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Therapeutic Equivalence of Generic Drugs Letter to Health Practitioners

January 28, 1998

Dear Colleague:

As you may be aware, certain individuals and groups have appeared recently before state legislatures, state boards of pharmacy, and drug utilization review committees, to express concerns about the interchangeability of certain products they characterize as narrow therapeutic index (NTI) drug products. A particular concern being raised by them is whether the safety and efficacy profile of these products could change if a switch were made from a brand-name product to an FDA-designated therapeutically equivalent generic product. FDA wishes to comment on the issue of interchanging any brand-name drug with a therapeutically equivalent generic drug and requests that you inform your association's members of this information.

For both brand-name and generic drugs, FDA works with pharmaceutical companies to assure that all drugs marketed in the U.S. meet specifications for identity, strength, quality, purity and potency. In approving a generic drug product, the FDA requires many rigorous tests and procedures to assure that the generic drug is interchangeable with the brand-name drug under all approved indications and conditions of use. For these reasons, FDA approved product labeling does not recommend that any additional tests need to be performed by the health care provider when a switch occurs from a brand-name drug product to a generic equivalent drug product, from a generic equivalent to a brand-name product drug, or from one generic product to another when both are deemed equivalent to a brand-name drug product. Brand-name drug products and therapeutically equivalent generic drug products are identified in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," frequently called the "Orange Book."

In addition to tests performed prior to market entry, FDA regularly assesses the quality of products in the marketplace and thoroughly researches and evaluates reports of alleged drug product inequivalence. To date, there are no documented examples of a generic product manufactured to meet its approved specifications that could not be used interchangeably with the corresponding brand-name drug. Questions have been raised in the past, as well, regarding brand name and generic products about which there could be concern that quality failures might represent a public safety hazard. FDA has performed post-marketing testing on many of these drugs to assess their quality. In one instance, more than 400 samples of 24 marketed brand-name and generic drug products were tested and found to meet the established standards of purity and quality. Because patients may pay closer attention to their symptoms when the substitution of one drug product for another occurs, an increase in symptoms may be reported at that time, and

anecdotal reports of decreased efficacy or increased toxicity may result. Upon investigation by FDA, no problems attributed to substitution of one approved drug product for another has occurred.

FDA works with both brand-name and generic drug product manufacturers after a drug product is in the marketplace to assure its quality. For example, brand-name and generic drug product manufacturers may want to change the drug formulation, site of manufacture, or manufacturing process after the drug is in the marketplace. These types of changes can be put in place only after the drug manufacturer provides the FDA with sufficient evidence that the drug identity, strength, quality, purity and potency will not change.

There are products in which small changes in the dose and/or blood concentration could potentially result in clinically important changes in drug efficacy or safety. Usually, these drugs require frequent adjustments in the dose of the drug and careful patient monitoring irrespective of whether the drug is a brand or generic drug product. These drugs may sometimes be described in FDA approved drug labeling as narrow therapeutic range drugs.

FDA may recommend to the manufacturers additional tests for approval of both brand-name and generic products, depending on the complexity of a drug substance or drug product and also depending on whether small changes in the dose and/or blood concentration could result in changes in drug efficacy or safety. It may also require additional tests for certain post-approval changes in manufacturing. The agency's recommendation to the manufacturer for these additional tests is designed to give the practitioner and patient additional assurance of product quality and interchangeability. These additional requirements should not be construed to mean that additional clinical scrutiny is necessary when interchange occurs. If anything, the additional tests required of pharmaceutical manufacturers are designed to reduce, not increase, concerns on the part of patients and practitioners.

Based on FDA's determination of therapeutic equivalence between generic and innovator drug products, the FDA concludes that:

- Additional clinical tests or examinations by the health care provider are not needed when a generic drug product is substituted for the brand-name product.
- Special precautions are not needed when a formulation and/or a manufacturing change occurs for a drug product provided that the change is approved according to applicable laws and regulations by the FDA.
- As noted in the "Orange Book," in the judgment of the FDA, products evaluated as therapeutically equivalent can be expected to have equivalent clinical effect whether the product is brand name or generic drug product.
- It is not necessary for the health care provider to approach any one therapeutic class of drug products differently from any other class, when there has been a determination of therapeutic equivalence by FDA for the drug products under consideration.

In considering drug product selection decisions, FDA acknowledges and supports the importance of good communication between the patient and the health care provider, particularly with regard to medications that require frequent monitoring of performance. We hope this information is useful to health care providers when making decisions regarding drug product selection. We thank you for seeing that this information reaches the members of your organization.

Sincerely,
Stuart L. Nightingale, M.D.
Associate Commissioner for Health Affairs



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