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Who is making the pharmaceutical supply chain safe?

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KEYWORDS: Counterfeit, falsified, supply chain security, supply chain integrity, pharmaceutical supply chain, anticounterfeiting.

ABSTRACT *Counterfeit medicines are an acknowledged crisis that takes patient risk to unacceptable levels – the authors argue that this is but the visible part of the iceberg. Counterfeit APIs are the much larger submerged part of the iceberg. Counterfeit APIs are a more serious issue as it represents a threat to the integrity of the legal supply chain of medicines, it potentially impacts a much larger number of patients and European and Japanese authorities do not yet perceive it as a threat – as such they may well remain outside the scope of proposed falsified medicines legislation and enforcement objectives. The pharmaceutical industry and its supply chain appear alone at taking steps to address this criminal threat.*

WHAT HAPPENED?

Globalization and hyper-competition in the off-patent medicines business has led to perfect conditions for the growth of falsified APIs. In 25 years the pharmaceutical industry witnessed a complete re-design of its supply chain - the majority of its manufacturing has now delocalized to India and China. The Medicine Agencies, responsible for protecting the patient, were caught by surprise by these changes. Established in the 20th century and designed to regulate a national industry Regulators today find themselves inspecting based on proximity and not risk. Absent any effective enforcement of compliance, and a marked amplitude of ethical values across the regions of the world, 80 percent of today's European medicines are made from active pharmaceutical ingredients (APIs) that come from Indian and Chinese factories that have almost never been checked by an EU inspector. Furthermore an unknown proportion of such ingredients are manufactured by chemical plants that do not observe good manufacturing practices - known as "shadow" factories these plants provide back-up production to those EU registered pharma fine chemicals plants in India and China whose success has exceeded their own capacity. This non-GMP production is fraudulently re-labelled to match DMF filings that numerous European Marketing Authorizations refer to as the source of API. Once shipped to Europe and formulated into medicines it is no longer possible to detect the counterfeit nature of the API in the medicine.

Absent effective deterrence Purchasing departments will continue to seek ever lower prices of APIs. Criminals have seized this opportunity and have created an industry around counterfeit APIs.

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WHAT IS INDUSTRY DOING?

To address this state-of-affairs the Pharmaceutical industry has worked to develop tools to ensure the security and authenticity of the Supply Chain. Regulators also have started to collaborate internationally to share information and take action faster in order to compensate for the head-start counter-fitters have enjoyed.

Most pharma companies -Innovators and Generic alike- have for some time managed large international audit programs to qualify their suppliers and to ensure that a minimum level of quality was observed. However absent an arbiter of quality increased price competition is likely to take its toll and a floor of quality may not be assured. Furthermore smaller generic firms that operate in single markets are unable to afford acceptable supplier audits, and often rely on brokers to do the sourcing of the APIs. In many European countries there is an actual trade in marketing authorizations with registration dossiers actually being bought and sold, often by traders who also assure the supply of the bulk active ingredient.

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Several industry initiatives across the globe have tried to reduce the cost of a professional vendor qualification through the sharing of the costs of the audits.
The Rx-360 consortium (www.rx-360.org) was founded in June 2009 and is one such initiative. This is an international pharmaceutical supply chain consortium that brings together small and large pharma companies, biotechs, innovators and generic firms, suppliers of APIs, intermediates, medical devices etc... Together they have been establishing a joint audit scheme that will allow industry to gather more information and improve the security of the supply chain. It has working groups that focus on Audit Standards, Audit Sharing and Auditor Qualification to support the joint auditing and sharing programs. Audit Guides for Basic Chemicals/Raw Materials, APIs/intermediates, Excipients and Supply Chain Security have been prepared and minimum qualification criteria for Auditors have been established. Industry now has a complete set of documents that closes the loop and will make the auditing activities more realistic and effective. There is a working group on Regulatory Affairs that has been establishing very positive relationships with regulators around the world ensuring that both industry and regulators' expectations and priorities are aligned.
Rx-360 consortium put together about a hundred people setting up a system, reviewing and selecting standards with an output never seen in such a short period of time. Companies are sharing their knowledge on suppliers and suppliers of suppliers. A joint audits scheme will cover a broader scope from Quality to Security topics. This will make auditors to stay longer at the sites audited but will save several audits per year to all those suppliers and contract manufacturers.
The consortium has now 41 members, working together in a dozen of working groups. Rx-360 also provides updated shared information freely available at www.rx-360.org. NewsFlash reports, e-newsletter and website registration are currently a valuable tool to keep you in the loop.

WHAT ARE THE AUTHORITIES DOING?

US FDA (Food and Drug Administration) has been very active at promoting the discussion and development of guidelines on Supply Chain Security. Last April, regulators and industry, including a number of Rx-360 members, met in Bethesda, MD for the conference entitled: "Enough Talk: Let's Find and Implement Solutions". Main working topics were:

- Enhancing Supplier Quality Management
- Increasing Control in the Supply Chain of Incoming Components
- Improving Analysis and Testing Strategies and Technologies
- Monitoring and Responding to Signals in the Market Place
- Enhancing Drug Product Distribution Supply Chain Controls and Use of Serilization, Track and Trace, and ePedigree

"The message throughout the workshop was clear: to be successful at securing the supply chain, we need to work together, embrace new technology, share information and best practices, and use common sense. Layered security, risk management, technology and communication were thematic tactics heard throughout the workshop as well".
Drug shortage is also a favourable factor to the increase of the demand on those products. Criminals are always paying attention to it and react instantaneously by offering counterfeit products to the market in a way that sometimes is impossible to be differentiated by the consumer. US FDA has published a new guidance to avoid drug shortages involving medicines. The document "Planning for the Effects of High Absenteeism to

Ensure Availability Medically Necessary Drug Products" recommends that manufacturers take actions that go from the development of a written plan that include Quality Risk Assessments and notifications to FDA, when applicable.

In July 2009, US FDA has also issued a draft guideline that will change the way we act in the future: "Draft guidance for industry on drug Anticounterfeiting". FDA is promoting the use of inks, pigments, flavour and other physical-chemical identifiers by manufacturers of drug products. This will make these products more difficult to copy by counterfeiters and easier to distinguish from counterfeits.

The World Health Organization (WHO) has also been working on this since early 80's, promoting programs for the prevention and detection of pharmaceutical products and assisting the Member-states in their efforts. IMPACT taskforce (www.who.int/impact/en) has been working with INTERPOL, World Customs Organization and other networks, improving coordination of operations and exchange of information. WHO is currently promoting a survey on terminology on counterfeit medicines or equivalent, only 30 percent of the member states have sent their comments; the final report is expected by October 2010.

EFCG (European Fine Chemicals Group) developed the Voluntary Guidelines, a proposed set of minimum requirements for all manufacturers in fine chemicals industry to minimize the risk in the quality of medicines.

The purpose is to combine elements of ISO and business ethics, inviting every company in the world to adhere and thus helping to raise manufacturing and distribution standards, promoting highest level of risk management and security of supply. A very interesting toolkit is available at www.efcg.cefic.org called BIEN (Business Integrity EvaluatioN) to be used to evaluate suppliers and suppliers of the suppliers.

In Europe a proposed Falsified Medicines Directive is currently being discussed at the European Parliament and at the Council. This is a modification of a Directive 2001/83/EC regarding "the prevention of the entry into the legal supply chain of medicinal products which are falsified in relation to their identity, history or source". Article 46 reinforces the requirements to use good manufacturing practices for excipients albeit in a more lenient form than for Active Pharmaceutical Ingredients. New Article (47a(2)) was introduced to clarify the legal responsibilities of manufacturing authorization holders that re-package medicinal products. However in its current form this proposed legislation would NOT consider a criminal act alleged heparin falsification that led to worldwide recalls in more than 14 countries across all the continents and left over 150 people dead.

Unfortunately the current text of the proposed EU directive is flawed in that its definition of a falsified medicine does not include any medicines made with falsified APIs. As such the major part of the iceberg lying below the waterline fails to be criminalized, and remains a very profitable business with no jail risk.

It would seem that anything that could result in an increase, even the slightest increase, in the cost of generics is a taboo topic.

Part of the raison-dêtre of this article is to alert to the apparent lack of understanding of the issue displayed by our politicians. It seems incomprehensible that legislators bring forward a directive that would allow the repetition of the heparin tragedy.

European legislators could also look across the Atlantic to America and check how FDA has managed to implement mandatory inspections for the last 40 years. Also if FDA, EMA and PMDA collaborated to make best use of resources and did not perform repeat inspections to well established API producers the patient would be better protected at little extra cost. The industry would also benefit from a level playing field.

It does seem odd that anyone that buys a banana or a shirt is legally provided with information as to the country of origin of the article. The medicine you buy for your children may have a very long package insert but nowhere is it disclosed where the API is made and where the formulation was manufactured.

The message throughout the workshop was clear: to be successful at securing the supply chain, we need to work together, embrace new technology, share information and best practices, and use common sense. Layered security, risk management, technology and communication were thematic tactics heard throughout the workshop as well

ABSENT ADEQUATE LEGISLATION…

Industry will work to assure it acts responsibly and provides quality medicines.

Management tools based on risk assessment methodologies are now seen as the tool to make more with less! In the next decade we will see all those companies that will have survived using it on a daily basis to identify where the risks are and to manage to secure them.

To assess the risks of a Supply Chain you can start by listing the criteria you consider relevant (e.g. criticality of the material supplied; level of internal testing before use), define a severity factor for each criteria and a probability for each case. The result will be a percent of risk that enables one to rank them and to prioritize the level of control, inspection, etc. Other more complex tools are also available and described at ICH Q9 guideline.

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Supply Chain Security is both a new discipline and a business opportunity. Securing the pharma channels will promote the development and implementation of new technologies and the development of better quality suppliers. Electronic finger-printing of products will not just assure quality but will prove pedigree. Sharing of supplier data on compliance will drive clients towards quality suppliers. Purchasing departments will cause cascading audits. As the pharma company audits its API suppliers, they in turn will audit their intermediates suppliers, etc... Advertising pharmaceuticals online will require accreditation. Patients will be able to send a code via text message to a database to check whether the medicine they purchased is authentic. Expect a broad set of actions along several dimensions to make the near future quite different. Counterfeits, business integrity, assurance of authenticity will become part and parcel of our language.

REFERENCES AND NOTES

1. Rx-360 newsletters available at www.rx-360.org.
2. www.fda.org
3. www.who.int
4. www.efcg.cefic.org
5. www.xavier.edu/xlc/med-xu/documents/XavierUnivpresentationHASSELBALCH.pdf
6. http://hosted.verticalresponse.com/427409/d87a06bb44/1754501101/d2376d4b0a/
7. www.ipqpubs.com/issues/ipq-monthly-update-july-2010/
8. www.gmp-compliance.com/eca_news_1059.htm