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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Rockville, MD 20857

April 20, 2004

Rick Potter  
New Hampshire Pharmacists Association  
2 Eagle Square, Suite #400  
Concord, New Hampshire 03301 -8905

Dear Mr. Potter:

Thank you for your April 7, 2004 letter where you raise questions related to Governor Benson's recent purchase of prescription drugs from Canada and questionable testing of these drugs by the New Hampshire State Police laboratory. The questions raised in your letter demonstrate the complex issues involved in the assessment of whether a drug purchased from outside the U.S. drug distribution system is equivalent to or is actually the FDA approved version and whether the quality of the product (e.g., potency, purity) has not been adversely affected. This assessment is not a trivial matter. As you are aware, qualitative testing for the presence of an active ingredient is not a substitute for thorough quantitative analysis (both in vitro and in vivo studies) that is necessary to ensure that the drugs are identical or interchangeable.

FDA shares with public officials and others the great concern for senior citizens and other patients who have difficulty paying for prescription drugs and we understand the need to find solutions to affordable access. However, these must be safe solutions. Public officials around the country are searching for ways to provide their constituents with more affordable prescription drugs, and many are looking to countries such as Canada as a source for such drugs. Indeed, it is often assumed that a drug sold in Canada is the same or very similar to American drugs, since Canada has a regulatory system analogous to our own. However, it is important to note that drugs are products that must be made with great care and under exacting specifications, without which drugs containing the same active ingredients may vary significantly. In fact, in the years since Congress authorized FDA to approve generic versions of brand name drugs, many consumers remain skeptical that the generic drug is the "same" as the brand name drug. FDA has gone to great lengths to ensure that the generic version of a drug is the same---is absorbed into the body, enters the blood stream,

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number of ways. Below is a description of why FDA believes that precision in the manufacturing of drug products is so important and why foreign drugs often will not meet the test of scientific accuracy.

**Assurance of Safety, Efficacy, and High Quality in U.S. Approved Drugs**

The longstanding regulatory and legal scheme for the manufacture, distribution, and sale of drugs in the U.S. reliably ensures that a patient receives a high quality drug that is safe and effective. FDA's evidence-based system of drug approval and science-based quality control requirements are the basis for the gold standard that provides Americans the great public health benefits from, and confidence in, the prescription drugs that they take. Drugs that do not meet this standard may be considered adulterated, misbranded, or unapproved new drugs under the Federal Food, Drug, and Cosmetic Act (the Act).

The current U.S. system is devised to maintain high pharmaceutical quality for U.S. approved drugs, starting at the manufacturing facility through to when the drug reaches the final end user, the patient. High quality of U.S. drug products is assured by:

- FDA approval of specific manufacturing procedures, product specifications, rigorous testing procedures, and labeling;
- FDA approval of any significant changes to the manufacturing process or facilities;
- Registration of all manufacturing facilities, repackagers, and relabelers, and listing of all marketed drugs;
- Comprehensive pre-approval and post-approval surveillance inspections by FDA of all manufacturing and testing facilities, both domestic and foreign, involved in producing the drugs. (These inspections verify data submitted to the agency and evaluate compliance with manufacturing and testing requirements);
- Compliance with current good manufacturing practices (cGMPs);
- Requirements for safe handling and storage by state licensed wholesalers;
- Notification requirements if problems occur. (FDA regulations (21 CFR 314.81(b)) require manufacturers to notify the agency within 3 days of any manufacturing problems, including contamination or degradation, or labeling mix-ups); and
- FDA health hazard evaluation to determine the risk posed by any defect and may take immediate action (e.g., recall initiation, seizures, injunctions) in response to serious risks.

The same requirements and procedures apply to FDA-approved drugs manufactured in FDA-registered facilities outside of the U.S.

These quality assurances are specific to drugs that are manufactured and maintained within the controls present in the U.S. drug production and distribution regulatory system. A foreign drug may be manufactured to meet quality standards in the country where it is approved; however, if it is not manufactured according to the same procedures and standards, with the same active and inactive ingredients, as the U.S. approved version, it is not the same as the U.S. approved version and may not work the same in the body and may produce different clinical effects.

**Foreign Versions of U.S. Approved Drugs Are Not Necessarily Interchangeable**

Many advocates of importation from foreign countries believe that a drug product in a

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In order to be interchangeable, drugs must be pharmaceutically equivalent and bioequivalent:

- 1) *Pharmaceutically equivalent* drugs have the same active ingredient, strength, dosage form, route of administration, and inactive ingredients (with a few exceptions) as the comparator drug.
- 2) *Bioequivalent* drugs must have the same rate and extent of absorption into the body. Bioequivalence is best understood in the context of generic drugs. For generic drugs, rather than replicate extensive clinical trials that have already been done in the development of the original, brand name pioneer drug product, the generic manufacturer must scientifically demonstrate that its generic product is bioequivalent to the pioneer drug product. To demonstrate bioequivalence, scientists must measure the time it takes for the test drug to reach the bloodstream and the amount that is absorbed in normal volunteers. This provides a measure of the rate and extent of absorption or bioavailability, which can then be compared to data from the brand name drug. The test drug must deliver the same amount of active ingredients into the bloodstream in the same amount of time as the brand name drug to be bioequivalent. Brand name drug manufacturers must perform the same bioequivalence tests when they reformulate their drugs, to demonstrate that the new formulation is interchangeable with the old formulation.

Pharmaceutical equivalence does not necessarily imply bioequivalence because even small changes in the manufacturing process can affect the drugs absorption into the body.

#### Different active or inactive ingredients

There may be situations where a drug product produced in another country may contain different amounts of active ingredients or different, or different amounts of, inactive ingredients or excipients, such as fillers, binders, lubricants, disintegrants, glidants, starch, colors, or flavorings. Due to the humidity or temperature in a country, different excipients may be needed to ensure adequate stability and potency of the dosage form. Even these changes in the formulation can affect the bioavailability of the drug, and consequently the two formulations may not be interchangeable. Changes in bioavailability can also influence the efficacy and side effects of the drug product.

#### Different time-release properties

Another example of where different formulations can affect interchangeability is if a drug product is marketed as delayed release, controlled release, sustained release, or extended release. Different formulations of a drug product used in other countries may use different release features that can result in different blood concentration profiles and bioavailability of the drug.

#### Different production lines

Even if a drug destined for a foreign market is manufactured in an FDA registered facility, there are several variables that could influence the specifications of the final product and could produce different bioavailability profiles and different identity, strength, purity, and quality of the drug product. For example, if a drug destined for marketing in the U.S. is made on one production line, possible differences in equipment operation and settings and even environmental conditions between that line and another line cannot guarantee that the

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### Narrow therapeutic range drugs

Therapeutic equivalence and bioequivalence are particularly critical for drugs that have a narrow therapeutic range, such as Dilantin, where small changes in the dose and/or the amount of drug in the blood could potentially result in dangerous effects. A patient who has been on a narrow therapeutic range drug for a while may require less frequent monitoring because the concentration of the drug in their bloodstream may have reached a steady state in the narrow range where the drug is safe and effective. However, if the were to change to a formulation that is not interchangeable, the change could allow their blood concentrations to vary and move outside the narrow range, causing their clinical condition to recur (due to a blood concentration below the narrow therapeutic range) or leading to toxicity (due to a blood concentration above the narrow therapeutic range).

### Chemical Analysis Cannot Reveal If A Foreign Version of a Drug Will Act The Same In the Body

Chemical laboratory analysis of a drug product is not sufficient to demonstrate interchangeability with a U.S. approved product or even determine if it is a U.S. approved product. Although chemical analysis can show whether the active ingredient is present and in what amount, as described above, even the slightest change in the manufacturing process, or different types or amounts of inactive ingredients, can affect interchangeability, yet not be apparent through simple chemical analysis.

Only *in vivo* studies that measure a series of blood samples from patients that directly compares the rate and extent of absorption of the drugs into the body, as well as demonstration of pharmaceutical equivalence, can support a finding that two drugs are therapeutically interchangeable. Studies such as these, along with several others, are the types that are required for generic drug approval in the U.S. to show that they are bioequivalent to the brand name drug.

It is not feasible to rely on basic qualitative spot testing to detect infrequent, albeit significant, quality deficiencies. A fundamental scientific premise is that *quality cannot be tested into a product*. Rather, *quality must be built into the product* throughout the manufacturing process; one cannot assure quality by testing for it at the end of the manufacturing process or at a later point.

Consequently, simple chemical analysis that detects the presence of an active ingredient may not reveal if a foreign drug is expired, contaminated, was stored under adverse or inappropriate conditions, or is counterfeit. For example, a product may require constant refrigeration through the chain of custody to maintain potency, but, a simple chemical analysis will not disclose if the potency was compromised.

### Conclusion

Americans have a high expectation that the prescription drugs that they take are of high quality and are reliably safe and effective. FDA is responsible for assuring that prescription drugs manufactured, distributed, and sold within the legal U.S. drug supply meet these stringent standards described above. FDA cannot make the same assurances for foreign drugs, and neither could proposals that purport to deem foreign drugs equivalent to U.S. drug products without determining whether they meet these stringent safety standards.

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/s/

William K. Hubbard  
Associate Commissioner for Policy and  
Planning

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