GPhA
Generic Pharmaceutical Association

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HAND DELIVERED

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Documents Management Branch
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: [Docket No. OOD- 160 1] Guidance for Industry and FDA Employees on Import Alert #66-66

Dear Sir or Madam:

The Generic Pharmaceutical Association (GPhA) is pleased to have the opportunity to comment on the Guidance for Industry entitled "Import Alert #66-66, Detention Without Physical Examination of API's that Appear to be Misbranded Under 502 (f)(l) because they do not meet the Requirements for the Labeling Exemption in 21 CFR 201.122.

GPhA is comprised of the manufacturers and distributors of generic medicines, as well as bulk API manufacturers and suppliers to these firms. Many members will be directly impacted by implementation of this level I guidance. We, therefore, submit the following comments for your consideration in the revision of this guidance.

On December 4, 2000, FDA's ORA issued the above Guidance as being "effective immediately because prior public participation to its implementation is not feasible or appropriate due to the risk to the public health."

The fact that the guidance was implemented without due process and input from the public is, in itself, creating a tremendous regulatory and financial burden on API manufacturers, import agents, and users of pharmaceutical APIs. This is counter to the FDA reform act, FDAMA which was intended to reduce the regulatory burden on pharmaceutical companies. Furthermore, this violates Good Guidance Practice (GGPs) by issuing a Level I guidance (effective immediately without comment period) which imposes additional burden and is a substantial change from current practice to the industry. Since December 2000, the number of days for which imported drug products have been detained has gone up tremendously. In some cases, firms have waited 3 and 4 weeks for a shipment to be released (reference actual examples in the next section). Delays in procurement of active ingredients have resulted in back orders and supply shortages in the marketplace, potentially resulting in loss of business by drug product manufacturers.

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The guidance is for the use for FDA field inspectors assigned to Import Alert.

There is no uniform guideline for FDA inspectors to assess whether an incoming drug product fits the above category. Moreover, a number of those products represent APIs that have been marketed to end users with approved applications. Labeling for these products meet 201.122 whereby adequate directions for use ("Caution: For manufacturing, processing, or repacking") are clearly indicated. However, since we are dealing with a paperless OASIS system at the FDA field offices, the inspectors never look at the labeling. The import operations FDA field inspectors are asking for any or all of the following documents: ANDA approval letters, DMF referral letters, Central File Numbers of Producer, File Registration Numbers of Producer, customer statements, NDC registration paperwork and the list goes on. Some of the information being requested is not readily supplied by industry but requires verification by the review divisions (i.e. linking the submitted API manufacturer or supplier with the original ANDA approval letter).

Specifically here are some "real life" examples of what has been occurring at ports of entry:

- *A standard production shipment was detained because FDA wanted to know the therapeutic use of the compound which has been approved for use in the US for at least 1.5 years).*
- *In another instance, FDA compliance officer requested an FDA issued document that defined the approved supplier for the ANDA. Since such a document does not currently exist, it could not be produced to release the detained material. Eventually, FDA agreed that such a document does not exist, and accepted the DMF referral letter from the API manufacturer.*
- *API material for R&D work was detained because the quantity of less than 1 Okg was "excessive" in FDA's judgment for developmental work.*
- *An API was detained for 2 months. The supplier had provided all requested information when originally contacted by FDA. However, for unknown reasons, it took 2 months to finally release the shipment during which time no new information was ever requested or supplied.*
- *Some older APIs (ANDAs approved prior to 1988) have been detained for over 2 months because certain FDA databases are only complete back to 1990. Even though end user letters and drug listings have been sent to the field office to attest the authenticity, documentation from FDA Rockville is being requested from the ANDA holder.*
- *In several cases where the ANDA had received a tentative approval, the FDA field inspector stated that in order to release the shipment, specialpermission must now be granted from CDER's Jim Hamilton. The reason given was that FDA is concerned with companies stockpiling material for a pending ANDA. Mr. Hamilton is requesting information such as batch size of the dosage form, whether the intended use is commercial or R&D, expected ANDA approval date, and other information not relevant to the import alert.*

With industry's input, the FDA needs to issue a clear set of guidelines to the FDA field inspectors as to what is necessary to make the required assessment and to synchronize FDA's review and compliance divisions. Additionally, the FDA needs to issue a set of guidelines to the producers and importers of the APIs which clearly defines what additional information is required to streamline the importation process and which does not impose an undue regulatory burden.

For APIs which are imported for commercial pharmaceutical products manufactured under an ANDA, an API may be imported for more than one ANDA holder.

Does the FDA field inspector require all the ANDAs to be listed on the paperwork? What are the requirements?

Many of the APIs which are imported are used for pre ANDA development work. Until now, it was sufficient to label them as "For Research and Development Purposes Only". According to part I.A, paragraph 4, of the guidance, the new required statement seems to be "Caution: For manufacturing, process, or repacking in the preparation of a new drug or new animal drug limited by Federal law to investigational use". Further, in part I.A. paragraph 5, the guidance asks for a valid IND in order to release the detained APIs.

It appears that the new statement proposed in the guidance is confusing in that it seems to combine two existing statements previously described in other regulations. The investigational use statement, which pertains to material used under an IND does not typically pertain to ANDAs where INDs are not usually required The repacking statement is one, however, that is already routinely placed on all incoming shipments of APIs, as this material is intended for further processing.

The intent of this guidance is to eliminate the importation of counterfeit/diverted pharmaceuticals. In particular, the guidance is directed for APIs.

In reality, more than just APIs are affected The FDA import field inspectors are detaining finished dosage forms. GphA is unclear as to the scope of this guidance, and if dosage forms are included that should be clearly stated. Furthermore, FDA import filed inspectors are even detaining APIs not listed on the Import Alert list IA6666.

In the FDA Homepage, Import Alert IA6666 is regularly listing all the detained APIs, by country, company name and address, and name of the API.

This notice specifically states, ''FOI: No purging is required" However, in reviewing entries for shipments recommended for D WPE (Detention without Physical Examination>, information such as the identity of the API, the supplier/manufacturer of the API, date of entry, and the home district for the shipment's destination. This information is typically considered privileged and would supply a competitor with confidential information about the sourcing status of a project (R&D or approvedproduct). Additionally, any information about batch size, status of the ANDA approval, or purpose of the batch would also be considered very confidential. Finally, there is no clearly defined mechanism to remove the API manufacturer or an API from the list IA6666.

GPhA recognizes the need for FDA and the Customs Authorities to have complete traceability. Thus a guidance which addresses one set of reasonable requirements which is understood, applied, and enforced uniformly by all FDA compliance staff is an effort which is supported by GPhA.. However, the current practice cannot continue, and detentions of legitimate shipments must end.

GPhA members supply 90% of the generic drugs in the USA. Originally, we welcomed the intent of the above document to eliminate the entry of misbranded counterfeit drug substances in the USA. However, in practice, the guidance has caused an unnecessary burden on the producers, importers, users, and ultimately will delay the access of low cost generic pharmaceutical products to the American consumers. Members of GPhA who are in the business of importing bulk APIs follow cGMPs and record keeping and are fully committed to providing high quality, safe APIs to its customer who formulate them for use in generic pharmaceutical products. Several of these member companies have been in the business of importing APIs for over 30 years and are cognizant of, and in compliance with the regulatory requirements for importation of APIs without this guidance. The guidance imposes unfair regulatory burdens on our industry.

Having said this, GPhA would like to propose a simple approach which we believe would be easy to manage by the FDA, easy to comply with by industry, and provide the necessary traceability to catch and control counterfeit shipments. For unapproved products in development, each end user would issue a letter which would reside in the files of the supplier. This letter, on end user letterhead, would state the name of the API manufacturer, the product, the intended use (i.e. R&D batch, ANDA batch, validation batch, pre-launch batches). For approved products, the end user would issue a letter on end user letterhead including the name of the product, ANDA number, and the intended use in the commercial manufacture of the approved dosage forms under that ANDA number. Then, at the time of importation, these documents could be produced to the FDA and preempt any detention. As previously stated, this information would be for FDA and customs officials only and would be considered confidential and not accessible under FOI.

GPhA welcomes this opportunity to provide comments and look forward to working with the FDA to implement these urgently needed revisions.

Sincerely,

William Nixon
President and CEO