Cover Page

Universiteit Leiden

The handle http://hdl.handle.net/1887/35437 holds various files of this Leiden University dissertation

Author: Bellanti, Francesco
Title: From data to models: reducing uncertainty in benefit-risk assessment: application to chronic iron overload in children
Issue Date: 2015-09-24
Summary, conclusions and perspectives

Growing awareness about the relevance of formal evaluation of the efficacy and safety in children has resulted into important changes in the legislation defining the requirements for the approval of medicines for children (1–4). In parallel to these developments, methodological advancements have taken place in terms of the level and type of evidence required to establish the so-called benefit-risk profile of an intervention (5–8). Whilst a considerable number of approaches have been evaluated over the last decade, their utilisation has often been limited to post-approval data. Most importantly, they summarise a \textit{fait accompli}, i.e., the evidence is gathered after the facts. Whilst risk management and mitigation measures are intrinsic components of a risk management plans (5–8), current approaches do not provide a quantitative framework for regulators, clinical scientists and drug developers on how to integrate knowledge about drug- and disease-specific properties, thereby enabling the prediction of treatment response across a range of possible scenarios before evidence is generated. The availability of such a framework would not only permit optimisation of risk management plans, it would also represent a more robust basis for addressing clinical and scientific questions during drug development and at the time of approval.

Throughout this thesis we have focused on the advantages of introducing quantitative clinical pharmacology concepts, and more specifically modelling and simulation, as an ancillary tool for evidence generation and evidence synthesis. We have illustrated how model-based predictions can be used in conjunction with established benefit-risk methodologies to support the decision-making process underpinning the approval of paediatric medicines. The examples used in previous chapters also offer insight into the deficiencies associated with data generation and unravel opportunities for the optimisation of clinical protocols in children.

Two main features need to be highlighted, which differentiate the work proposed here from previous research in paediatric clinical pharmacology. In contrast to previous work in which population pharmacokinetic-pharmacodynamic models have been developed to describe a
single endpoint, it is the first time that multiple drug-disease models are implemented in parallel, taking into account eventual correlations between measures of efficacy and safety. This represents an important advancement in the way one assesses treatment response i.e., not as a primary endpoint in a clinical protocol, but rather as a means to characterise disease- from drug-specific properties, thereby providing a **parametric representation of the efficacy and safety profile of an intervention**. A second feature of our work is the application of clinical trial and not-in-trial simulations as complement to data obtained from clinical trials. Here simulated data (i.e., imputations) from virtual scenarios were intertwined with real data and used as input for the multi-criteria decision analysis. An immediate advantage of the approach is the possibility of **exploring in a quantitative manner the benefit-risk profile of a medicinal product in situations which have not been tested prior to its approval**. This aspect is particularly relevant for the evaluation of medicines for children, for whom limited evidence can be generated and physiological processes associated with maturation and growth may affect the benefit-risk balance.

The aforementioned features were embedded across the different chapters, where chelation therapy associated with iron overload is used to illustrate the implementation of the proposed framework. Here we present an overview of the results and conclusions from these investigations, emphasising the contribution of modelling and simulation as a tool for more effective data generation, evidence synthesis and decision making regarding the evaluation of paediatric medicines.

Our work is based on the premise that when a drug is granted its first marketing authorisation the decision is based only on the evidence generated throughout the drug development phases in the target paediatric population (1,3,2,4). However, at this stage no quantitative evaluation is performed of the benefit-risk balance (BRB); usually a full BR appraisal takes place during the post-marketing phase, when additional evidence arises from clinical practice as well as from additional randomised controlled trials. Clearly, this situation is not ideal, as it imposes a reactive rather pro-active attitude towards benefit-risk. Despite the acknowledgement by different stakeholders about the need for a more consistent, transparent framework to support (decision-making for) the approval of new medicines (9–12), inferential methods by modelling and simulation have been ignored or have limited role as a statistical analysis tool. Thus far little has been done to enable the use of inferential methods by modelling and simulation as an integrative tool for evidence synthesis and benefit-risk assessment.

In **chapter 1**, we review the available literature on benefit-risk evaluation to identify suitable methods for the development of the proposed framework. In spite of the vast number of
methodologies (both qualitative and quantitative) are available in the public domain, the majority of them are not appropriate for a more general application (13–15). Among other things, we highlight the relevance of quantitative methods as enablers or keys to the answer to clinical, regulatory and scientific questions regarding the benefits and risks of an intervention. Growing consensus suggests that a combined approach involving qualitative and quantitative methods is required to ensure meaningful evaluation and interpretation of benefit and risk data. Here we identify MCDA as the method of choice for further integration with mechanism-based modelling and simulation. Despite its limitations in the way uncertainty is handled, MCDA offers the opportunity to evaluate a multidimensional aspects drug and disease which arise in drug development and in the clinical practice. In revisiting the drug approval process and the requirements for paediatric drug development, it becomes evident that the use of drug-disease modelling and simulation represents a formal extension of the clinical pharmacology concepts into the realm of evidence synthesis and evaluation of novel therapeutic agents. This advancement can be compared to the introduction of receptor pharmacology in drug discovery, which replaced empirical evidence from experimental protocols (16–18). Then receptors were just a concept, not a substrate, whose properties could be used to understand drug properties and optimise the development of novel molecules. Similarly, today response scenarios in virtual patients are still seen as concepts, rather than as substrates that can be used for further characterisation of the benefit-risk profile.

Having identified a suitable methodology enabled us to formalise the scope and intent of the investigations described in the subsequent chapters of this thesis. In fact, in chapter 2 we introduce details on the implementation of a framework in which MCDA is applied in an integrated manner with modelling and simulation. The primary intent of the framework is to have a tool for more effective data generation, evidence synthesis and better decision making. Focus is given to the opportunities for optimising data generation in children and most importantly to the possibility of integrating knowledge by mechanism-based parameterisations, which enable us to discriminate between drug- and disease-specific properties. The implementation of these concepts is illustrated by the use of clinical trial and not-in-trial simulations to complement data generation and improve benefit-risk assessment. For the sake of clarity, the proposed work is presented into three separate sections in this thesis. In section 2, attention is paid to importance of data quality in the context of paediatric bridging studies and the implications for the estimation of the parameters of interest in subsequent steps, i.e., evidence synthesis. Our investigation also shows how critical pharmacokinetic data are for the selection of the dosing regimen in the target population. In section 3, we discuss the hurdles for the assessment of efficacy in children and show that disease processes may determine the time course of response,
making drug effects no more than a covariate factor for efficacy and safety. We illustrate how treatment response can be characterised by integrating certain physiological measures (i.e., markers of pharmacology) with disease-related factors. In this context, it also worth mentioning that further insight into the mechanisms underpinning pharmacological effects provides a systematic approach to the evaluation of safety findings. In fact, drug-disease models were developed for a series of clinically relevant outcomes, taking into account the physiological or pharmacological correlation between them. The examples presented here also provide a first insight into the concept of knowledge propagation, not as a statistical prior, but as time variant and time-invariant parameter distributions. These predictive distributions are essential in the context of chronic diseases, as they enable prediction of long-term complications or changes in response due to physiological factors as well as patient behaviour. Finally, in section 4, we demonstrate how MCDA can be implemented in conjunction with modelling and simulation. The models developed in the previous sections are used to generate virtual responses in clinical trial and not-in-trial simulation scenarios, mimicking a Phase III efficacy trial and a long-term follow-up pharmacovigilance protocol. The availability of a range of scenarios which have not been evaluated in an empirical setting, including predictions of long-term changes in the benefit-risk profile, provides a more robust basis for decision making regarding the approval and risk management of medicines for children.

10.1 Optimising evidence generation in paediatric trials

One of the major issues in paediatric drug development is that ethical and practical constraints often limit the generation of evidence (19,20). This has implications for the subsequent use in the evaluation of the benefit-risk profile of an intervention. In brief, there is an imperative for acquiring data with high quality and high informative value. Obviously, both the quality and informative value of data acquire in children cannot be taken for granted. Empirical experimental evidence based primarily on feasibility yields a potentially distorted picture of reality, in that drug-specific properties may not be disentangled from the role of disease-related factors and experimental design.

Given the role of extrapolation and bridging in paediatric research, in chapters 3, 4 and 5 we demonstrate how knowledge integration can be use applied in conjunction with optimal design to evaluate which study protocol designs are more informative, whilst taking into account feasibility issues. Here we have focused on the sample size and sampling frequency required for obtaining accurate estimates of systemic exposure in children with < 6 years of age undergoing chelation therapy with deferiprone. The study was based on the assumption that pharmacokinetic properties can be bridged from adults and adolescents. Affected by transfusion-dependent diseases and therefore
provide evidence of the dosing regimen(s) that ensures comparable drug exposure across the overall patient population. Therefore in chapter 3 we developed a population pharmacokinetic model using available data in adults receiving oral doses of deferiprone as a 100 mg/ml solution. Our results show how a model-based approach can be used to assess the effect of demographic and physiological factors on drug exposure and subsequently provide the basis for evaluating the design of prospective clinical trial protocols. Our analysis also illustrates how pharmacokinetic models can be used with a set of assumptions to explore the implications of factors such as co-morbidities, hepatic or renal impairment on drug exposure and consequently on dosing recommendations. In chapter 4, the population pharmacokinetic model describing the pharmacokinetics of deferiprone in adults and adolescents is used in conjunction with allometric scaling concepts to optimise the sampling algorithm for a prospective PK trial in children aged < 6 years. The analysis also provided an opportunity to assess the feasibility of reducing the number of patients per dose level. A sampling scheme with 5 samples post-dose per subject was found to be sufficient to ensure accurate characterization of the systemic exposure to deferiprone. Despite the assumptions regarding the changes in clearance and volume of distribution, our results reveal that the use of predefined (fixed) sampling schemes and sample sizes do not warrant accurate model structure and parameter identifiability in paediatric pharmacokinetic studies. Of importance is the accurate estimation of the magnitude of the covariate effects, as they may determine the dose recommendation for the population of interest. Furthermore, the analysis shows that the optimisation of study design does not require necessarily the use of the final model for the population of interest; the combination between ED-optimisation and the information carried by a hypothetical model is sufficient to significantly increase the quality of the information collected in a prospective clinical trial. Finally, in chapter 5 we have performed the analysis of the pharmacokinetics of deferiprone in children aged < 6 years after administration of three different dose levels in the DEEP1 PK study (EudraCT, 2012-000658-67). The analysis also demonstrates the value of optimised protocol design, in that pharmacokinetic parameter estimates are obtained with high precision and accuracy despite sparse sampling and small sample size (i.e., 18 evaluable children with 5 samples per patients). Based on bridging concepts, a dosing regimen was recommended to this population of young children that ensures comparable exposure to adults and adolescents. An oral dose of 75 mg/kg/day deferiprone results in median AUC values of 340.6 and 318.5 µM/L*h in children and adults, respectively. Comparable values are also observed after a regimen of 100 mg/kg/day. Hence, a dosing regimen of 25 mg/kg t.i.d. should be used in children below 6 years, with the possibility of titration up to 33.3 mg/kg. The work carried out in this section allowed us to characterise the pharmacokinetics in the target population and supported the dose rationale for the subsequent assessment of the efficacy and safety of deferiprone in a non-inferiority study in the target population.
From a methodological perspective, our findings highlight the role of parameter-covariate correlations to establish accurate dosing recommendations, i.e., pharmacokinetic studies in children involve more than simply generating data in a small group of children: it demands some level of stratification of the covariate factors.

**10.2 Integrated evaluation of efficacy and safety by modelling and simulation**

In addition to the requirement for high quality of data, accuracy and precision in the parameters of interest, the evaluation of pharmacodynamics, efficacy and safety imposes the assessment of the multidimensionality and the complexity of the clinical context in which the treatment is used. In contrast to pharmacokinetics, where measures of exposure are all derived from the underlying pharmacokinetic parameters, the analysis of pharmacodynamic data needs to account for multiple endpoints, many of which are correlated with each other. Drug-specific and system-specific parameters need to be considered in an integrated manner in order to characterise the efficacy and safety profile of a drug. As illustrated in the previous chapters of this thesis, PKPD models provide an opportunity to quantify such correlations and account for them when drawing conclusions about the benefit-risk profile of an intervention. To this end, the integration oncoming clinical data with prior knowledge (e.g. epidemiological data on background rates of expected co-morbidities; or knowledge acquired on a different disease, population or drug of the same class) becomes essential to describe the dynamics of disease and its progression and consequently determine long-term outcome.

These concepts were illustrated for characterisation of the safety and efficacy profile of deferoxamine, which is currently the first line treatment for chronic iron overload in patients affected by transfusion-dependent diseases (21–24). First, in chapter 6 we developed a disease model for chronic iron overload based on available literature data in untreated patients. For the first time, the relationship between serum ferritin levels and blood transfusions has been characterised in a parametric manner. A turnover model was implemented in which a time-varying parameter describes the ferritin conversion rate taking into account the transfusion history and disease progression. This model provides a more mechanistic interpretation of the pathophysiological changes associated with iron overload observed during the course of transfusions. Among other things, it allows us to address some unanswered clinical questions in thalassaemia, such as to estimate the time required to achieve response based on the serum ferritin levels at the start of treatment.

This turnover model was used as a starting point in chapter 7 for the evaluation of the chelating effects of deferoxamine, as determined by the changes in serum ferritin levels. Deferoxamine binds iron at different extracellular levels, and within the cell it targets
lysosomal ferritin iron by stimulating ferritin degradation. The drug effect was therefore parameterised in the disease model as a proportional change in the degradation rate constant ($K_{out}$). Such a parameterisation can also be applied to the evaluation of other chelating agents. Most importantly, the availability of this model offers an opportunity to explore different scenarios that have been so far evaluated empirically in clinical practice. For example, it may be possible to evaluate the importance of different compliance patterns for the available chelating agents, and consequently, their impact on ferritin levels and/or risk of clinical failure. In fact, we found clear evidence that high compliance leads to stable ferritin levels over time and that poor adherence to deferoxamine therapy is strongly correlated to a poor clinical outcome.

We subsequently apply this drug-disease model as a framework for further optimisation of therapeutic interventions, whereby the impact of covariate factors such as dose, drug exposure, compliance, or disease status can be evaluated against short and long-term treatment outcome.

As the assessment of the benefit-risk profile of a treatment requires quantitative descriptors of efficacy and safety, in chapter 8, we have complemented the work described in the previous chapter for safety endpoints. Whilst different dimensions of a symptom or sign may need to be considering when assessing its clinical relevance, here we have focused on incidence only. This decision was purely based on didactic reasons, ensuring clarity about how modelling and simulation can be used to integrate different endpoints. Two survival models were developed to describe disease-specific complications, namely hypothyroidism and type II diabetes. Both co-morbidities evolve as a consequence of iron accumulation and as such can be causally correlated with ferritin levels. A hazard function including ferritin levels was found to be a predictor of the probability of the incidence of the co-morbidity. In addition two models were developed to characterise the incidence of acute drug-specific adverse events, namely arthralgia/myalgia and anaphylaxis. They reflect two typical features of the safety profile, in that the former refers to a frequent, dose-dependent event, whereas the latter a rare, dose-independent one. Of particular relevance for the implementation of BR assessment, is the possibility of exploring rare dose-independent AEs. The four models were used in parallel to assess the impact of different exposure levels and compliance patterns on short- and long-term complications of iron chelation therapy. It should be noted that such a comprehensive analysis would not have been possible without integration of epidemiological (literature) and pharmacological data. In doing so, we have ensured that interdependencies and correlations between the different endpoints under evaluation were taken into account in a quantitative manner.
10.3 Clinical Trial Simulations: accounting for exposure, disease progression and uncertainty in benefit-risk analysis

As highlighted in the scope and intent of investigations, throughout this thesis we have defended the use of model-guided evidence generation and subsequent evidence synthesis for characterising the benefit-risk profile of medicines for children. Our results have demonstrated that empirical evidence is not necessarily accurate and that any attempt to establish the benefit-risk profile of an intervention at the time of its approval presupposes that the available data suffices to support such an assessment. This assumption may not be appropriate in a considerable number of cases. In paediatric diseases one needs to consider that the natural time course of disease occurs in parallel to developmental (physiological) growth and maturation processes. By performing clinical trial simulations and not-in-trial simulations, intrinsic and extrinsic sources of variation as well as confounding factors can be appropriately evaluated and incorporated into the decision process. The approach also addresses the issue of uncertainty due to limited sample size in clinical trials.

In chapter 9 MCDA is used in conjunction with simulation scenarios to evaluate the benefit-risk profile deferoxamine in children with transfusion-dependent haemoglobinopathies. Here all five models developed in the previous section were used to simulate treatment response in virtual paediatric patients. Individual response data is obtained from a 1-year hypothetical phase III trial in conjunction with a follow-up safety study in which patients are evaluated up to 10 years after the start of the treatment. A reference scenario was proposed based on the currently approved dosing regimen of deferoxamine, i.e., 45 mg/kg/day (5/7). In this analysis, we have compared the results of the phase III trial with a range of alternative regimens and conditions, namely different fixed dose levels, weight-banded dosing regimens and ferritin-guided individualised regimens. The availability of simulated responses over a period of 10 years enabled us to assess the impact of long-term complications on the benefit-risk balance. Our approach clearly provides a more comprehensive evaluation of the implications of drug-specific and disease-specific factors on the overall benefit-risk profile of deferoxamine. Moreover, we show how interdependencies can be accounted for during the characterisation of long-term complications and how disease progression can be disentangled from drug-related events. The current findings open new avenues for a more structured evaluation of the BR balance of an intervention. It provides a framework for the integration of knowledge in a parametric manner, thereby 1) complementing the existing data to support the decision to be taken; 2) optimising the input data for the MCDA analysis; and 3) quantifying the relevant correlations among different endpoints and possibly determining whether personalised regimens would be of any benefit for the patient population.
10.4 Conclusions, recommendations and perspectives

Throughout this thesis we have highlighted important limitations in the assessment of BR profile of a medicinal product in children, especially if applied at the time of approval. In contrast to current practice, PKPD modelling provides a robust, mechanism-based opportunity to complement the clinical data to be used in BR assessment. Whereas different methods have been developed with the intent of enabling a more quantitative appraisal of the benefit-risk profile, none of them fully address the aforementioned limitations. Nevertheless, the MCDA appears to possess the necessary features to assess BRB in a more systematic and transparent manner, with the potential for a full integration with PKPD modelling. Yet, it should be noted that the use of MCDA has an illustrative purpose in this thesis. In principle, our approach could be implemented in combination with other quantitative BR methodologies. The major challenge lies in the steps that take place before a BR evaluation is performed. Traditional endpoints do not necessarily capture sufficient information about the treatment and the p-value of a clinical trial is not predictive of effectiveness, losing its importance in the context of BRB. This is compounded by the fact that ethical and practical constraints limit the level of clinical evidence that can be gathered in a randomised, controlled setting as well as by the effect of disease progression on the benefit-risk balance, especially in chronic conditions.

In summary, we defend the need for a development and approval paradigm in which both evidence generation and evidence synthesis form the basis for approval. Clinical events or the absence thereof are not spurious, random features of an intervention. They are greatly determined by the patient population, the context in which the treatment is assessed and by the dose rationale.

Even though some examples are available in literature where M&S is proposed in combination with clinical utility measures in the context of BR assessment (25,26), this thesis represents the first analysis in which PKPD modelling has been fully integrated with MCDA. This approach enables regulators, sponsors, and clinical experts to:

1. optimise study design, ensuring the quality of the data collected;
2. integrate available information (e.g., epidemiological data) to support data analysis and models assumptions;
3. simultaneously evaluate multiple endpoints and account for co-linearity and interdependencies and
4. most importantly, complement real data for a more comprehensive decision making.
What have we learned?
We have encountered a number of challenges that made the characterisation of treatment effects within a real-life clinical context rather complex. Currently, clinical data are generated for hypothesis testing and as such are focused on primary endpoints, not on the assessment of benefit-risk profiles. Often, the available were not sufficient to estimate all model parameters for each separate endpoint or to fully assess correlations between endpoints. Moreover, dose rather than exposure is still used as gold standard for defining treatment effects, ignoring the role of pharmacokinetics and covariate factors as explanatory variables for the variability in response.

Firstly, these challenges allowed us to learn that M&S tools provide an opportunity to describe and quantify relevant aspects of paediatric diseases even in the absence of individual data by making use of available literature as well as prior knowledge, as presented in chapter 6. We have shown also that despite limited evidence regarding the safety profile of deferoxamine, such a limitation does not prevent us from exploring the implications of treatment based on the integration of data from epidemiological studies as well as from a different population in which the same compound or another one of the same pharmacological/molecular class has been used. Secondly, we have shown the importance of defining a model for each endpoint to be evaluated in a BR analysis: an integrated approach with the use of multiple models is essential to characterise the multidimensionality of disease. Moreover, PKPD relationships cannot be ignored during the evaluation of the BR profile. Whereas this process was found to be resource-intensive and time-consuming, we have no doubt about its superiority in terms of establishing the true benefit-risk profile and enabling better decision making. It is also clear that implementation of the approach in a prospective manner requires efforts to be allocated as early as phase I. Finally, we have learnt that the clinical interpretation of benefit-risk estimators is fraught with a relatively large degree of uncertainty, varying considerably among the different stakeholders. These differences do not facilitate consensus regarding the consequences of an intervention. M&S allows a reduction in this uncertainty thanks to the use of underlying PKPD relationships. Such relationships are causal in nature and as such provide a somewhat more objective readout of the different criteria and their relative consequences: exposure-response data can be used to guide the expert judgment and dismiss implausible correlations. Nevertheless, we are aware of the fact that subjectivity cannot and most likely will never be fully eliminated during the appraisal of the benefit-risk profile of a medicinal product.

Requirements and recommendations
In the next paragraphs, we aim at summarising how a model-based approach can be applied to future appraisals using MCDA as a quantitative method. The first point to consider is that the clinical data generated is not sufficient for a comprehensive BR evaluation. In table 1 a
visual overview of the elements that differentiate our proposal from current practices in benefit-risk assessment. The most important message from our work is that any available knowledge on the pharmacological properties as well as on the disease and its progression cannot be omitted from a more structured and comprehensive analysis of the benefit-risk profile.

Table 1. Overview of the differences between the proposed model-based approach and the current approach for BR appraisals. CTS: Clinical Trial Simulations; NITS: Not In Trial Simulations.

<table>
<thead>
<tr>
<th>CURRENT APPROACH</th>
<th>MODEL-BASED APPROACH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data from phase II-III trials</td>
<td>SOURCE</td>
</tr>
<tr>
<td>Pharmacokinetic data</td>
<td>Epidemiological data: background incidences (co-morbidities and AEs)</td>
</tr>
<tr>
<td>Longitudinal data</td>
<td>Prior knowledge on: mechanism of action; disease progression; other drugs; other populations</td>
</tr>
<tr>
<td>Evidence generated</td>
<td>INPUT</td>
</tr>
<tr>
<td>Evidence generated + virtual scenarios (CTS and NITS*)</td>
<td>OUTPUT</td>
</tr>
<tr>
<td>Tested dosing regimen vs. placebo or standard of care</td>
<td>Alternative options: possibility to achieve personalised medicine</td>
</tr>
</tbody>
</table>

The proposed approach is versatile in that it does not necessarily rely on the characteristics of MCDA. However, if we consider M&S in the context of MCDA, as described throughout this thesis, the chart shown in figure 1 can be used to illustrate what exactly changes in benefit-risk assessment. In figure 1, the different stages of MCDA are aligned to the contributions of M&S.
Figure 1. Contributions of the proposed model-based approach to the different stages of MCDA.

Future perspectives and conclusions
The regulation of drugs is undergoing rapid worldwide change in response to the advances in pharmaceutical sciences, drug development, and changes in public expectations. The
interest towards BR assessment is expanding and more and more projects have started focusing on the use of a more structured and transparent process by combing ideas and inputs from different stakeholders (5–8,27,28). The major effort of these groups appears to be focused on the following aspects (29–37):

1. more systematic use of available clinical evidence;
2. better graphical representation of the overall BRB;
3. re-evaluation of the BRB during the whole life cycle of the drug based on data accumulation and integration of clinical data with real data (progressive licensing);

Unfortunately, as depicted in Figure 2, it appears that today’s efforts rely primarily on data accumulation, making it central to the implementation of BR analysis. By contrast, we envisage the joint used of available data with drug-disease models as basis for clinical trial simulations (CTS) and/or not-in-trial simulations (NITS). The concept of extrapolating to real life population is not new and has been already applied and proposed in the context of safety management (39).

Figure 2. Process of the Public Health Benefit assessment. Adapted with permission from Massol et al. (38)
One major area that requires further development and discussion is uncertainty. While statistical uncertainty is captured well in most decision approaches, work remains to be done with regard to better articulating the consequences of any gaps in the efficacy and safety data (e.g., dropouts) and the level of evidence available on the benefit–risk profile. We acknowledge the fact that the models developed and used in this thesis carry a certain degree of uncertainty. Nevertheless, they allowed us to explore scenarios that could not be considered during drug development. They also provided answers to clinical questions (e.g., impact of long-term complications on the BRB of iron chelators) that could not necessarily be addressed directly in a real setting. Drug development and therapeutics will greatly benefit from a framework that describes how drug- and disease-specific properties interact with each other and ultimately determine the benefit-risk profile during development (i.e. randomised clinical trials) as well as during clinical use of the drug.

Our approach could form the backbone for the recently proposed progressive licensing model, which was initiated by Health Canada to develop a drug regulatory system for the future (36). The progressive licensing model consists in sound scientific evidence and risk management. It is aimed at supporting access to promising new drugs and the continuous monitoring of safety, quality, and efficacy. It is being developed on the assumption that knowledge and experience can be gained from every stage of a drug's life cycle. A well-designed regulatory framework should support the collection, analysis, and communication of knowledge and experience about a drug throughout its life cycle so that it can be used wisely. In addition, in contrast to network meta-analysis which relies in stochastic parameterisation of the trade-offs between risk and benefit, the use of drug disease models suits the same purpose using a biologically, clinically plausible parameterisation (40).

In conclusion, it should be highlighted that models do not make decisions, people do. A collaborative effort between industry and regulators will be required to continue to advance the science of benefit–risk methodology, since, as we have argued above, there is no single or simple approach that would address all benefit–risk assessments. Eventually, we expect a set of common principles, standards and a toolbox of methods will emerge. Ultimately, patients, clinicians, drug developers and regulators need to acknowledge that decisions are better made when data are presented and communicated in a clear, systematic manner. PKPD modelling can complement evidence generation by providing stakeholders the opportunity to explore conditions that have not been experimentally tested at the time of BR analysis. Regardless of the limitations models and simulation scenarios may have, model-based evaluation is likely to outperform gut feeling, which currently prevails in clinical decision-making.
References


