

**UNITED STATES HOUSE OF REPRESENTATIVES,
COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS**

**One Page Summary of Testimony
John B. Dubeck, Esq.,
Keller and Heckman LLP
on behalf of the
Bulk Pharmaceutical Task Force of the
Synthetic Organic Chemical Manufacturers Association
November 1, 2007**

The Bulk Pharmaceuticals Task Force of the Synthetic Organic Chemical Manufacturers Association submits that the Commissioner of Food and Drugs should reduce the health risk to American consumers posed by imported drug products by taking the following actions:

1. rank foreign and domestic drug manufacturing firms together according to FDA's risk-based approach to inspections;
2. list "foreign facility" as a significant risk factor for purposes of its risk-based approach;
and
3. implement a testing program to monitor imported drugs for patterns that create the appearance of underlying problems with current good manufacturing practices (cGMP), so that FDA may refuse entry to such products as being adulterated.

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**Written Testimony of John B. Dubeck, Esq.,
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In January of last year, the Bulk Pharmaceuticals Task Force of the Synthetic Organic Chemical Manufacturers Association submitted a Citizen Petition to FDA urging that it take specific actions to better manage the manufacturing-related public health risks posed by the majority of pharmaceuticals consumed today. My testimony today will explain that these risks to the American consumer arise because inspections of foreign manufacturing facilities are so infrequent that the risk to a manufacturer of being found out of compliance is virtually non-existent. Given the magnitude of the problem, we are disappointed that the only communications we have received from FDA regarding the petition have been its administrative assignment of a docket number, *viz.*, 2006P-0049, and an equally administrative automatic notification approximately 180 days later stating that FDA had not yet reached a decision.¹

By way of background, the Bulk Pharmaceuticals Task Force (also known as the BPTF) is an association for manufacturers of active pharmaceutical ingredients (also known as APIs), excipients, and intermediates. The BPTF is a subgroup within the Synthetic Organic Chemical Manufacturers Association – also known as SOCMA. 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.

¹ Pursuant to 21 C.F.R. §10.30(e)(2), FDA is required to respond to petitioners within 180 days, indicating either that the petition is approved, denied, or providing a tentative response indicating why FDA has been unable to reach a decision. FDA's response to the BPTF said that the Petition raised "significant issues requiring extensive review and analysis by Agency officials." See FDA's July 20, 2006 Response Letter at www.fda.gov/ohrms/dockets/dockets/06p0049/06p-0049-let0001-vol1.pdf.

Once the safety and effectiveness of a drug has been established, the only assurance that on-going production will yield products with the same assurance of safety and effectiveness is if the products are manufactured in accordance with current good manufacturing practice (cGMP).² Compliance with cGMP is the responsibility of the drug manufacturer. FDA determines whether a manufacturer is in compliance with its cGMP obligations by conducting inspections. A manufacturer's failure to adhere to cGMP renders a drug adulterated, *per se*, even if the drug product is analytically within specifications. This is an essential distinction between the quality assurance obligation imposed on drug manufacturers and mere quality control. The goal is to ensure that every single dosage is of appropriate quality, not just that specifications are met on average.

FDA is required to inspect domestic drug establishments every two years.³ These inspections are unannounced. Indeed, BPTF members have had to abruptly alter plans to attend task force meetings because an FDA inspector had arrived at one of their facilities. A single inspection can extend over many weeks and may involve several separate visits of one or more days. The law imposes no comparable obligation on FDA to inspect foreign facilities. Since FDA must be invited to perform its official duties on foreign soil, a foreign facility always receives several weeks notice of an impending visit by an FDA investigator and the length of the inspection is typically driven by travel schedules rather than the compliance status of the facility. To FDA's credit, it is undisputed that its cGMP inspections are the most demanding in the world. Accordingly, the fact that the statute permits FDA to enter into cooperative arrangements with foreign officials to determine whether drug(s) should be refused admission into the United States⁴ is a poor substitute for a visit by the FDA.

The drug manufacturing industry today is structured vastly different than it was thirty, twenty or even ten years ago. No longer are drugs primarily manufactured in-house by the major pharmaceutical companies and sold as branded products. The major pharmaceutical companies

² See FDCA § 501(a)(2)(B).

³ See FDCA § 510(h).

⁴ See FDCA § 510(i).

have greatly expanded the number of manufacturing steps that are out-sourced (increasingly to foreign manufacturers). The ever expanding number of generic drugs available are even more likely to include significant components from (or be entirely produced by) a foreign source. By 2004, firms in China, Hong Kong and India accounted for 49% of the drugs consumed in the U.S. By 2005, four out of every ten prescriptions came from foreign facilities.⁵ The percentage of active ingredients produced on foreign soil is substantially higher.

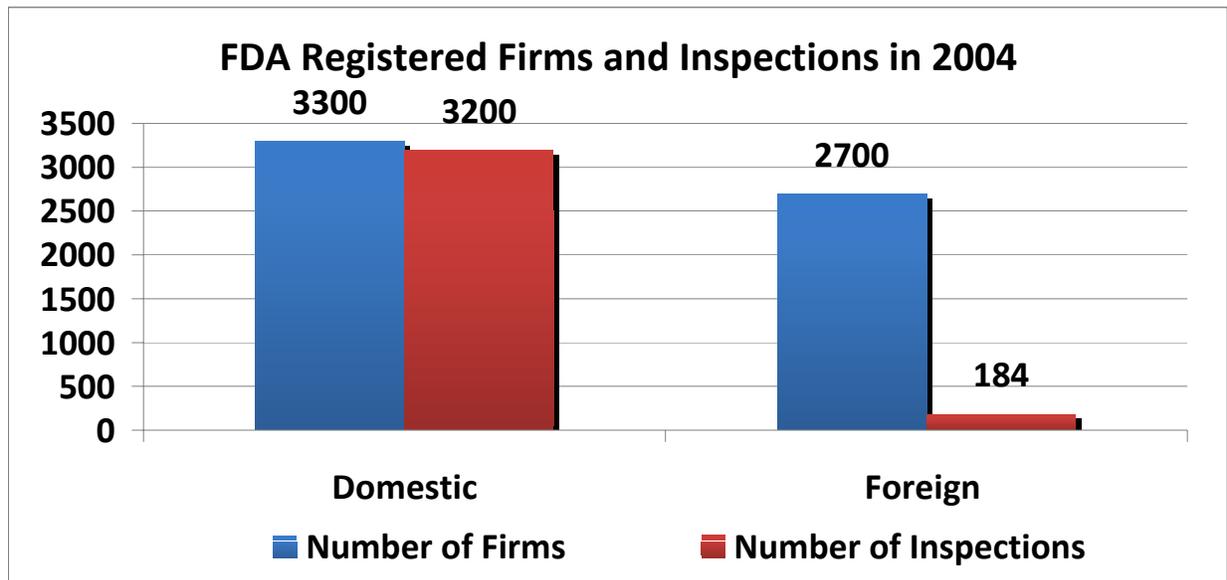
FDA's records indicate that in 2004 (the latest year for which reliable data is widely available), there were 3300 domestic drug manufacturing sites and 2700 foreign facilities.⁶ China and India led in the number of facilities, with 440 and 300 sites, respectively.⁷ In 2004, FDA conducted cGMP inspections on 1825 or 55% of the domestic facilities, but only 184 or just under 7% of the foreign facilities.⁸

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 This number excludes the 4500 domestic sites registered solely for the production of medical gases.

⁷ Kristen Evans, *CDER 2005 Compliance Update*, 29th International cGMP Conference, Univ. of Georgia, March 2005

⁸ Source: CDER Reports to the Nation (for years 1999 to 2004).



As a practical matter, a foreign manufacturer is unlikely to be inspected for cGMP compliance at all except in the context of a pre-approval inspection. As I explain below, these pre-approval related cGMP inspections have less value than you might think with respect to assuring on-going compliance.

For purposes of understanding the various inspection statistics that have been reported by FDA and GAO, it is important to note that not all foreign drug establishments manufacture products that trigger a preapproval inspection. I will return to the significance of this later in the context of an FDA notice of proposed rulemaking related to over-the-counter dosage forms of ibuprofen.

Briefly, drugs that are not generally recognized as safe and effective and (even if so recognized) have not been used to a material extent and for a material time are defined to be New Drugs. New Drugs require prior approval of a New Drug (or Abbreviated New Drug) Application (NDA/ANDA) before they may be legally marketed. As a general rule, FDA inspects each site identified in an NDA/ANDA that performs a critical production or quality control function prior to approving the application. Such pre-approval inspections look at the design and development of the manufacturing process and the adequacy of the systems in place to assure compliance with cGMP by that facility. It may or may not include an actual inspection of the management's ability to operate the facility in accordance with cGMP at production capacity. In

trying to best allocate scarce inspection resources, the responsible FDA field office may decide that the processes for manufacturing the product undergoing approval are so similar to an already inspected process at the facility that nothing of value would be gained by conducting an inspection; if a recent cGMP inspection of the site found no significant deficiencies for similar types of production operations, a new inspection for compliance with cGMP also may appropriately be skipped. The statistical discrepancy this creates between the number of New Drug Applications approved, the number of pre-approval inspections, and the number of cGMP inspections conducted by FDA is not a concern. More likely, however, is that the equipment and procedures in place to be inspected during a pre-approval inspection are only appropriate for or being operated at pilot scale.

There is a big difference between having procedures that may allow operations to comply with cGMP and actually implementing the procedures to achieve cGMP and maintaining operations at a high state of on-going compliance. Also, post-approval scale up changes may or may not require prior approval; even if prior approval of a supplemental NDA/ANDA is required, it does not follow that a new pre-approval inspection would be conducted; the cGMP status of a scaled up operation is typically only reviewed as part of a routine cGMP inspection. If a routine cGMP inspection is unlikely to occur in a timely fashion, it is very tempting for management to skimp on validating procedures and otherwise paying close attention to cGMP requirements. If the first routine cGMP inspection does not occur for another 12 years, the degree of control exercised during the scale up process and early production will be ancient history.

Statistics presented at a cGMP Conference in 2005 indicate that cGMP inspections of foreign firms result in significantly more violations than seen in domestic firms.⁹ When comparing pre-approval inspections, the same discrepancy is seen: deviations from cGMP were more serious in foreign facilities than in U.S. facilities.¹⁰ These numbers cry out for FDA to conduct more frequent inspections of foreign facilities and underscore the significance of the factors identified

⁹ See *id.*; see also Philip S. Campbell, *2004 Inspection Records & Compliance Issues*, 29th International cGMP Conference, Univ. of Georgia, March 2005.

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

in the BPTF petition which uniquely invite managers of foreign facilities to spend less time, attention and money on ensuring that manufacturing operations comply with cGMP. A drastic and dramatic overhaul of FDA's approach to the risks posed by foreign manufactured drugs is long overdue. The manufacturing side of the pharmaceutical industry has changed substantially in recent years and yet FDA's allocation of inspection resources remains unchanged from an earlier era.

In order for FDA to give cGMP inspections of foreign facilities the priority it deserves, the BPTF proposes that FDA do three things. Our first proposal is that FDA should abandon its policy of separately prioritizing facilities for inspection based on whether they are domestic or foreign facilities.^{11, 12} Instead, FDA should rank domestic and foreign facilities together, based on the risk that products from each facility pose to the American consumer. If there are 100 foreign facilities with higher risk profiles than the highest risk-ranked domestic firm, the American consumer is ill-served unless those 100 foreign facilities are inspected before the domestic firm. This obviously would require either an easing of the demand that domestic facilities be inspected every two years, which would allow a reallocation of scarce resources, or it would necessitate additional funding.

Some may argue that unified rankings will be problematic because fair implementation would require equal access to foreign and domestic facilities, something that is not within even Congress' authority to grant. The U.S. market for pharmaceuticals is large and lucrative. As recently evidenced by the import restrictions FDA implemented with respect to melamine contaminated proteins, FDA already has broad authority to refuse the importation of any product that appears to FDA to be adulterated. It is arguably within FDA's discretion to determine that a refusal to allow an inspection of a foreign facility creates the appearance of non-compliance, and that therefore it is permissible to refuse imports from the facility until an inspection is allowed. While such a policy would likely have trade implications and could subject U.S. manufacturers

¹¹ 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.

¹² 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.

to retaliatory prohibitions on their efforts to export to other countries, the health justification for the policy and the ease with which such refusals could be avoided make it seem reasonable that diplomatic solutions to these concerns could be reached.

Our second proposal is that FDA should specifically list “foreign facility” as a significant risk factor in its risk-based inspection program. As noted in the BPTF petition and as borne out by the statistics noted above, foreign facilities, in general, pose a greater risk to public safety. When a facility is inspected infrequently, there is a natural tendency for management to become complacent. 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-traveled road from minor deviations to serious quality failures. Since each step away from cGMP compliance can be a short term cost savings, profits can displace cGMPs in the absence of creditable regulatory oversight.

If the frequency of foreign inspections were increased proportionate with risk, an additional (but smaller risk factor) should still be assigned to foreign facilities. As a practical matter, any inspection that provides prior notice, is constrained by travel arrangements and therefore must be concluded within a defined window of time, and suffers from the communications problems inherent when dealing with facilities that operate in a foreign language through a translator provided by the facility, is bound to be less effective than an unannounced inspection of indeterminate duration conducted in the investigator’s native language.

The final request in the citizen petition is that FDA actively monitor the impurity profiles of active pharmaceutical ingredients (APIs) produced in facilities which FDA has not inspected. This monitoring would be a poor substitute for on-site inspections, but given budget and staffing considerations, it would be a great improvement compared to doing nothing to assure the safety of these important drug components. As noted above, cGMP is all about assuring quality; it is much more demanding than simply determining that the final product meets specification when sampled at some defined frequency and sample size. Just as a stopped clock is correct twice a day, a process that is not in compliance with cGMP will produce product that meets specifications occasionally. It is reasonable to assume that non-cGMP-compliant foreign

manufacturers will cherry-pick production lots and ship to the U.S. only those lots that meet specifications. Impurity profiles are highly sensitive to minor process variations. An active ingredient manufactured in accordance with cGMP will have a consistent impurity profile, while cherry-picked production from a non-complaint process will vary widely. It is virtually impossible to deconstruct an impurity profile to reconstruct the process conditions that created it, but one does not need that degree of knowledge to know that two different batches of product coming from the same facility with significantly different impurity profiles did not come from a process that is in control. If FDA gathered samples and discovered that products from a particular facility had variable impurity profiles, it would be justified in concluding that the facility was not being operated in accordance with cGMP. Therefore, the product would “appear” to be adulterated and future imports could be summarily refused admission until an inspection visit could be arranged and the presumption of non-compliance rebutted.

This monitoring of imports for a consistent impurity profile is an interim solution at best. It would raise production costs and reduce that amount of material available for export from a foreign manufacturer since even fewer batches could be cherry-picked if a consistent impurity profile is an additional requirement. Also, such monitoring is only useful for bulk active ingredients. Once an active ingredient is formulated with other ingredients, the impurity profile will reveal little about the control involved in the manufacturing process because of the presence of additional ingredients; their associated impurities will overwhelm the relatively subtle variations that can serve as a window on the degree of control inherent in the manufacturing process.

As noted above, not all drugs are subject to the new drug approval process and its associated prior approval inspection. Many of these “non new” drugs are available over-the-counter and are lawfully marketed as long as their composition and labeling are consistent with a final or tentative final monograph or an applicable enforcement policy pending adoption of a final monograph.¹³ Because there are no regulatory pre-approval barriers to entry for these products, formulators are free to obtain raw materials from any manufacturer and may change suppliers

¹³ 21 C.F.R. Part 330.

freely and frequently to obtain the lower costs. Quality assurance is a good investment only if there is a higher price to pay for poor quality. In the absence of effective oversight, quality assurance investments become unnecessary and unrecoverable costs. As long as the only production of imported monographed 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 even to implement cGMP, let alone invest the time and attention required to stay up to date with cGMP.¹⁴

Indeed, if an OTC product or its components are manufactured in a foreign facility, the risks to public health are further amplified. The 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 a particular drug product does not mean such product does not pose additional risks. 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.

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."¹⁵

¹⁴ 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.

¹⁵ 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.

Although there are many economic factors that have resulted in nearly half of all drugs marketed in the U.S. being produced in foreign facilities, the fact that such production attracts less aggressive FDA oversight surely contributes to the trend. A significant and prompt reordering of priorities by FDA with respect to the inspection of foreign facilities is essential to protect Americans from facing more crises due to unsafe drugs. Absent a new approach to inspecting imported products, the risks to public health will only increase.

In closing, I would like to note that the number of drugs entering the country without any oversight of their manufacturing process is likely to increase further and even more creative enforcement techniques than outlined in the Citizen Petition may be necessary. A factor that is expected to drive this increase is the fact that a number of prescription drugs have been converted to OTC status. One of the earliest such switches was the OTC dosage for ibuprofen. In August 2002, FDA proposed to substantially deregulate the manufacture of the 200 mg tablet form of ibuprofen by adding it to the monograph for internal analgesics. If this rule making were to be finalized as proposed, bulk ibuprofen would freely enter this country without FDA having any clue as to the manufacturing process employed or the degree of manufacturing control that existed. The impurity profiling technique described above is unlikely to be effective since it will be just as easy (and more profitable for the foreign manufacturer) to import fully formulated dosage form product. In short, FDA is proposing to allow ibuprofen of unknown quality to be sold in the U.S. without any prior approval on the basis that such products are generally recognized as safe and effective and have been used to a material extent and for a material time.

This ibuprofen proposal is significant for two reasons. First, it is a landmark event; there are many drugs that have made the Rx to OTC switch since ibuprofen and, in time, will also have been on the market for a material time and extent. They will all be candidates for conversion to “not new” drug status. Second, the same blind spot that allows FDA to ignore the risks of improperly manufactured imported drugs underlies the FDA proposal. The products that have created a favorable record of safety and effectiveness over a material time and extent have all been manufactured under the strict controls of the NDA/ANDA process. Further, the ibuprofen API used in these products for this material time and extent has been produced to an

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overwhelming extent in a limited number of domestic establishments and FDA has a history of demanding more detailed information from these manufacturers than simple compliance with the specifications in the United States Pharmacopoeia (USP). How this history supports the notion that uncontrolled manufacture of product that may only nominally meet USP specifications constitutes uses for a material time and extent of a generally recognized as safe product is a mystery. Although the context is different, it is the same mystery that concerns the Subcommittee today and suggests that the issue runs deeper than simply a lack of funding to perform more frequent inspections of foreign facilities.

On behalf of SOCMA and its Bulk Pharmaceuticals Task Force, I thank you for your time and attention to this serious matter.

JOHN B. DUBECK

PRACTICE OVERVIEW

A specialist in matters relating to product approval and clearance requirements, as well as compliance and enforcement actions under statutes administered by FDA, CPSC, USDA and EPA (particularly related to products subject to TSCA and FIFRA). Mr. Dubeck has been teaching the popular course "Practical Food Law" since 1982, and other courses offered by Keller and Heckman LLP as well as those sponsored by the Food and Drug Law Institute.

EXPERIENCE

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|--------------|---|------------------|
| 1976–Present | Keller and Heckman LLP | Washington, D.C. |
| ▪ | Associate, 1976 – 1981 | |
| ▪ | Partner, 1981 to present | |
| ▪ | Chair, Management Committee, 2005 to present | |
| 1971–1976 | United States Navy | Arlington, VA |
| | <i>Nuclear Propulsion Engineer, NavSea 08</i> | |
| ▪ | Licensing of transportation containers for radioactive and fissile materials. | |
| ▪ | Nuclear submarine refueling procedures | |

EDUCATION

- | | | |
|-----------|---|------------------|
| 1972–1976 | Georgetown U. Law Center | Washington, D.C. |
| ▪ | Juris Doctor | |
| 1972–1972 | Bettis Atomic Power Lab | W. Mifflin, PA |
| ▪ | Post-graduate studies in nuclear propulsion engineering | |
| 1967–1971 | Cornell University | Ithaca, N.Y. |
| ▪ | B.S. ChemE, with distinction | |

PROFESSIONAL ORGANIZATIONS

Admitted to the Bar of the Supreme Court and District of Columbia Ct of Appeals, District of Columbia and Commonwealth of Virginia

Tau Beta Pi, Engineering Honorary Fraternity

American Chemical Society, Cornell Society of Engineers

**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)
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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.

2006 P-0049

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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 prescription 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

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"

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 firms¹⁴ 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

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

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 monographed 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

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.

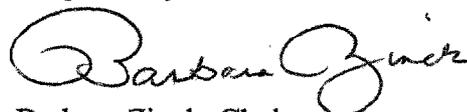
IV. ECONOMIC IMPACT STATEMENT

An economic impact statement is not required at this time.

* * *

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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