Comment on the EU Commission Public Consultation
Key Ideas for Better Protection of Patients against the Risk of Counterfeit Medicines

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It is a pleasure to have the opportunity to comment on the European Commission Enterprise and Industry Directorate-General's proposal "Key Ideas for Better Protection of Patients against the Risk of Counterfeit Medicines." I believe that the plan addresses an important public health problem and support efforts aimed at both studying the problem of counterfeit medicines and securing the supply chain to guard against the threat to public health. Beginning with my doctoral dissertation at the University of California, Berkeley, my research agenda has largely focused on the markets for counterfeit pharmaceuticals and the economic incentives surrounding their production. For more than a decade, I have examined the questions surrounding pharmaceutical innovation, access to medicines, and intellectual property protection. The security of the pharmaceutical supply chain as well as the adoption of anticounterfeiting strategies have been a significant focus of much of my work.

Counterfeit and substandard medicines are increasingly prevalent and sophisticated, ranging from worthless inert substances to lethal mixtures that both pose a growing threat to public health. Counterfeiters have extended their reach to encompass products as diverse as simple painkillers, expensive lifestyle treatments, and anti-cancer medicines, distributing their fakes on a global scale. Advancing technology has reduced the cost of producing sophisticated counterfeits which are increasingly discovered in industrialized countries. Motivated by the money, counterfeiters have a dual focus: very expensive drugs (lifestyle, HIV/AIDS and anti-cancer medicines) and high volume medicines (common antibiotics, inexpensive generics). Both are very lucrative as pharmaceutical counterfeits are high value relative to their bulk, and in very high demand. The Centre for Medicines in the Public Interest estimates that global sales of counterfeit pharmaceuticals will reach $75 billion by 2010 -- a 90% increase over 2005.[1] Given such profitability it is not surprising that counterfeiters invest in avoiding detection rather than in the quality of their fakes. As such, efforts by the Enterprise and Industry Directorate-General are an important step in reducing the threat of counterfeit medicines.

The Public Consultation proposes three areas of regulation of medicinal products in order to improve the regulatory framework and enhance the safety of the EU market. The focus is on: medicinal products placed on the market; issues surrounding the export, import and transit of pharmaceuticals; and the regulations surrounding active ingredients and excipients. The principle advantage of this focus is the complementarity between the elements, encompassing the quality and security of the pharmaceutical supply chain from the production of ingredients to manufacture of the final product and through to drug distribution. Thorough oversight of each step in the production process and supply chain is essential to securing the quality of medicines and the Public Consultation identifies important areas of focus.

[1] As cited by the World Health Organization (2006), p.2.

After reviewing the Key Ideas, I have organized my comments to accomplish two things:
1. Identify the strengths of the proposal, offering suggestions to further improve the strategy; and
2. Target the aspects of the proposal that may be ineffectual or difficult to implement, providing suggestions to facilitate their adoption.

In an effort to evaluate the strategies suggested in the Proposal, it is worth reflecting on the factors that contribute to pharmaceutical counterfeiting. The World Health Organization has determined that counterfeiting is facilitated where "there is weak drug regulatory control and enforcement; there is a scarcity and/or erratic supply of basic medicines; there are extended, relatively unregulated markets and distribution chains, both in developing and developed country systems; price differentials create an incentive for drug diversion within and between established channels; there is lack of effective intellectual property protection; due regard is not paid to quality assurance" (World Health Organization 1992, pp.11-12). These characteristics provide a valuable context for appraising the effectiveness of anticounterfeiting strategies.

Strengths of the Proposal and Suggestions for further Improvement**:**

Good Manufacturing Practices Perhaps the greatest strength of the proposal is the European Commission's emphasis on the adoption of Good Manufacturing Practices in section 4.3.2. For greatest effectiveness, the regulations should apply across active pharmaceutical ingredients (APIs), excipients, and finished products. In addition, the EU regulatory regime should establish a minimum standard for national regulations. The regulations should provide for state-of-the-art review, compliance and inspection policies. These policies should reflect current pharmaceutical science and facilitate the industry's rapid adoption of technological innovations in order to improve safety, quality and efficiency in pharmaceutical manufacturing.[2] Effective policies will reduce the risks of cross contamination, as well as errors in production and labeling. As described by the World Health Organization, the primary risks are "unexpected contamination of products, causing damage to health or even death; incorrect labels on containers, which could mean that patients receive the wrong medicine; insufficient or too much active ingredient, resulting in ineffective treatment or adverse effects" (WHO 2008).

Uniformity in the established Good Manufacturing Practices would reduce the uncertainty surrounding expectations across national markets. This would also make enforcement easier by establishing a single set of regulations across the industry and providing additional security. Moreover, common knowledge of Good Manufacturing Practices and existing standards allow for vigilance in markets with less protection, those just meeting the minimum levels of EU standards. A single standard across member states and production components would reduce the legal uncertainty surrounding different practices and simplify enforcement across markets that vary in size and sophistication.

Transparency The European Commission's proposal repeatedly describes the importance of increased transparency.[3] Greater transparency will reinforce and strengthen the proposal's other strategies for

[2] These objectives mirror those outlined by the final report on good manufacturing practices of the U.S. FDA in September 2004.

[3] References to increased transparency appear at least four times in a variety of contexts, on pages 3, 5, 10 and 12.

securing the pharmaceutical supply chain. Specifically, this is a valuable complement to the emphasis on Good Manufacturing Practices.

In the context of increasing transparency, there are two ways in which this can be particularly effective at reducing the insertion of counterfeit medicines into the supply chain. These are: minimization of the number of links in the supply chain and elimination of repackaging and relabeling. At a joint meeting with the World Health Organization, the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) advocated no more than three stages in the distribution chain: from the licensed manufacturer to the wholesaler and from the wholesaler to the dispensing pharmacist (IFPMA 1997, p. 3). This limits the opportunities counterfeiters have for incorporating their products into the supply chain.

In like manner, discontinuing the practices of relabeling and repackaging will increase the security of the supply chain by reducing the variation across product packaging and increasing the standardization in labels, seals, and packaging. Relabeling and repackaging have been identified by the World Health Organization as factors that encourage pharmaceutical counterfeiting (WHO 2008b). As the following recommendation to the WHO's International Medical Products Anti-Counterfeiting Taskforce (IMPACT) describes, a few policy changes would eliminate the need for repackaging. "Tamper evident packaging should not be tampered with or removed during repackaging activities. Instead, packaging could be over-labeled with country specific requirements. Product Information Leaflets (PIL's) should be in 5 languages to accommodate the European Community, thereby eliminating the need for repackagers to replace the PILs contained within the package" (Rittenburg 2007, p.3).

By restricting the presence of additional actors (e.g. brokers, traders, secondary wholesalers) and eliminating repackaging, the integrity of the supply chain is better protected. In addition, such strategies will reduce manufacturing costs, eliminating the need for repeated handling and additional packaging materials. Finally, they will ease product recalls and enhance traceability of medicinal products.

<u>Ineffectual or Unfeasible Aspects of the Proposal and Suggested Improvements</u>**:**

Pedigree In addition to the unique manufacture seal, the proposal also recommends a pedigree to address the fragmentation of information throughout the supply chain (section 4.1.4). The pedigree, a centrally accessible record of the product's movements through the supply chain, is attractive for reasons of transparency and traceability.[4] Clearly such a record would be useful for tracking drugs when counterfeiting is suspected and on the occasion of a product recall. A traceable pedigree would enhance supply chain integrity and provide a reliable record of transport. Since products could be more easily traced to their source, this would increase the level of accountability at every link in the supply chain. With thorough implementation, such a system would increase the cost of introducing counterfeit drugs into the legitimate supply chain, thus reducing the ease and likelihood of such an insertion. Any strategy

[4] The State of California (2007) has determined a single pedigree "shall include every change of ownership . . . from its initial manufacture through to its final transaction to a pharmacy or other person for furnishing, administering, or dispensing the drug, regardless of repackaging or assignment of another National Drug Code (NDC) Directory number".

that raises the cost of counterfeiting, either through higher production cost or an increased probability of detection, will reduce the profitability of counterfeiting.[5]

At a practical level, the adoption of a pedigree system is more difficult than perhaps envisioned. A universal pedigree system would require the adoption of costly track-and-trace technology by producers, distributors and every other entity along the supply chain. In order to trace a product from manufacturer to consumer, every link in the supply chain must coordinate on and adopt a single technology and record-keeping system. A unique identifier must be affixed at the point of manufacture to the smallest container saleable at the pharmacy level. This is also true of the proposal's mass serialization recommendation. Unfortunately, small distributors will be disproportionally burdened by the sizeable cost of such technology and may charge that the forced adoption of readable technology is anticompetitive. Although the 1988 Federal Prescription Drug Marketing Act mandated pedigrees in the United States, they are still provided voluntarily. In the US, their use has been repeatedly delayed because the "wholesale industry has argued that attaching pedigree papers to all drug shipments would be too great a burden on them" (WebMD 2004, p.2). This raises another issue, the cost burden. It is important to determine who is responsible for the cost of adopting the readable technology. Will the cost be absorbed by the government or manufacturers? Is each distributor or wholesaler along the supply chain expected to individually assume this cost? If sufficiently costly, small producers and distributors may be forced to exit.

Beyond the cost of the readable technology, an additional practical consideration is the necessity that a uniform standard be established. This may be difficult and given the tremendous scale of adoption, competing technologies will certainly be proposed. Of utmost importance is transparency in the decision-making process, and the security of the adopted technology. While the e-pedigree has not been uniformly adopted in the US, California and Florida are the states that have the greatest amount of experience with the technology and efforts to establish universal standards. In this process, EPCglobal is the primary standards-setting entity most experienced in this area, having established the standards for the UPC bar code (State of California, 2007). They have been most actively engaged in this work and worked most closely with industry participants.

Finally, it is important to recognize that a pedigree system is most valuable when combined with established Good Manufacturing Practice Standards and regulations against repackaging and relabeling. Only when the quality of the medicines that enter the system is assured can the pedigree system be relied upon to contribute to a secure supply chain. Following that, preventing repackaging and relabeling preserves the integrity of product and packaging as well as the ability to track medicines. To perform effectively, every entity at every link of the supply chain must be able to access the pedigree information in whatever format it is embedded in.

Unique Manufacture Seal The proposal advocates the adoption of a unique seal from the manufacturer to improve product integrity (section 4.1.3). Regrettably, this is an overly simplistic solution perhaps

[5] Lybecker (2007) models the counterfeiting decision as a function of costs and benefits. Anticounterfeiting strategies can effectively reduce the risk of counterfeiting by either increasing the likelihood of detection or raising the cost of producing a counterfeit version.

indicating a naïve perception of the problem of counterfeiting. Rapidly changing technology has facilitated the increasingly sophistication production of counterfeit drugs and removed many of the obstacles faced by counterfeiters. Unfortunately, manufacturers' seals are easily copied. Desktop publishing and other technologies enable counterfeiters to accurately replicate the look and feel of original packaging. Labels, seals, blister packs, inserts, and even holograms are all reproduced with varying degrees of accuracy.[6] In addition, counterfeiters "can even buy their packaging from the same companies as the legitimate manufacturers, making it impossible for authorities to identify the fakes without expensive chemical analysis" (Schofield 2001, p.1564). Given this, the European Commission may wish to reconsider the adoption of a unique manufacturing seal. Such a feature may easily increase the cost of production without providing any additional security.

Anticounterfeiting technology is rapidly advancing and is increasingly intricate. Many of the newest technologies are difficult to replicate and make counterfeiting more difficult and expensive. Security features may be categorized as overt, covert and forensic. Overt elements are applied to external packaging and are easily identifiable by sight or touch. Covert feature provide an additional level of security and may involve chemical taggants or machine-readable inks. Finally, forensic technologies comprise isotopic tags or molecular markers, directly incorporated into the product or packaging. These elements are usually verified through laboratory testing and kept quite confidential. The use of multiple technologies, especially covert and forensic, constitutes a greater obstacle to counterfeiters and is most effective when elements are used jointly. Optimally, this combines consumer awareness (overt) with secretive technologies verifiable by very few personnel (forensic).

It is important to recognize that the most advanced anticounterfeiting technologies are not a universal solution and are only appropriate for the most vulnerable products. Due to the cost of these technologies, they should be strategically utilized. As an example, consider the recent judicious use of radiofrequency identification (RFID) technology in cases of the greatest security need. Pfizer adopted RFID tags for use on all bottles of Viagra (sildenafil), globally one of the most widely counterfeited drugs. Purdue Pharma elected to protect bottles of OxyContin (oxycodone) with RFID tags following numerous incidents of abuse, theft and diversion of the controlled substance.[7] Moreover, security technologies are most beneficial when combined with a ban on repackaging. The challenge for both the manufacturers and the European Commission is determining how to best utilize security technologies to protect public health and discourage counterfeiting without needlessly increasing the costs of production.

In summary, the European commission Enterprise and Industry Directorate-General is undertaking an important process, securing the EU pharmaceutical supply chain and protecting public health from the risks and dangers of counterfeit and substandard medicines. Ensuring the safety and quality of the pharmaceutical supply chain must originate with comprehensive oversight of each step in the production and distribution process: from the chemical ingredients and inert excipients to the transport of the finished product. Fortunately, the strategies proposed do exactly this and the attention to the complementarity of the elements proposed here comprise its principle advantage. The suggestions

[6] Cockburn et.al. (2005) present examples of remarkably convincing fake holograms found in Southeast Asia.

[7] These examples are cited in the FDA Consumer Magazine (March-April 2005) as effective use of advanced technologies.

identified here examine the strongest elements of the proposal (establishment of Good Manufacturing Practice Standards and Increased Transparency) and also describe two areas for reconsideration (Pharmaceutical Pedigree and Unique Manufacture Seal). The Public Consultation has clearly identified important areas of focus and the development and pursuit of these requirements will further the goals of public health policymakers and result in a safer drug supply.

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