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VIRAL RISKS OF PLASMA-DERIVED MEDICINAL PRODUCTS

M.P. Janssen¹, C.L. van der Poel², B.A. van Hout¹, J. Over², H.T.M. Cuijpers²

¹ UMC Utrecht, Utrecht, Netherlands

² Sanquin Blood Supply Foundation, Amsterdam, Netherlands

Background: The prevention of transmission of viral infections by plasma-derived medicinal products has, since the transmission of HIV and HCV in the past, been a point of concern for manufacturers, legislators and patient groups. At present new European legislation (EMA guideline CPMP/BWP/5180/03) requires a viral risk assessment for HBV, HCV, HIV, Parvo B19 and HAV for all new marketing applications.

Aims: The risk model that was developed for the Dutch Sanquin Blood Supply Foundation will be laid out together with modeling assumptions and perceived model limitations. The results of model sensitivity analyses will be presented to show the impact of various parameters on the residual risk for different viruses.

Methods: To enable a proper assessment of the final product related residual viral transmission risk, all individual steps in blood collection and the production process are modeled as close to actual practice as possible. The residual risk is assessed using discrete event Monte-Carlo simulations. This approach allows for incorporation of both variability and uncertainty of model parameters and enables modeling of conditional decision strategies. Variability and uncertainty refer to donor epidemiology, donation intervals, blood screening tests, quarantine period, size and composition of the production pool, production time of the product, viral reduction capacity of the production process and product yield. Decision strategies during the production process are for example related to timely discarding of on-hold plasma in case a subsequent donation from a repeat donor is found infected.

Results: The analyses show that the residual risk is mainly determined by the viral incidence rate, screening test sensitivity, viral reduction capacity and the product yield. The production pool size and type of donation (apheresis or whole blood donation) have (almost) no impact on the residual risk. Increasing the inventory hold period has a modest impact on the residual risk, only 0.5 logs for 1 year increase in hold period. The results show that there is large dispersion in the residual risk estimates (2 to 6 logs) depending on the virus type. This is caused by the uncertainty in virus titer of an infected donation and the uncertainty with respect to the exact viral reduction capacity of the production process.

Summary/Conclusions: The use of probabilistic Monte-Carlo simulations is essential when estimating residual risks. This approach in contrast to traditional residual risk estimation allows incorporation of complex process specific decision strategies into the risk model. It also allows modeling of uncertain model parameters, like incubation time, duration of the window phase or viral load of an infected donation. A counter-intuitive finding was that production pool size and type of donation e.g. apheresis or whole blood donation have a limited impact on the residual risk.