Modeling Complex PK Profiles of Long Acting Injectable Products Using a Convolution-Based Approach

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Objectives: The active pharmaceutical ingredient (API) in long acting injectable (LAI) products is usually encapsulated in microspheres (i.e., glycolide/lactide matrix) that extend the release of API into the systemic circulation, giving relatively long apparent half-lives and unique PK profiles. The PK profile of these products usually consists an initial release phase where APIs on the surface of the formulation ingredients are absorbed systemically, a lag phase with minimal API release, and a main release phase in which the ingredients in the formulation degrade allowing the API to be absorbed into the systemic circulation completely. The objective of this study was to apply a convolution-based methodology to characterize the PK profile of LAIs, to link in-vivo release with in-vitro dissolution data and finally to assist development of optimized LAI products.

Methods: Convolution-based methods are used to directly relate the time course of the plasma concentrations to the time course of the fraction of the dose released in-vivo. A novel approach is proposed to implement joint models describing the time course of the in-vivo drug release and the disposition and elimination processes of LAI products. The model describing the time course of the fraction of the dose released in-vivo is implemented using the same models used to describe the in-vitro dissolution profiles. This approach provide a modelling framework for linking the in-vivo release with in-vitro dissolution data, to assist development of optimized LAI products and to define new bioequivalence criteria for LAI formulations. The model has been implemented in NONMEM 7.3.

Results: The proposed methodology was successfully applied using single or dual Weibull in-vivo release models for fitting the PK profiles of: a) four long-acting subcutaneous risperidone formulations, b) four long acting olanzapine microspheres formulations, and c) RISPERDA CONSTA® formulation.

Conclusions: A new modeling approach has been proposed to characterise the complex PK profiles of LAI products. The estimated in-vivo release rate has been used to evaluate the in-vitro/in-vivo correlation and the define criteria for assessing comparative bioequivalence of LAI products.