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Commentary

Considerations for Conducting Bioequivalence Studies on Complex Delayed-release, Long Acting Injections and Sustained-release Formulations

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Abstract

Generics have been on the market since the Waxman-Hatch bill was passed in 1984 and the approval process has worked well. However, there are new issues to be resolved. Among these are products with a delayed, sustained, long acting injections or complex absorption. Based upon these absorption issues, how well does adult data predict children. These areas are discussed in the commentary.

Keywords: Injections; Generics; Children

Since the passing of the Waxman-Hatch act [1], also known as the "drug competition and patent term restoration act of 1984" one of the guiding principles of that act is that all generic drug studies should be done in adults for practical reasons using either a two-way crossover or parallel statistical design [2]. These results should then be applicable to children since the drugs have previously shown efficacy in pediatrics and children. That is a good rule of thumb, not to unnecessarily expose children to drugs without a therapeutic benefit which has worked for 30 yrs. In addition, doing drug studies in children has many difficulties beyond just safety concerns.

However, with the advent of drugs with complex absorption mostly related to extended release, long acting injectables and multiple release formulations, this practice was brought into question with the methylphenidate generics for Concerta which were prescribed for ADHD (attention deficit hyperactivity disorder). The Mallincrodt and Kudco generics were initially compared to the innovator Concerta via the standard two-way crossover designed bioequivalence studies. However there were complaints from patients (e.g.,children) that the generic drugs were not effective. The drugs were subsequently removed from the marketplace [3]. A resolution to the problem was based upon statistics. The objective was to be certain that the test should be no more variable than the reference. However, this was not possible to be determined with the established two-way cross-over design thus a design change was proposed [4]. All future generic drug studies for these formulations would have to be conducted as replicated design studies to define the subject-by-formulation interaction with a value above 15% being problematic [5]. Therefore, to additionally improve metrics for methylphenidates, the new FDA guidance recommended the determination of several partial area-under-the-curve values (pAUC0-3, pAUC3-7, and pAUC7-12) in addition to Cmax to assure curve shape adherence in these formulations [5]. To date this seems to be okay; however, one of the lingering questions has been to determine how well adult data predicts the outcome in children including both pharmacokinetics and pharmacodynamics. The other concern would be the impact of efficacy prediction especially for extended release, long acting injections and complex formulations. Current research efforts have been related to these matters with work on the comparison of children 4-12 yrs old vs adults for the same methylphenidate formulation. In addition, studies are being

conducted via simulations to determine the impact of two-way crossover vs replicated designs on bioequivalence and if indeed when the pharmacokinetics fails to meet the 90% confidence intervals of 80-125% of the reference how does efficacy reflect these changes. This could be a key question because if it does not, then how well does adult pharmacokinetics predict the pharmacokinetics and efficacy in children. This would be especially relevant for products with delayed or complex absorption (e.g., long acting injectables). For some drugs, the efficacy may depend on only one end of the confidence interval such as Naloxone [6]. Answers to this question can be addressed via simulation utilizing the pediatric efficacy studies submitted to support drug registration for pediatrics and children.

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