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Regulation of stability studies to enhance the efficiency of drug registrations to regulatory authorities

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Stability testing is an important tool to assess the quality of drug substances and products which may vary with time under influence of variety of factors such as temperature, humidity and light. Stability studies of drugs are designed according to the climatic zones to establish a retest period for active drug substance or a shelf life for the finished product as well as to recommend the storage conditions. The strict regulatory requirements on designing, performing evaluating stability study to claim the expiry date and shelf life of drug products are based on a series of regulatory requirements and advisory guidelines that have been developed by regulatory authorities of US, Europe and Japan which were harmonized through the development of the 5th International Conference and Exhibition on Harmonization (ICH) procedures. To assess the stability of drug substances and products, the design and conduct of stability studies, defining relevant thresholds for impurities testing is required with a current good manufacturing practice based risk management approach to achieve a robust stability of pharmaceutical dosage forms. There are relevant requirements that cover new drug substances and products as well as new dosage forms containing existing active ingredients and vice versa.

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Piperaquine and Lumefantrine resistance in Plasmodium berghei ANKA associated with increased expression of Ca2+/H+ antiporter and glutathione associated enzymes

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We investigated the mechanisms of resistance of two antimalarial drugs Piperaquine (PQ) and Lumefantrine (LM) using the rodent parasite Plasmodium berghei as a surrogate of the human parasite, Plasmodium falciparum. We analysed the whole coding sequence of Plasmodium berghei chloroquine resistance transporter (Pbcrt) and Plasmodium berghei multidrug resistance gene-1 (Pbmdr-1) for polymorphisms. These genes are associated with quinoline resistance in Plasmodium falciparum. No polymorphic changes were detected in the coding sequences of Pbcrt and Pbmdr-1 or in the mRNA transcript levels of Pbmdr-1. However, our data demonstrated that PQ and LM resistance is achieved by multiple mechanisms that include elevated mRNA transcript levels of V-type H+ pumping pyrophosphatase (vp2), Ca2+/H+ antiporter (vcx1), gamma glutamylcysteine synthetase (ggcs) and glutathione-S-transferase (gst) genes. These mechanisms are also known to contribute to chloroquine resistance in P. falciparum and rodent malaria parasites. The increase in 'ggcs' and 'gst' transcript levels were accompanied by high glutathione (GSH) levels and elevated activity of glutathione-S-transferase (GST) enzyme. Taken together, these results demonstrate that Pbcrt and Pbmdr-1 are not associated with PQ and LM resistance in P. berghei ANKA, while vp2, vcx1, 'ggcs' and 'gst' may mediate resistance directly or modulate functional mutations in other unknown genes.

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