PKPD relationships and dose rationale in analgesic drug development : towards the prediction of target engagement

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Cover Page

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Title: PKPD relationships and dose rationale in analgesic drug development : towards the prediction of target engagement
Issue Date: 2013-11-20

Stellingen

behorende bij het proefschrift

"PKPD Relationships and Dose Rationale in Analgesic Drug Development -Towards the Prediction of Target Engagement"

1. The lack of construct validity of pre-clinical models used in drug screening, the irreversibility of changes introduced by signalling dysfunction and the absence of early diagnostic tools explain the differential pharmacological effects of analgesic drugs in animals and humans. *This thesis*

2. Poor experimental design can lead to inaccuracies in parameter estimation and consequently to biased selection and ranking. *This thesis*

3. The characterization of exposure-response relationships is a *conditio sine qua non* for the dose rationale of analgesic drugs, regardless whether they are aimed at symptomatic pain relief, disease modification or prophylaxis. *This thesis*

4. In contrast to the maximum tolerated dose and other empirical approaches in Phase 1 and 2 trials, the use of biomarkers offers a basis for the personalization of therapy from the very start of clinical development. *This thesis*

5. The intrinsic refractoriness to treatment with analgesic drugs reflects disease heterogeneity, irrespective of the exposure levels. *This thesis*

6. The reasons for discontinuation of a drug discovery program are neither well investigated nor published, leading to speculative and unsubstantiated claims. Whiteside *et al*. Neuropharmacology, **54**:767-775, 2008

7. Since the accurate characterization of PKPD relationships is not a formal requirement for the regulatory approval of new analgesic drugs, the evidence generated may be uninformative or even biased. (*EMEA guideline on Clinical Medicinal Products for the Treatment of Nociceptive Pain*, London, 2002)

8. Treatment of neuropathic pain is often poorly understood by healthcare professionals and consequently not managed well. The selection of tricyclic antidepressants and anticonvulsants as the drugs of choice, in terms of effectiveness, can therefore be compared to using cannons to shoot a duck. (Allen, *CEACCP* **5**: 134-137, 2005)

9. The most commonly used numeric rating scales for pain screening have only modest accuracy for identifying patients with clinically important pain and are consequently inadequate for the quantitative assessment of efficacy. (Krebs *et al.*, *J Gen Intern Med.* **22**: 1453–1458, 2007)

10. The yardstick for evaluating a good scientist are the number of publications and successful grants. It's rarely good science.(Author's view).

11. Everything should be made as simple as possible, but not simpler. (Einstein)

12. I have often heard ABDs (all but dissertation) remark, 'If only I could finish my thesis, my troubles would be over'. (David Sternberg, *How to complete and survive a doctoral dissertation.* New York, 1981)

13. In today's digital era the printing of hard copies of a thesis only contributes to increasing our carbon footprint, and is thus an outdated practice. (Author's view)

Amit Taneja, 20th November 2013