U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Petition to Request the Food and Drug Administration to Rank Foreign and Domestic Drug Manufacturing Firms Together for Purposes of the Agency's Risk-Based Approach to Inspections and Take Other Steps to Reduce the Public Health Risks Associated with Imported Drugs	)	Docket No. _____

CITIZEN PETITION

The Synthetic Organic Chemical Manufacturers Association's (SOCMA's) Bulk Pharmaceuticals Task Force (BPTF) submits this petition to request that the Food and Drug Administration (FDA) take specific actions designed to allow it to better manage the risks to public health associated with the use of drugs manufactured or processed at foreign facilities.

The BPTF is an association for manufacturers of active pharmaceutical ingredients (APIs), excipients, and intermediates. The BPTF's primary objective is to seek clarification of current regulatory requirements and to interact with governmental agencies on emerging issues that may impact SOCMA members. SOCMA is the leading trade association of the specialty batch and custom manufacturing chemical industry, representing 300 member companies with more than 2000 manufacturing sites and over 100,000 employees.

I. ACTION REQUESTED

The BPTF respectfully submits this petition to request the Commissioner of Food and Drugs to allocate its resources to reduce the public health risk that imported drug products pose by:

1. ranking foreign and domestic drug manufacturing firms together according to FDA's risk-based approach to inspections;
2. listing "foreign facility" as a significant risk factor for purposes of its risk-based approach; and
3. implementing a program of monitoring the impurity profiles of imported over-the-counter (OTC) drugs for patterns that create the appearance of underlying problems with current good manufacturing practices (cGMP), so that FDA may refuse entry under 21 U.S.C. § 381(a) to products that appear adulterated.

II. STATEMENT OF GROUNDS

A. Background

Domestic and foreign establishments importing drugs must register their establishment and list all drugs in commercial distribution.[1] A review of establishment registrations and drug lists reveal several important trends in drug manufacturing. In 2004, 2700 foreign drug manufacturing establishments were registered with the FDA versus 3300 domestic sites (excluding the 4500 domestic sites registered solely for the production of medical gases).[2] China and India led in the number of FDA registered facilities with 440 and 300 sites, respectively.[3] Approximately 51% of the registered foreign sites are API manufacturing facilities; the remaining are other establishment types, such as finished dosage plants and control laboratories.[4]

The number of finished drug products manufactured abroad for the U.S. market is increasing, accounting for four of ten prescriptions drugs now sold in this country.[5] A review of the FDA Type II DMF database also reflects the trend toward increasing foreign drug manufacturing: 87 percent of the 510 DMFs filed with the FDA in fiscal year 2004 were for products/APIs manufactured outside of United States.[6] Even if not all of these DMFs have yet been cross-referenced into approved applications, the numbers suggest that a greater proportion of drugs are likely to come from foreign countries in the future.

FDA is responsible for ensuring that all domestic and imported drug products are safe, effective, and in compliance with current good manufacturing practices (cGMPs).[7] It is cGMP that provides the assurance that each pill we consume has the same identity and strength and the same quality and purity characteristics as the product approved by FDA. FDA is required to inspect registered domestic establishments in any state every two years.[8] NDA/ANDA pre-approval inspections are conducted for specific new products, but domestic facilities also receive periodic, unannounced inspections for cGMP compliance. Based on CDER inspection statistics of 1999-2003 (Table I below), and the estimated number of domestic manufacturing sites registered, it

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[1] *See* Federal Food, Drug and Cosmetic Act (FDCA) § 510, 21 C.F.R. § 207.20, 21 C.F.R. § 207.20.

[2] Kristen Evans, *CDER 2005 Compliance Update*, 29th International cGMP Conference, Univ. of Georgia, March 2005.

[3] Kristen Evans, *CDER 2005 Compliance Update*, 29th International cGMP Conference, Univ. of Georgia, March 2005

[4] *See id.*

[5] *See* GOVERNMENT EXECUTIVE *at* http://www.govexec.com/dailyfed/1204/121404cdpm1.htm (*last visited* October 20, 2005). The proportion of APIs that are imported is even higher; at least 80 percent of APIs used by U.S. manufacturers to produce prescription drugs are imported. *See* GAO/HEHS-98-21: General Accounting Office, GAO, Report to the Chairman, Subcommittee on Oversight and Investigations, Committee on Commerce, House of Representatives, Food And Drug Administration, *Improvements Needed in the Foreign Drug Inspection Program* (March 1998) [hereinafter 1998 GAO report].

[6] www.fda.gov/cder/dmf/index.htm

[7] *See* FDCA § 501(a)(2)(B).

[8] *See* FDCA § 510 (h).

appears that FDA is reasonably close in meeting the biennial inspections mandated of the domestic facilities.

Table I
CDER Manufacturing Plant Inspections

Fiscal Year	Domestic Inspections		Foreign Inspections
	NDA/ANDA	cGMP	
1999	2548	1844	220
2000	2229	1436	248
2001	2090	1497	249
2002	2166	1519	210
2003	1453	1512	184
2004	1375	1825	184

Source: CDER Reports to the Nation (for years 1999 to 2004)

FDA is not required to inspect foreign facilities every two years for the simple reason that FDA has no authority to enter a facility in a sovereign country unless invited. As partial compensation for FDA's lack of authority to inspect foreign facilities, the statute invites FDA to enter into cooperative arrangements with foreign officials to determine whether drug(s) should be refused admission into the United States.[9] Nonetheless, FDA is falling short of meeting its responsibility to safeguard the public from adulterated or misbranded drugs manufactured or processed at foreign facilities. Even though as much as 80 percent of APIs used by U.S. manufacturers to produce prescription drugs are imported,[10] the Agency inspects foreign API suppliers and foreign suppliers of drug products for OTC applications infrequently, if at all. Indeed, inspections of foreign pharmaceutical manufacturers occur with far less frequency than the two-year interval Congress deems necessary for domestic manufacturers.

In fact, at the current rate of inspection, a foreign manufacturer is unlikely to be inspected for cGMP compliance at all, unless the firm is listed in an ANDA/NDA. In October 2000, Jane M Henney, M.D. testified before the Subcommittee on Oversight and Investigation that based on the Establishment Evaluation System database, 242 foreign API manufacturers, in 36 countries, appeared to have exported products into the U.S. in 1999, without having been inspected by FDA.[11] Forty-six of these firms were located in China and Hong Kong and eleven in India; according to 2004 data, firms in these countries now account for 49% of the drugs consumed in the U.S. It is worthy to note that the final rule requiring registration of foreign establishments did not take effect until February 11, 2002; therefore, the actual number of foreign facilities not inspected by the FDA may have been substantially higher than 242.

According to FDA's Center for Drug Evaluation and Research (CDER) Office of Compliance, 90 percent of the international drug inspections of facilities were limited to "pre-approval"

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[9] *See* FDCA § 510 (i).

[10] *See* 1998 GAO report, *supra* note 5.

[11] Jane M. Henney, M.D., Testimony to Chairman Fred Upton, Subcommittee on Oversight and Investigations, House of Representatives, October 3, 2000.

inspections, with the remainder being cGMP compliance or post-approval surveillance.[12] Thus, a majority of the foreign drug manufacturing sites were not inspected for cGMP compliance at all, and those that were inspected had little or no follow-up on the corrective action implemented in response to previous inspections.

In China and India, for example, more than five years may elapse between FDA inspections of a drug manufacturer. Moreover, FDA is still experiencing delays in taking enforcement action against foreign pharmaceutical manufacturers. In one case, FDA allowed a manufacturer in India to continue exporting its products to the United States despite an investigator's finding that the manufacturer could not adequately test for impurities in its product and water system; nearly two years passed before FDA determined that enforcement action had never been taken against this manufacturer. [13]

Statistics also show the number of Form 483s issued to foreign firms after an inspection is significantly higher in percentage than are issued to domestic firms[14] and serious deviations from GMPs were identified more often in foreign than U.S. pre-approval inspections.[15] If there had been enough cGMP inspections of foreign firms to generate comparable statistics, it is reasonable to assume that the higher violation rate for foreign facilities would be repeated.

Foreign facilities, in general, pose a greater risk to public safety because when a facility is inspected infrequently, as is the case for foreign manufacturers, there is a natural tendency for management to become complacent that what was adequate at the last inspection is still adequate. In the absence of a credible threat of reasonably frequent inspections, the "c" in cGMP gets lost. Maintaining cGMP compliance requires constant effort and vigilance. Minor deviations may not cause any apparent lack of quality, but it is a well-paved road from minor deviations to serious quality failures. Each step away from cGMP compliance appears to be a short term cost savings. Without creditable regulatory oversight, profits can displace the assurance of cGMP. Furthermore, the consequences for a foreign firm that fails an FDA inspection is loss of the US market; however, if a foreign firm complies with local laws, it may continue to operate and produce for its own domestic, and many other, markets. This, of course, is not the situation for U.S. drug manufacturers, which risk a much greater penalty for failing FDA inspections.

B. Risk-Based Inspection Ranking

FDA has stated that as part of its cGMPs for the 21st Century Initiative, it will pilot a risk-based inspection model for prioritizing drug manufacturing establishments for routine inspection.[16] We

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[12] Charles M. Edwards, *FDA International Inspections*, 27th International cGMP Conference, Univ. of Georgia, March 2003.

[13] *See* 1998 GAO report, *supra* note 5.

[14] *See id.*; *see also* Philip S. Campbell, *2004 Inspection Records & Compliance Issues*, 29th International cGMP Conference, Univ. of Georgia, March 2005

[15] *See* 1998 GAO report, *supra* note 5.

[16] *See* FDA's *Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model* (September, 2004), *available at* http://www.fda.gov/cder/gmp/gmp2004/risk_based.pdf.

understand that as part of this initiative, the Agency has started using a computer program to select manufacturers for inspection, which ranks domestic facilities, using risk factors such as specific product, processes used, recalls, violation history, and contamination potential.[17] We also understand that the agency will use this program for foreign manufacturers in 2006, but will rank domestic and foreign facilities separately.[18] In this regard, we urge FDA to risk-rank domestic and foreign facilities together. Additionally, we request that, based on the considerations noted above, the Agency specifically list "foreign facility" as a significant risk factor for purposes of its risk-based approach to inspections. Such action will assure that resources are actually allocated consistent with the risk, and thereby reduce the likelihood that quality problems associated with drugs would lead to injury, and even death, as happened in 1998-1999, when seventeen patients who were treated with gentamicin sulfate died – the common denominator linked to the deaths was the API of the drug originated from a Chinese supplier with varying levels of endotoxin and notable chemical impurities.[19]

One difficulty that may be perceived with risk ranking foreign and domestic firms together, however, is FDA's lack of authority to demand access to foreign facilities. In theory, this lack of authority could undermine the unified rankings because FDA would have to skip over facilities to which it could not gain access. In our opinion, this problem is more theoretical than real, at least in the case of facilities that are named in approved New Drug Applications. Foreign facilities that supply NDA holders typically establish Drug Master Files (DMFs) that describe the portions of the chemistry, manufacturing, and control operations associated with new drug production performed at the site. Because information provided in a DMF is incorporated by reference into the customer's New Drug Application, if a supplier were to deny access to FDA, for example to check records, the customer's NDA would be in jeopardy. As a result, the relationship between supplier and NDA holder (customer) gives FDA leverage over the suppliers—leverage that can be used to gain access to foreign suppliers.

C. Impurity Monitoring as a Surrogate for cGMP Inspections

A different approach, however, is required for foreign establishments that supply products other than those subject to a NDA. Most over-the-counter (OTC) drugs are not the subject of NDAs and ANDAs; rather, they are marketed pursuant to regulations referred to as "monographs" or an enforcement policy pending adoption of a final monograph.[20] Because there are no regulatory pre-approval barriers to entry for these products, formulators are free to source raw materials from any manufacturer and may change suppliers freely and frequently to obtain the lowest cost of goods. Quality assurance is a good investment only if there is a higher price to pay for poor

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[17] *See* presentation by Alicia Mozzachio, FDA inspector, *APIs and the Foreign Inspection Program*, at SOCMA's cGMP Compliance Conference for Pharmaceutical Ingredient Suppliers, Oct., 6, 2005; *see also* Pat Phibbs, *U.S., Foreign Firms Ranked Separately in Tool FDA Uses to Target Inspections*, Daily Report for Executives, Oct. 11, 2005.

[18] *See id.*

[19] A review of all the evidence indicated it was unlikely that endotoxin alone was responsible, but that it might have acted synergistically with a non-endotoxin pyrogen. *See* James F. Cooper, LAL TIMES, *Pyrogenic Reactions to IV Gentamicin*, December 1999; *see also* Steve Sternberg, USA TODAY, *FDA Probe Into Antibiotic Deaths Called Inadequate*, May 11, 2000.

[20] 21 C.F.R. Part 330.

quality. In the absence of effective oversight, quality assurance investments become unnecessary and unrecoverable costs. As long as the only production of imported mongraphed products (or ingredients) that are offered for import to the U.S meet the applicable specification requirements of the U.S. Pharmacopeia, there is virtually no incentive for such manufacturers to even implement GMP, let alone invest the time and attention required to stay up to date with cGMP.[21]

Indeed, if an OTC product or its components are manufactured in a foreign facility, the risk factors discussed above with respect to foreign suppliers to NDA/ANDA holders are further amplified. At this time, use of unproven or hazardous excipients in the formulations is possible because there currently is no systematic mechanism for detection or prevention of their use in such products. Additionally, just because adverse events are not associated with an OTC, does not mean there are no additional risks associated with foreign sites. Adverse events are difficult to correlate to an actual source or problem, especially considering that many OTC manufacturers may use numerous different suppliers over time for the same product with the same API and adverse effects of poor quality OTCs could take considerable time to appear.

Since cGMP non-compliance can be inferred by observing inconsistent impurity profiles in different batches of products, we ask that FDA implement a program to monitor the impurity profiles of imported OTC drugs for patterns that create the appearance of underlying cGMP violations. We recommend that FDA coordinate the priorities for this program based on the risk ranking of the facility that produces the product.

D. Conclusion

While the FY 2006 budget was signed into law on November 10, 2005,[22] we understand that the 2006 budget with regard to the foreign inspection programs is still unclear but, based on the proposed 2006 budget,[23] likely includes cuts to nearly all FDA's inspection programs, potentially reducing the foreign drug establishment inspection program by 5.8%. We sympathize with FDA's limitations in resources, but believe that if the agency is to fulfill its mandate to protect US consumers, it is imperative that the foreign manufacturing facilities responsible for exporting 80% of the bulk APIs into U.S. be inspected, at a minimum, to the same extent as domestic facilities. As Bernard Schwetz, D.V.M., Ph.D., Acting Principal Deputy Commissioner of FDA in 2001 stated, "FDA must improve foreign inspection and physical inspection coverage and oversight of foreign producers to be able to maintain the safety of products on that [sic] market that we believe Americans expect and demand."[24]

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[21] Although it is common for drug product manufacturers in the U.S. to qualify their suppliers, there is no explicit regulatory requirement for such inspections. *Cf.*, 21 C.F.R. Part 211.

[22] *See:* PL 109-97 http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=109_cong_public_laws&docid=f:publ097.109.pdf

[23] Julie Appleby, USA TODAY, *Budget Cuts FDA Safety Checks*, Feb.14, 2005.

[24] Bernard Schwetz, D.V.M., Ph.D, Acting Principal Deputy Commissioner, FDA, Testimony before the U.S. House of Representatives Committee on Appropriations, Subcommittee on Agriculture, Rural Development, and Related Agencies, March 8, 2001.

We urge FDA to properly allocate its limited resources to reduce the overall risk to consumers. FDA could increase the compliance stakes for foreign establishments by more aggressively exercising its prerogative under 21 U.S.C. § 381(a) to refuse entry to products that appear adulterated. Warning Letters and resource consuming formal enforcement efforts are not prerequisites to keeping suspect foreign drug products out of domestic commerce. Exercising this prerogative does not impose a significant burden on the budget and will raise the compliance stakes for foreign manufactures.

Although nearly half of all drugs marketed in the U.S. are produced or manufactured in foreign facilities, and this number is rapidly increasing, the vast majority of FDA inspections occur domestically. Neglecting to adequately inspect foreign drug establishments not only places domestic pharmaceutical manufacturers at an economic disadvantage, it also clearly places U.S. consumers and patients at risk. Contaminated gentamicin from a foreign drug supplier was the apparent cause of seventeen deaths in 1998-1999. Arguably, insufficiently aggressive foreign drug establishment inspections led to the flu vaccine shortage last fall. In order to help protect Americans from facing more crises due to unsafe drugs, the BPTF urges FDA: 1) to utilize its authority to refuse entry under 21 U.S.C. § 381(a) to products that appear adulterated; 2) to rank foreign and domestic drug manufacturing firms together according to FDA's risk-based approach to inspections; 3) to list "foreign facility" as a significant risk factor for purposes of its risk-based approach; and 4) to implement a program of monitoring the impurity profiles of imported over-the-counter (OTC) drugs for patterns that create the appearance of underlying problems with current good manufacturing practices (cGMP).

III. ENVIRONMENTAL IMPACT STATEMENT

The action requested does not involve the introduction of any substance into the environment and is subject to categorical exclusion of 21 C.F.R. § 25.30(a) because it involves inspections. To the petitioner's knowledge, no extraordinary circumstances exist.

IV. ECONOMIC IMPACT STATEMENT

An economic impact statement is not required at this time.

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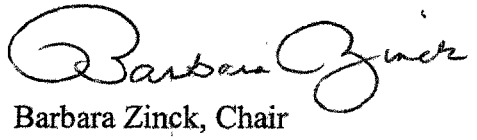
The undersigned certify that, to the best of her knowledge and beliefs, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,



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