Stability Study to Ensure Abuse Deterrent Properties During Shelf Life of Abuse Deterrent Formulation of Opioids

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Abuse of Opioid drug products has become a national health crisis in the US. These drugs are being abused in several ways by administering either oral, nasal or parenteral routes that potentially increases the mortality rates. To deter abuse, a number of drug products with abuse-deterrent (AD) properties have been approved by the US Food and Drug Administration (FDA) (1). For AD labeling, various strategies including physical barriers, chemical barriers, antagonists, aversive agents, and prodrugs have been investigated (1). To deter abuse effectively, it is critical to maintain AD properties during product shelf life. However, no information on the stability of AD properties during product shelf life is publicly available. To support the development and safe use of Abuse Deterrent Formulation (ADF) of Opioids, this study is designed to evaluate the stability of AD properties of surrogate ADF of Opioids at various storage conditions. Surrogate extended release (ER) AD tablets were prepared by direct compression using Diltiazem HCl (model drug), polyethylene oxide (PEO) polymer and suitable excipients followed by curing at 70°C for 30 mins. PEO provides abuse deterrence by exerting physical barriers via enhancing hardness and viscosity of the formulation. Following the FDA Guidance (2), *in vitro* characterization and evaluation of AD properties of tablets including content uniformity, drug-excipient interaction (DSC, FTIR), hardness, friability, Scanning Electron Microscope (SEM), dissolution, physical manipulation using coffee grinder, particle size distribution, drug extraction potential in solvents at room and elevated temperatures, syringeability/injectability etc. have been performed. The stability study was conducted at 25°C/60% RH and 40°C/75% RH following the ICH guidelines (3).

Based on the data collected on freshly prepared samples, the dissolution study confirmed the desired ER of drug from the tablet matrix. Curing process remarkably increases the crushing strength of tablets. However, surrogate tablets can be consistently manipulated using a coffee grinder in less than 5 mins at room temperature to a size less than 1 mm. Such a manipulation leads to a significant enhancement in the amount of drug extracted in solvents, regardless of temperature as well as storage condition and time. Furthermore, the viscosity of the manipulated sample (prepared from tablets stored at 40°C/75% RH) hydrated in water is decreased after 3 months, indicating possible degradation of PEO used in AD tablet formulation. In addition, it is indicated that a shorter hydration time of the manipulated sample in water eases syringeability, and thereby may increase potential drug abuse by IV route. The identified potential critical quality attributes will guide to recommend the selection of suitable excipients, manufacturing method as well as storage condition for adequate AD properties during the shelf life of AD Opioid drug products.

References: **1.** Maincent J, Zhang F. *Int J Pharm*. 2016;510(1):57-72. **2**. General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: Guidance for Industry, 2017. **3**. ICH guidelines, Q1A(R2), 2003.