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Bristol-Myers Squibb Company

May 7, 2008

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods
Pharmaceuticals
entr-pharmaceuticalscounterfeit@ec.europa.eu

Re: Public Consultation in Preparation for a Legal Proposal to Combat Counterfeit Medicines for Human Use: Key Ideas for Better Protection of Patients Against the Risk of Counterfeit Medicines, Brussels, 11.03.2008

Bristol-Myers Squibb is a global healthcare company of approximately 43,000 employees providing medicines to fight cancer, cardiovascular and infectious diseases including HIV/AIDS and serious mental illness. Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. We are pleased to have the opportunity to offer comments on the *Public Consultation in Preparation for a Legal Proposal to Combat Counterfeit Medicines for Human Use: Key Ideas for Better Protection of Patients Against the Risk of Counterfeit Medicines.* Our comments are set forth in the attachment to this letter.

Bristol-Myers Squibb appreciates the opportunity to provide comment and respectfully requests that European Commission, Directorate General Enterprise and Industry, give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Richard L. Wolgemuth

Richard L. Wolgemuth. Ph.D.
Sr. Vice President
Global Regulatory Sciences

SUBMISSION OF COMMENTS ON:
"Public Consultation in Preparation for a Legal Proposal to Combat Counterfeit Medicines for Human Use: Key Ideas for Better Protection of Patients Against the Risk of Counterfeit Medicines"

FROM: Bristol-Myers Squibb Company

Areas of Regulation	Key ideas for changes to EC legislation submitted for public consultation	Comments
4.1 Tightening requirements for manufacture, placing on the market of medicinal products and inspections		
4.1.1 Subject all actors of the distribution chain to pharmaceutical legislation	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.	a) Security of the drug distribution chain is comprised of two components: the financial transaction of product ownership and the security of the physical product itself. Brokers, traders or agents should be accountable as they perform some of the same functions as wholesalers and should participate at a comparable level of effort in order to further the security of the drug distribution chain. To that end, where existing pharmaceutical legislation is currently applicable to wholesalers, it is recommended that this legislation be extended to cover these other entities. b) Audits demonstrate a company's due diligence of its business partners providing evidence and assurance that their partners are reliable and trustworthy. A risk-based approach to auditing either by the company or by an independent accredited third party focuses resources in the areas of the distribution chain where gaps in security could most likely occur. Consideration of the following criteria for determining high risk entities are: where a company has no or little previous experience with a business partner, when there has been a significant change in their senior management, or when the business partner fails to meet contractual/regulatory requirements. Mandating audits based on risk provides increased transparency into the drug distribution chain where it is most needed.
4.1.2 Tightening rules on inspections	• Strengthen provisions on inspections and supervisions, in particular regarding inspections in third countries. For example, make application of the Community procedures on inspections and supervision ("Compilation of Community Procedures on Inspections and Exchange of Information") mandatory. • Include specific harmonized provisions for inspections by competent authorities of parties in the distribution chain (e.g. wholesalers, brokers, traders, agents, business-to-business platforms).	No comment provided.

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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	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).	Overt security features such as seals provide a layer of security relative to its packaging but not the product. There are limitations to seals in that they can be readily duplicated or mimicked. Some seals can be removed and reapplied without showing any evidence that the package had indeed been previously opened. In addition, overt features are generally compromised within several months requiring the manufacturer to change the feature. This continual replacement of the seal design/type makes it difficult for the end user to police and verify the large number of various manufacturers' seals that would be in the marketplace at any one time. The end user logistics and practicality of verifying seals may not hold much value in that they offer relatively little assurance that the product is genuine. However, tamper evident container closure systems that leave a visible trace if removed, in addition to overt and/or covert authentication features are an important element to addressing counterfeiting. It must be clearly evident to the customer that tampering has occurred prior to use and there are a number of technologies and approaches which can be employed and must be part of an overall anti-counterfeiting strategy. Anti-counterfeiting approaches such as risk-based and technologies selected for use on products need to be at the discretion of the manufacturer. With respect to R&D comparator studies performed by bio/pharma companies or government agencies with the need to conduct studies or investigate product situations, the right to open the outer packaging should be broadened to include these entities. A prohibition on repacking is supported as eliminating this type of handling alone will minimize the opportunity for counterfeits to be inserted into the distribution chain. Consider that the statement in the EC legislation should be modified to include facilities licensed for repacking, beyond the license holder and the end-user. However, it is recommended that an exemption for entities conducting clinical studies where repackaging of products may be necessary for blinding purposes.

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4.1.4 Centrally accessible record to facilitate traceability of batches throughout the distribution chain	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.	Manufacturers typically track their drug product shipments by batch number. By extending this requirement further into the distribution chain, there would be more transparency even without a pedigree record if the legislation mandated that each distribution entity maintain their own records with the appropriate information needed to communicate among one another should there be need to do so. With respect to comparators used in clinical studies, it is recommended that consideration be given to how pedigree would be handled as this visibility to others in the supply chain would expose proprietary and confidential information to others and compromise competitive advantage. A centrally accessible record requires an interoperable system among the actors of the distribution chain. A strategy around the many local country databases that would be in operation needs to be considered and should include who owns, manages and pays for the centralized system. The state of California of the United States has similar legislation that has been delayed primarily due to the technological challenges required to implement such a system. The two primary challenges of a batch pedigree include agreed upon technology standards which are still evolving within GS1 Healthcare and the issue of data sharing/ownership. It Is recommended that a centralized record system not be legislatively imposed but rather guidelines be developed to help collaboratively move the entire industry towards a futuristic central record system. It should also be noted that at the national level of the United States, the FDA is developing Technologies for Prescription Drug Identification, Validation, Track and Trace, or Authentication and Standards for Standardized Numerical Identifier, Validation, Track and Trace, and Authentication for Prescription Drugs. Therefore, it is recommended that this idea become an international harmonization effort as counterfeiting is a global issue.

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4.1.5 Mass serialization for pack-tracing and authenticity checks on a case-by-case basis	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.	In addition to the interoperable system and technological challenges noted in 4.1.4, there are two others: the reliability of technology and the fact that there is no agreed upon technology among the actors of the distribution chain. Implementing mass serialization on product packaging requires significant changes to both the manufacturers' packaging lines and their distribution centers and will also require their clinical operations to have appropriate equipment to read serialized marketed product for use in clinical studies. Other distribution chain actors also need to make changes to their operations in their warehouses in order to read each pack and verify it. Mass serialization technology is still evolving for real world practice and it requires many more years for it to be fully developed and sufficiently robust for use on drug products. Other considerations include: how mass serialization on serialized products used in clinical studies would be handled should a recall be necessary be considered and the manufacturer's obligation for maintaining the serial number record over a period of time. The state of California of the United States has similar legislation for implementing mass serialization on drug products but that has been delayed primarily due to the technological challenges previously discussed. At the national level of the United States, the FDA is also developing *Technologies for Prescription Drug Identification, Validation, Track and Trace, or Authentication* and *Standards for Standardized Numerical Identifier, Validation, Track and Trace, and Authentication for Prescription Drugs*. Therefore, it is recommended that this idea become an international harmonization effort as counterfeiting is a global issue.

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4.1.6 Increasing transparency concerning authorized wholesalers through a Community database	• 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.	BMS supports the idea of certifications of wholesalers upon successful GDP inspections as well as a centralized database that allows the distribution chain to verify an actor's GDP compliance. However, manufacturers who already hold appropriate marketing authorizations are currently held to GMP practices that include the handling and shipment of products into the marketplace, and therefore GDP compliance/certification is not needed for the manufacturers of drug products.
4.2 Tightening requirements for the import/export/transit (transhipment) of medicinal products		
4.2 Tightening requirements for the import/export/transit (transhipment) of medicinal products	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.	It is recommended that manufacturers be exempt for the requirements related to qualitative and quantitative analysis of the imported medicinal products they manufacture outside of the EU as their plants adhere to GMP requirements. Specifically, intra-company shipments that include export/import activities should be exempt from specific import testing requirements as manufacturers have tracking capability for these internal transfers to assure that the product remains under their control and use good tracking tools that adhere to GMP requirements. With respect to qualitative and quantitative analysis of the imported medicinal (Article 51(1)(b) and (2) Directive 2001/83/EC) , in the case of comparator product for clinical trials, the relevant methods are unlikely to be available from the innovator company, and hence development times would be extended. The onus should be on providing evidence that a robust pharmaceutical quality system is in place, rather than requiring full and routine re-testing.

Areas of Regulation	Key ideas for changes to EC legislation submitted for public consultation	Comments
4.3 Tightening requirements for manufacture, placing on the market of active substances and inspections		
4.3.1 Requirement of a mandatory notification procedure for manufacturers/ importers of active substances	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.	While establishment of this type of database may bring more transparency to the sources of active substances, this information exists in manufacturers' filings and is available to regulators. In addition, it is not clear who would have access to this proposed database of information or how it would be used. Other issues surrounding this idea include disclosure of a company's proprietary information, intellectual property, internal business matters and competitive information. Until this idea is further defined, it is not recommended that this type of notification become a mandatory requirement. Particularly as it could have unintended consequences.
4.3.2 Enhancing audit and enforceability of GMP	1. Make regular audits of active substance suppliers on GMP compliance by manufacturers and importers of medicinal products mandatory. Auditors should be sufficiently qualified. 2. 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. 3. 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.	1. As part of our internal business practice as a manufacturers, we currently audit our active substance suppliers to ensure GMP compliance. Additionally, we augment our audit program by establishing Quality Agreements with our active substance suppliers. As a mandate to audit, it is recommended that allowance be made for establishing and implementing a risk based audit program. 2. A Certificate of Analysis is required from our suppliers indicating that it passed certain analytical testing specifications and upon receipt of the active substance, we perform additional testing based on our internal procedures. Based on item 1. above (high risk supplier), it is recommended that rather than require additional analytical techniques, guidelines for this additional testing be developed which can then be applied based on an overall risk assessment approach. 3. Although strengthening GMP principles for active substances by making them Directives offers potential value in assuring the integrity of those substances, it may not be possible to effectively enforce. It is recommended that manufacturer purchasing the active substance ultimately assure the integrity of that material based on items 1 & 2 above.

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4.3.3 Enhancing GMP inspections	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.	BMS supports the expanded inspectional coverage by the Community of active substance manufacturers based on the principles of good manufacturing practice for active substances placed on the Community market.