Catalent

May 9, 2008

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods
Pharmaceuticals

via E-Mail: entr-pharmaceuticalscounterfeit@ec.europa.eu

RE: PUBLIC CONSULTATION IN PREPARATION OF A LEGAL PROPOSAL TO COMBAT COUNTERFEIT MEDICINES FOR HUMAN USE KEY IDEAS FOR BETTER PROTECTION OF PATIENTS AGAINST THE RISK OF COUNTERFEIT MEDICINES

Dear Sir/Madam:

Catalent Pharma Solutions (hereafter referred to as Catalent) serves the pharmaceutical industry as a contract manufacturer. This letter is written to provide comments and suggestions regarding the above-cited proposal to Combat Counterfeit Medicines For Human Use.

We appreciate and support this proposal to better protect patients against the risk of counterfeit product. Therefore, please accept our response to the Key Ideas for Changes to EC Legislation Submitted for Public Consultation sections as provided in the attached.

Thank you for this opportunity to comment.

Respectfully submitted,

Edward Thiele
Senior Vice President, Quality and Regulatory Affairs

4.1.1. Subject all actors of the distribution chain to pharmaceutical legislation

Key ideas for changes to EC legislation submitted for public consultation

a) Clarify that the obligations for wholesalers apply to all parties in the distribution chain, except for those directly distributing or administering to the patient. Brokers, traders and agents would be considered as wholesalers, with the respective obligations stemming from the pharmaceutical legislation

b) Make regular audits of GMP/GDP compliance mandatory by qualified auditors

- of (contract) manufacturers by manufacturers;

- between suppliers (wholesalers, manufacturers) at least in cases of suspicion of non-compliance with GMP and/or GDP.

Catalent Pharma Response:

Recommendation: This proposal should not be applied to investigational medicinal products "IMP's". IMP's do not go into the commercial distribution channel, they are distributed to an administrator or end user. In addition, IMP's are provided free of charge to clinical trial subjects and as such, should not be the target of counterfeiting operations. Please provide clarification that this guidance does not apply to IMP's.

Recommendation: Comparator products used for IMP clinical trials require blinding for the clinical trial process. Comparator products are marketed products that are purchased and used by packaging operations for clinical trial use. The use of comparators products in the clinical trial process should allow them to be exempted from the intent of this guidance. The releasing company would maintain records of which batches of comparator product were used in the clinical trial; and, the QP releasing the stock would be responsible for providing the final verification.

Recommendation: Stricter licensing/registration requirements should be considered by regulatory authorities to make it more difficult for illegitimate wholesalers, manufacturers, etc to get into business.

Recommendation: Imprisonment along with high monetary fines should be considered available as penalties for any guilty conviction of handling and/or distributing in a counterfeiting business.

Recommendation: We agree with the Commission's vision for combating counterfeit medicines. Definition of the supply chain should be explained in

more depth to ensure the various entities will understand the guidance (e.g., contractors, contract givers, movement of product between facilities owned by the same company). The Commission should consider providing guidance in the use of the Quality Agreement to delineate the role of each actor in the supply chain.

Recommendation: Clarification is requested on the scope of duties of the QP with respect to oversight of the overall supply chain.

4.1.3 *Improving product integrity through a unique seal from the manufacturer to the retailer or wholesaler, using a risk-based approach, supported by a ban on repackaging*

Key ideas for changes to EC legislation submitted for public consultation

Require the outer packaging of medicinal products to be sealed. This would reveal any subsequent opening of the packs.

Such a requirement could be applied to certain categories of products chosen on a risk-based approach, i.e. by taking into account the public health impact of the appearance of a counterfeit product and the profit strategies of counterfeiters.

The right to opening the outer packaging would be restricted to the market authorization holder and end-user (hospital, health care professional, or patient).

Catalent Pharma Response:

Recommendation: It is recommended that the proposal wording be modified to reflect the circumstances when repackaging is acceptable. There are certain cases when repackaging is a legitimate business such as comparator blinding for clinical trial studies. Such circumstances should be eligible for exemption to the proposed ban on repackaging and the right to open the outer packaging in this case would not be restricted to the market authorization holder and/or end user.

Recommendation: For the wording, "*This integrity should be secured by an obligatory product sealing*", we recommend rewording to reflect the phrase '*tamper-resistant seal',* to align with wording used by other regulatory agencies and pharmacopeias. However, it is anticipated that additional costs to our business will be incurred in proceeding with this recommendation.

Recommendation: Regarding the right to open the outer packaging, it is recommended that the Commission considers how Federal Customs inspections may be effected if there is a ban on their ability to open containers for inspection. This must be considered as product moves across the world and may enter the EU more than once before it is used.

Recommendation: It is recommended that finished pharmaceutical packaging, including all containers, closures and printed materials be non-recycled and there should be a provision for proper destruction through appropriately documented channels (incineration, shredding for land-fill) so as to render unusable.
Consider a provision for how printed packaging materials and container/closure systems should be recycled and/or destroyed.

4.1.4. *Centrally accessible record to facilitate traceability of batches throughout the distribution chain*

Key ideas for changes to EC legislation submitted for public consultation

Require the possibility of tracing ownership and transactions of a specific batch. This should be achieved by making a specific record (pedigree) obligatory. The record should be accessible by all actors in the distribution chain.

Catalent Pharma Response:

Recommendation: Solutions adopted for product integrity and traceability need to take into account a risk benefit to the patient, which has to consider a cost element. Centrally accessible records could be used as a means of providing the supply chain with information which could further a counterfeiter's process. Further, it is anticipated that there would be a significant impact to the cost of medicinal products, the social security systems as well as the clinical research and product innovation to pharmaceutical companies. The consideration that it is mandatory to provide access to records at each stage of the supply chain appears to be more practical and realistic as anti-counterfeiting measures.

Recommendation: Clarification on the types of systems for traceability is required.

4.1.5. *Mass serialization for pack-tracing and authenticity checks on a case-by-case basis*

Key ideas for changes to EC legislation submitted for public consultation

Require the possibility to trace each pack and perform authenticity checks. This could be attained by a mass serialization feature on the outer packaging. Technical details would be further defined in implementing legislation and/or by standardization organizations.

Catalent Pharma Response:

Recommendation: Consideration must be given to the impact of the costs of implementing systems to support such an initiative.

4.1.6 Increasing transparency concerning authorized wholesalers through a Community database

Key ideas for changes to EC legislation submitted for public consultation

• Require GDP certificates to be issued after each inspection of a wholesaler.

• Establish a Community database of wholesalers (including distributing manufacturers) documenting GDP compliance. This could be achieved via extension of the EudraGMP database.

Catalent Pharma Response:

Recommendation: Clarification is needed on whether or not the regulators will be satisfied with manufacturers relying purely on the GDP certification without a site audit. It may be construed as contradictory to the regulatory requirement for other service providers.

4.2 Tightening requirements for the import/export/transit (transhipment) medicinal products

Key ideas for changes to EC legislation submitted for public consultation

Directive 2001/83/EC would be clarified to the effect that imported medicinal products intended for export (i.e. not necessarily subject to marketing authorization) are subject to the rules for imports of medicinal products. The following provisions would apply:

• the obligatory importation authorization under the conditions set out under Article 41 Directive 2001/83/EC, e.g. relating to premises and the qualified person;

• the relevant obligations for the importation authorization holders set out under Articles 46 and 48 Directive 2001/83/EC, e.g. relating to staff and access for

inspection;

• the obligations stemming from Article 51(1)(b) and (2) Directive 2001/83/EC, relating to qualitative and quantitative analysis of the imported medicinal product; and

• the relevant obligations stemming from Directive 2003/94/EC on good manufacturing practice.
The corresponding rules on inspections would apply.

Catalent Pharma Response:

Recommendation: Consideration must be give to the impact of the costs of implementing systems to support such an initiative.

4.3.1 Requirement of a mandatory notification procedure for manufacturers/importers of active substances

Key ideas for changes to EC legislation submitted for public consultation

Submit the manufacturing/import of active ingredients to a mandatory notification procedure.

• Render information on notified parties available in a Community database. This could be achieved via extension of the EudraGMP database.

Catalent Pharma Response:

Recommendation: Clarification should be given on how the above impacts exported products.

Recommendation: A risk based approach should be defined; and, considered relative to EU GMP Appendix 8 regarding sampling. Reference should be made to ICH Q9.

4.3.2 Enhancing audit and enforceability of GMP

Key ideas for changes to EC legislation submitted for public consultation

• Make regular audits of active substance suppliers on GMP compliance by manufacturers and importers of medicinal products mandatory. Auditors should be sufficiently qualified.

• Require, where scientifically feasible, control of active substances via sufficiently discriminating analytical techniques, such as fingerprint technologies, Near Infrared Spectroscopy (NIR), as a mandatory method for identification by the manufacturer of the medicinal product. Such a testing is meant to identify deviations of the manufacturing process and manufacturing site for each batch.

• Turn principles of good manufacturing practice for active substances placed on the Community market into a legal act of Community law (e.g. a Commission Directive) in order to enhance enforceability.

Catalent Pharma Response:

Recommendation: Clarification of the definition of terms 'qualified' auditor and 'regular' audits is required.

4.3.3 Enhancing GMP inspections

Key ideas for changes to EC legislation submitted for public consultation

The competent authority may carry out announced or unannounced inspections of active substance manufacturers in order to verify compliance with the principles of good manufacturing practice for active substances placed on the Community market.

The competent authority shall carry out these inspections if there is suspected noncompliance with GMP.

The competent authority shall carry out repeated inspections in the exporting country if the third country applies standards of good manufacturing practice not at least equivalent to those laid down by the Community or if mechanisms for supervision and inspections are not at least equivalent to those applied in the Community. To this end, a Member State, the Commission or the Agency shall require a manufacturer established in a third country to undergo an inspection.

Catalent Pharma Response:

Recommendation: Clarification on the possibility of sharing these inspection reports or reliance on these inspections for qualification purposes for all the companies that use the supplier. Enhancing GMP inspections of API suppliers by competent authorities is seen as a positive step to providing additional security within the supply chain.

Final recommendations/questions:

Clarification on how products that are donated to charitable organizations are covered within this proposal document (e.g., control of supply chain in world wide distribution).

Clarification on how are dietary supplements/health and nutrionals covered within this proposal document.

Has the commission determined the root causes that have allowed counterfeit drugs to have such an impact?

How do the proposed legislative changes address counterfeiting; and, prevent further underground activity?

The Commission should consider developing increased education for consumers.

The products that are highly likely to be counterfeited should be publicized in journals, in newspapers and through television, internet methods.

The Commission should consider working collaboratively with other regulatory agencies and bodies. Collaboration should be global to have a lasting affect on counterfeiting. This collaboration should include a sharing of international information.

Lastly, how does this proposed document affect the purchase of medicines via the internet?