Pediatric Formulations and Challenges beyond Technological Development: Identification and in silico Qualification of Impurities in 5 mg Primaquine Tablets.

Thamara de Carvalho Mendes[a]; Maria Eduarda Correia Furtado[a]; Juliana Johansson Soares Medeiros[b], Ivone de Jesus do Nascimento Lopes[a], Flávia Furtado de Mendonça Sousa[a], Diogo Dibo do Nascimento[a]; Livia Deris Prado[a]; Camila Areias de Oliveira[a] *

[a]Laboratório de Desenvolvimento e Validação Analítica - Farmanguinhos, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brazil.

[b]Coordenação de Desenvolvimento Tecnológico– Farmanguinhos, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brazil.

INTRODUCTION: The present work outlines the crucial analytical procedure undertaken for the registration of primaquine 5 mg tablets specifically intended for pediatric use. Given the importance of ensuring the safety and efficacy of pharmaceutical formulations administered to children, rigorous analytical methodologies are essential in the drug development and registration process.**OBJECTIVE:**In compliance with current regulatory guidelines, our primary objective was to identify and qualify the impurities that were detected during the long-term stability study of the tablet formulation. This step is fundamental for ensuring product safety throughout its shelf life and for supporting regulatory submissions.**MATERIAL AND METHODS:**To achieve accurate and reproducible results, a stability-indicating chromatographic method was developed using a C18 column. Chromatography was performed employing a binary mobile phase system. Mobile phase A consisted of trifluoroacetic acid (TFA) 0.05% and acetonitrile (ACN) in a volumetric ratio of 78:22, while mobile phase B was 100% ACN. The analysis was conducted in gradient mode at a flow rate of 0.8 mL/min, and the detection wavelength was set at 265 nm, monitored using a Diode Array Detector (DAD). This method allowed for the clear separation and detection of degradation products under stability conditions.**RESULTS:**The degradation products that reached the identification threshold after 24 months were eluted at 15.87 minutes and 19.46 minutes, identified as DP-2 and DP-3, respectively. LC-HRMS analysis revealed protonated molecule peaks at m/z 517.32599 for DP-2 and 461.21567 for DP-3. Their respective elemental compositions were determined to be $C_{30}H_{41}O_2N_6$ and $C_{26}H_{29}N_4O_4$. DP-2 was qualified through *in silico* safety assessment using a quantitative structure-activity relationship (QSAR) model, with an established specification of 0.6%. For DP-3, although full structural elucidation was

not achieved, a conservative specification limit of 0.5% was assigned.**CONCLUSION:**This study highlights the critical role of advanced analytical development in assessing the quality and safety of pharmaceutical products, especially during regulatory submission. It also underscores the complexities encountered during the product lifecycle, reinforcing the need for robust scientific approaches in drug development.