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CHAPTER 2
Model-informed benefit-risk assessment of iron chelation in transfusion-dependent haemoglobinopathies

Scope and intent of the investigation

2.1 General introduction
Drug approval by regulatory agencies is granted on the basis of the evidence on the safety and efficacy profile of a drug, which has been generated throughout the drug development phases (1–4). At this stage, decisions about the benefit-risk balance rely on the assumption that the data collected are sufficient to allow an unbiased evaluation of the safety and efficacy of a given intervention. This assumption may not be valid for all drugs, with a vast number of conditions and diseases in which numerous clinical questions cannot be fully addressed at the time of approval. In fact, the use of a question-based approach for the review of regulatory submissions by some regulatory agencies has highlighted the relevance of understanding which clinical and scientific questions need to be considered for the approval of a new drug. To be effective, such a regulatory process requires sponsors, researchers and clinicians to reflect on which data need to be generated, what is already known and how both existing and new data are integrated and processed. Moreover, as widely recognised by different stakeholders, including regulatory authorities, industry and patients (5–7), a clear framework for the assessment of benefit-risk balance (BRB) in which quantitative methods are used to translate findings obtained during the development process into measures that summarise favourable and unfavourable effects of treatment, is still lacking. This situation has resulted in undefined, inconsistent and non-transparent decision making (8–10).

Clarity about which clinical and scientific questions need to be addressed as well as the availability of quantitative methods to translate findings into summaries of favourable and unfavourable effects are requirements that apply to all drugs, but they become even more relevant when dealing with special populations, such as the paediatric population, where practical and ethical constraints make the process of generating evidence extremely
challenging (11–14). These hurdles limit the level of evidence available at the time of the first-marketing authorisation, as compared to other populations. In this thesis we focus on the current challenges in evidence generation during paediatric drug development. We demonstrate how modelling and simulation (M&S) can be applied for evidence synthesis and decision making; by the integration of existing and new data, to address essential clinical and scientific questions and to support a more comprehensive evaluation of the benefit-risk balance of a medicinal product prior to its approval. In addition, the implementation of such a framework will allow for better understanding of consequences of an intervention, and consequently improve risk management and therapeutic use of medicinal products. The examples provided in the following chapters were developed in the context of paediatric diseases, but the concepts underpinning the proposed framework can be extrapolated to a broader range of diseases and conditions across any patient population.

In order to demonstrate the contribution of modelling and simulation as a tool for more effective data generation, evidence synthesis and better decision making, the work presented in this thesis will be divided into three main sections, namely:

1. Optimisation of study protocol design and data generation in children;
2. Integration of existing knowledge and mechanism-based parameterisation of drug- and disease-specific properties;
3. Use of clinical trial and not-in-trial simulations to complement data generation and improve benefit-risk assessment.

An outline of the scope of the research and details on the implementation of the different sections are presented in the next paragraphs.

In chapter 1, an overview of the different methodologies currently available for benefit-risk assessment (BRA) is presented. Focus is given to differences between qualitative and quantitative approaches and the relevance of the latter for accurate decision making about the benefit-risk profile of a medicinal product. As recently suggested by EMA, amongst the available approaches the use of Multi Criteria Decision Analysis (MCDA) appears to have the right features to address the lack of transparency in the way benefit-risk balance is assessed, enabling integration of different dimensions or levels of clinical concern during the process (15).

Our review highlights how MCDA can benefit from the use of M&S in order to better define the BR balance of a given drug and vice versa, i.e. how concentration-effect relationships can provide a stronger basis for understanding benefit and risk, and how pharmacologists can gain insight into the therapeutic value of an intervention by jointly evaluating multiple
endpoints. The advantages of such an integrated approach are illustrated by the few available examples in the published literature.

The theoretical concepts presented in chapter 1 form the basis for the experimental work proposed in this thesis, which will be described in the subsequent paragraphs in this chapter. We will make use of chronic iron overload by transfusion-dependent haemoglobinopathies as a case study. Iron overload provides all the necessary elements, i.e., a complex multidimensional disease condition with short- and long-term complications that can lead to different clinical presentations over time. Moreover, it has a sufficiently low incidence to allow lessons learned to be applied in other rare paediatric diseases.

2.2 Transfusion-dependent haemoglobinopathies

Among the transfusion-dependent diseases, β-thalassaemia major is one of the most common disorders. It belongs to a group of hereditary blood disorders characterised by reduced or absent beta-globin chain synthesis. As a result, patients suffer from reduced haemoglobin (Hb) levels in red blood cells (RBC) and decreased RBC production followed by anaemia (16).

Historically, the majority of thalassaemia patients are located in the Mediterranean countries, in the Middle East and Asia. According to the Thalassaemia International Federation (TIF), around the world only about 200,000 patients are alive and registered as receiving regular treatment (17). Children are usually diagnosed between 6 and 24 months after birth. Early clinical symptoms include feeding problems, diarrhoea and progressive enlargement of the abdomen caused by spleen and liver enlargement. In some developing countries, patients also suffer from growth retardation, poor musculature and skeletal changes (18). Individuals affected by β-thalassaemia major require regular RBC transfusions to survive. Without transfusions or in the presence of poor management of the disease, patients often die before the third decade of life. According to the guidelines for the clinical management of thalassaemia (17) transfusion intervals should aim to maintain a pre-transfusion Hb level between 9 and 10 g/dl and a post-transfusion level of 14 to 15 g/dl. This requirement implies the need for frequent blood transfusions, with the most common transfusion interval being once every two to four weeks (equal to two to three blood units per three weeks).

A graphical overview of iron distribution and storage is provided in figure 1. In the context of transfusion-dependent diseases, it worth mentioning that there is no innate mechanism that is able to clear any iron excess from the body. Under normal physiological conditions, iron is almost completely recycled within the body.
Figure 1. Iron homeostasis. In a balanced state, 1 to 2 mg of iron enters and leaves the body each day. Dietary iron is absorbed by duodenal enterocytes. It circulates in plasma bound to transferrin. Most of the iron in the body is incorporated into haemoglobin in erythroid precursors and mature red cells. Approximately 10 to 15 percent is present in muscle fibres (in myoglobin) and other tissues (in enzymes and cytochromes). Iron is stored in parenchymal cells of the liver and reticuloendothelial macrophages. These macrophages provide most of the usable iron by degrading haemoglobin in senescent erythrocytes and reloading ferric iron onto transferrin for delivery to cells. Adapted from: Andrews et al, N Engl J Med. 1999 (19).
Iron entry into the cells is regulated by the uptake of iron-transport protein transferrin from the plasma. Once chronic RBC transfusion therapy has started, iron exposure in macrophages increases, which results in the saturation of transferrin transport capacity. This leads to the release of non-transferrin bound iron (NTBI) in plasma. NTBI can then enter important tissues (e.g., in heart and liver) and accumulate over time. As iron is stored in tissues mainly as ferritin complexes, once ferritin storage capacity has saturated small clusters of ferritin particles will be formed and degraded by lysosomes leading to the formation of insoluble masses of hemosiderin (20–26). Over time these masses can cause severe organ damage (19,27–31).

**Iron overload and chelation therapy**

Even though significant improvements have been achieved in the management of the chronic transfusion regimens in the past decades, RBC therapy will eventually lead to a series of complications. Iron overload is the most common and relevant one and it is associated with several (lethal) co-morbidities such as cardiac dysfunction, liver fibrosis, hypogonadism, hypothyroidism, hypoparathyroidism and diabetes mellitus (28,30). Cardiac disease caused by myocardial siderosis is the most relevant complication, causing death in 71% of the patients affected by transfusion-dependent diseases (27). In the absence of an innate mechanism that allows removing iron excess from the body, treatment with iron chelators is essential to prevent iron accumulation and related complications (32–35). An overview of iron chelators currently approved for the treatment of iron overload is shown in table 1 (33).
**Table 1.** Summary of the available iron chelators. Adapted with permission from: Kwiatkowski JL. Pediatr Clin N Am. 2008; 55:461-82 (33)

<table>
<thead>
<tr>
<th>Property</th>
<th>Deferoxamine</th>
<th>Deferiprone</th>
<th>Deferasirox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chelator:iron binding</td>
<td>1:1</td>
<td>3:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Subcutaneous or intravenous</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Usual dosage</td>
<td>25-50 mg/kg per day</td>
<td>75 mg/kg per day</td>
<td>20-30 mg/kg per day</td>
</tr>
<tr>
<td>Schedule</td>
<td>Administered over 8-24 hours, 5-7 days per Week</td>
<td>Three times a day</td>
<td>Daily</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Local reactions</td>
<td>Agranulocytosis/neutropenia</td>
<td>Gastrointestinal disturbances</td>
</tr>
<tr>
<td></td>
<td>Ophthalmologic</td>
<td>Arthralgias/Arthritis</td>
<td>Renal Insufficiency</td>
</tr>
<tr>
<td></td>
<td>Auditory</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advantages</td>
<td>Long-term data available</td>
<td>May be superior in removal of cardiac iron</td>
<td>Once daily administration Only oral chelator licensed for use in US</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Toxicity Compliance Problems</td>
<td>Not licensed for use in United States. Frequent blood count monitoring required</td>
<td>Long-term data lacking</td>
</tr>
<tr>
<td>Drug cost</td>
<td>$</td>
<td>$$</td>
<td>$$$</td>
</tr>
</tbody>
</table>

Iron chelators possess a similar mechanism of action. They act by 1) preventing the uptake of NTBI into organs, such as liver and heart; 2) chelating intracellular iron and thus preventing its incorporation into ferritin; or 3) intercepting iron released from degraded ferritin (36).

**Clinical assessment of iron overload**

The symptoms and signs associated with iron overload can be initially diagnosed and assessed by different clinical biochemistry parameters. The most common marker of iron imbalance is serum ferritin, which indirectly reflects the correlation between circulating levels and total body iron stores (37). The use of serum ferritin alone, as a single clinical marker however is not always sufficiently robust to detect iron overload. Ferritin levels are also be influenced by other factors such as inflammatory disorders and liver disease (38).
Therefore, serial measurements of serum ferritin are still the easiest and least invasive method to evaluate iron overload and efficacy of chelation therapy. Other methods for the assessment of iron overload focus more on tissue specific accumulation. Liver iron concentration (LIC) is considered as the gold standard for the evaluation of iron overload. LIC has been shown to correlate well with total body iron accumulation (39). The measurement of liver iron concentration requires, however, an invasive technique, which may lead to potential clinical complications and bias, such as in the case of false negative results (40). Magnetic bio-susceptometry (SQUID) is another option for measurement of liver iron accumulation (41). However, it is only available in a limited number of centers worldwide. Furthermore, cardiac complications due to iron accumulation in the heart have been associated with 50-70% of deaths in thalassaemia major patients, mainly at young age (42). Methods for cardiac monitoring were developed under the assumption that keeping serum ferritin and LIC level below a certain threshold (<2500 μg/L and <7 mg/kg dwt respectively) would lead to decreased cardiac risks. However, cardiac dysfunctions were often identified at relative late stage of treatment, suggesting that this method was not sufficient for effective intervention. In recent years, magnetic resonance imaging (MRI) techniques for assessing iron loading in the liver and heart have been introduced and validated for the evaluation of tissue specific accumulation (43).

Clearly, understanding and integration of knowledge about the short and long term mechanisms underlying iron overload are lacking. The ability to predict iron organ accumulation based on systemic, non-invasive markers such as ferritin will depend on further characterisation of dynamic, homeostatic processes. In this context, accurate details of the transfusion history and assessment of the effects of chelation therapy are equally important.

In the next sections we present details of the investigations, which will provide the basis not only for the characterisation of the disease, but also for the design and optimisation of clinical protocols in children. These concepts are followed by the introduction to methods supporting evidence synthesis as a means to better understand the safety and efficacy profile of a drug. Two important aspects reflect the novelty in the approach described here. First the use of a multi-model analysis in which different measures of efficacy and safety are derived according to underlying biological or pharmacological correlations, where applicable. Second, the integration of clinical data from real and virtual patients, whose responses are simulated from the aforementioned models, to improve the assessment of benefit-risk profile by multi-criteria decision analysis (MCDA).
2.3 Optimising evidence generation in paediatric trials

Practical and ethical constraints to the implementation of clinical trials in the paediatric population (11,12,14), make evidence generation in most paediatric diseases extremely challenging. The value of the new data is tremendously higher than in a standard protocol involving adults. Yet, little attention has been paid to the opportunities to ensure that high quality data are obtained whilst keeping the burden for the children to a minimum.

As indicated previously, the approval of a medicinal product relies on the ability of a sponsor to address clinical and scientific questions regarding the efficacy and safety profile of the drug under investigation. Here factors such as how knowledge is generated in this population and which type of data is needed to approve a given therapeutic intervention ultimately underpin the validity of the experimental evidence provided in a regulatory submission. In a very simplistic manner, it can be said that three scenarios have been used to determine the rationale for paediatric programs, while relying on adults as a reference population: 1) if the disease has different features in adults and children, then both pharmacokinetic and efficacy/safety data must be generated; 2) if the disease and its progression as well as the main endpoints of interest are similar in the two populations bridging concepts can be applied and pharmacokinetic and eventually pharmacodynamic data should be sufficient to prove comparable efficacy; 3) in some cases it is also conceivable that pathophysiological processes and pharmacological mechanisms are sufficiently understood to allow extrapolation of efficacy findings from the adult population without the need of generating new evidence in children. In all three cases the quality of the data collected is crucial to establish not only the effect size of a treatment, but also to define the actual benefit-risk profile of the intervention.

From a clinical and scientific point of view, this implies that high accuracy and precision are desirable, irrespective of the nature of the trial.

Whilst the aforementioned scenarios are valuable steps to mitigate the burden of evidence generation in children, they also imply the need for generating evidence prior to approval as a key requirement. None of these scenarios formally considers how current understanding of a drug, disease or patient population in adults can contribute to the decision making process for children. We foresee the integration of available knowledge with clinical data can significantly improve one’s ability to assess the benefit-risk profile of a treatment and reduce the uncertainty associated with gaps in the data available at the time of submission.

From a clinical pharmacology perspective, this implies that the concept of bridging could be expanded to situations where the disease is different in children and adults. If, such differences are simply due to the natural course of the disease, then these differences may be predicted by parametric (mathematical) representation of the underlying processes in a drug-disease model. This is the situation that we deal with throughout this thesis, i.e.,
haemoglobinopathies, in which long-term complications, which are the primary consequence of iron overload, clearly mark the difference between adults and children and can be anticipated using prior knowledge.

Amongst the opportunities for increasing the informative value of data collected in children is the possibility of using population pharmacokinetic or pharmacokinetic-pharmacodynamic modelling in conjunction with optimal design concepts to reduce sample size and frequency in the so-called bridging studies.

Despite the wide clinical experience with iron chelators, and more specifically with deferiprone, there is no pharmacokinetic data in children below 6 years of age. Given the nature of the disease and its progression, a model-based approach can be used to optimise a prospective pharmacokinetic study in children and consequently define the dosing requirements in this subgroup. First, we demonstrate in chapter 3 how available pharmacokinetic data from adults and adolescents can be characterised by means of a population pharmacokinetic model. We then explore how uncertainty about the changes in pharmacokinetic properties of deferiprone can be evaluated in conjunction with optimal design theory. A proposal for sampling schedule and group size is presented in chapter 4, where ED-optimality concepts are used to identify the most suitable sampling scheme in the absence of data in the population under investigation. This information will be used to support the design of a prospective bridging study in children with less than 6 years of age. Subsequently, we show how modelling and simulation enables the evaluation of the pharmacokinetics of deferiprone based on sparse data. Dosing recommendations are proposed based on the predicted exposure to deferiprone taking into account the parameter distributions in the target patient population. In this investigation, it is worth mentioning that dosing recommendations involve more than simply the data obtained in a small group of children: it encompasses parameter-covariate interactions, which may not be well represented in the trial population.

Whereas these concepts have been implemented for a specific drug, a similar approach can be applied for the evaluation of biomarkers or clinical response.

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

The concepts underpinning the optimisation of pharmacokinetic data collected in prospective clinical trials are also extremely important in the evaluation of the pharmacodynamics of a drug. In this sense, population PKPD modelling can be applied as a tool for evidence synthesis. In addition to the opportunities to increase the informative value of data collection in prospective studies, PKPD modelling also address a critical aspect
of clinical pharmacology research, i.e., the integration of information as the basis for the evaluation of treatment response when complex and multiple factors are involved. Moreover, the approach enables one to account for multidimensionality, i.e., to evaluate in an integrated manner multiple endpoints. The correlation or interdependency between endpoints or measures of drug response is currently overlooked when quantitative BR analyses are performed. Experimental evidence from clinical trials is handled in empirical manner, which disregards the (pathophysiological or pharmacological) mechanisms associated with the underlying correlations or interdependencies. PKPD models provide an opportunity to quantify such correlations and account for them when performing BR analysis and drawing conclusions about the benefit-risk profile of an intervention. It is also worth mentioning that understanding of the dynamics of disease and its progression is critical to assess the long-term implications of a therapeutic intervention. Such an integrated approach will be illustrated by combining clinical data with available 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).

More specifically, in the context of chronic iron overload serum ferritin levels are often used as markers of total body iron accumulation. Despite known limitations of instantaneous serum ferritin levels as a predictor of iron organ accumulation, model-based approaches can be developed which incorporate MRI data as well as other measurements (e.g., SQUID or LIC) to better describe tissue specific accumulation (see paragraph 2.2.2). However, a challenge remains in that such measurements may not be easily performed or feasible in young patients. Therefore, situations exist in which decision-making will have to be guided by evidence arising from endpoints which do not reflect drug-disease interaction in the target population. An attempt will be made to demonstrate how evidence synthesis by modelling and simulation may provide a more robust basis for extrapolating findings from adults to children and for translating short-term results into long-term predictions.

In chapter 6 we develop a disease model based on available literature data, in which changes in serum ferritin levels are correlated with RBC transfusion regimen. The approach is developed in a stepwise manner; first we evaluate basal, physiological changes in serum ferritin in healthy individuals by means of a turnover model. Then, the effect of RBC transfusions is added into the model to quantify changes in the production rate of ferritin. Our investigation provides for the first time in a parametric way, evidence of the relationship between blood transfusions and serum ferritin levels. This physiological turnover model forms the basis for a more structured evaluation of chelation therapy in transfusion-dependent iron overload. The approach is subsequently validated in chapter 7, where data
from 27 patients affected by transfusion-dependent diseases are used to predict the effects of deferoxamine on ferritin levels.

The scope of the drug-disease model for iron overload is not only to establish the relevance of ferritin levels as a measure of effective chelation therapy. The ultimate goal will be to demonstrate its value as a tool to support decision making in benefit-risk analysis. Of note is the opportunity to explore different scenarios in addition to available clinical evidence. Such scenarios may provide further insight into the role of differences in patient population characteristics and dosing regimens on treatment response as well as enable one to predict potential long-term complications based on short-term effects. Given the multidimensional nature of benefit-risk profile, our approach involves not only the integration and parameterisation of a drug-disease model for efficacy measures, but also for safety endpoints. Therefore, in chapter 8, we evaluate the acute and long-term complications of iron chelation therapy using the data obtained from patients undergoing chelation with deferoxamine. Different adverse events are considered, which reflect typical features of adverse drug reactions, including short and long term events, as well as dose-dependent and dose-independent effects. Such a comprehensive analysis is proposed by integrating epidemiological (literature) and pharmacological data. In doing so, we also ensure that interdependencies and correlations between the different endpoints under evaluation are taken into account in a quantitative manner.

As in many other chronic diseases, compliance to the prescribed dose and dosing regimen is an important factor in chelation therapy. We illustrate how patient behaviour regarding compliance to treatment contributes to changes in ferritin levels and consequently affect the overall benefit-risk profile of an intervention. Simulation scenarios are evaluated in which different compliance patterns are used to assess changes in the magnitude and incidence of acute and long-term complications.

2.5 Clinical trial and not-in-trial simulations: accounting for exposure, disease progression and uncertainty in benefit-risk analysis

Throughout this thesis we have hypothesised that model-guided evidence generation and subsequent integration of new clinical data with available knowledge (i.e., evidence synthesis) provides a robust framework for characterising the benefit-risk profile of any intervention. We also highlight the limitations of current practice in that any attempt to establish the benefit-risk profile at the moment of drug approval relies only on the evidence generated (e.g. treatment arms tested throughout the drug development phases). Such an approach presupposes that the available data are representative of the response profile in
target population and suffice to support key decisions about the favourable benefit-risk profile and suitability of the recommended dose and dosing regimens. The underlying assumptions appear to overlook the fact that in children the natural time course of disease occurs in parallel to developmental (physiological) growth and maturation processes. The interaction between these processes may lead to significant changes in the benefit-risk profile over time and such changes are not evident at the time of approval, nor necessarily well captured by long term safety monitoring, as implemented in pharmacovigilance plans. Once more we show that a model-based approach can be used in which virtual scenarios are created taking into account clinical trial design features, as well as real life factors which are known to play a role in clinical practice, such as variable compliance patterns. 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.

Clearly, most of the points-to-consider described in the previous paragraph are currently overlooked or excluded from quantitative BR analysis, independent of the methodology used. The highlight of this thesis is therefore presented in chapter 9, where we illustrate how new evidence (from typical clinical programmes) can be integrated with existing knowledge in a parametric manner, using drug-disease models in the context of clinical trial protocols or real-life use of the drug. This simulation framework provides a more robust basis for establishing the benefit-risk profile of treatment in children. In fact, clinical trial and not-in-trial simulations offer the opportunity to explore scenarios in which the impact of covariate factors can be assessed without being limited only to the data available. Moreover, we propose the use of Multi Criteria Decision Analysis (MCDA) as the method of choice for evaluating real and virtual data together. As discussed in the introduction of this thesis, MCDA appears to have the necessary features to characterise and summarise the BR profile of a treatment in a systematic and transparent manner. In chapter 9, we perform MCDA to establish the benefit-risk profile of iron chelation therapy with deferoxamine in thalassaemic patients undergoing frequent transfusions. The drug-disease models developed in the previous chapters are used to simulate a range of scenarios; describing typical clinical trials and long term follow up. During the analysis the same relative weight is given to both types of data, i.e., the available data from clinical trials and the predicted profiles inferred from the models. A standard phase III trial (“real data”) is used as a reference scenario and a number of alternative dosing algorithms are proposed and compared (“virtual data”). For the sake of clarity, here we only look at the optimisation of the dosing regimen and how the different options proposed can influence the BR profile. The intent of these scenarios is to illustrate how drug-disease models in conjunction with simulations can better support regulatory and clinical decision making. A range of applications can be considered, in that
the proposed simulation framework could also be used to optimise study design before the implementation of clinical trials. But most importantly, it could form the basis for personalised medicines. Clinical trial and not-in-trial simulations allow us to quantify the impact of relevant covariate factors on treatment outcome, thereby demonstrating the implications of treatment and population stratification.

2.6 Conclusions and perspectives
The results and conclusions drawn from our research are summarised and discussed in chapter 10. In this concluding chapter, we revisit the different examples presented in this thesis and we attempt to shed light on the issues currently faced by clinicians, sponsors and regulators involved with the evaluation of the benefit risk profile of a treatment. We make clear that evidence generation has been the paradigm for the development and approval of new drugs. This paradigm is inefficient and should be questioned for a number of reasons. The assumption that arising evidence from clinical trials discriminates drug-specific properties from the underlying progression of disease overlooks shortcomings such as limited accuracy and precision of the estimates for endpoints, which will be subsequently used for BR assessment.

We defend the need for a development and approval paradigm which relies on a framework which supports evidence generation and evidence synthesis as 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. In addition, we emphasise in this last section, how clinical trial and not-in-trial simulations can be used to complement clinical evidence. We envisage that such a framework will provide a more structured basis for BR analysis, reducing uncertainties about the changes in benefit-risk profile, which are intrinsic to the progression of disease and take place in parallel to maturation developmental growth in children.

We conclude this thesis with a set of answers to longstanding clinical questions regarding the use of iron chelators in chronic iron overload. The approach used to address those questions also highlights opportunities for future research in quantitative pharmacology, especially with regard to the development of multidimensional models and the relevance of Bayesian statistical inference for the implementation of such models. In our final remarks we include suggestions regarding the requirements for the prospective implementation of this framework as a tool for regulatory approval and risk management for paediatric medicines.
CHAPTER 2

References


