Review Report on PhD Thesis of Nikunjkumar K. Patel
entitled

„Prediction of pro-arrhythmic activity in humans with the use of physiologically based pharmacokinetics and pharmacodynamics modeling"

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Nikunjkumar Patel submitted the doctoral thesis based on research findings presented in four peer-revieved publications. The key idea investigated in these papers is to find the relationship between side-effect of treatment - torsade de points and secondary to the pharmacotherapy QT interval elongation, to find models to determine patients at high risk of life-threating arrhythmias.

Prolongation of the cardiac action potential and its electrocardiographic symptom - QT interval elongation have been linked to a potentially fatal but rare tachyarrhythmia known as torsades de pointes. Nonclinical studies analyzed the action potential duration effect and the QT interval performed on the hERG channel current in vivo, have been developed to predict the risk of QT interval prolongation and torsades de pointes in humans. On the other hand, there is a lot of evidence showing that an increase in the QT interval does not necessarily lead to torsades de pointes. Thus, it appears that while standard assays are very good, although perhaps not infallible, at predicting the risk of QT interval prolongation in man they do not predict the proarrhythmic risk. For last years there has been a plethora of publications suggested that there are electrophysiological markers associated with drug-induced torsades de pointes other than hERG channel activity, APD and the QT interval, and these markers may be better predictors of torsade de pointes. Electrophysiological markers are important but the risk of that kind of procedures is significant. In this condition important is to prepare simulation basing on mathematical models. Thus, application of physiologically based pharmacokinetics simulations of drug exposures models of arrhythmias and cardiac mortality risk assessment starting in drug development could guide drug development decisions in pre- and post-approval risk management to define a clinical safety.

In this condition, topic of presented dissertation seems to be very current. Every novel method of prediction of secondary to pharmacotherapy arrhythmias is important, because potentially is able to reduce cardiovascular mortality.

Nikunjkumar Patel based his dissertation on four publications.

1. First publication entitled "*Virtual Thorough QT (TQT) Trial-Extrapolation of In Vitro Cardiac Safety Data to In Vivo Situation Using Multi-Scale Physiologically Based Ventricular Cell-wall Model Exemplified with Tolterodine and Fesoterodine.*" was published in *American Association of Pharmaceutical Scientists Journal* (AAPS J. 2018 Jul 11;20(5):83. doi: 10.1208/s12248-018-0244-3. 2017 Impact Factor: 3.804, MNiSW: 40). Nikunjkumar Patel is first author of this paper and he was the author for correspondence. Authors in their study performed

virtual thorough QT/QTc simulations , as surrogate to identify the proarrhythmic risk, have been exemplified with use of two related drugs tolterodine and fesoterodine. Moreover the influence of bio-relevant concentrations: plasma vs estimated heart tissue analyzed. Performed model was able to accurately simulate the QT prolongation at therapeutic and supra-therapeutic dose levels of tolterodine well within 95% confidence interval limits of observed data. The model was able: to predict the QT prolongation difference between CYP2D6 extensive and poor metabolizer subject groups at different doses, to simulate the negligible QT prolongation observed with fesoterodine establishing its differential metabolism. Authors demonstrated the utility of the quantitative systems toxicology and safety approaches to simulate virtual TQT trials.

2. Second publication entitled "*Towards Bridging Translational Gap in Cardiotoxicity Prediction: an Application of Progressive Cardiac Risk Assessment Strategy in TdP Risk Assessment of Moxifloxacin.*" was published in *American Association of Pharmaceutical Scientists Journal* (AAPS J. 2018 Mar 14;20(3):47. doi: 10.1208/s12248-018-0199-4. 2017 Impact Factor: 3.804, MNiSW: 40). Nikunjkumar Patel is again the first author of this paper and he was the author for correspondence. Authors analyzed occurrence of torsade de pointes, special form of drug-induced cardiac arrhythmia. Torsades de pointes is one of leading reasons of mortality especially in drug naïve, resistant patients with pro-arrhythmic medication. Thus risk of torsades de pointes is a leading cause of attrition and post-approval re-labeling and withdrawal of many medicaments. The measurable parameter modifying the risk of torsade de pointes is the QT interval elongation. Nikunjkumar Patel and his team used multi-scale mechanistic modeling framework consisting of physiologically based pharmacokinetics simulations of clinically relevant drug exposures combined with Quantitative Systems Toxicology models of cardiac electro-physiology to describe applications of this simulations in torsade de pointes risk prognosis. They show approach in cardiac risk assessment as exemplified by moxifloxacin, an anti-bacterial agent, 4th generation quinolone, with abundant clinical cardiac safety data. Simulations of moxifloxacin concentrations in plasma and heart tissue estimated were linked with in vitro measurements of cardiac ion channel inhibition to predict the magnitude of QT prolongation in healthy individuals. Authors concluded that application of a progressive physiologically based pharmacokinetics simulations of clinically relevant drug exposures combined with quantitative systems toxicology models of cardiac risk assessment paradigm starting in early development could guide drug development decisions and later define a clinical safety for post-approval risk management.
3. Third publication entitled "*Real Patient and its Virtual Twin: Application of Quantitative Systems Toxicology Modelling in the Cardiac Safety Assessment of Citalopram.*" was published in *American Association of Pharmaceutical Scientists Journal* (AAPS J. 2017 Nov 27;20(1):6. doi: 10.1208/s12248-017-0155-8. 2017 Impact Factor: 3.804, MNiSW: 40). Nikunjkumar Patel is also the first author of this article. In this study authors established quantitative systems toxicology model for citalopram to simulate and predict the occurrence of cardiotoxic events previously reported in patients under various clinical conditions. The model

considered the effects of citalopram and its most notable active metabolites, on cardiac electrophysiology. Through the use of model including multiple ion channel current inhibition and metabolites in the simulation with unbound plasma citalopram concentration provided the lowest prediction error. Moreover authors veriffied the predictive performance of the model with three additional therapeutic and supra-therapeutic drug exposure clinical cases. Authors concluded that mechanistic modelling can help bridge the gaps existing in the quantitative translation from preclinical cardiac safety assessment to clinical toxicology.

4. Last, fourth publication was published in *Theoretical Biology and Medical Modelling* and entitled "*Age and gender dependent heart rate circadian model development and performance verification on the proarrhythmic drug case study.*" (Theor Biol Med Model. 2013 Feb 9;10:7. doi: 10.1186/1742-4682-10-7., 2017 Impact Factor: 2.000, MNiSW: 25). Using in silico implemented mathematical and statistical modelling to translate the in vitro findings into the human in vivo situation at the population level authors analyzed publicly available data set describing the circadian changes of the heart rate of 18 healthy subjects for the heart rate model development. Model was validated with the use of a clinical research database containing heart rate measurements derived from 67 healthy subjects and then incorporated into the ToxComp platform to simulate the impact of heart rate circadian variation on QTc interval. The usability of the combined models was assessed with moxifloxacin as a model drug. Authors concluded that simulations performed at the population level proved that the combination of the IVIVE platform and the population variability description allows for the precise prediction of the circadian variation of drugs pro-arrhythmic effect thus practically useful model describing the heart rate circadian variation has been developed and moreover its performance was verified.

Publications form a coherent whole which presents one of the solutions to the problem of modeling of the risk of adverse events in pharmacotherapy. Moreover, considering the importance of the research topic, the creation and evaluation of models simulating the risk of adverse reactions are important new contribution to the existing literature. Topic is a kind of bridge between theoretical pharmaceutical sciences and clinical medicine.

I am pleased to conclude that the doctoral dissertation of Mr Nikunjkumar Patel presents an original contribution to science in the field of pharmacy and I recommend it to be accepted by Collegium Medicum of Jagiellonian University in Kraków in partial fulfillment of the requirements for the doctor's degree.

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