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VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

On behalf of a pharmaceutical manufacturer, Alston & Bird submits this petition under Sections 505 and 704 of the Federal Food, Drug, and Cosmetic Act ("FFDCA" or "Act") (21 U.S.C. §§355 and 374), 21 C.F.R. Part 314, and 21 C.F.R. §10.30. We appreciate your review and consideration.

I. Action Requested

Petitioner requests the Commissioner of Food and Drugs take the following action with respect to the scheduling and conduct of inspections associated with drugs manufactured or processed at domestic and foreign facilities:

- Establish a reliable and publicly available database of foreign and domestic pharmaceutical-product manufacturing firms registered with the Food and Drug Administration ("FDA") and selling product in the United States, and therefore subject to inspection for compliance with current good manufacturing practices requirements (cGMPs).
- Rank foreign and domestic manufacturing firms together according to FDA's risk-based approach to cGMP inspections.

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- Establish publicly available written criteria which determine how frequently and under what circumstances a firm is to be inspected for cGMP compliance.
- Ensure that those criteria are applied evenly and equally to all firms, both domestic and foreign.

II. Statement of Grounds

A. Background

FDA conducts inspections of pharmaceutical-product manufacturing firms for any of three primary reasons: (1) pre-approval inspections to ensure that before a new drug application (“NDA”) or abbreviated new drug application (“ANDA”) is approved, the manufacturer of the finished drug product, and each manufacturer supplying a bulk pharmaceuticals used in the finished product, complies with current good manufacturing processes (“cGMPs”); (2) routine postapproval inspections to periodically assess the regulatory status and quality of marketed drug products; and (3) “for-cause” inspections when FDA receives information suggesting problems in the manufacture of marketed products, or when it follows up on previous inspections in which problems were reported by investigators.

There have long been concerns about the consistency of FDA inspections and subsequent enforcement actions taken against pharmaceuticals manufacturers. These inconsistencies have been reported among domestic manufacturers as well as between domestic and foreign firms. FDA has offered different explanations for such inconsistencies, such as differences from district to district, scheduling practicalities, and differences in how field investigators and headquarters staff evaluated foreign inspection results and determined appropriate follow-up action. There is also a recognized perception that FDA has relied on foreign facilities to correct earlier problems because of insufficient resources to conduct follow-up inspections on-site.¹

B. Foreign vs. Domestic

There has also long been a perceived disparity regarding the frequency and intensity of inspections of foreign v. domestic firms. This disparity has not been resolved or mitigated. In fact, it appears to have worsened based on publicly available statistics, fueled by the dramatic increase in the number of FDA-regulated products, including pharmaceuticals, which are manufactured overseas and marketed in the United States.

FDA’s 1988 and 1993 internal evaluations found that while FDA routinely conducted surveillance inspections of domestic pharmaceutical manufacturers, foreign manufacturers were

¹ GAO, Report to the Chairman, Subcommittee on Oversight and Investigations, Committee on Commerce, House of Representatives: “Food and Drug Administration, Improvement Needed in the Foreign Drug Inspection Program (March 1998) [hereafter 1998 GAO Report], available at <http://www.gao.gov/archive/1998/he98021.pdf>

typically inspected only when they were listed in new drug applications.² More recent statistics reflect that this problem continues. FDA reported that in fiscal year 2005, it conducted 188 domestic approval inspections and 234 foreign preapproval inspections. However, FDA conducted, 1,437 domestic cGMP inspections and only 213 foreign cGMP inspections.³

In the 1998 GAO Report, it was reported that, according to FDA, as much as 80 percent of the bulk pharmaceutical chemicals used by U.S. manufacturers to produce prescription drugs was imported.⁴ That percentage is surely higher today. Yet routine inspections of foreign pharmaceutical manufacturers occur with far less frequency than the 2-year interval required for domestic manufacturers pursuant to 21 U.S.C. §360h. As FDA acknowledged in the 1998 GAO Report, most foreign pharmaceutical manufacturers may never receive a routine surveillance inspection.⁵

This situation is untenable in this era of increasing globalization. FDA is responsible for the safety and quality of domestic and imported pharmaceutical products under the FFDCA. Such products include both prescription and over-the-counter medications, and their active pharmaceutical components. While there is no specific statutory provision mandating routine inspections of foreign manufacturers every two years, there is no sound reason why such firms and their products should not be inspected as rigorously as domestic firms and their products. Certainly, recent recalls suggest that more scrutiny is needed.

FDA's foreign inspection program has been predominantly a preapproval inspection program. While that is an important and necessary activity, it should be remembered that all parties involved—the ANDA/NDA sponsor and the API supplier—are amply motivated to achieve compliance in order to qualify for approval. However, there is no reason to assume that same level of compliance will be maintained in the years ahead. Routine surveillance is intended to address that issue.

C. The Longstanding Weaknesses of the Foreign Inspection Program Remain Uncorrected

On November 1, 2007, the status of FDA's foreign drug inspection program was recently reviewed at hearing by the House Energy and Commerce Subcommittee on Oversight and Investigations. During that hearing, GAO presented its preliminary findings from its investigation of that inspection program. GAO Health Care Director, Marcia Crosse, stated: "... [M]ore than nine years after we issued our last report on this topic, FDA's effectiveness in

² 1998 GAO Report at p. 21.

³ 2005 CDER Report to the Nation at p. 47, available at <http://www.fda.gov/cder/reports/rtn/2005/rtn2005.PDF>.

⁴ 1998 GAO Report, p. 1.

⁵ 1998 GAO Report, p. 4.

managing the foreign drug inspection program continues to be hindered by weaknesses in its data systems.”⁶

Other significant findings by GAO included the following:

- FDA does not know how many foreign establishments are subject to inspection. FDA relies on information from several databases that were not designed for that purpose (pages 3 and 13).
- GAO found that the agency may inspect about 7 percent of foreign establishments in a given year. At this rate, it would take FDA more than 13 years to inspect each foreign establishment on this list once, assuming that no additional establishments are subject to inspection (pages 3 and 13).
- The number of establishments is not static. For example, according to GAO’s analysis of International Trade Centre data, the value of pharmaceutical imports increased 42 percent from 2001 to 2005 adjusted for pharmaceutical inflation (page 1).
- FDA does not have a dedicated staff to conduct foreign inspections. It does not arrive unannounced. It lacks the flexibility to easily extend inspections. It relies, where necessary, on translators provided by the foreign establishment itself (page 4).
- For fiscal years 2002 through 2007, 88 percent of FDA’s inspections of foreign establishments were conducted as part of the preapproval process. FDA often includes a cGMP inspection when it visits an establishment for a preapproval inspection (pages 15-16).
- FDA conducts fewer cGMP surveillance inspections of foreign establishments than it does of domestic ones. Of the 1,445 foreign establishment inspections conducted from fiscal year 2002 through fiscal year 2007, 1,177 inspections included a cGMP component, of which 998 were conducted in conjunction with a preapproval inspection. In contrast, FDA conducted 9,694 domestic establishment inspections that included a cGMP component, of which 7,742 were not conducted in conjunction with a preapproval inspection (page 17).
- The DRLS database shows that in fiscal year 2007, approximately 3,000 foreign establishments were registered with FDA but that according to

⁶ Drug Safety, Preliminary Findings Suggest Weaknesses in FDA’s Program for Inspecting Foreign Drug Manufacturers, Statement of Marcia Crosse, Director Health Care, <http://www.gao.gov/new.items/d08224t.pdf>, at page 3.

OASIS, 6,760 foreign establishments manufactured drugs that were imported into the United States (pp. 10-12).

While acknowledging that the quality of foreign inspections, when they do occur, appear to be thorough and professional, the Subcommittee's Staff Trip Report—"FDA Foreign Drug Inspection Program: A System at Risk"—voices many of the same concerns as expressed by GAO. See http://energycommerce.house.gov/cmte_mtgs/110-oi-hrg.110107.StaffTripReport.pdf. In an October 2, 2007 letter from the Subcommittee to FDA, attached to the Staff Trip Report, the following figures are presented which highlight the disparity between inspections of domestic and foreign drug establishments:

- As of August 23, 2007, there were 2,967 pharmaceutical product-manufacturing firms registered with the U.S. that are likely shipping to the U.S. and would be subject to: (a) pre-approval inspection; and (b) ongoing surveillance inspections.
- Of these nearly 3,000 firms, they break down as follows: (a) 183 are making both dosage/active pharmaceutical ingredients (API) products; (b) 1,146 are making API only; (c) 1,036 are making dosage only; and (d) 600 firms are making products "unknown to the FDA."
- FDA has conducted approximately 1,379 foreign inspections since Fiscal Year 2002—1,196 were both pre-approval and cGMP inspections, 107 were pre-approval inspections only, and 76 were cGMP inspections only.

D. Disparity Among Domestic Firms

There is another disparity that is a frequent topic of discussion within the industry, but usually behind closed doors: not all domestic firms are treated similarly by FDA. To put it bluntly, some firms are inspected an inordinate number of times, when the use of those agency resources may not be justified. The reasons cited may vary and include the District in which they are located, the type of products they manufacture, their history with FDA, a need to train new inspectors or model new inspection procedures, and specific personalities. Those reasons are beyond the scope of this Petition. We do ask FDA, however, to establish and apply criteria for inspections in a transparent and even-handed manner, for both domestic and foreign establishments. The resources consumed by the agency and by manufactures subject to inspection are just too great, and too preciously scarce, to not follow specific written standards.

We also note that FDA frequently cites limited resources as an explanation of why more foreign inspections are not conducted. We observe that to the extent FDA expends inordinate and unjustified time revisiting domestic establishments, that time could be directed toward strengthening an admittedly weak foreign inspection program. As an example, one client of our firm was inspected 16 times during the period 1999-2007, with a total of 88 days spent by

investigators during those audits. This is a company with a stellar inspection history and few significant 483 observations. While a few visits constituted preapproval inspections, most were for other purposes, including: cGMPs, sample collection, stability data review, and follow up to complaints.

Another concern voiced by domestic firms involves reinspections. For domestic manufacturers with a prior inspection of cGMP observations, FDA typically conducts a reinspection to verify that promised corrective actions have been implemented. Often a reinspection will demonstrate such implementation, but occasionally observations might remain uncorrected. While demanding near perfection in this scenario, competing products of foreign origin may never be inspected, and, reinspection of foreign establishments almost never occurs.⁷ This is a question of priorities. Senior managers must maintain a consistent procedural mechanism to determine if the level of risk inherent in what are often minor violations justifies the current degree of domestic scrutiny. Could agency resources be deployed more effectively to protect the public health?

E. Risk-Based Inspection Ranking

In June 1997, FDA's foreign inspection working group proposed using risk-based criteria to prioritize the foreign manufacturers inspected by FDA. Proposed criteria included inspection history, and whether products were to be sterile or otherwise posed higher public health risks. However, these recommendations were never successfully implemented.⁸

More recently, FDA 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.⁹ As reported in a 2006 Citizen Petition filed by the Synthetic Organic Chemical Manufacturer's Association's (SOCMA's) Bulk Pharmaceuticals Task Force, FDA stated that it will use this program for foreign manufacturers, but will rank domestic and foreign and domestic facilities separately.¹⁰ We support the Petition's recommendations that FDA "risk-rank domestic and foreign facilities together," and that the Agency specifically list "foreign facility" as a significant risk factor for purposes of its risk-based approach inspections.¹¹

F. Recent Congressional Inquiries

It is clear from the foregoing that problems with FDA's inspection program, particularly deficiencies regarding products manufactured in foreign establishments, have worsened, not

⁷ 1998 GAO Report, pp. 21-26.

⁸ 1998 GAO Report, pp. 21-27.

⁹ 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_method.htm.

¹⁰ SOCMA Citizen Petition (June 24, 2006), Docket No. 2006P-0049, page 4-5, available at <http://www.fda.gov/ohrms/dockets/dockets/06p0049/06p-0049-cp00001-01-voll.pdf>.

¹¹ Id.

abated. The red flags are all around us, whether it is Chinese fever medications containing diethylene glycol, or counterfeit Indian or Chinese methotrexate or Viagra. Recently, FDA received letters from the House Committee on Energy and Commerce and its Subcommittee on Oversight and Investigations (letter of October 2, 2007), and from Sen. Charles Grassley (R-IA), ranking member of the Senate Committee on Finance (letter of August 8, 2007). That correspondence requested information regarding FDA's inspections of foreign pharmaceutical manufacturing facilities.¹² For example, Sen. Grassley asked what protocols FDA has in place regarding such inspections, what strategies it has to improve the program, and how it is planning to respond to the shift of manufacturers from domestic to foreign facilities. The House Committee asked for several similar pieces of information and chastised FDA for its deficient adverse event information system, its inability to track and manage foreign inspections and its inability to know reliably and confidently which foreign firms are manufacturing and exporting products to the United States.

More recently, on October 30, 2007, Sen. Grassley sent a followup letter to FDA, requesting its response to additional questions following an August 23, 2007 FDA staff briefing.¹³ Sen. Grassley expressed concern about FDA's annual foreign inspection budget, emerging exporters that have never been inspected, the import of generic and over-the-counter drugs, and the practice of FDA inspectors permitting foreign pharmaceutical manufacturing plants to ship samples directly to the Forensic Chemistry Center, with no assurance that the samples are indeed from the plant that is the subject of inspection.

G. Conclusion

For the reasons set forth above, Petitioner urges FDA to begin to address the weaknesses of its foreign inspection program and the inequities in its inspection of domestic and foreign establishments, by taking, at a minimum, the following steps:

- Establish a reliable and publicly available database of foreign and domestic pharmaceutical-product manufacturing firms registered with the Food and Drug Administration ("FDA") and selling product in the United States, and, therefore, subject to inspection for compliance with cGMPs. Include a listing of dates and circumstances of establishment inspections.
- Rank foreign and domestic manufacturing firms together according to FDA's risk-based approach to cGMP inspections.
- Establish criteria to determine frequently and circumstances of firm cGMP inspections.

¹² See <http://energycommerce.house.gov/Investigations/DrugSafety.100207.FDA.ltr.pdf> and http://grassley.senate.gov/public/index.cfm?FuseAction=PressReleases.View&PressRelease_id=52eae135-1d37-477a-906c-127ff685ee04.

¹³ See http://insidehealthpolicy.com/secure/data_extra/dir_07/he2007_3913_1.pdf.

- Ensure that those criteria are applied evenly and equally to all firms, both domestic and foreign.

Environmental Impact

The petitioner claims a categorical exclusion from the environmental assessment requirement under 21 C.F.R. § 25.31.

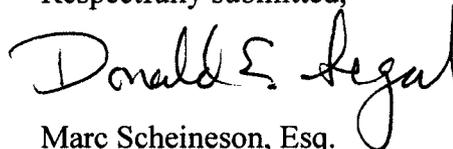
Economic Impact

Petitioner will submit an assessment of the economic impact of the actions it is requesting herein should the Commissioner determine such assessment is necessary in evaluating this petition.

Certification

We certify to the best of our knowledge and belief: (a) this petition contains all information and views upon which the petition relies; (b) this petition contains representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) we have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to us. We further certify that the information upon which we have based the action requested herein first became known to the party on whose behalf this petition is submitted on about November 1, 2007. We received or expect to receive no payments, including cash and other forms of consideration, to file this information or its contents (other than by virtue of our retention by our client). We verify under the penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



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