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Pharmacogenomics in drug development : implementation and application of PKPD model based approaches

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Propositions

To the doctoral thesis

Pharmacogenomics in Drug Development:

Implementation and Application of PKPD Model Based Approaches

1. Incorporating PK-PD modelling into pharmacogenomics (PGx) research enables quantitation of the contribution of genetic variability relative to the overall interindividual variation. *This thesis*

2. The relationship between genotype and phenotype should not only focus on the mean differences between genotype groups but also on the variation within each phenotype group. *This thesis*

3. Clinical trial simulation can be used to quantitatively compare study designs incorporating genetic information, and will lead to improved therapeutic outcomes. *This thesis*

4. Genotype differences in pharmacokinetics should always be considered relative to the exposure response relationship. *This thesis*

5. PB-PK models incorporating information from non-clinical sources should be used to optimise the design of first in human trials for drugs which undergo biotransformation by polymorphic enzymes (Jones H and Rowland-Yeo K, CPT Pharmacometrics Syst. Pharmacol. 2013:2, e63).

6. Modelling PK, PD, PGx, and systems pharmacology will not only enhance the power of predicting a personalized drug response but will

also shed light on our understanding of living systems in a broad sense (Xie L et al. PLoS Comput Biol. May 2014; 10(5)).

7. Genetic heterogeneity alone cannot completely explain interindividual variations in drug responses (Lam YW, ISRN Pharmacol. 2013:641089).

8. For most drugs, pharmacogenomic testing has not been endorsed by expert committees, since we still lack evidence that clinical outcomes will improve (Kitzmiller J et al Cleve Clin J Med. Apr 2011; 78(4): 243–257).

9. Everything is theoretically impossible until its done (Robert A. Heinlein).

10. Valid criticism does you a favour (Carl Sagan).

Frances V. Stringer

Leiden, 13 January 2015