Common Deficiencies in Abbreviated New Drug Applications with In Vitro Bioequivalence Studies
U.S. Food and Drug Administration

Purpose
Abbreviated new drug applications (ANDAs) with in vitro bioequivalence (BE) studies have numerous preventable deficiencies which unnecessarily prolong the ANDA review and approval process, thereby significantly increasing the regulatory burden on the Agency and generic industry. The purpose of the present study is to bring forth commonly occurring deficiencies in ANDA submissions containing in vitro BE studies and provide useful information to generic drug industry to avoid preventable deficiencies in future submissions.

Methods
Internal databases of the United States Food and Drug Administration (US FDA) were searched from January 2001 to December 2014 for the most commonly occurring deficiencies in ANDA submissions with in vitro BE studies. For the purpose of this evaluation, we focused solely on ANDAs containing in vitro BE studies from three (3) different classes of drug products: Category 1: locally acting drug products (Eg. Resins that bind phosphate in the GI tract), Category 2: drug products that require equivalent release of the active pharmaceutical ingredient (API; Eg. Quantitative capsule rupture testing; QCRT), and Category 3: drug products classified as Biopharmaceutical classification system (BCS) Class I drugs. The common deficiencies identified were categorized into different categories for each drug product category and descriptive statistical analysis was performed to determine commonly occurring deficiencies.

Results
Data from a total of 126 ANDA submissions from January 2001 to December 2014 were collected to identify commonly occurring deficiencies. The breakdown of 126 ANDA submissions based on aforementioned categories is as following: 18 ANDAs belong to Category 1 drug products, 54 ANDAs belong to Category 2 drug products and 54 ANDAs belong to Category 3 drug products. The two (2) most common deficiencies for Category 1 drug products are as following: 61% submissions have inadequate optimization of the QCRT with USP Apparatus II and IV and 44% submissions are inadequate due to deficiency related to inadequate API equivalence and Inactive ingredient equivalence testing. Four (4) major deficiencies, identified for Category 2 drug products, are as following: i) 74% ANDAs have deficiencies related to inadequate pre-study analytical method validation, ii) 72% ANDAs have deficiencies related to inadequate sample analysis and repeat analysis, iii) 56% ANDAs have deficiencies related to inadequate study design of kinetic binding and pivotal equilibrium binding studies, and iv) 43% ANDAs have test product formulation deficiencies. Four (4) common deficiencies identified for Category 3 drug products, are as following: i) 39% submissions have deficiencies related to inadequate study design of solubility testing of the drug product, ii) 28% submissions have deficiencies related to inadequate study design of solubility testing of the drug product, iii) 24% submissions have deficiencies related to inadequate study design of permeability testing of the drug product, and iv) 18% submissions have deficiencies related to inadequate dissolution testing

Conclusion
By providing examples of common deficiencies from historical data, the present study aims to provide useful information to generic drug industry submitting ANDAs with in vitro BE studies in order to avoid common preventable deficiencies, resulting in the submission of higher quality ANDAs. The submission of higher quality ANDAs will subsequently make the drug approvals process less time-consuming, which will go a long way in significantly decreasing the regulatory burden, especially in the age of Generic Drug User Fee Agreement (GDUFA).