.d.)</td>
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Simulations of systemic exposure in children from 1 month to 4 years, in combination with actually observed data, were used as a support that this dosing regimen would result in the expected systemic exposure. The simulations covered worst-case scenarios, i.e., a 1-month child with a very low body weight and a 6-month child with a high body weight. The calculated fraction of the dose required to achieve the same exposure as a 4-year-old was 0.58 for a 1-month-old child, which substantially exceeded the minimum threshold established by the applicant prior to simulations, i.e., a change of 20%, necessitating a dose adjustment. The proposed cut-off for dose adjustment, i.e., 6 months, was found reasonable because the fraction of the reference dose was equal to 0.8 at this age and considering that the maturation of glomerular filtration is essentially complete by the age of 6–12 months. The 30% reduction of the dose (e.g., 7 vs. 10 mg) in children 1–6 months was a compromise resulting in systemic exposure similar to or slightly lower compared to a 4-year-old and was considered reasonable from a safety point of view. From an efficacy point of view this dose was deemed sufficient because the dosing involves an up-titration and the dose recommendation in children 1–6 months was also consistent with the dose used in this age group in the pivotal efficacy study.

In conclusion, although there was limited pharmacokinetic data in infants below 1 year of age the modeling of the pharmacokinetic data, in conjunction with a priori information on maturation of renal function and body weight distributions for children, contributed in making relevant predictions of systemic exposure of levetiracetam in the youngest children where actual data were missing. These efforts strengthened the view that the proposed dose titration schedule was adequate and served as a significant regulatory aid for the assessment of safety and efficacy in very young children. However, this pharmacokinetic M&S exercise assumed that the same exposure-response relation was valid for children from 1 month to 4 years of age as compared to older children and adults. This assumption was not proven.
but because there was sufficient evidence of efficacy this was not further pursued. Both from an efficacy and safety point of view the limited number of patients <1 year old was of concern, in particular because of the heterogeneity of epileptic syndromes in this age group and the limited long-term safety data available. Therefore, the MAH committed to further assess the long-term efficacy and safety in this age range postapproval through an observational sentinel site study. The MAH also committed to submit specific safety reports every 6 months for children <4 years old. The limitation of data in children from 1 month to 4 years of age was also reflected in the product information.

2.4.2 Celsentri (Maraviroc)

Celsentri (Maraviroc) is a CCR5 antagonist used in combination with other antiretroviral agents in treatment of HIV-1. Maraviroc has relatively complex pharmacokinetic behavior with highly variable absorption, dose-dependent oral bioavailability and food effect, likely because of saturation of efflux at higher doses and a combination of more efficient efflux because of slower absorption (less saturation) and to some extent complex formation when administered with food. Moreover, being a substrate for CYP3A4 and P-gp, the interaction potential with other antiretroviral drugs is high. Although the contribution of renal elimination is low when maraviroc is administered as a single drug, the importance of this elimination pathway increases significantly when administered together with CYP3A4 enzyme inhibitors.

Sophisticated pharmacokinetic-pharmacodynamic models have been applied during the development of maraviroc (Rosario et al. 2005, 2006, 2008; Jaqmin et al. 2008). Both pharmacokinetic and pharmacokinetic/pharmacodynamic models were presented in the submitted application for marketing authorization. For example, the probability of failure, where failure was defined as a patient having HIV-1 RNA (>50 copies/ml), in the Phase 2b/3 studies has been related to average exposure.

Because of its relatively complex pharmacokinetic behavior and interactions with other antiretrovirals, it was not reasonable to clinically study all possible scenarios. Simulations of the systemic exposure of maraviroc have therefore been used in the assessment and these were evaluated in combination with the suggested exposure-response relationship to answer questions such as:

1. What happens with the exposure if maraviroc is administered with inhibitors of various potency in combination with food?
2. What is the effect of impaired renal function when maraviroc is administered in combination with potent inhibitors of CYP3A4/P-gp?

M&Ss together with observed data from Phase 2b/3, where maraviroc had been administered with or without food in combination with various antiretroviral agents, resulted in dose recommendations that were expected to yield sufficient exposure regardless of food intake. Because of some uncertainties in the model, a study in subjects with renal impairment was requested as a follow-up measure. Based on the result of this study and further simulations the dose recommendations have been amended.
2.4.3 **Bridion (sugammadex)**

Bridion contains sugammadex, which reverses neuromuscular block induced by the nondepolarizing neuromuscular blockers rocuronium and vecuronium by forming complexes with these drugs. The assessment of safety issues related to drug–drug interactions because of the mode of action was greatly enhanced by the use of population model predictions as follows: the mechanism of interactions may be due to the possibility of (1) sugammadex’s binding to other molecules, reducing their effect or (2) displacement of the neuromuscular blocking agent from sugammadex, resulting in reduced reversal of the neuromuscular blockade or reoccurrence of neuromuscular blockade. Because investigating all interactions *in vivo* is not feasible, the applicant developed a strategy to screen for the interaction potential. In this strategy the knowledge from two major data sources was combined:

1. Binding affinity to sugammadex for several drugs estimated as the association constant determined by isothermal titration calorimetry
2. Predictions of systemic exposure and pharmacodynamic effects using a population pharmacokinetic-pharmacodynamic interaction model, including pharmacokinetics of rocuronium and sugammadex, the complex binding interaction and pharmacodynamic effects of rocuronium (with and without sugammadex).

Although several assumptions were made in the model predictions, the approach was considered acceptable from a regulatory perspective. One important reason for this opinion was that the model, which was developed using data from healthy volunteers and patients, exhibited adequate predictive properties as demonstrated by external validation, independent of the data used to build the model. Furthermore, model predictions for worst case scenarios were performed, and drugs that were identified with a risk for interaction were included in the product information. Model predictions of pharmacodynamic outcome also supported clinical recommendations concerning duration of surveillance for re-occurrence of blockade because of concomitant administration of a drug potentially being able to displace rocuronium from sugammadex. In addition, model predictions of pharmacodynamic outcome, such as time to recovery from neuromuscular blockade, supported the use in patients with renal impairment, which at the time for approval of marketing authorization was based on limited clinical data.

### 2.5 Future Perspectives and Summary

Obtaining a complete description of the population intended for treatment within the clinical development program is usually not feasible. Hence, the collected clinical trial data do not represent the entire target population and there is a need for better approaches to extrapolate efficacy and safety data to various subpopulations. M&S of pharmacokinetic, pharmacodynamic and clinical endpoints offer such a tool and the contribution in regulatory decision making by this type of
documentation is predicted to increase. It is anticipated that the use of M&S will increase in pharmaceutical development. Accordingly, the regulatory agencies will need to increase their capability to assess and utilize this type of information. Moreover, discussion and cooperation among regulatory agencies is necessary to provide more unified guidance to drug developers. The demand for collaboration is not limited to a European level, but should also be placed in a global perspective.

Thus, an increased awareness of the utilities of M&S at the European agencies is essential. To move forward, it is crucial to spread knowledge within regulatory authorities about the use and possible gains of M&S. Moreover, there is a need for more regulatory pharmacometricians, i.e., assessors of M&S documentation. These assessors should, in addition to technical skills (Holford and Karlsson 2007), have the knowledge to determine the importance of model deficiencies, to recognize when M&S may be useful and to judge the appropriateness of endpoints used. The latter points toward the multidisciplinary aspects of pharmacometrics (Barrett et al. 2008), which demand frequent communication between clinical and pharmacometric assessors.

From a short-term perspective, it is likely that the type of regulatory requests forwarded to applicants today will continue and that results from model-based analyses will constitute a larger part of the critical knowledge prior to marketing approval compared with the present situation. Moreover, physiology-based models and software are readily available tools for predicting (1) the effect of varying renal function or (2) drug interaction potential based on in vitro data, etc. It is envisaged that the usage will increase (Rowland et al. 2010). For example, it is of particular interest to forecast systemic exposure in the paediatric population. For simple cases, such as intravenous administration of drugs that are purely eliminated by glomerular filtration, limited pharmacokinetic data would be sufficient when combined with model predictions.

From a long-term perspective, it would be of great value to have a European regulatory forum or discussion group, e.g., a pharmacometric network for assessors, where continuous dialogue on the use of M&S in drug applications can take place to form consensus among the member states. Organizing a formal network will permit better priority ranking of issues and the creation of an agenda. The network should preferably include regulatory statisticians and should have good communication with relevant Working Parties that develop guidelines in the clinical area.

In summary, drug development needs appropriate tools for more efficient interpretation of collected data and for extrapolation of knowledge to the entire target population. M&S is considered to be useful in this respect and European regulatory agencies will promote and encourage the increased use of these methodologies. The contribution in regulatory decision making by this type of documentation may gradually increase. To assist drug developers and provide more unified guidance, an interactive process among regulatory agencies is needed on a global level.

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