

Statement of

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Before the

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A. Introduction:

Mr. Chairman, members of the Subcommittee on Oversight and Investigations, I thank you for this opportunity to discuss the status of FDA's oversight of the foreign-based pharmaceutical manufacturing industry and related drug products. I retired from FDA in February 2005 after 32 years of government service, 28 of which I served in the U.S. Food and Drug Administration, Office of Regulatory Affairs (ORA). Besides serving as a senior special agent with FDA's ORA/Office of Criminal Investigations, I served in capacities as a consumer safety officer carrying out duties as a field investigator, a resident-in-charge, a field compliance officer, a first line supervisor of a field unit dedicated to import operations, lead compliance officer with the original Team Biologics Core Team based in ORA headquarters, and, finally, for nearly six years, I served as Director of ORA's Division of Import Operations and Policy (DIOP). Since my retirement I have been self-employed as a regulatory consultant as C. Nielsen Consulting and am co-founder of FDAImports.com.

I understand it is the purpose of this Subcommittee's hearing to evaluate FDA's ability to oversee the foreign drug industry to ensure public health and safety. The short answer – the current paradigm is grossly inadequate, is held together by bailing wire, and is incapable of determining or verifying the safety and efficacy of most imported drug products. Product liability is protecting us more than FDA's oversight of the international supply of pharmaceuticals. Not only are financial and human resources woefully inadequate, the current FDA organization is not designed and funded to adequately oversee the foreign industry, to effectively manage and administer the related programs, and to ensure the delivery of safe and effective imported drug products into the United States through secure supply chains.

B. Importance of Surveillance Drug Manufacturer Inspections

The traditional first and internationally recognized primary method for the agency to ensure drug products are safe and effective after product approval is to conduct current good manufacturing practice (cGMP) inspections to ensure the firms are in compliance with requirements of the current good manufacturing practice regulations (cGMPRs) and conditions promised in the drug applications. Drugs emerging from cGMP compliant firms means they were made in adequate facilities using appropriate systems and practices are in place to ensure the safety and effectiveness of each batch of finished drug. cGMP compliant firms have systems in place to ensure incoming components including ingredients meet quality specifications.

Prescription (Rx) drug manufacturers are required to identify their sources of ingredients, including Active Pharmaceutical Ingredients (API's), used to make their finished drugs are the same ones identified in their drug applications. The applicants must also submit information describing product specifications and manufacturing methods for the API's. This is usually done through the Drug Master File (DMF) process in which the API manufacturer submits the information to the Agency. Today, most API's are made by foreign manufacturers.

The finished Rx drug manufacturer must also demonstrate the ingredients they use in the manufacturing process consistently produces finished products that meet all relevant specifications. Part of establishing a stable manufacturing process is ensuring the ingredients going into the process meet specifications and are of adequate purity and quality. In other words, the manufacturer of the finished drug essentially performs pilot manufacturing using the API from a specific source to make sure the finished drug meets final specifications described in the application. Use of API's from sources other than those identified in the approved drug application can result in a finished product that will not do what it is supposed to do.

During counterfeit imported API investigations in the early 1990s, we found an instance, for example, in which a patient died because a finished carbamazepine drug, an anti-convulsant, which was made with an imported counterfeit carbamazepine API, did not work. Other patients who experienced seizures using the same product became seizure free once they used another carbamazepine product. The counterfeit carbamazepine API

met identification and potency testing requirements. The investigation determined the crystalline structure of the counterfeit altered the compression characteristics of the tablet which had an adverse effect on dissolution characteristics. Consequently, the tablet did not dissolve and the carbamazepine was not delivered to the target organ to manage the seizure disorder. It apparently just passed through the intestinal tract.

Finished product testing alone is inadequate to ensure a batch of product is safe and effective. Finished product testing does have value in determining expiration dating, monitoring manufacturing processes, establishing baselines for impurity profiles and other analyses useful to identify and verify important product characteristics. But testing alone can not put the quality and safety into the product. It is the manufacturing processes and application of effective quality assurance programs that determine the quality and safety. An adequate correction for a failed product that is detected or confirmed by testing is not to just do more testing. Rather, it is to identify the cause of the failure and to implement corrective steps in the manufacturing processes to best ensure the same failures are not repeated. It is the well designed, stable manufacturing process that ensures product safety and effectiveness from one pill to the next, from one vial to the next, and one bottle to the next.

C. FDA Organizational Weaknesses Undermine Effective cGMP Compliance Programs

It is primarily FDA's Office of Regulatory Affairs' (ORA's) job to ensure the drug industry is complying with cGMP requirements by conducting inspections of the physical

plant, processes and materials. However, ORA is not directly funded to maintain baseline infrastructure to ensure appropriate inspection coverage of regulated industry. Resources are negotiated between ORA and the Center for Drug Evaluation and Research (CDER) through an annual, on-going, ORA work planning process that determines which and how many field activities will be supported for a fiscal year. These activities include domestic and foreign inspections and border operations.

The number of activities the agency plans for the year is based on the number of activities that can be accomplished by FTEs (Full-time Equivalents). The number of FTE's, though, do not directly translate to the number of warm bodies performing the activities such as inspections and entry review. In my six years as Director of the Division of Import Operations and Policy, no one could provide me a roster of personnel assigned to import duties fulltime, nor was I able to develop one. In a September 24, 1998, statement Mr. William B. Schultz, then FDA's Deputy Commissioner for Policy, stated before the Permanent Subcommittee on Investigations of the Senate's Committee on Government Affairs, " In 1992, we received approximately 1.1 million line items of imported foods and had 631 supported Full Time Equivalent employees (FTEs) to look at those items. By 1997, our line items more than doubled to approximately 2.7 million but budget limitations caused us to cut our supported FTEs to 565. Of these 565 FTEs, only 314 are what we refer to as "operational," with 112 actual investigators and 202 analyzing samples in the laboratories. (The others are support staff, including those at headquarters.)". This statement was provided in the context of describing FDA's oversight of imported foods.

From Mr. Schultz's statement one can readily see FTE's do not directly relate to the number of inspectors with feet on the ground. Out of the referenced 565 FTE's, there were 112 investigators (inspectors) to conduct entry reviews, collect samples, and examine cargo. About 1/5 of the FTE number translated to actual investigators (inspectors). FDA's FTE model means more than half the resources are spent on non-descript support staff who do not report time into the tracking systems that keep count of FDA's activities, e.g., entry review, domestic and foreign inspections, investigations, sample collections, examinations, laboratory analyses, etc. The math behind this FTE resource model is very questionable. The FTE appears to be little more than time accounting. However, only the activities of the field inspectors, investigators and laboratory analysts are accountable and only they report their time into the systems used to create the FTE model. The ORA work planning process and organizational structure need a major overhaul.

D. Disparity in FDA Inspections of Domestic vs. Foreign Drug Manufacturers

The statute requires FDA to inspect the domestic drug manufacturers every two (2) years. Historically, FDA does pretty well meeting this 2 year obligation with its scant resources. However, the industry trend for more than a decade has been to move drug manufacturing for finished drugs and API's off-shore. Unfortunately, without the external pressure on the agency, the current FDA organization has not re-deployed, and

will not re-deploy significant resources away from the domestic industry to the international arena commensurate with this industry trend.

The current FDA organizational structure and administrative processes are entrenched in overseeing the domestic industry while largely ignoring the foreign industry. Very few foreign surveillance inspections are conducted annually, and most are conducted in a very short-time frame of 2-3 days in order to save money and to get the greatest number of inspection numbers accomplished on a foreign trip. Regardless of the outcome or scope of the foreign inspections, the agency uses the number of completed foreign inspections to argue it is providing adequate coverage of the foreign industry using the least amount of resources. FDA still uses the number of completed inspections and other activities, the work widgets, to measure performance instead of the outcome of the widgets. If FDA plans 700 foreign inspections per year, for example, and the 700 foreign inspections are completed in that year, then FDA considers the planning a success. If 701 or more inspections are conducted then the work obligations and performance goals have been exceeded and performance awards may even increase.

Certainly fiscal constraints to some extent have tied the agency's hands adding to its inability to adequately oversee the foreign industry. But why would management continue to spend the same resources on the domestic industry when it is known at least the same number, or more, of the manufacturing firms are located overseas? It doesn't make sense. Certainly it is logical to expect greater risks will arise from drug industries in countries that do not have the same or similar oversight regulatory capabilities as the

United States. Simple infrastructure issues such as potable water, power supply, personal hygiene of employees and air quality can be very significant for producing products of high quality and safety. Yet, FDA's focus on domestic manufacturing – to the exclusion of foreign inspections – persists.

There is an FDA culture of not wanting to know there may be more regulatory problems outside the traditional domestic industry because the agency is already strapped with domestic regulatory issues. This “know no evil” culture enables FDA to say that no one has identified a specific risk, thus, there must be no risk – thus there is no cause for FDA action. A real comprehensive risk management approach does not just pick a subset of the universe and ignore the rest. Instead, the agency should put more value into knowing the compliance status of the entire foreign industry as thoroughly as it pursues the compliance of the domestic industry. If the agency knew the compliance status of the universe of foreign manufacturers, it would be able to develop appropriate strategies to better ensure only safe imported drugs are allowed entry into the United States. The agency would be able to direct resources to particular firms or countries or regions to facilitate compliance with U.S. requirements or prohibit access to the U.S. market.

Compliance by the foreign industry with cGMP requirements will reduce the potential risks to drug product safety and efficacy. And, a rare 2-3 day foreign inspection by itself will not adequately assess compliance with cGMP requirements. FDA's persistence of focusing resources on the inspection of the domestic industry and PDUFA pre-approval inspections, creates greater opportunity for the foreign industry to cut corners with cGMP

and other requirements without detection by FDA. The lack of credible FDA inspection presence in the foreign industry can make unbearable the temptation to reduce costs by taking short-cuts in proper cGMP controls because the likelihood of being caught is quite remote. It can become a very dangerous race and slippery slope to the lowest competitive drug price if there is no robust FDA oversight of manufacturing conditions for both domestic and foreign industries. Further, there must be a robust, risk-based border operation that integrates all relevant information including cGMP compliance as criteria for admissibility. Current FDA border operations will not, can not, readily detect shortcomings in manufacturing conditions that could cause the imported products to be unsafe. The integration of foreign inspection data with FDA's import operations requires significant resources to develop Information Technologies (IT) platforms capable of taking in, managing, evaluating, and delivering relevant information to create an effective border operation.

E. Unfair Competitive Advantages in the Foreign Industry

The lack of credible FDA inspection presence in foreign industry also creates an unfair competitive advantage for the foreign industry. The domestic industry is accustomed to experiencing an FDA inspection of 2-3 weeks duration when significant, or questionable practices are discovered. This is in stark contrast to the routine 2-3 days FDA spends inside a foreign manufacturer, regardless of inspectional findings. Obviously, the scope and detail of the 2-3 day foreign inspections are dramatically reduced, as well as FDA's ability to conduct a comprehensive assessment of the manufacturer's cGMP compliance.

One should expect the results of domestic inspections to show a greater rate of compliance with FDA requirements by U.S based firms when compared to the foreign industry, unless the brief foreign inspections are just too shallow to uncover significant cGMP issues.

Unlike the domestic industry, the foreign industry is given extensive opportunities to micromanage and influence FDA inspections. The current foreign inspection process puts the manufacturer in almost a totalitarian position to control the inspection from the time an investigator lands to the time of departure. Generally, the domestic industry is subject to unannounced inspections under FDA's statutory authority. Meanwhile, the foreign industry receives several weeks' advance notice of FDA's intent to inspect. This interlude provides foreign industry an opportunity to prepare and put on the best face for the FDA inspector knowing the inspection will likely be of a specific duration and knowing the likelihood of a timely re-inspection is remote. The FDA investigator generally is at the mercy of the foreign firm for logistic support including land transportation, food, translation of records and oral statements, and a work station other than a motel room. In essence the FDA foreign inspector or inspection team is on its own in a foreign land and is expected to be a self-sufficient traveling station with a laptop and portable printer, and maybe a government issued cell phone as a tether to Agency support on U.S. shores.

F. These Weakness are not Isolated to Prescription Drugs

Weaknesses in FDA's current regulatory paradigm to ensure safety of imported goods are consistent across all imported regulated goods. This includes oversight of imported pharmaceuticals, Rx and OTC alike. FDA's current import program is the primary means of overseeing the products actually arriving from foreign sources. The current import paradigm primarily focuses mostly on sampling at the border and the review of information contained in an invoice. Except for information in a few Import Alerts, the FDA decision to allow the importation of a drug shipment is not based on information related to the conditions of manufacture that can effect product safety. Even though there are a few data points beyond invoice information that are reviewed during the entry review process, information related to the current status of cGMP compliance is not one of the criteria for admissibility. ORA entry reviewers have access to the text information in multiple CDER and ORA databases, but they still do not know the current condition of manufacturing for most drugs. Few commercial shipments are physically examined outside of operations at international mail facilities and courier hubs. Shipments of less than \$2000 value are essentially given a free pass as an informal Customs entry.

The ORA entry reviewers check technical requirements such as registration and listing information that have little to do with product safety, and are certainly not linked to evidence of compliance with cGMP's. Using the stove-piped databases, the reviewers try to determine whether the entry of Rx drugs, finished or API, are covered by a current drug application. Entry reviewers have to spend significant time just logging in and out of the databases in the search of information that may be related to the shipments. And even after all that time and effort, the entry reviewers still do not know what the current

manufacturing conditions are for the vast majority of the entries. It appears FDA presumes the foreign Rx drug industry complies with conditions in the approved drug applications or DMF's without a verification process.

There are similar shortcomings in the foreign inspection program for foods and drugs. For example, many of FDA's regulated foreign food processors, if inspected by FDA at the current rate, are on nearly a 200 year inspection cycle. Based on my experience and recollection, I estimate the inventory of foreign manufacturers of Rx finished drugs and API's to range from approximately 3,000 to 5,000 firms, maybe up to 6,000 firms or more. If FDA were to continue inspecting the foreign Rx industry at the historical rate of 200-300 firms per year, the manufacturers of Rx Active Pharmaceutical Ingredients (APIs) and finished drugs would be completed on an inspection cycle up to 30 years (6,000 firms divided by 200 inspections per year). Such a cycle would mean a 2-3 day inspection once every 30 years in the worst case to make sure drugs are made in a manner to ensure safety and efficacy. The best case scenario may be approximately a 10 year inspection cycle (3,000 divided by 300).

The inspection rate of foreign OTC manufacturers may range into several decades, maybe a 50 year cycle or more. As I recall, the number of foreign firms related to OTC drugs could be several thousand, maybe tens of thousands or more, above the Rx industry. Oversight of OTC drugs (finished drugs and API's) at the border is even less rigorous than that for Rx drugs. They simply are not on the radar as they are not funded in the ORA work plan. There is no requirement for the OTC industry to submit an

application that describes manufacturing processes including the source of Active Pharmaceutical Ingredients (API's) and other ingredients. The OTC finished drugs must meet monographs and labeling requirements. The monographs are basically product formulation requirements coupled with labeled uses allowed by the agency. OTC drug manufacturers are also required to comply with the same current good manufacturing regulations (cGMP's) as the Rx industry. And, failure to implement good manufacturing practices can result in unsafe and ineffective drug products. But in foreign OTC manufacturing, cGMPs are virtually never assessed.

It was reported in October 2006, that an outbreak of DEG (diethylene glycol) poisoning occurred in Panama, resulting in multiple cases of illnesses and death. The tainted product was an OTC drug. It is my understanding the DEG (diethylene glycol) found in toothpaste made in China discovered in Panama and the United States in May 2007 was not a result of product tampering of the finished product, but a result of deficient cGMP practices that failed to verify the identification and specifications of the incoming raw materials. The DEG was not related to the API, but was related to the quality of the excipient or inactive ingredient of the toothpaste. Good manufacturing practices could have prevented the incident, and robust oversight could have verified good manufacturing practices were implemented.

The OTC industry market may even have greater impact on public health and safety than the Rx industry since the exposure is so great. Most people self-medicate minor ailments using OTC products. It's the first cost-effective treatment plan for the consumer, if used

properly. However, there's even less known about the conditions of manufacture of the imported OTC products. Historically, inspection of the OTC industry has been a very low FDA priority compared to the Rx industry. While at FDA, I do not recall any discussions about conducting inspections of foreign OTC firms in any FDA work plan process. I seriously doubt any surveillance inspections have been done in recent years, if ever, unless it was connected to an Rx manufacturer or follow-up activity related to an injury or illness.

Consequently, the FDA oversight of OTC products from foreign sources are largely relegated to the current border operations, and that should not make anyone feel better. The absence of reliable information about current manufacturing conditions of most foreign manufacturers results in a lot "unknowns". This includes the release by FDA of foreign made OTC products of unknown quality and safety. There is no process to routinely identify the conditions of manufacture or compliance with requirements of the monograph before allowing entry into the U.S. market. Compliance with cGMPs by the foreign manufacturer and a risk-based border operation, similar to the one proposed in the FDA 2003 Import Strategic Plan, could have prevented incidents like the discovery of DEG in imported toothpaste.

G. Foreign Made Drugs – a Close Cousin to other Foreign Made Goods

There are an estimated 300,000 + foreign manufacturers of all FDA regulated products dispersed among 200+ foreign countries. Products enter through approximately 300 U.S.

Customs ports of entry. For years FDA has allocated less than 200 inspectors (on average of less than 1 per port) to conduct entry reviews, collect samples and conduct physical examinations and investigations of all imported products including foods and drugs. FDA typically inspects 500-900 foreign firms per year, the vast majority of which are drug or device approval driven (and funded). There are approximately 18 million lines of entry for all FDA regulated products, of which approximately 10% are drug related. About 60% of the entries are food and cosmetic related. Approximately 25-30% of the lines of entry are radiation emitting and medical devices.

Do the math. The current FDA organization, IT systems and regulatory paradigm have not, and can not effectively manage the foreign industries or mitigate the related risks. More money alone may not be enough.