CHAPTER 9

Summary / Samenvatting

This thesis covers a variety of topics around the central theme of pharmacological research involving children, with a specific focus on the development of minimally invasive methodology that can be employed in future studies involving children. Children form a unique group within the area of pharmacological research and pharmacotherapy. The heterogeneity even within this group is large, covering the range of preterm neonates weighing 500 grams up to adolescents. Obviously, therapeutic needs change across this range, as among others disease epidemiology, drug disposition, pharmacodynamic response, and suitable drug formulations change with age. The same holds true for the design of drug trials involving children: where pharmacokinetics in adults can be studied simply by recruiting a number of healthy volunteers, such a study with a number of healthy toddlers is clearly not feasible and not acceptable. Therefore, approaches and new methodology are needed to circumvent these issues.

CHAPTER 1 of this thesis provides a background scope on the topic of pharmacological research involving children. Until recently, the pharmaceutical industry was not required to submit data concerning children to the competent authorities. This changed in the late 1990's (US) and in 2006 (Europe) when the authorities started requiring the industry to present data on the pediatric population when applying for a novel marketing authorization, and at the same time offering rewards for new research on already marketed compounds. This has led to an impulse for research infrastructure specifically focused on the pediatric age group. On the other hand it has led to industry exploiting the new regulation by placing the 'center of gravity' of research on their blockbuster drugs, thereby creating substantial additional revenue. This chapter also shortly comments on the issue of ethics in trials involving children. Non-therapeutic research is almost inevitable in the process of adequate drug research (e.g. dose-finding, toxicity, basic pharmacokinetics). In minors, non-therapeutic research may not entail more than minimal risk and/or burden. The interpretation of minimal risk and burden are a subject of intense debate. Finally, the first chapter contains a short overview of the contents of the thesis.

CHAPTER 2 evaluates the effects of the pediatric exclusivity provision under the American Food and Drug Administration Modernization Act (FDAMA), later followed by the Best Pharmaceuticals for Children Act. This pediatric exclusivity essentially provides a drug manufacturer 6 months of additional market exclusivity, once this manufacturer delivers results of research in the pediatric population that is satisfactory to the FDA. We have reviewed the types of studies that have been performed in response to this legislation, and for which compounds. We found that 135 entities were granted pediatric exclusivity between 1998 and 2006, involving research with at least 40,000 patients from the pediatric age group. The spectrum of compounds researched closely matched the adult utilization patterns rather than utilization patterns of children. In addition, the amount of blockbuster drugs granted pediatric exclusivity was considerable. We concluded that although the development of a research infrastructure is certainly a positive development, but have also drawn attention to the facts that the additional profits to drug companies might be viewed as disproportionally large, and that an increased focus should be put on actual therapeutic needs of children.

The availability of formulations suitable for children is not always obvious. In **CHAPTER 3**, Levothyroxin is covered as an example of problems associated with suitable formulations being unavailable. In the Netherlands, common practice is to administer levothyroxine in the form of crushed tablets administered with water. Where this is referred is commonly referred to as a solution, it turns out to be a suspension due to very poor solubility of levothyroxine in water. We have shown that administration through a nasogastric feeding tube leads to loss of considerable amounts of drug in the tube, probably due to non dissolved tablet

particles remaining in the nasogastric feeding tube. Also administration of crushed tablets with water on a spoon leads to uncertainty, as most of the drug will be in the bottom of the spoon and not dissolved in water. We have recommended use of a preparation commercially available in other European countries. In contrast to the suspension described above, this commercial product is a solution. We have shown that this solution can be administered through nasogastric feeding tubes without problems.

CHAPTER 4 is an example of a study collecting combined pharmacokinetic and pharmacodynamic data. We have studied clonidine, a centrally active antihypertensive drug, which has been demonstrated to elicit growth hormone release in the late 70's. It is used as a diagnostic tool in patients, including children, with a suspected growth hormone deficiency. The diagnostic procedure, involving administration of clonidine, is associated with several untoward effects such as hypotension, sedation and hypoglycemias. By combining the collection of pharmacokinetic data with pharmacodynamic data, we were able to perform a combined analysis of the two using non-linear mixed effect modeling, an advanced mathematical method working with likelihood models to predict the true relationship of drug concentrations versus observed effects. Based on our data, we have concluded that the clonidine concentrations reached are probably well above those needed for maximum intentional and unintentional effects. Ideally, one would want to predict a lower effective dose level using the PK-PD model, but the highly complex underlying pattern of spontaneous growth hormone release has made a solid prediction difficult. We have therefore concluded that a lower dose is likely to be sufficient, but prospective studies are needed to test this hypothesis and to establish an evidence-based lower dose level.

In **CHAPTER 5** and **6**, we have employed neurocognitive tasks form the Neurocart in children aged 8-12 years of age. The Neurocart is a battery of neurocognitive tasks frequently used and extensively validated at the Centre for Human Drug Research. In **CHAPTER 5** we report on a group of healthy children performing 3 consecutive runs of neurocognitive testing. We identified learning effects for a number of tasks, which should be considered in future trial design. We also evaluated how children tolerated participation in the study, and demonstrated that this type of study is well-tolerated by children from this age group. In **CHAPTER 6**, we used the same battery in children with attention-deficit hyperactivity disorder. We designed a placebo controlled, 2-way crossover trial in which participating children were tested with several runs of neurocognitive testing after administration of placebo and after administration of methylphenidate. Significant differences between the placebo and methylphenidate condition were identified for a number of tasks, and in one case (adaptive tracking) there was a clear suggestion of a relationship with (expected) plasma methylphenidate concentrations. The plasma methylphenidate concentrations were not measured during the study, but saliva samples were collected. These data will be used to predict plasma concentrations of the participating children, using pharmacokinetic modeling with data obtained from a study in adults, in whom paired plasma and saliva samples were taken.

A bedside device for measurement of the activated partial thromboplastin time (APTT) is evaluated in **CHAPTER 7**. The bedside requires only a drop of blood for assessment of the APTT, whereas conventional methods require a tube to be sent off to the central lab. This means that the bedside device is less invasive, as it requires a substantially smaller amount of blood. We demonstrate why thorough validation of new methodology such as this bedside device is necessary. Paired samples were taken from infants on heparin therapy, one of which was measured using the bedside device, the other sample analyzed using the central lab as 'gold standard'. It turned out that the bedside device led to substantial overestimation of the APTT, especially at higher APTT levels. We have therefore concluded that the bedside device should not be used to monitor heparin therapy

in infants. The findings in this chapter should also be seen as a generic advice to thoroughly evaluate novel methodology.

The thesis concludes with a general discussion (**CHAPTER 8**). Apart from shortly summarizing the contents of the thesis, we have once again drawn attention to the financial aspects of legislation regarding drug research involving children. The current list of top 10 selling drugs in the United States contains 8 compounds for which pediatric exclusivity was granted. The nature of these drugs (including statins, antipsychotics and anticoagulant) reaffirms our prior statement that there is a mismatch of research performed under the pediatric exclusivity provisions with actual therapeutic needs. To address the true therapeutic needs, public funding will be needed (through the 7th Framework Programme in the EU and the NIH in the US), as there is no prospect of large revenue in this category of drug compounds. Once such research is performed, governments also have a responsibility to make the obtained information accessible to the public and prescribers. In the Netherlands, the open access and web-based Children's Drug Formulary is an excellent example of how newly obtained knowledge can be disseminated effectively. This example also illustrates the need for public funding: open access of unbiased information would be hard to achieve without support from public funds.