DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Re: Docket No. FDA-2006-P-0139
Docket No. FDA-2007-P-0187

Dear Ms. Zinck, Mr. Scheineson, and Mr. Segal:

This is a combined response to your citizen petitions asking the Food and Drug Administration (FDA or Agency) to take various actions regarding drugs manufactured or processed at foreign facilities.

The petition submitted by the Synthetic Organic Chemical Manufacturers Association (hereafter the SOCMA petition) was received by the Agency on January 24, 2006.[1] The SOCMA petition requests that the Agency:

- Rank foreign and domestic drug manufacturing firms together according to FDA's risk-based approach to inspections;
- List "foreign facility" as a significant risk factor for purposes of its risk-based approach; and
- 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 practice (CGMP), so that FDA may, under 21 U.S.C. 381(a), refuse entry to products that appear adulterated.

The petition submitted by Alston & Bird (hereafter the A&B petition), received by the Agency on December 10, 2007,[2] reiterates the SOCMA petition request to rank foreign and domestic manufacturing firms together according to FDA's risk-based approach to CGMP inspections, and in addition, asks the Agency to:

[1] The SOCMA citizen petition was originally assigned docket number 2006P-0049/CP1. The number changed to FDA-2001-P-0139 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] The Alston & Bird citizen petition was originally assigned docket number 2007P-0475/CP1. The number changed to FDA-2007-P-0187 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

FDA-2006-P-0139

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- Establish a reliable and publicly available database of foreign and domestic pharmaceutical-product manufacturing firms registered with the FDA and selling product in the United States, and therefore subject to inspection for compliance with CGMP;
- Establish publicly available written criteria that determine how frequently and under what circumstances a firm is to be inspected for CGMP compliance; and
- Ensure that those criteria are applied evenly and equally to all firms, both domestic and foreign.

For the reasons discussed below, the petitions are granted in part and denied in part.

I. BACKGROUND

A. Legal Framework

Under section 505 of the Federal Food, Drug, and Cosmetic Act (the Act), prior to approval of a new drug application (NDA), abbreviated new drug application (ANDA), or certain manufacturing supplements, FDA determines that the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the applicant's drug are adequate to preserve the drug's identity, strength, quality, and purity. Similarly, under section 351 of the Public Health Service Act (the PHS Act), prior to approval of a biologics license application (BLA), FDA determines that the biological product that is the subject of the application has been demonstrated to be safe, pure, and potent, and that the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to ensure that the biological product continues to be safe, pure, and potent. Domestic or foreign facilities that manufacture drugs (including biological drug products) for the U.S. market must meet FDA's CGMP requirements under section 501(a)(2)(B) of the Act. These statutory CGMP requirements apply to the manufacturer's facilities that produce the active pharmaceutical ingredients (API) as well as the finished drug product.

Section 801(a) of the Act provides the Agency with the authority and establishes a process to refuse entry of products imported or offered for import that appear to be adulterated. A product is adulterated if, among other reasons, it is manufactured in an establishment that fails to conform to CGMPs.[3] The appearance of adulteration on such a basis could be, but does not need to be, based on an FDA inspection.

[3] See 21 CFR parts 210 and 211 and section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

B. Overview of FDA's Foreign Inspection and Import Sampling Program

FDA's foreign drug inspection and surveillance program encompasses several distinct elements based upon the laws and regulations FDA enforces. This program includes registration of drug manufacturing establishments and listing of drug products, evaluating manufacturing practices at foreign facilities, and ensuring that firms have systems in place to prevent the distribution of products that do not meet FDA's quality standards. Elements of this program include:

- Required registration of foreign drug manufacturing establishments and listing of products under sections 510(i) and 510(j) of the Act. Section 510(p) of the Act requires electronic drug listing in addition to establishment registration (see also FDA guidance for industry on *Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Listing,* May 2009).

- Inspections of both API and finished dosage form product manufacturers.[4] Other facilities, including contract laboratories, are also inspected. These firms are inspected under FDA's preapproval and surveillance programs. In addition, FDA inspects firms on a "for cause" basis when we learn of an issue that we believe needs prompt follow-up at the firm's physical facility. Finally, each year a risk-based surveillance plan identifies specific foreign facilities for special focus. We have made significant progress in increasing these international inspections. From fiscal years 2007 to 2008, FDA increased its total number of risk-based international surveillance inspections. Similarly, in fiscal year 2009, we once again expect our inspections of these facilities to increase.

- Careful review of all foreign inspection outcomes by Agency compliance officers. Compliance officers review inspection reports of an establishment, an establishment's written response to Form FDA 483 ("Inspectional Observations"), the firm's commitments and documentation provided in the response, and an establishment's history of compliance. Based on their review, compliance officers consider whether the findings warrant further FDA regulatory action.

Agency pre- and postapproval inspection and postapproval surveillance activities include assessments for CGMP compliance and risk-based sampling, as appropriate. Sampling may be

[4] Agency policy has been, and continues to be, that we approve drugs after verifying that the standards set forth in section 505 of the Act, or section 351 of the PHS Act, are met based upon a recent inspection of the manufacturing facility or facilities named in the application. If we have a recent, satisfactory inspection on record for a given facility named in the application, we may not conduct a new preapproval or prelicense inspection of that facility before approving the application. However, even if there has been a recent satisfactory inspection, we will inspect again if we determine that the circumstances warrant it. For example, FDA will inspect again if FDA believes that the manufacturing facility may not be in compliance with CGMPs, if the application raises questions that need to be resolved by inspection, or if the facility is using a new or unique technology for the product that warrants evaluation by inspection.

conducted at a foreign manufacturing site when a product is offered for import, or, in rare cases, after it is released into interstate commerce. Decisions to sample certain articles offered for import are based on current Agency assessments of risks and the judgment of field personnel. FDA is continually seeking ways to strengthen the sampling of imports.

In addition to the activities described above, the Agency is engaged in a number of ongoing and future initiatives[5] that address the dramatic growth rate of imported FDA-regulated products and the challenges this represents to the Agency. These include:

- Maximizing foreign prescription drug preapproval inspections
- Enhancing our foreign presence (the Agency recently established several offices in China and is planning more)
- Instituting the Beyond Our Borders Initiative, which involves cooperative arrangements with foreign counterparts, potentially expanded use of third party certification to verify compliance with U.S. safety and security standards, and providing technical assistance to help foreign regulators understand FDA standards
- Issuing Good Importer Practices to help the importing community take appropriate steps to ensure the safety of their products
- Developing a pilot program that would reduce the delay for firms that take proactive measures when they import finished drug products and APIs
- Implementing foreign vendor registration verification to help increase information about foreign facilities
- Sharing foreign inspection records with trusted foreign counterparts
- Building a modern information technology (IT) infrastructure to ensure the accuracy and validity of the data in the Agency's registration and import IT systems, including an initiative, Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT), an automated entry screening system that has the potential to make a dramatic change in FDA's business practices by incorporating relevant risk data from all points in the import life cycle, including data currently outside FDA databases, to predict and prioritize the highest risk import entries

[5] See testimony by Andrew C. von Eschenbach, Commissioner of Food and Drugs, before the Committee on Energy and Commerce's Subcommittee on Oversight and Investigations, April 22, 2008 (http://www.fda.gov/ola/2008/foreigninspection042208.html).

- Increasing surveillance inspections to help ensure compliance with CGMP standards and prevent product problems

- Holding U.S. manufacturers accountable to help ensure that importers are aware of their responsibility for safe and effective medical products

- For fiscal year 2009, doubling the number of inspections in FDA's annual work plan as compared with fiscal year 2008 specifically to increase the number of CGMP inspections of foreign human drug manufacturing establishments

- Staffing a team of investigators who will be dedicated for an extended period of time to perform inspections of foreign drug manufacturing establishments

The Agency is also undertaking rapid response initiatives to address emerging safety risk and product problems. All told, as is evident from the discussion above, there are comprehensive efforts already in place and in development to implement a systematic, life cycle approach that addresses the globalized system of drug development.

C. Overview of Compliance Framework

When an imported drug appears to be adulterated, whether through testing, a CGMP inspection, or otherwise, it can be denied entry into the United States, subject to an opportunity for the importer to show that the drug is not adulterated. If it appears that future shipments from an establishment appear to be adulterated due to non-compliance with CGMPs, FDA may issue an import alert to communicate this information to Agency field staff. (For more information on Import Alerts, see http://www.fda.gov/ora/compliance_ref/rpm/ chapter9/ch9.html.) To notify a foreign firm of the need to correct serious CGMP findings, FDA may send a warning letter to the responsible establishment.

II. DISCUSSION

A. Request To Identify "Foreign Facility" as a Significant Risk Factor

- Both the SOCMA and A&B petitions requested that the Agency designate "foreign facility" as a significant risk factor for surveillance inspections as part of the implementation of the Agency's CGMP risk-based initiative announced in 2004[6] (SOCMA at 4-5; A&B at 6). Both petitioners assert that this action is warranted because of the relatively lower inspection rate of foreign facilities compared to domestic facilities and the increasing number of drug products manufactured abroad. The petitioners also

[6] Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach (Fall 2004).

> assert that there is a relatively higher incidence of CGMP violations for foreign facilities compared to domestic facilities. Among other things, both petitioners cite to a 1998 and 2007 GAO report concerning FDA's inspection of foreign drug establishments.

We acknowledge the cited statistics that FDA has conducted inspections of foreign facilities at a relatively lower rate than domestic facilities, as well as the increasing numbers of drug components and finished drug products manufactured abroad. However, as discussed above in section I.B, FDA has undertaken numerous significant initiatives to address the dramatic growth rate of imported FDA-regulated products and the challenges this represents to the Agency, including increasing the number of foreign surveillance inspections to help ensure compliance with CGMP standards and prevent product problems. We do not believe that characterizing all "foreign facilities" as a significant risk factor for surveillance inspections would be helpful for these efforts.

We note in particular that the request is not adequately tailored to specific evidence of risk. The petitions fail to provide evidence that *all* foreign facilities should be classified as a significant risk factor. In fact, similar to the variation in risk among domestic firms, the amount of variability of risk among foreign firms is so great that considering all foreign facilities to be a significant risk for inspection ranking decisions would be overly broad and not meaningful. We also do not believe that a review of Form FDA 483 data, as undertaken by the SOCMA petitioner in support of its assertion of greater risk from foreign drugs, is an appropriate comparator of risk, particularly because such a review does not account for different product types and different types of inspection.

As for the petitioners' assertions concerning the alleged disincentives for foreign firms to comply with CGMPs because of the limited likelihood of FDA surveillance inspections, we believe that the petitioners do not adequately consider other important incentives, aside from FDA inspections, for foreign manufacturers to comply with CGMPs. Foreign manufacturers are obligated to follow the applicable laws of their own countries and may, in fact, be inspected by regulatory authorities other than FDA who are charged with surveillance of their domestic industry. The Agency has established a number of working agreements with foreign governments.[7] These agreements have been invaluable in extending Agency resources to increase our knowledge of foreign facilities and enhance our risk management efforts. For example, FDA in many cases obtains copies of inspection reports from our international

[7] For example, the European Union (EU)-U.S. Bilateral Technical Working Group on Medicines Quality and Manufacturing, established in 2007, will focus on sharing resources through information exchange of inspectional data for plants in the United States and the European Union. Similarly, FDA has applied to join the Pharmaceutical Inspection Cooperation Scheme (PIC/S), which fosters cooperation among pharmaceutical inspection authorities in pharmaceutical good manufacturing practices and in developing and promoting harmonized CGMP standards and inspections.

counterparts. This information is coupled with our foreign inspection program to provide FDA with knowledge of facility compliance status. We also note that, with respect to products manufactured by foreign facilities, FDA can refuse entry of such products that are imported or offered for import based on the appearance of adulteration, under section 801(a) of the Act.

FDA is continuously seeking ways to improve oversight of imported drugs, including upgrading information technology systems to enhance the accuracy and reliability of data that track foreign firms, enhancing cooperative relationships, and initiating new formal agreements with foreign regulators. These efforts are outlined in section I above.

Thus, for the reasons described above, we deny the petitioners' request.

B. Request That FDA Risk-Rank Foreign and Domestic Drug Manufacturing Firms Together

Both the SOCMA and A&B petitions request that the Agency risk-rank foreign and domestic firms together (SOCMA petition at 4-5; A&B petition at 1).[8] These petitions urge risk-ranking foreign and domestic drug manufacturing together as a means of addressing their asserted "foreign facility" risk factor. Specifically, these petitions cite:

- The need to ensure that resources are allocated consistently, thereby reducing the likelihood that quality problems associated with drugs would lead to injury or death, such as the gentamicin incidents, where deaths were thought to be linked to the API of the drug containing varying levels of endotoxin and chemical impurities, and originating from a Chinese supplier (SOCMA petition at 5).
- A disparity between the frequency and intensity of inspections of foreign as opposed to domestic firms.
- Preliminary findings from GAO presented at a November 1, 2007, hearing by the House Energy and Commerce Subcommittee on Oversight and Investigations (A&B petition at 3).

As explained above, we acknowledge that FDA has conducted inspections of foreign facilities at a relatively lower rate than domestic facilities, as well as the increasing numbers of drug components and finished drug products manufactured abroad. However, as discussed above, FDA has undertaken numerous significant initiatives to address the dramatic growth of

[8] We note that the A&B petition also requests that FDA ensure that the inspection criteria are applied evenly and equally to all firms, both domestic and foreign. This request is part of A&B's request to risk-rank foreign and domestic firms together, which is addressed in this section. We address A&B's request to establish publicly available criteria in section II.C.

imported FDA-regulated products and the challenges this represents to the Agency. While the Agency's efforts to collaborate with foreign jurisdictions and enhance the Agency's presence on foreign soil will vastly enhance our program efforts, the Agency does not currently have the resources to inspect foreign firms as frequently as domestic firms. Thus, the Agency is not risk-ranking foreign and domestic firms together at this time. However, as discussed in section C below, inspections of foreign and domestic firms are being prioritized using the same risk-based method.

For these reasons, we deny the request to risk-rank foreign and domestic firms together.

C. Request to Establish a Reliable and Publicly Available Database and Criteria for Inspection

The Alston & Bird petition requests that the Agency establish a reliable and publicly available database of foreign and domestic firms registered with FDA (A&B petition at 1-2). In addition, the petition requests that the Agency make publicly available written criteria that establish how frequently and under what circumstances a firm is to be inspected for CGMP compliance, both domestic and foreign.

As grounds for the request, A&B asserts that FDA does not know how many foreign establishments are subject to inspection, and that the Agency relies on information from several databases that were not designed for foreign inspection purposes (A&B at 4).

We agree that a comprehensive and appropriately accurate inventory of sites is needed. FDA is developing an electronic drug registration and listing system that will, among other things, help ensure that data are accurate and complete.[9] This information will be made publicly available to the extent permitted under applicable law.

[9] The Agency's Electronic Drug Registration and Listing System (eDRLs) is a registration and listing system for drug manufacturers and other types of drug establishments. The system will provide FDA with more comprehensive, accurate, and real-time information to ensure the quality and integrity of U.S. drugs, wherever they are made. FDA will use the information from the registration and listing system to identify drugs and drug manufacturers, repackers, and relabelers. This information will allow FDA to conduct greater oversight of the supply chain involved in the manufacture of drugs. As described in FDA guidance for industry on *Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Listing,* May 2009, as of June 1, 2009, the Agency intends to accept all drug establishment registration and drug listing information in electronic format only, unless a waiver is granted.

In terms of criteria for prioritizing inspections, FDA has made publicly available its risk-based method for inspections.[10] Our foreign inspection prioritization is governed by risk-based decisions using our previously described risk model and, among other things, whether the establishment's product is in fact imported to the United States, logistical considerations in planning foreign establishment inspection trips, and leveraging other foreign regulatory authorities' efforts. FDA does not disclose individual risk-factor weights and final scoring information, or specific information used to generate the weights and scores. FDA does not intend to publish or disclose such details of a site's individual score or ranking, in order to be able to effectively enforce the law.

We note that we are addressing your requests in the context of the Agency's evolving inspection and registration and listing programs. For the reasons provided above, the requests for FDA to establish a reliable and publicly available database of foreign and domestic pharmaceutical product manufacturing firms registered with the FDA, as well as to establish publicly available written criteria that determine how frequently and under what circumstances a firm is to be inspected for CGMP compliance, is granted in part and denied in part.[11]

D. Request To Establish a Program To Monitor the Impurity Profiles of Imported OTC Drugs

The SOCMA petition requests an approach other than foreign CGMP inspections for OTC drugs or their components that are manufactured in a foreign facility not subject to an NDA.[12] Specifically, SOCMA requests that the Agency instead implement a program of monitoring the impurity profiles of imported OTC drug products for patterns that create the appearance of underlying problems with CGMPs so that FDA may refuse entry to products that appear adulterated. They suggest that the previously asserted risk of foreign manufactured products is amplified when the products manufactured are OTC drugs. As grounds for their assertion, they

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[10] See http://www.fda.gov/cder/gmp/gmp2004/risk_based_method.htm; see also http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/CompliancePrograms/ucm095419.pdf (Compliance Program Guidance Manual 7345.848) for a description of CBER's risk-based management approach to biological drug product manufacturer inspections. As noted in the Compliance Program Guidance Manual, FDA's statutory authority establishes a 2-year frequency for inspection of domestic establishments (section 510(h) of the Act). The Act does not include a frequency for foreign drug establishment inspections.

[11] FDA's risk-ranking method is used for both foreign and domestic firms for prioritizing inspections. However, in applying this method, there are additional considerations that influence prioritization decisions for foreign firms, as described above. For this reason the criteria for the prioritization of inspections for foreign and domestic firms differ. Therefore, your request that FDA ensure that the criteria that determine how frequently and under what circumstances a firm is to be inspected for CGMP compliance are applied evenly and equally to all firms, both domestic and foreign, is denied.

[12] SOCMA describes its suggested approach in the section heading as a "surrogate" for CGMP inspections.

state that because many OTC drugs are not subject to preapproval requirements, OTC drug manufacturers are less likely to comply with CGMPs (SOCMA petition at 6). In addition, SOCMA states that there is no systematic mechanism for detecting or preventing unproven or hazardous excipients in OTC formulations. As a result, SOCMA argues, the public health risks for OTC drug products are similar to those for prescription drug products manufactured outside the United States.

We note that finished drug product manufacturers are required by 21 CFR 211.84(d)(2) to ensure through testing, or appropriate validation of the supplier's test results, that each component of a drug product conforms with all appropriate written specifications for purity, strength, and quality. Thus, the manufacturers of OTC drug products not subject to an NDA must ensure that all components, including excipients, used in manufacturing the finished product meet such specifications. It would not be acceptable under CGMP requirements for a manufacturer to use an excipient that raises safety concerns. FDA inspects finished drug product manufacturers, including domestic manufacturers that receive excipients from foreign manufacturers, to ensure that they comply with these CGMP requirements applicable to drug components.

Furthermore, FDA already has a sampling and testing program that covers drug products, including OTC drugs, manufactured in domestic and foreign facilities and marketed in the United States. Among other things, this program helps ensure that these OTC drugs conform to their established specifications.

In addition to the sampling and testing plan discussed above, our current strategy for fostering the safety of imported OTC products includes (1) leveraging information from foreign counterparts; (2) continuing to maximize our CGMP inspection and surveillance program to include foreign manufacturers of OTC drug products; and (3) issuing specific guidance when it appears that raw materials of a class of drug product may be vulnerable to contaminants.[13] Our guidance on glycerine and a more recent guidance on melamine are examples. (See FDA guidance for industry on Testing of Glycerine for Diethylene Glycol at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070347.pdf and Pharmaceutical Components At Risk Components for Melamine Contamination at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175984.pdf).

[13] We note that the dosage form manufacturer has primary responsibility to ensure the quality of each lot of components received from a supplier, and this includes appropriate examination and testing as mandated by CGMP requirements.

To the extent that the SOCMA petition requests that FDA conduct tests to look for "patterns" of impurities, we believe such efforts would not be useful for FDA to ensure the safety of imported OTC drugs. Impurities in drug products may arise from the ingredients used in their formulation and by the production process used to create the dosage form. The presence of impurities in a finished product is acceptable when the impurities are limited and monitored. Changes to ingredients and methods of processing can result in a change to a product's impurity profile. Such changes are not CGMP violations when properly managed and validated to ensure the finished product continues to meet appropriate specifications. Therefore, the detection of changes to an impurity profile or a pattern of impurities would not, on its own, support a conclusion that a product appears adulterated under the Act. The Agency believes that its more targeted sampling and testing efforts, along with oversight of the actual conditions of manufacturing, are more effective in identifying any underlying CGMP problems with imported OTC drugs.

For the reasons explained above, we believe that our approach is more comprehensive and appropriate than the more limited intervention suggested by the SOCMA petition. We do not believe that increased testing (e.g., monitoring impurity profiles), particularly as a surrogate for CGMP inspections, would adequately address the petitioner's concerns regarding the level of CGMP compliance and degree of safety associated with imported OTC drugs compared to drugs that are evaluated through NDA or ANDA submission. As noted throughout this response, we expect that our risk-based approach for using our limited resources and collaborative international efforts is also an effective means of minimizing the safety risks of drug products manufactured by foreign establishments. Consequently, we deny your request that FDA create a new testing program to monitor impurity profiles in imported OTC drugs.

III. CONCLUSION

The SOCMA petition requests that FDA (1) list "foreign facility" as a significant risk factor; (2) rank foreign and domestic drug manufacturing firms together; and (3) implement a program of monitoring the impurity profiles of OTC drugs for patterns that create the appearance of underlying problems with CGMPs. These requests are denied for the reasons set forth in this response.

The A&B petition request to rank foreign and domestic manufacturing firms together according to FDA's risk-based approach to CGMP inspections is denied for the reasons set forth in this response. The request that FDA ensure that those criteria are applied evenly and equally to all firms, both domestic and foreign, is denied for the same reasons. The request to designate "foreign facility" as a significant risk factor is also denied for the reasons set forth in this response.

Docket Nos. FDA-2006-P-0139 and 2007-P-0187

The additional A&B requests for FDA to establish a reliable and publicly available database of foreign and domestic pharmaceutical product manufacturing firms registered with FDA and establish publicly available written criteria that determine how frequently and under what circumstances a firm is to be inspected for CGMP compliance is granted within the parameters of the Agency's evolving foreign inspection and registration and listing programs, as discussed in this response.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research