Stellingen behorende bij het proefschrift:

First-pass and systemic metabolism of cytochrome P450 3A substrates in neonates, infants, and children

JM Brussee

1. Inflammation and organ failure lead to an increased exposure to CYP3A substrates in critically ill children. *This thesis*

2. Intestinal and hepatic CYP3A activity can be quantified by application of advanced physiological population pharmacokinetic modelling approaches. *This thesis*

3. The very low presystemic and systemic metabolism of midazolam in preterm neonates is due to immature CYP3A activity not only in the liver, but also in the gut wall. *This thesis*

4. Clearance of most CYP3A substrates with a low or intermediate extraction ratio can accurately be scaled from adult clearance values down to children using a pediatric covariate function for CYP3A-mediated midazolam clearance. *This thesis*

5. Modelling approaches in the pediatric population that incorporate both drug-specific and system-specific properties, lead to more physiological knowledge in neonates, infants, and children. *Barret JS et al. Clin Pharmacol Ther. 2012*

6. The impact of intestinal metabolic extraction on bioavailability is often neglected. *Yang J et al. Curr Drug Metab. 2007*

7. A PKPD model is useful only when it can be used to answer a (clinical) question. *Standing JF, Br J Clin Pharmacol. 2017*

8. Mechanistic models taking into account developmental changes affecting absorption and (presystemic) clearance in children can optimize pediatric drug development. *Edginton AN, Paediatr Anaesth. 2011*

9. Despite the fact that saunas do not affect the pharmacokinetics or pharmacodynamics of midazolam (*Vanakoski J et al. Eur J Clin Pharmacol. 1996*), they positively affect the completion of a PhD thesis.

10. Those who have knowledge, do not predict; those who predict, lack knowledge or data. *Lao Tzo*

11. Less pressure to publish and inspiring role models in science lead to better research quality.

12. Working hard is important, but something else is even more important: believing in yourself.