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Learnings from Generic Substitution in US and Suggestions to Korean Food and Drug Administration

Bong Kyu Yoo

College of Pharmacy, Yeungnam Univerisity, Kyungsan, Kyungbuk, Korea

Virtually every state in US has adopted laws and regulations that mandate the generic substitution of brand-named prescription drugs in order to reduce sky-rocketing drug costs. In the late 1970s, many state governments began to recognize the need of generic substitution and requested Food and Drug Administration (FDA) to consult with this issue. FDA did consult which drugs were interchangeable each other based upon the available scientific and experimental evidences given to the agency along with New Drug Application (NDA) and Abbreviated New Drug Application (ANDA). Soon, however, it became apparent that FDA could not serve the needs of each state on an individual basis.

FDA Center for Drug Evaluation and Research (CDER) released first publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" commonly known as "Orange Book" in Federal Register (45FR 72582) on October 31, 1980. This publication contains FDA's advice to the public, to practitioners, to pharmacists, and to the state governments regarding drug product selection based on scientific evidence, while generic substitution may involve social and economic policy administered by each states. Orange Book has been updated yearly and we have 23rd Edition on January 2003.

Therapeutic equivalence evaluations in the book reflect FDA's application of specific criteria to the approved multi-source prescription drug products. These evaluations are presented in the form of code letters that indicate the basis for the evaluation made. Code letters composed of "A" and "B" which mean "considered to be therapeutically equivalent" and "considered not to be therapeutically equivalent at this time", respectively.

"A" code means drug products that are considered therapeutically equivalent to other pharmaceutically equivalent products. FDA classifies as "A" for those products that meet the

following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredients in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.

"B" code means drug products that are considered not to be therapeutically equivalent to other pharmaceutically equivalent products. Drug products disignated with "B" code fall under one of three main policies: (1) the drug products that have been identified by the agency as having documented bioequivalnece problems or a significant potential for such problems and for which no adequate studies demonstrating bioequivalence have been submitted to FDA; or (2) the quality standards are inadequate or FDA has an insufficient basis to determine therapeutic equivalence; or (3) the drug products are under regulatory review.

Generic substitution is mandatory by every state law unless prescription bears "brand name prescription is medically necessary", "dispense as written", or "no substitution" etc. Therefore, claim reviewers in most insurance companies and state-run Medicaid are highly alert on prescriptions filled with brand-name drug. Some are employing formulary, which is even tougher system to protect their budget. Bluecross Blueshield, for example, allows only one kind of angiotensin receptor blockers (ARBs) to be filled for their members. If a prescriber wants to stick to the specific brand-named drug, then he/she has to contact the insurance with documented medical reason and get the prior authorization (PA) before the prescription is filled.

Suggestions to KFDA are; (1) to expedite the classification which drugs are considered "A" without bioequivalence evaluation and which drugs need to be further evaluated; (2) to publish a Report on Therapeutic Equivalence Evaluation to the public and health professionals; (3) to encourage the pharmaceutical companies to use a generic name for their generically copied products. Drug products that do not present a known or potential problem for therapeutic equivalence should not be forced to go through the time-consuming and national energy-consuming evaluation arena. Finally, KFDA should employ the concept of therapeutic euivalence in the place of bioequivalence because bioequivalence does not imply therapeutic equivalence.