Pharmaceutical
Security
Institute

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Ms. Victoria A. Espinel
United States Intellectual Property Enforcement Coordinator (IPEC)
Office of Management and Budget

Via Email: intellectualproperty@omb.eop.gov

Comment Letter on Joint Strategic Plan Formulation

Dear Ms. Espinel:

I am pleased to submit this comment letter on behalf of the Pharmaceutical Security Institute ("PSI") in response to a request for public comment on the formulation of the Joint Strategic Plan against counterfeiting and infringement (the "Request") issued by the Office of Management and Budget (the "OMB") on February 18, 2010 and published in the Federal Register on February 23, 2010 (75 Fed. Reg. 8137), providing a blueprint for the implementation of the mandate of Section 303 of the Prioritizing Resources and Organization for Intellectual Property Act of 2008 ("Section 303"). I can provide you with valuable recommendations because my organization's member companies are among the most successful pharmaceutical innovators in the world and have dealt extensively with the global counterfeiting issue under a wide variety of circumstances.

PSI is a not-for-profit, membership organization dedicated to protecting health, sharing information on the counterfeiting of pharmaceuticals, and initiating law enforcement actions through the appropriate authorities. The Institute is headquartered in Vienna, Virginia where it manages a unique database, the Counterfeit Incident System ("CIS"), which is used to document incidents of counterfeiting, theft and illegal diversion around the world. PSI recorded 1,834 such incidents occurring in 2008 affecting 651 different pharmaceutical products. CIS incidents come from a variety of sources, including open media reports, PSI member company submissions, and public-private sector partnerships. On a daily basis, incidents are identified by the careful work of a multi-lingual analytical team which gathers the facts from news accounts, police reports and drug regulatory authorities. PSI supports its member's efforts to engage law enforcement in order to disrupt multi-national pharmaceutical counterfeiting operations.

I commend the Office of the IPEC and its staff on an extremely well-written, logical and helpful Request setting forth the general concepts implementing Section 303. In general, the Request covers the applicable statutory requirements with admirable

clarity and precision and for the most part reaches what we consider to be the clearly correct conclusions concerning the goals of the Joint Strategic Plan.

The Office of the IPEC sought comments on two major areas. Part I comprises the costs to the U.S. economy resulting from the infringement of intellectual property and the threats to public health and safety. Part II includes recommendations for accomplishing the objectives of the Joint Strategic Plan. I have chosen to address: (1) the risk to public health and safety represented by counterfeit pharmaceuticals from Part I, and (2) the formulation of public-private collaborations and information sharing related to Part II.

1. Public Health Risk of Counterfeit Pharmaceuticals

The consequences of the administration of infective or harmful counterfeit pharmaceuticals have long being outside the scope of aggregate mortality and disease statistical reporting. Public health statistics fail to accurately account for them. Sometimes mortality or morbidity is masqueraded by the underlying illness and the effect of the pharmaceutical therapy is not counted as a relevant factor. In other instances, the event is just reported as an unusual adverse or secondary effect of the drug but not tied to quality issues. Finally, the episode can go unreported altogether. PSI has gathered, however, evidence of a significant number of cases where deaths and illness have been directly linked to the consumption of counterfeit pharmaceuticals.

The counterfeit pharmaceuticals found on the market may contain no active ingredient at all, the correct dosage of the active ingredient, or the right active ingredient in the wrong dosage. Oftentimes, the active ingredient is not the compound approved but an untested infringing variation known as an "analog" that may cause serious harm.[1] They may also contain dangerous impurities or contaminants. In the U.S. pharmaceuticals are subject to extensive clinical testing requirements to ensure their efficacy and safety before receiving approval for marketing. All manufacturers seeking approval including manufacturers of generic drugs, copies of already approved products, have to demonstrate equivalent formulation in accordance with the current good manufacturing practices ("cGMP"), which is verified during marketing approval and requires submission of a full clinical trial and cGMP dossier, or for generics to submit the results of bioequivalence testing before receiving marketing authorization.[2] Consequently, even a counterfeit product that contains the correct amount of active ingredient is unsafe because it cannot show compliance or verified to have been manufactured under cGMP, or prove similar therapeutic effects in-vivo.

The following are a few examples of deaths linked to counterfeit drugs that PSI has found over almost a decade of research on pharmaceutical counterfeiting. In October 2004, the Ministry of Health in Venezuela reported that during a period of one and a half

[1] *See* Reepmeyer JC, d'Avignon DA, Structure elucidation of thioketone analogues of sildenafil detected as adulterants in herbal aphrodisiacs, J. Pharm. Biomed Anal., 49(1):145-50, (Jan. 15 2009).
[2] *See generally* 21 U.S.C. § 355(j).

years six children have died because of illicit medicines including counterfeit anesthesia.[3] In December 2004, a 22- year-old woman suffered acute liver failure and died after being injected with a counterfeit iron supplement at a public hospital in Argentina. Two other women also died after receiving the same drug. It was also reported that approximately a dozen women suffered harm after being injected with the product at the hospital. Many of these women were pregnant.[4]

In June 2005, following the discovery of a counterfeit hypertension drug which was dispensed by an accredited pharmacy in Canada, eleven reported deaths were examined for a link to these medicines. The regional coroner reported that of the eleven deaths, four might have been caused by counterfeit heart medication but there was not sufficient evidence to determine whether it was the cause either way.[5] In June 2006, it was reported that a 23- year-old man in Burma with malaria died because the medicine he received was counterfeit. He was treated with the anti-malarial drug artesunate, labeled as made by the company Guilin Pharmaceutical in China. The drug is one of the most effective to treat the disease, yet he lapsed into a coma and died. Subsequent testing of the medicine found it to contain ten milligrams of artesunate per tablet, rather than the fifty milligrams a genuine tablet would have contained.[6] In November 2006, a 28-year-old bodybuilder died in Spain after taking counterfeit anabolic steroids distributed by a criminal network.[7] In January 2009, two people died in the Xinjiang Uygur Autonomous Region of China after taking a counterfeit version of a drug used to treat diabetes. The drug contained six times the normal dose of the blood-sugar-lowering active ingredient glibenclamide.[8]

The presence of dangerous chemicals or contaminant is another risk of counterfeit pharmaceuticals. It is not unusual for counterfeit drugs to contain heavy metals, arsenic or industrial chemicals, depending on the environmental contaminants present at the manufacturing location. In August 2007, a 28-year-old man suffered a serious illness in

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[3] Yira Yoyotte, Farmacias y MSDS alertan sobre venta ilegal de medicamentos, PRENSA AN, (Oct. 27, 2004), at http://asambleanacional.gov.ve/ns2/noticia.asp?numn=6124.

[4] Una Embarazada Quedó al Borde de la Muerte Después de Recibir una Inyección de Hierro, CLARÍN, (Dec. 22, 2004), at http://www.clarin.com/diario/2004/12/22/um/m-891949.htm; Otra mujer en terapia intensiva por una inyección de hierro falsa, CLARÍN, (Dec. 31, 2004), at http://www.clarin.com/diario/2004/12/31/sociedad/s-03215.htm.

[5] Bhusmang Mehta Labelling errors, failure to keep records, misidentified or inadequately identified drugs, Pharmacy Connection, (Jun. 26, 2008), at http://www.newontariopharmacist.com/client/ocp/ocphome.nsf/ab26815c7d6d78e58525732b00626f24/aa6045f7b9733ec9852570d10060b1d1?OpenDocument.

[6] Call for Global Action to Prevent Spread of Counterfeit Artesunate, The Pharmaceutical Journal, Vol. 276, No. 7405 , p 711, (Jun. 17, 2006), at http://www.newontariopharmacist.com/client/ocp/ocphome.nsf/ab26815c7d6d78e58525732b00626f24/aa6045f7b9733ec9852570d10060b1d1?OpenDocument.

[7] Desarticulan una red que falsificaba productos dopantes, tras la muerte de un culturista, EL PAIS, (Jun. 8, 2007), at http://www.elpais.com/articulo/deportes/Desarticulada/red/dopaje/relacionada/muerte/culturista/elpepudep/20070608elpepudep_9/Tes.

[8] China orders arrest of suspect in fake drug deaths, China.com, (Feb. 5, 2009), at http://english.china.com/zh_cn/health/news/11020771/20090205/15311072.html.

Hong Kong after taking an erectile dysfunction drug which contained an analog of the active ingredient sildenafil. He suffered a drug-related neurologic disorder because the drug contained an "analog" version of the approved active ingredient.[9] In 2008, the Health Sciences Authority of Singapore reported 240 adverse events submissions, including ten deaths, which were related to an illegal sexual stimulant which contained dangerous doses of a diabetes drug.[10] The main ingredient of an erectile dysfunction drug seized by customs in New Zealand in 2009 was bat and bird droppings. Other drugs seized contained insects, dust mites, hair and charcoal.[11] In January 2010, the U.S. Food and Drug Administration (FDA) warned consumers about the sale of a counterfeit over-the-counter weight-loss drug online. The counterfeit product contained the controlled substance sibutramine instead of orlistat, the actual approved active ingredient. Sibutramine is dangerous to people who have a history of cardiovascular disease.[12]

Another significant threat is the development of microbial resistance as a consequence of the use of counterfeit medicines. Antimicrobials require close professional supervision for their use to be safe and effective. According to the CDC, the Institute of Medicine has identified antibiotic resistance as one of the key microbial threats to health in the United States.[13] The emergence of resistance to therapeutics is not a new phenomenon among microbes, whether viral, bacterial, or protozoan. Following the introduction and subsequent widespread use of penicillin, in the early 1940s, microbiologists soon discovered that a number of bacterial strains had become resistant to this antibiotic. What is perhaps most notable today is the increasing degree to which microbial resistance has become an important health threat, and the continuing failure to deploy an effective response to this threat.

Although microbial resistance results primarily as a consequence of selection pressure placed on susceptible microbes by the use of therapeutic agents, a variety of factors also contribute to the emergence and spread of resistance. An important one is the use of counterfeit medicines that contain the wrong active ingredient or the right active ingredient in the wrong dosage, to treat infections. In Angola, a health care task force created to develop strategies to control serious cases of malaria found a resurgence of such cases. The spokeswoman for this group stated that they increasingly receive notifications of very serious cases of malaria affecting people in areas of the country where the disease is endemic and serious cases are rare. She mentioned fourteen cases in

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[9] Lilian Goh, Adulterated impotence drugs spark call for stricter regulations, SOUTH CHINA MORNING POST, p 4, (Aug. 10, 2007).

[10] Consumers are warned not to buy bogus products marketed as 'herbal' treatments for erectile dysfunction, MHRA, (Dec. 16, 2009), at http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalmedicines/HerbalSafetyNews/Currentsafetyissues/CON065616.

[11] Rebecca Todd, More buy risky drugs on internet, The Press, p 1, (Mar. 6, 2010), at http://www.stuff.co.nz/the-press/news/3411488/More-buy-risky-drugs-on-internet.

[12] http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm198557.htm

[13] Antibiotic Resistance Questions & Answers, CDC, at http://www.cdc.gov/getsmart/antibiotic-use/anitbiotic-resistance-faqs.html.

the city of Luanda in 2009 alone.[14] One of the potential causes for this trend is the sale of counterfeit drugs with no active ingredient that makes the treatment ineffective and increases the likelihood of microbial resistance after an intermittent course of treatment. All across Africa has been reported that once efficacious malaria treatments are becoming increasingly ineffective because of pervasive drug resistance. This is the result of the sale of counterfeits that do not contain enough active ingredient to eradicate the parasite, but sufficient to make it tolerant to the chemical. Even the newer drug artemisinin is showing reduced effects.[15] Although malaria is not endemic in the U.S., this problem also affects drugs to treat bacterial infections and HIV-AIDS. Further, the lack of effective malaria treatments in poverty-stricken countries promotes economic and social instability and the emergence of failed states, a threat to U.S. national security.

The Joint Strategic Plan should make the international fight against counterfeit pharmaceuticals a priority. The consequences of the spread of counterfeit pharmaceuticals across the globe go well beyond a mere trademark or patent violation matter. Here is where drug regulatory standards and intellectual property rights intercept. These products contain very specific ingredients and need to be manufactured at approved facilities and in accordance to very strict specifications. The U.S. has created very stringent standards and a tight supply chain controlled by a specialized agency, the FDA. Any product that deviates from these standards is a public health danger, including all counterfeits. Thus, the IPEC should adopt, and incorporate into the Joint Strategic Plan, a policy of strong protection of pharmaceutical intellectual property rights and create the adequate venues for participation of all private sector and government agency stakeholders.

2. Formulation of Public-Private Collaborations

The nature of the counterfeit pharmaceutical problem requires the participation of multiple sectors including health regulatory agencies, law enforcement, and private industry because this is a unique and tightly-regulated consumer product category that demands a multidisciplinary approach. The OMB oversees strategic planning, interagency coordination and budgeting, and it is seen as a successful coordinator of programs that span multiple agencies. The Office of the IPEC is, thus, well-equipped to set priorities and recommend specific resource allocation strategies for a plan that must include multiple agencies and public-private partnerships. Regarding this last item, PSI has gained substantial experience over the past decade so I would like to make specific recommendations on how to create and manage effective public-private partnerships.

One example that I want to bring to you attention in terms of allocation of resources and information sharing within the Federal Government is FDA's Office of Criminal Investigations ("OCI"). OCI is responsible for investigations of many violations of the Food, Drug and Cosmetics Act ("FDCA") violations, including

[14] Casos graves de malária preocupam autoridades angolanas, Jornal OJE, (Jul. 8, 2009), at http://www.alphatrad.pt/news/1406.php?pays=6.
[15] Fake Drugs – Counterfeiting Human Life, The Herald (Harare), (Mar. 5, 2010).

counterfeiting activities. The OCI's budget of $41 million in fiscal year 2008 pales in comparison to a total FDA budget of $2.1 billion for the same year.[16] Clearly, only 2% of the Agency's budget is insufficient for an organization such as OCI which has many important and competing priorities. Further, FDA has opened ten international offices since 2008. The Agency now operates offices in China, India, Europe, Chile and Costa Rica but no OCI agents have been deployed abroad.[17] Also, a recent Government Accountability Office ("GAO") analysis found that FDA's oversight of OCI's investigations of individuals and companies external to FDA is limited, curtailing effective exchange of information and accountability.[18] OCI is strategically positioned to serve as a key liaison between the FDA, law enforcement, and private industry. The Joint Strategic Plan must be formulated to strengthen the OCI and have it play a more central role in coordinating counterfeiting investigations with other government agencies and with private industry.

The complex nature of pharmaceutical regulation, the numerous manufacturers, and thousands of brand-name products marketed make close interaction between law enforcement, FDA and private right-holders crucial. Law enforcement needs the technical expertise and training that only FDA or the manufacturer of the product can lend to correctly identify the product and the associated regulatory issues. In turn, the manufacturer has to enjoy open channels of communication to share information with law enforcement and regulators to respond quickly to any public health threat created by counterfeit pharmaceuticals. The global footprint of some pharmaceutical manufacturers and the U.S. Government should be leveraged to tackle criminal organizations that nowadays are global in nature. For instance, PSI's experience has demonstrated that the technical capabilities of the pharmaceutical manufacturers to swiftly test and identify the origin of the product, and to facilitate industry-specific resources for an investigation, yield better enforcement outcomes.

In sum, while national and state laws may provide tools to partially address the challenges, PSI emphasizes public-private partnerships that lead to better management of resources, targeted training and improved exchange of information in the long run. Accordingly, the Joint Strategic Plan should include the appropriate channels for pharmaceutical manufacturers to provide continued input during the development of multi-agency anti-counterfeiting policies. We must make sure that all parties understand the scope of the issues, and that failing to maintain and improve the security of the pharmaceutical supply poses risks for public health and economic development. The understanding of the nature of organized counterfeiting groups that PSI has developed leads to the logical conclusion that increased international coordination and collaboration

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[16] FY 2008 Budget Summary, US FDA, at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/BudgetReports/2008FDABudgetSummary/ucm082723.htm.

[17] FDA opens Mexico City office, United Press International, (Dec. 15, 2009), at http://www.upi.com/Science_News/2009/12/15/FDA-opens-Mexico-City-office/UPI-16461260898398/.

[18] Improved Monitoring and Development of Performance Measures Needed to Strengthen Oversight of Criminal and Misconduct Investigations, GAO, (Jan. 2010), at http://www.gao.gov/highlights/d10221high.pdf.

by law enforcement agencies and public-private partnerships are the only way to address pharmaceutical crime.

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PSI and its members are committed to working with the U.S. Government to eliminate the threat of counterfeit pharmaceuticals. PSI thus looks forward to further collaborating with the IPEC on the formulation and implementation of the Joint Strategic Plan.

Thank you for requesting the public's input on this matter so critical to the U.S. economy and the welfare of the American people.

Respectfully submitted,

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