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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

***Re: Docket No. 2004N-0115
Request for Comment on Prescription Drug Importation***

Dear Sir or Madam:

King Pharmaceuticals, Inc. ("King") submits the following comments in response to questions posed by the Department of Health and Human Services (HHS) Secretary's Task Force on Drug Importation (the "Task Force"), including questions posed by members of the Task Force at the April 14, 2004, public meeting. For your convenience, a copy of King's April 14 presentation to the Task Force, including the slide deck, is attached as Tab 1.

King develops, manufactures, and markets drug products across a range of therapeutic categories, including cardiovascular, endocrinology, neuroscience, women's health, critical care, respiratory, and anti-infectives. We are headquartered in Bristol, Tennessee, and we have research, development, and manufacturing operations in the Eastern and Midwestern United States.

As outlined at the April 14 public meeting, King has been conducting an investigation into foreign Internet pharmacies that purport to offer King's products to U.S. consumers. We have grave concern about the effect that importation may have on the safety of U.S. consumers; the chilling effect that importation is likely to have on certain pharmaceutical alliances that have produced hundreds of innovative remedies for U.S. consumers; and the concern that the importation of foreign drugs will result in the exportation of U.S. jobs. A more detailed discussion of each of these issues follows.

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I. SAFETY

After King's presentation at the April 14 public meeting, the Task Force asked the following:

Can you think of any importation regime that would be viable and still have the sort of safety and efficacy concerns that we've always had in this country? Given the results of King's investigation, do you have any suggestions as to steps that could be taken to protect consumers in this situation, in going onto the Internet and purchasing their pharmaceuticals? 1/

As we stated at the meeting, King believes that any such regime or program will, as a necessary consequence, compromise patient safety and drug efficacy. We have reached this conclusion based on our own diligent investigation into the importation of two of King's leading products, Levoxy^l® (levothyroxine sodium) and Altace® (ramipril). We have also concluded that the proposed efforts to limit the scope of an importation program, to mitigate patient safety risks, are likely to be easily circumvented.

A. Patient Safety Will Be Compromised

King has reviewed the evidence published by the Food and Drug Administration (FDA) and the U.S. Bureau of Customs and Border Protection (CBP), as well as our own investigation. It is clear that U.S. consumers are increasingly turning to Canadian Internet sources for their medications despite the fact that doing so is contrary to federal law. 2/ According to FDA, the increase in volume of such personal drug importations has been dramatic in recent years. 3/

If the Secretary certifies a drug importation program, the rate at which U.S. consumers will seek foreign sourced medications will increase exponentially. This increase will result in a corresponding increase in the number of foreign Internet sites offering prescription drugs to U.S. consumers. As a result, U.S. patients will be

1/ See HHS Import Task Force Public Meeting, Wednesday, April 14, 2004 at <http://www.hhs.gov/importtaskforce/session3/transcript.html>

2/ 21 U.S.C. 381(a). See Statement of W. Hubbard, FDA Associate Commissioner for Policy and Planning, before the Subcommittee on Energy and Commerce, U.S. House of Representatives at <http://www.fda.gov/ola/2002/drugimportation0725.html> (July 25, 2002) ("Under the Federal Food, Drug, and Cosmetic (FD&C) Act, unapproved, misbranded, and adulterated drugs are prohibited from importation into the United States. In general, all drugs imported by individuals fall into one of these prohibited categories.")

3/ See Hubbard, *supra*.

confronted with the impossible task of distinguishing between purportedly “certified” Internet outlets, on the one hand, and other Internet sources that offer deep discounts, on the other. As explained more fully below, proposed certification schemes, such as those limiting reimportation to an “approved list of medications” or approving/certifying certain “safe and reliable” Canadian pharmacies, will be insufficient to protect U.S. consumers in search of low cost medicines.

For example, King’s investigation has shown that foreign Internet pharmacies often fill prescriptions for two of King’s leading products – Levoxyl[®] (levothyroxine sodium) and Altace[®] (ramipril) – with unapproved substitutes. In the case of Levoxyl[®], foreign exporters, shippers, and pharmacy operators have substituted different brands of levothyroxine sodium for Levoxyl. Many of these products, to the extent they are even approved in the United States, are listed as “BX rated” in FDA’s publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (known as *The Orange Book*). As such, they are not considered to be interchangeable with Levoxyl and their use may lead to serious and potentially life-threatening adverse effects. ^{4/}

We also must emphasize that the risks presented by such products may go unnoticed, until the effect reaches an extreme state. Levoxyl and Altace are, for example, intended to maintain patients with chronic conditions (hypothyroidism and hypertension, respectively), within a healthy, normal range. These conditions may be asymptomatic, and a patient who receives a substandard product is at serious risk of harm – *but may not even know it*. When U.S. patients look outside the U.S. drug distribution system to fill prescriptions for maintenance drugs, this risk of harm may escape immediate detection. The patient and his or her physician may never have an opportunity to evaluate this risk until the effect is irreversible.

Finally, it is our expectation that the demand under an authorized drug importation system will be greatest for maintenance drugs. These drugs are taken on a long-term, chronic basis and, understandably, their use can put relentless pressure on fixed-income households. That said, the apparent savings from the use of imported versions of such drugs will be offset by the residual healthcare costs associated with the

^{4/} See, e.g., Tab 2, *FDA Guidance for Industry: Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing* (Dec. 2000) (discussing the narrow therapeutic range within which a patient must be maintained, and the adverse health effects of under- and over-dosing of levothyroxine patients); see also FDA Press Release, *Recent FDA/U.S. Customs Import Blitz Exams Continue to Reveal Potentially Dangerous Illegally Imported Drug Shipments* (Jan. 27, 2004) (stating that levothyroxine therapy requires “very careful dosing in order to avoid serious and potentially life-threatening side effects”); American Association of Clinical Endocrinologists, *Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hyperthyroidism and Hypothyroidism*, 8 *Endocrine Practice* 457, 464 (2002) (“Because levothyroxine has a narrow therapeutic range, small differences in absorption can result in subclinical or clinical hypothyroidism or hyperthyroidism.”).

long-term health consequences of relying on foreign-sourced drugs of uneven and unknown quality.

B. Proposed Restrictions Will Not Mitigate The Safety Risks

Based on our first-hand experience, King believes that the types of risks described above cannot, as a practical matter, be mitigated by various proposals for restricting imports, certifying Internet sites, or channeling foreign drugs through commercial vendors or large-scale pharmacies.

Currently, in the absence of an authorized reimportation program, the volume of misbranded and unapproved drugs reaching U.S. patients appears to be overwhelming. ^{5/} Certifying a reimportation program, even for an approved drug list, would “open the floodgates” in a manner that would immediately exceed the limits of FDA and CPB.

First, our experience with Internet purchases shows that – no matter how tightly the program is drawn – too many opportunities for fraud will remain. FDA will, at best, have only limited resources and limited authority to investigate such abuses because businesses that operate Internet sites are often located in foreign jurisdictions. And, irrespective of the language or design of a certified program, FDA and CBP inspectors would still have to open thousands of packages per day just to ensure they contain drugs identified on an approved list and from an approved site. The number of these packages that will be offered for importation, however, will increase exponentially as foreign sites seize upon the opportunity to present themselves as certified and approved. ^{6/} Even if some type of authentication system were developed, for each site or even for each package, experience has shown that such systems are prone to counterfeiting and fraud.

King’s investigation has demonstrated that foreign pharmacies, even those who provide safe and reliable services under their own country’s requirements, are unlikely to

^{5/} See Statement of W. Hubbard, FDA Associate Commissioner for Policy before the Subcommittee on Foreign Affairs, Foreign Commerce, and Tourism and the Senate Committee on Commerce, Science, and Transportation, at www.fda.gov/ola/2001/importation0905.html (Sept. 5, 2001).

^{6/} For instance, in 2001, FDA and CBP initiated the Carson Mail Facility Pilot to determine how many packages containing drugs were flowing in the United States through international mail facilities. FDA and CBP estimated two million such packages, most of which contained unapproved, misbranded, or adulterated drugs, were imported into the United States by individuals each year. See Hubbard, n.2, *supra*. See also Statement of Elizabeth Durant, Executive Director of Trade Programs, U.S. Customs Service before the Subcommittee on Oversight and Investigations Committee on Energy and Commerce of the U.S. House of Representatives, at <http://energycommerce.house.gov/107/hearings/06072001Hearing267/Durant398.htm> (June 7, 2001). In March 2004, FDA Associate Commissioner Hubbard estimated the number of packages to have grown to a range of five to ten million packages per annum.

hue to U.S. dispensing standards. Several states, such as Wisconsin, have attempted to provide citizens with “the ability to buy certain prescriptions at significantly lower prices directly from Canadian pharmacies that [the] state has visited and found to be safe, reputable, and reliable.” See www.drugsavings.wi.gov. Wisconsin’s Internet site lists Total Care Pharmacy as one of the three Canadian pharmacies that Wisconsin has determined to be “safe, reputable, and reliable.” ^{7/}

During King’s investigation, however, Total Care Pharmacy filled a prescription for King’s Levoxyl® with a Canadian version of Synthroid®. Consistent with FDA’s *Orange Book* rating, the Synthroid® bottle Total Care Pharmacy dispensed had been clearly labeled by the manufacturer as “Not Interchangeable With Other Brands.” The pharmacy label Total Care Pharmacy placed on the bottle, however, asserted that Synthroid® is the “Canadian Equivalent for Levoxyl.” This assertion is false and misleading.

A more recent attempt by our investigator to fill a prescription for 30 capsules of Altace® 2.5 mg through Total Care Pharmacy’s crossborderpharmacy.com website resulted in the sale of a bottle of *100 capsules* of the Canadian version of Altace® 2.5 mg. In this instance, Total Care Pharmacy filled our investigator’s prescription with more than three times the amount ordered and prescribed by the treating physician of an unapproved drug that is illegal in this country. See www.crossborderpharmacy.com purchase order, prescription submitted with the order, and Total Care Pharmacy invoice, attached as Tab 4.

King believes the results of its investigation are not simply anecdotal but are symptomatic of a more complex problem with Canadian pharmacies routinely dispensing medications to U.S. patients. Regardless of whether Total Care Pharmacy can pass a one-time, pre-announced inspection by Wisconsin regulators, King doubts that Canadian pharmacies are able to function with an appropriate level of care when routinely filling foreign prescriptions from foreign doctors for medications approved by a foreign regulatory agency. U.S. patients that have been titrated for King’s Levoxyl® are *different* than Canadian patients. Canadian pharmacies that fill Levoxyl® prescriptions for U.S. patients with Synthroid® are putting the health and safety of these U.S. patients at risk. ^{8/}

^{7/} Total Care Pharmacy appears to own and operate www.crossborderpharmacy.com, an Internet pharmacy that targets U.S. customers for prescription drug sales. A “WebWhois” search on February 17, 2004 found that Total Care Pharmacy was the registrant of the crossborderpharmacy.com domain name. A repeat search on May 17, 2004, however, found that registration had been changed on May 7, 2004. Subsequent to the April 14 public meeting, the www.crossborderpharmacy.com domain now has a private registration, which lists “Domains by Proxy, Inc.” as the administrative contact. See Tab 3, WebWhois data.

^{8/} The Canadian Pharmacist Association lists the Canadian approved monograph for Synthroid®. That monograph recommends “patients who are switched from one levothyroxine formulation to another be retitrated to the desired thyroid function.” See Synthroid® Canadian monograph, available at <http://129.33.165.73/cpha/monographs.aspx>.

Finally, permitting states to develop and run their own reimportation regimes will be unworkable. FDA and CBP inspectors would be forced to know and understand the distinctions between the various programs. Federal agencies already face this difficulty when implementing FDA's personal importation policy or DEA's "50 dosage unit" traveler's policy. ^{9/} Both programs require a prescription that is valid in the importer's U.S. state. But laws and rules that establish the criteria for validity of a prescription can vary. Furthermore, in order to reduce their own costs, some states are likely to rely upon the safety review of other states in recommending Canadian pharmacies to their consumers. For instance, very recently Rhode Island launched a new website referring its citizens to Canadian Internet pharmacies for obtaining and importing prescription drugs. See <http://204.17.96.7/rirx/>. Yet every link on Rhode Island's website for choosing a Canadian pharmacy or ordering Canadian drugs redirects the consumer to the Wisconsin website. ^{10/}

For these reasons, King believes certifying a drug importation program will harm patients, will result in an unmanageable increase in personal importation of dangerous drug products, and proposals to mitigate these risks will prove to be ineffective.

II. INTELLECTUAL PROPERTY AND CONTRACTS

The Task Force asked King:

How could an importation regimen be disruptive of different licensing arrangements among different manufacturers and countries? How prevalent are these types of different country licensing and manufacturing arrangements? Why, in your view,

^{9/} See, e.g., W. Tauzin and J. Dingell letter to FDA, Customs, and DEA regarding confusion associated with DEA's and FDA's policies on permitting personal importation of drug products across land borders, at www.house.gov/commerce_democrats/press/107ltr24.htm (Mar. 14, 2001).

^{10/} The "Ordering Information" link on Rhode Island's website automatically redirects you to drugsavings.wi.gov/section.asp?linkid=25, which is the Wisconsin website page entitled "Ordering Information". The "Find Prices" link and the "Find Prices/Order Here" button on Rhode Island's website both redirect to drugsavings.wi.gov/medicinelist.asp?locid=2, which is the Wisconsin website page entitled "Prescription Medicine List". In this case, Rhode Island is relying entirely upon Wisconsin's pre-announced one-time "visits" to refer consumers to Canadian Internet pharmacies. Yet King's investigation has demonstrated practices by at least one of the three Canadian pharmacies listed on Wisconsin's website that raise significant questions about whether that pharmacy is "safe, reliable, [or] reputable".

is this a beneficial practice? Why should these arrangements not be interfered with? 11/

Pharmaceutical companies do not, as a general matter, unilaterally research, develop, manufacture, distribute, promote, and sell their own products. Instead, the norm in the industry is to form strategic alliances, to bring together and optimize the available resources and expertise. These alliances directly benefit patients by allowing research-based entities to move new discoveries more quickly from development to commercial-scale manufacturing and distribution. See M. Liebman, *Strategic Alliances Propel Industry Productivity*, Medical Marketing & Media, May 2000, attached as Tab 5. These pharmaceutical alliances fill the gap between capacity and capital by permitting R&D companies to leverage the value of their discoveries, on the one hand, and manufacturing facilities to leverage their excess production capacity, on the other. *Id.* Under this paradigm, patients benefit when relatively small R&D entities can take advantage of manufacturing and sales capacity that is available in the marketplace.

A key component of this paradigm involves contracting for U.S. marketing rights, where the U.S. market is considered to be the largest in the world for state of the art medicines and healthcare. King's business strategy, for example, focuses on acquiring U.S. rights to promising drug products. King has contracted for exclusive licenses to manufacture, promote, distribute, market, offer for sale, and sell products, such as Altace®, in the United States. King pays considerable licensing fees in exchange for these exclusive rights. An importation scheme that authorizes the importation of foreign versions or other purported substitutes for King's products will directly undermine King's U.S.-based intellectual property and contract rights. We urge the Task Force to take this into consideration as an integral part of the nature and value of drug development.

King is not unique in developing alliances with other pharmaceutical companies. Between July 2001 and June 2002, a reported 779 pharmaceutical alliances were formed, the majority of which involved R&D funding as well as marketing/licensing rights. See Windhover Information Inc., *Pharmaceutical Strategic Alliances*, vol. XIV (Sept. 2003), attached as Tab 6. Pharmaceutical companies who negotiate in good faith for U.S. marketing rights rely on the integrity of the legal system to enforce these rights. If drug importation were given official sanction, the value of such rights would be put in jeopardy.

Pharmaceutical companies also rely on strategic alliances to combine sales forces when launching a new drug product, leverage commercial presence through a larger pharmaceutical partner, and create synergies between complementary interests. *Id.* Research indicates that these alliances are expected to not only increase the number of new chemical entities developed but also to reduce the time it takes to bring the drug to

11/ See April 14 Public Meeting Transcript, n.1 *supra*.

market. *Id.* These alliances, therefore, directly benefit patients by bringing more new drugs swiftly to the market.

If the law no longer supports the licensing of intellectual rights, innovators will be limited in their ability to generate capital for future projects. Even more, if a government certified program is put into place, it will directly affect U.S. contract rights and undermine a basic business model upon which virtually every level of the drug industry currently relies.

III. JOBS

Finally, at the April 14 meeting, the Task Force asked King whether there are “any studies that have been done to demonstrate importation, if expanded could cost domestic jobs?”

We believe that the impact on jobs, particularly for a U.S.-based company such as King, is self-evident. King is headquartered in Bristol, Tennessee. Our products are manufactured in more than a dozen U.S. cities, including Bristol; St. Petersburg, Florida; Kansas City, Missouri; Rochester, Michigan; and Middleton, Wisconsin. King’s drug sales are supported by American workers who manufacture King’s products in more than a dozen U.S. cities. King cannot continue to pay workers to manufacture drugs that people will not buy because purported and, potentially, certified “substitutes” can be imported from Pakistan, Mexico, or even Canada.

If the previously described business model is put at risk, investment for small entrepreneurial companies developing new drugs will be negatively affected. These concerns are supported by recent statements made by U.S. Commerce Undersecretary Grant Aldonas. Undersecretary Aldonas testified before a Senate panel asserting that, if Congress allows consumers to import medicines from Canada, “there will be disinvestments in the United States, a loss of employment opportunities and frankly a loss of an industry that is a huge multiplier” in terms of benefits to the overall U.S. economy. *See Reuters, Drug import bill could cost US jobs – Bush aides* (April 27, 2004), attached as Tab 7.

King believes that permitting non-U.S. drug manufacturing and distribution companies access to the U.S. market through any means other than the existing FDA approval and inspection process, translates into lost sales to U.S. consumers that King cannot make. As volumes of such imports increase, demand for domestically manufactured and distributed pharmaceuticals will decrease, resulting in reduced revenues to U.S. industry.

Companies facing such a dilemma will be forced to choose between continuing under an existing business model that is no longer sustainable or seeking alternatives to reduce costs. King believes a certified importation scheme will result in

too many companies choosing to open facilities elsewhere to reduce costs. Any scheme that permits U.S. patients to purchase unapproved or non-interchangeable substitutes of King's drug products will reduce King's sales and, in turn, its ability to support U.S.-based jobs.

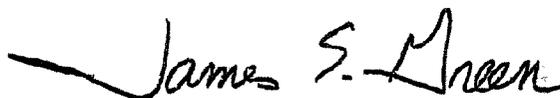
IV. CONCLUSION

Any reimportation proposal, regardless of how narrowly its scope is drawn, will increase unacceptable risks to patient safety. Furthermore, given the evidence King has already developed, it is clear that the opportunities for foreign Internet pharmacies to profit from supplying unsafe and illegal drugs to unsuspecting U.S. patients will likewise increase. Limiting the reimportation scheme to commercial shipments of specified drugs, from specified pharmacies, will not significantly hinder the potential for fraud. Moreover, permitting importation of foreign versions of FDA-approved drug products will directly impact U.S. contractual and intellectual property rights, and will do substantial harm to a business model that has proven to be a benefit to patients. Finally, drug importation will result in the loss of U.S. jobs that are important to the local and national economies.

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We look forward to assisting the Drug Importation Task Force and its members in any way we can.

Respectfully,

A handwritten signature in black ink that reads "James E. Green". The signature is written in a cursive style with a long horizontal stroke at the beginning.

James E. Green