Implementation of an Anti-Counterfeiting Device – Enhancing Supply Chain Robustness by a Risk Management Approach

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Abstract

The global phenomenon of falsified medicines is on the **increase**, with more and more medicines now being falsified.
Thus, in July 2011, the EU strengthened the protection of patients and consumers by adopting a new Directive on falsified medicines for human use.
This Directive aims to prevent falsified medicines entering the legal supply chain and reaching patients. It introduces harmonised safety and strengthened control measures across the supply chain, such as the obligation to implement Safety features in medicines.
The Directive came into force on 21 July 2011. Member States had to start applying these measures in January 2013.
Pharmaceutical supply chains are naturally complex and additionally, there are potential increases in costs involved in the implementation of an anti-counterfeiting device. Therefore this is not an issue that can be dealt as an equal. The best way for an organization to approach this issue is by adopting a Risk Management Approach.
This thesis presents a method for implementation of Risk Management to supply chains (of OM Pharma, more specifically).
It is based on the model proposed by ICH Q9[1] using some of the most basic quality tools for the first iteration (as suggested by the ICH Q9).
It comprises the identification and analysis of potential counterfeiting risks of the 3 identified major supply chains of OM Pharma and presents solutions for strengthening and enhancing their protection. This is materialized by the implementation of anti-counterfeiting devices chosen by a method that takes into account and balances the overall risk of counterfeiting, the potential severity of harm and the cost of the implementation process.

Keywords: Risk Management, Anti-counterfeiting, falsified, medicines, supply chain.

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1. Introduction

Counterfeiting is the crime of the XXI century! It is a global phenomenon, affecting individuals and communities from small villages to major cities right to big retail stores and pharmaceutical companies. The dual impact of globalization and growth of internet trade has made the problem considerably more acute.

Counterfeit products circulate via unregulated channels but can also enter legitimate supply chains. In many cases it is very difficult to distinguish them from genuine products.

Counterfeiters now have the ability to produce higher quality packages, which enables fake medicines to slip into supply chain more easily.

At present counterfeiters are able to copy most anti-counterfeiting technologies within 18 months. As a result an estimated 7-10% of all goods sold worldwide were counterfeited at the cost of ca. 450 billion € (statistics from 2007). [2]

This issue is so alarming that to combat this threat, the European Parliament and the Council of the EU amended the anti-counterfeiting directive (Directive 2001/83/ES)[3] and issued the new Directive 2011/62/ EU of 8 June 2011[4] that includes the requirement for features that enable the identification, authentication and traceability of medicines.

It is than imperative that pharmaceutical manufacturers examine and invest in a solution as soon as possible.

There are many paths by which this can be accomplished. Nonetheless, when it comes to traceability, serialization seems to be the more consensual resource. This does not mean that other traceability or anti-counterfeiting systems should not be used.

It is up to every each organization to make the decision to implement or not an anti-counterfeiting system and which one to choose.

The subjacent factor here is the increase in overall integrity of patient's safety, through the enhancement of the supply chain integrity and security.

The model of choice by which this is achieved is, again, up to each organization individually. Regarding this matter, many documents have been written but the great

majority have in common the choice of a Risk Management approach as suggested by ICH Q9.

This is a very dynamic and iterative model that acts as a guidance and if fully and correctly implemented can lead to an overall effective increase in the supply chain control, security and integrity.

The objective of this work was to create a model (and test it) for the implementation of an anti-counterfeiting device as a way to enhance the supply chain robustness mainly based on the guidance provided by the ICH Q9.

Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011. [4]

This new directive is an amendment to the Directive 2001/83/EC, on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.
It comes into play due to, as previously explained, "an alarming increase of medicinal products detected in the Union which are falsified in relation to their identity, history or source. Those products usually contain sub-standard or falsified ingredients, or no ingredients or ingredients, including active substances, in the wrong dosage thus posing an important threat to public health."[4]
There are 5 main topics addressed in this new directive:

- Unique identity (serialization): technology choice and implementation;
- Governance of the system: deciding who sees what data and on what terms;
- Modalities of verification: deciding how packs will be verified and what level(s) of authentication feature(s) will be required;
- Whitelist and blacklist criteria: determining which prescription drugs are excluded from key requirements (deemed safe) and which non-prescription drugs are included (deemed risky);
- Mechanism of notification: of whitelisting and blacklisting.

The first and most relevant point of this directive is the definition of falsified medicinal product, as follows:

"Any medicinal product with a false representation of:

(a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;

(b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or

(c) its history, including the records and documents relating to the distribution channels used.

This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights." [4]

Besides this important definition of falsified medicinal product, this Directive also refers to the following points:

- Introduces the concept brokering for finished medicinal products and provides a new definition for brokering medicinal products.
- Introduces a requirement that brokers have to register with the Competent Authority of the EEA Member State in which they are established.
- Extends the requirement for a wholesale dealer's licence for export of medicines to third countries.
- Extends existing obligations for wholesale dealers and provides new obligations, in particular reporting any suspected falsified medicines.
- Formalises current regulatory expectations for the manufacturer of the medicinal product to have audited their suppliers of active substances for compliance with the relevant Good Manufacturing Practice ("GMP"), and provides a solid legal basis in the Directive for the written confirmation of audit (the "QP Declaration").
- New rules on the API importation from countries outside the EU.
- Introduces a formal requirement for manufacturers of medicinal products (or a third party acting under contract) to audit their suppliers of active substances for compliance with the requirements of Good Distribution Practice ("GDP") particular to active substances.
- Formalises the regulatory expectation that manufacturers of the medicinal product will verify the authenticity and quality of the active substances and excipients they use.
- Introduces a new obligation on product manufacturers to inform the Competent Authority and Marketing Authorisation Holder should the manufacturer obtain information that products (manufactured under the scope of the manufacturing authorisation) may be falsified, whether those products are being distributed through the legitimate supply chain, or by illegal means.
- Makes a number of significant changes to the controls on active substances and excipients intended for use in the manufacture of a medicinal product for human use, and in particular introduces two new definitions for Active substances and Excipients.
- Introduces a new requirement for manufacturers, importers and distributors of

active substances to be registered with the Competent Authority of the Member State in which they are established.

- Introduces a new requirement for companies selling medicines at a distance to members of the public to be registered and a requirement for a common internet logo on their website.

This directive should be fully implemented as of July 2013 and from the day it was issued, all member states have 36 month to transpose this the their National Law. Obviously this Directive represents major changes on the Pharmaceutical Companies working routines.

One of the most important points to be addressed by the Pharmaceutical Industries regards to the new rules on the importation of API from countries outside the EU.

These new rules state that as of 2nd of January 2013, all imported active substances must have been manufactured in compliance with standards of good manufacturing practices (GMP) at least equivalent to the GMP of the EU. The manufacturing standards in the EU for active substances are those of the 'International Conference for Harmonisation' – ICH Q7. As of 2nd of July 2013, this compliance must be confirmed in writing by the competent authority of the exporting country. This document must also confirm that the plant where the active substance was manufactured is subject to control and enforcement of good manufacturing practices at least equivalent to that in the EU. [5]

Another very important point of the new Directive states that: "Medicinal products subject to prescription shall bear the safety features referred to in point (o) of Article 54. The point (o) of article 54 states that: "for medicinal products other than radiopharmaceuticals referred to in Article 54a(1), safety features enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to:

— verify the authenticity of the medicinal product, and

— identify individual packs, as well as a device allowing verification of whether the outer packaging has been tampered with."[4]

Despite the general importance of all changes that this new directive proposes, these 2 last referred points are perhaps the ones that have been creating the most discrepancy and raising more concerns in the Pharmaceutical World.

Concerning the implementation of safety features, it is referred in the introductory not that these systems should be harmonized: "Safety features for medicinal products should be harmonised within the Union in order to take account of new risk profiles, while ensuring the functioning of the internal market for medicinal products."[4] It is broadly accepted that a system like Data Matrix would be a perfect example of a harmonized safety feature, nevertheless the information to be codified is up to each industry to define. Additionally, because it is more of a traceability feature then an anti-counterfeiting one, it is also generally accepted that more systems should be implemented.

On the next chapter some of the most common safety features available to the pharmaceutical companies will be presented and explained. It is because of this immense range of solutions that confer different grades of protection, that the pharmaceutical companies must be very smart while choosing an appropriate feature.

Anti-counterfeiting technology review

The alarming increase in counterfeited medicines has, fortunately, prompted the development of a number of anti-counterfeiting solutions, from simple holograms and watermarks, to sophisticated barcodes that enable track and trace, tagged packages, and even technologies that can be applied directly to individual tablets.
Although the majority of medicines do not, at this time, display any anti-counterfeiting devices / measures, the recent changes in the legal / regulatory scene are making the pharmaceutical companies change this pattern.
The most commonly used and available anti-counterfeiting measures are the use of barcoding and any sort of simple tamper evident systems.
In this chapter, it will be made a review to the existing technologies available to the pharmaceutical industries.
In order to better systematize this review, it was opted to differentiate the anti-counterfeiting devices / measures according to the following 4 categories [6]:

1. Overt, or visible features;
2. Covert, or hidden features;
3. Forensic techniques;
4. Serialization/ Track and trace.[6, 7]

There is a wide range of possible solutions ranging from the very simple to the highly complex, from zero cost to highly expensive and from fragile to highly secure against compromise. As for the overt options, they represent an attempt to put authentication into the ends of general public. However, to be effective they demand public education and awareness, which is especially difficult in the most challenged developing markets. It should also be noted that the more widely used one overt technology becomes, the more attractive it is for counterfeiters to defeat it.
The covert features are most effective in the hands of industry specialists. They are a very valuable investigative tool, but a counterfeiter will be able to copy many of the simpler features unless they are skilfully applied and their details kept a well-guarded secret. However there is almost unlimited scope of possibilities, given imagination and ingenuity on the part of the technologist and designer, and the costs can be minimised or even eliminated when applied in-house. In-house application also has advantages of limiting involvement of third party suppliers, who may not be trustworthy in some environments. Only the most secure covert features can be safely used in an overt

context but then fall under the need to use forensic techniques.

Regarding the forensic markers, there are some very robust and secure options available, which may enable their use to be more widely known and therefore accessible to trustworthy authorities and investigators. However these tend to be subject to patent protection and therefore restricted in availability and pricing.

Unique pack serialisation has the potential to deliver robust solutions to fraud and counterfeiting pharmaceuticals, but it is not yet fully developed. Barcode systems use proven existing technology, but lack the advantage of automation and remote scanning possible with RFID. Unfortunately RFID systems are not yet proven or robust enough, and standards must be defined and agreed. Also, RFID tags may be vulnerable to deliberate or invisible alteration or corruption. [6, 7]

Supply Chain Control and Risk Management

Supply chain management can be a big asset for companies because it can reduce costs, improve the profit margin, and offer a better return on investments. However, those advantages do not mean there are no potential problems related to supply chain management that companies may need to deal with, thus the reason to develop a group of actions / procedures to gain and maintain control over the supply chain.

Unfortunately due to the nature of its own activity, the supply chain of the typical pharmaceutical company can be quite complex. With this level of complexity it is easily understandable that it is very difficult, and probably ineffective to try and solve the counterfeiting problem only from one side, without the collaboration of different parties involved in the Supply Chain control.

At this point, finding a solution that establishes the framework to involve the distributors in the control of the supply chain is necessary. However, because the ultimate responsibility remains within the Pharmaceutical Industry that should always look after the assurance of quality and integrity of their products in order to be able to provide the best medicines to the end user while maintaining economic viability. A risk management approach then presents itself as the most natural choice when dealing with an issue this complex that involves multiple players across different countries. A flexibly-designed risk-based strategy incorporates robust process of data gathering, analysis and presentation of valuable and target oriented results. This would ultimately allow the definition of an automated decision process. This allows an institution to strike a balance between the need to remain compliant and the minimization of fraud and risk exposure.

According to the International Conference for Harmonization (ICH) Q10[21], that describes a pharmaceutical quality system, the accountable organization is the ultimate responsible for ensuring that processes are in place to assure the control and quality of purchased materials and activities. Then, it requires that these processes incorporate Quality Risk Management as defined in ICH Q9 and includes:

- Assessing the suitability (prior to the establishment of a business relationship) and competence of other parties to carry out the activity or provide the material using a defined supply chain by use of, for example, audits, evaluations and qualification;
- Defining the responsibilities and communication processes for the quality related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and the contract acceptor;
- Monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and the identification and implementation of any needed improvements;
- Monitoring the incoming materials to ensure they are from approved sources using the agreed supply chain.[1, 9]

2. Methods

The development of this work, had as a base, the Quality Risk Management model detailed in the ICH Q9 (as shown below in figure 1), where Risk Management is defined as:"The systematic application of quality management policies, procedures and practices to the tasks of assessing, controlling, communicating and reviewing the risk".[1]
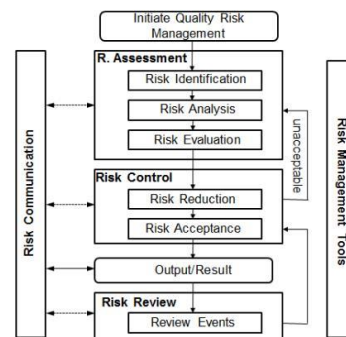

Figure 1 - ICH Q9 Quality Risk Management Model

It should be clear by now that this is a very dynamic and on-going process about anticipating hazards and controlling risk through a continuous of risk awareness, reduction and / or acceptance, and review. [10]Hazards and their associated risks can be present anywhere throughout the supply chain. Risks may be compounded or increased by further processing, thus creating a hazard at a later stage. In the worst case, those hazards may not become apparent until too late, even after finished product has been released to the market. For the accountable organization and their respective suppliers to manage risk effectively, it is also of the upmost importance to understand that the sources of risk throughout the tiers of the supply chain can be both external and internal to the company and its suppliers.

To materialize this statement, as an example, some examples of these risks are shown on the next table (table 1). It is worth noting that external risks are identifiable and possibly controllable through careful planning and action whilst internal risks can be managed, mitigated or even eliminated. [11]

External Risks	Internal Risks
Increase / decrease in demand	Non-conformity
Political climate / instability	Rejection of a batch / Product recall
Legal restrictions in individual markets and of supplier	Capacity / resource issues
Counterfeit / fraud	Reduced inventory
Materials, product, service supply interruption	Single sourcing versus dual / multiple sourcing
Termination of material or services	Inadequate supplier selection / qualification process
Uncontrolled variation in materials	Longer / more complex supply chains
Unexpected contaminants in supplied product	Non-conformance with contracts / agreements
Deliberate or accidental adulteration	Staying with poorly performing supplier & not progressing improvement or exit strategy
Unknown or poorly controlled use of brokers / agents	Inadequate communication
Distribution / transportation / storage events	Transportation / storage events
Inadequate communication	Personnel / organizational changes
Lack of adequate documentation control	Lack of adequate documentation control
Complex processes	Increasing process variability

Table 1- Examples of External and Internal Risks

Risk Management Process

1. Risk management team and responsibilities

The risk management process should be undertaken by a multidisciplinary team within the organization. It should be noted that for smaller organizations and / or smaller / less complex supply chains, this may be limited to a small group of individuals (sometimes as small as 2).According to their roles, they can be divided in 4 categories:

- Responsible – those that do the work to achieve the task.
- Accountable – there should be only one accountable person specified for each task. His responsible for approving the work developed by the responsible(s).

- Consulted – People whose opinions are sought and with whom there is a constant (need to basis) two-way communication.
- Informed – People that are updated on the progress of the work developed, normally once a task is finished or at key milestones of the project.

2. Risk Assessment

The very first step (step 0) of the process is to initiate the Quality Risk Management. This is often materialized as the characterization of the supply chain. This includes the identification of all involved agents. The functions and activities that the agent performs should be specifically identified as well. After every agent in the step 0 is identified and included in the risk management process, the next step of the Risk Assessment itself can begin. This assessment shall consider the following stages:

- Risk identification:
  Is as systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, trend analysis, informed opinions, etc. Risk identification addresses the question "What might go wrong?" including identifying the possible consequences.
- Risk Analysis:
  Is the estimation of the risk associated with the identified hazards. It is the process of linking the likelihood of occurrence, severity of harms and detectability. In some cases, an audit is necessary to complete this assessment.
- Risk Evaluation:
  Compares the identified and analysed risk against the given risk criteria.

3. Risk Control

The Risk control encompasses all activities of the decision-making nature that result, in this case, in action (through Risk Reduction / Mitigation) or inaction (through Risk Acceptance).
It is, of course, the main purpose of Risk Control to reduce the risk to an acceptance level. It is worth pointing that at this stage, the higher the risk, the more decisive and effective action is required. [1, 10-12]

3.1. Risk Reduction

Risk reduction can be defined as:
"Actions taken to lessen the probability of occurrence of harm and the severity of that harm" [ICH Q9]
This stage then focuses for control and / or avoidance of risks that were previously identified as above the tolerance level.

3.2. Risk Acceptance

Pending the result of the previous step, there may be a residual risk. This is the stage where the decision of accepting the residual risk, and taking no further actions, is made.
There should be a formal record of this acceptance by the management or by the people with is kind of power of decision making. It should be noted that the residual

risk may not be further prosecuted or at least is not at that moment feasible/ practical to procure further reduction. However the action of accepting a residual risk, enable the company to monitor these risks and therefore, this can be considered as a mitigating factor since, it provides the company with the ability to act more rapidly should the situation change at any time.

4. Risk communication

It is widely accepted that an effective communication is critical to an effective Risk Management process. Therefore it is important to develop a communication plan in at an early stage, in order to properly and timely communicate and manage any problems that may surface during the Risk Management process. The communication can and will be established between internal and external sources either for the mere purpose of reporting results (or issues) or for consultation. An effective consultation will, or at least, should ensure that those involved in the process are aware and comprehend the outcomes and decisions of every stage of the process. [1, 10-12]

5. Risk Review

Risk review is defined as:
"Review or monitoring of output / results of the risk management process considering (if appropriate) new knowledge and experience about the risk" [ICH Q9].

As previously stated, a supply chain and consequently its risk management are a very dynamic process, since many changes may occur at a given time. Thus it would not be wise not to have a stage that allow the organization to revisit the risks previously identified and worked on and reassess them. This process can be done periodically, by planning, or whenever an event occur or new information comes to light.

If a proper review method is not established, the risk model becomes outdated and obsolete and may not be valid and / or useful. As a consequence, the new potential risks are not identified and assumptions will not be validated or moderated and the supply chain control will be lost destroying the initial resource consuming investment in risk management. [1, 10-12]

Risk Management Tools

Risk management tools can be used, in generic terms, to:

- Gather / organize data;
- Structure data / information;
- Manage project;
- Process and facilitate decision making;
- Analyse data and transform it into easy to understand / work information;

The trigger to use one tool in detriment of another can vary and may depend on the scope, the experience of the user itself, the process in question, the type of risk, the availability of proper "workable" information, the time that can be used, etc. [1, 9-13]

All tools herein referred are well known thus a complete description will not be the focus of this paper rather, for better understanding, a table (see table 2) is presented

with the most used tools and their respective possible applications in the risk management process.
During the development of this work the following tools were used:

- Flowcharts/ process mapping
- Brainstorming
- Risk ranking and filtering (through risk and criticality matrixes)
- Carrot diagram
- Root cause analysis

Risk Management Tool [1]	Description / Attributes	Potential Applications [2]
Basic Tools		
Diagram Analysis • Flowcharts • Check Sheets • Process Mapping • Cause/Effect Diagrams	▪ Simple techniques that are commonly used to gather/organize data, structure risk management processes, and facilitate decision making.	✓ Compilation of observations, trends, or other empirical information to support a variety of less complex deviations, complaints, defects, or other circumstances.
Risk Ranking and Filtering	▪ Method to compare and rank risks ▪ Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and weighting factors and risk scores.	✓ Prioritize operating areas / sites for audit/assessment. ✓ Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool.
Advanced Tools		
Fault Tree Analysis (FTA)	▪ Method used to identify all root causes of an assumed failure or problem. ▪ Used to evaluate system/sub-system failures one at a time, but can combine multiple causes of failure by identifying causal chains. ▪ Relies heavily on full process understanding to identify causal factors.	✓ Investigate product complaints ✓ Evaluate deviations.
Hazard Operability Analysis (HAZOP)	▪ Tool assumes that risk events are caused by deviations from the design and operating intentions ▪ Uses a systematic technique to help identify potential deviations from normal use or design intentions.	✓ Access manufacturing processes, facilities, and equipment ✓ Commonly used to evaluate process safety hazards.
Hazards Analysis and Critical Control Points (HACCP)	▪ Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring ▪ Bottom-up approach that considers how to prevent hazards from occurring and/or propagating ▪ Emphasizes strength of preventive controls rather than ability to detect ▪ Assumes comprehensive understanding of the process and that critical process parameters (CPPs) have been defined prior to initiating the assessment. Tool ensures that critical process parameters will be met.	✓ Better for preventive applications rather than reactive ✓ Great precursor or complement to process validation ✓ Assessment of the efficacy of CPPs and the ability to consistently execute them for any process
Failure Mode Effects Analysis (FMEA)	▪ Assesses potential failure modes for processes, and the probable effect on outcomes and/or product performance. ▪ Once failure modes are known, risk reduction actions can be applied to eliminate, reduce, or control potential failures. ▪ Highly dependent upon strong understanding of product, process and/or facility under evaluation. ▪ Output is a relative "risk score" for each failure mode.	✓ Evaluate equipment and facilities; analyze a manufacturing process to identify high risk steps/critical parameters.

[1] Sample list of key risk management tools – others (not listed here) may apply for a specific application
[2] Examples only

Table 2- Risk Management tools description and possible applications [9]

3. Results and Discussion

The previously described method was applied to OM Pharma's work context. OM Pharma commercializes products to fulfil not only the national market but also other countries within and outside the EU.

For these reason, their associated supply chains are quiet variable. Nonetheless, following the first step of the risk management process it is possible to group them into the following categories:

- Exportation:
  - o Direct delivery
- National Market:
  - o Direct delivery
  - o Indirect delivery

In regards to the Direct Exportations supply chain, it can be described as follows (refer to figure 2):
Raw materials are sent by the supplier (broker or manufacturer) trough a haulier. Products are analysed and the pharmaceutical form is manufactured at OM Pharma's facilities.
Once the batch is released it is picked up by the distributor using their own transportation means and product is taken to their warehouse (in Portugal).
Product is then shipped by the distributor to the Forwarder Agent that handles the customs and the transportation from National territory until the destination agent / Client.
The destination agent then distributes the product using their means of transportation to their end clients (Pharmacies / Hospitals).
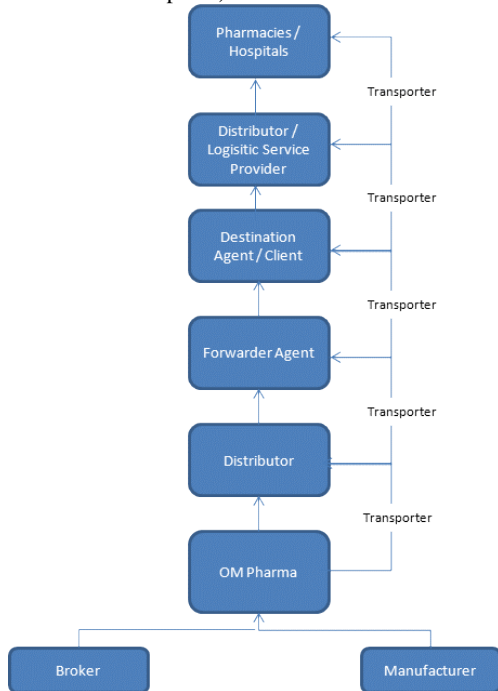

Figure 2 - Direct Exportation Supply Chain

Regarding the Direct Delivery to the National market the supply chain is as follows (please refer to figure 3):
Raw materials are sent by the suppliers (Broker or manufacturer) trough a haulier. Products are analysed and the pharmaceutical form is manufactured at OM Pharma's facilities.
Once the batch is released it is picked up by the distributor using their own transportation means and product is taken to their warehouse (in Portugal).
From the distributor it is sent directly to the end client (Pharmacies / Hospitals / Clinics).
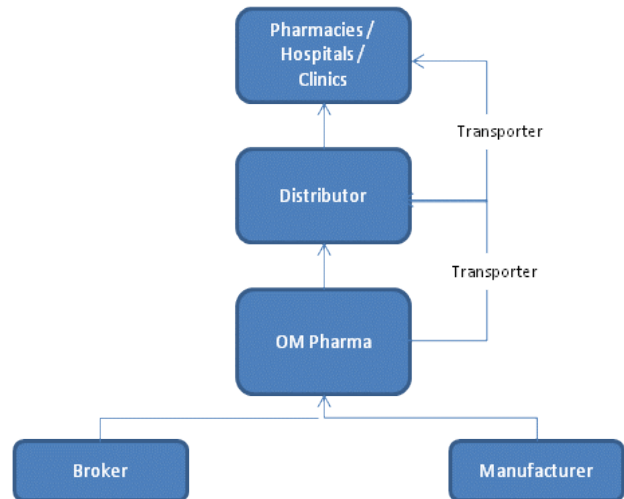

Figure 3 - National Market Direct Delivery Supply Chain

As for the Indirect Delivery to the National market the supply chain is as follows (please refer to figure 4):
Raw materials are sent by the suppliers (Broker or manufacturer) trough a haulier. Products are analysed and the pharmaceutical form is manufactured at OM Pharma's facilities.
Once the batch is released it is picked up by the distributor using their own transportation means and product is taken to their warehouse (in Portugal).
From the distributor it is sent to wholesalers.
The wholesaler than sells the product directly to the end client (Pharmacies / Hospitals / Clinics).
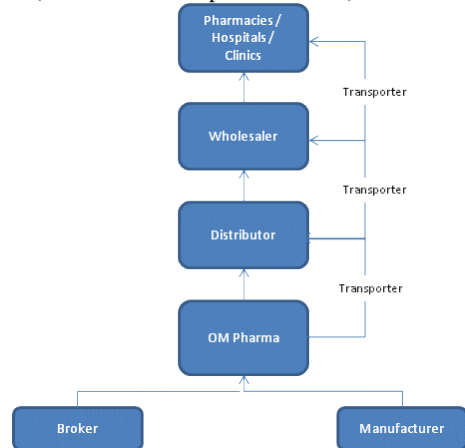

Figure 4 - National Market Indirect Delivery Supply Chain

Although the term indirect delivery is not totally correctly applied for this supply chain, it is meant to reveal the main difference between the two types of supply chains that regard the National distribution.
In direct delivery, the product is sent directly to the end client trough OM Pharma's distributor, whereas for the indirect delivery, the product is sold to wholesalers that in turn are responsible for the product through the rest of the supply chain.

The next logical step was the risk identification. For the three supply chains, using the empirical knowledge, flowcharts and brainstorming the following risks were identified / considered.

Direct Exportation supply chain identified risks:
- Cartoons and literature suppliers do not destroy properly the remaining (lightly damage and / or reusable product) of a production.
- If an anti-counterfeiting device (covert) is already in place, the information is leaked and becomes of general knowledge (either at supplier and / or OM Pharma)
- Complex supply chain with multiple agents involved including different transporters and distributors.
- Product is being delivered to countries with different rules and health authority systems.

National Market Direct Delivery:
- Cartoons and literature suppliers do not destroy properly the remaining (lightly damage and / or reusable product) of a production.
- If an anti-counterfeiting device (covert) is already in place, the information is leaked and becomes of general knowledge (either at supplier and / or OM Pharma)

National Market Indirect Delivery:
- Cartoons and literature suppliers do not destroy properly the remaining (lightly damage and / or reusable product) of a production.
- If an anti-counterfeiting device (covert) is already in place, the information is leaked and becomes of general knowledge (either at supplier and / or OM Pharma)
- Slightly complex supply chain (more transporters / handling).

It was identified different numbers of risks that contribute to the global risk of counterfeiting, respectively:

Direct Exportation supply chain – 4 factors
National Market Direct Delivery supply chain – 2 factors
National Market Indirect Delivery supply chain – 3 factors

Each of these factors was ranked a score according to a likelihood of happening versus the consequences of happening (using the matrix on figure 5). After which, an arithmetic sum was made to establish the overall risk value of counterfeiting happening within a certain supply chain.

Figure 5 - Risk analysis matrix

The results are as follows:
Direct Exportation supply chain total score: **27**
National Market Direct Delivery supply chain: **9**
National Market Indirect Delivery supply chain: **12**

For the Risk Evaluation step, the carrot diagram was used.
For the Risk Evaluation step the results were as follow (please refer to figure 6):

Figure 6 - Carrot diagram

The supply chains concerning the exportation were deemed unacceptable with the National Market Indirect Delivery considered as tolerable and the National Market Direct Delivery within the acceptable region.

Considering this output, the risk management will advance to the Risk Control phase which encompasses the Risk Reduction and the Risk Acceptance.

At this stage, the Root Cause Analysis (RCA) tool was used, to assess the potential root causes for this risk to occur.

The following basic steps were followed:
1. define the risk to be reduced = output of Risk Evaluation
2. define potential root causes for this risk to occur
3. define which root causes if removed will prevent or reduce the risk
4. implement risk reduction measures = address the root causes
5. document & observe the effect of implementing the Risk Reduction measures
6. review and repeat as required

These basic 6 steps were applied to all 4 supply chains, even to the two related to the National Market, on the

principle that it is good practice to try and mitigate the risk as much as possible.

It was verified that for point 4 of the RCA, for all supply chains, the implementation of an anti-counterfeiting device was a suitable solution for risk mitigation.

It is proposed in this work that the selection and implementation of an anti-counterfeiting device is made by combining a role o factors such as:

- the overall risk of the supply chain
- the level of protection given by the anti-counterfeiting measure
- the costs involved in such implementation
- Criticality level of the product.

The first step should the definition of the criticality level of the product. The criticality of the product should be a ration between how important the product is for the company (in terms of sales – in units or value) versus the potential to cause harm to the patient – should a counterfeiting occur. Using the next table (please refer to figure 7) by introducing the sales volume on the y axis versus the potential to cause harm on the x axis, the result will be the criticality of the product. For instance, if a product has a high volume of sales but is a relatively innocuous product, its criticality level should be medium / medium high.
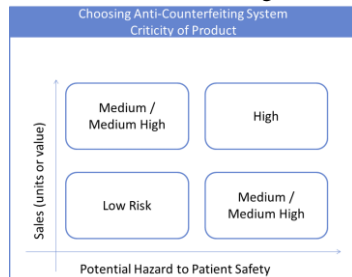

Figure 7 - Criticality level Matrix

Once the criticality level is found / defined, the next step is to select the Protection level of the anti-counterfeiting device that the organization should apply. This is done by inputting the criticality level on the y axis versus the overall supply chain risk on the x axis.

For instance, if the output of the last matrix was a medium / medium high level of criticality but that product is sold on the national market (which has a low level of supply chain risk) than the protection level to be chosen is medium (please refer to figure 8).
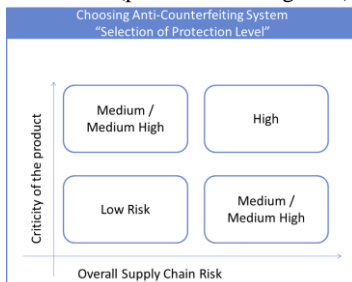

Figure 8 - Selection of Protection Level Matrix

The last factor to consider is the costs of implementation of the chosen anti-counterfeiting system.

There is no specific tool or method to easy a decision of this nature. It is up to the decision makers to assess how much the organization is willing to cut on the profit margin of a product in order to choose a more or less expensive anti-counterfeiting system.

It should be noted however that it is not necessary to invest a considerable amount of capital in one state-of-the-art anti-counterfeiting system.

The decision makers should be aware of the possibility of combining one or more anti-counterfeiting devices, with virtually no cost, in order to provide a higher degree of protection.

This matrixes where used for all three supply chains, considering a volume of sales of the same medicine (units) as follows:

- Direct Exportation: 140000 un
- National Market Indirect Delivery: 300000 un
- National Market Direct Delivery: 15000 un

The results for the selection of protection level were as follows:

- Direct Exportation: High
- National Market Indirect Delivery: Medium
- National Market Direct Delivery: Low

With the previous results, for each supply chain and the range of anti-counterfeiting systems widely available for the pharmaceutical companies, having in mind the degree of protection that each one can provide (described previously in the technology review chapter), the following systems or combination of system could be chosen:

- Direct Exportation:

Tamper evident secondary packaging with serialization to provide total traceability to the product combined with a personalized hologram and a micro-impression.

Alternatively a combination of virtually costless anti-counterfeiting systems such as serialization, micro-impression, tamper evident and special unique cutters.

- National Market Indirect Delivery:

Tamper evident secondary packaging with unique cutters, micro-impression and serialization.

- National Market Direct Delivery:

Tamper evident secondary packaging, micro-impression and serialization.

In the case of the implemented measures on all 3 supply chain, since it would eliminate the root causes of potential risk, it is safe to assume that the risk of counterfeiting occurring would be reduced to tolerable (Direct exportation) and acceptable levels (National Market Indirect delivery).

On this next step of Risk acceptance the decision makers will decide whether the residual risk is tolerable enough for acceptance or if they feel that enough controls were applied.

In this case, given the identified risks and the selected applied measures, the risk of all 3 supply chain are acceptable. The results of the last stage should be formally documented and communicated to all involved

or need to know parties. After this there is only the last but very important step of Risk Review.

At this point there must be already a considerable knowledge of all supply chains and their potential risks. Additionally, proper methods and or Standard Operation Procedures should have already been in place in order to create mechanisms that allow for a suitable monitoring of the events that may occur that have potential impact on the supply chain. For example, using KPI's may indicate that something is going wrong with the supplier, or a formal communication process for all changes that affect the raw materials is in place, etc.

This will act as an indicator of when the process must be reviewed, either periodically for safeguarding and updating or triggered randomly by an event with impact on the supply chain / product.

It is the dynamics of this step (if well implemented) that will allow for a continuously better risk management process. It is worth noting the while reviewing the Risk Management process, not only the tools used in all steps may and should evolve to more complex (and accurate) but also the reviewing process and monitoring procedures should be reviewing.

Updating and enhancing the reviewing process is a critical point on the road to a successful risk management approach.

4. Conclusions

The new DIRECTIVE 2011/62/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 8 June 2011enters the pharmaceutical industry world as long needed and waited review on the alarmingly growing counterfeiting issue. It brings several key notions and rules that will influence the pharmaceutical industry across the world in order to provide safer medicines to the patients.

One of the measures stated on the new directive is the use of anti-counterfeiting systems.

While reviewing the technology behind the anti-counterfeiting systems it can be verified that there are a considerable range of options that any pharmaceutical organization can choose from.

Some of these technologies are completely new while others are adaptations of already existing technologies used by other types of industries. It is being noticed that the adaptation of technologies and notions with given proofs on other industries are rapidly being adopted more and more by the pharmaceutical world.

Nevertheless, there is a great deal of decisions to be made on the choosing process of an anti-counterfeiting device. While only the bigger industries in the world can either afford the state of the art anti-counterfeiting systems or even have an in-house development department, the majority of the pharmaceutical companies will have to cope with what the suppliers have to offer. This will implicates that for the majority of the industries, the focus of the implementation of an anti-counterfeiting system should not rely on the device itself but also (and perhaps more intensely) on the mechanisms of choice of the device and all the procedures involved in updating its effectiveness and confidentiality throughout the product lifecycle.

Implementation of an anti-counterfeiting device should then be viewed as a critical step on the security of the supply chain, and as one of the tools an organization can use to enhance and maintain the integrity and security of the supply chain.

One approach to choose for controlling and enhancing the security of a supply chain is through Risk Management.

Although Risk Management can be interpreted differently by any organization, the ICH Q9 provides guidance on how to implement and use such a process / approach.

The Risk Management process guidance provided by the ICH Q9 should be viewed by an organization as pointing tool to use and adapt according to each individual needs.

This is a quite generic guidance but also very dynamic and by being so, also allows the flexibility and adaptation space that every organization needs to for the implementation of this iterative process.

Following the principles of ICH Q9, with its due adaptations, a starting point model was created for OM PHARMA SA (LIS) to implement a Risk Management process to its supply chains.

This model was created, and tested, using the simplest "quality" tools, as per suggestion of ICH Q9. In the future, as more reviews and iterations on the model are performed, the knowledge of the process and of the risks will grow significantly but with it so will the chosen tools and procedures that will allow for a better risk identification, analysis, evaluation, mitigation and acceptance tools.

This than will counterbalance the potential risks that may be identified and will allow for continuously improvement of the safety of medicines delivered across the globe.

Using this model, the major supply chains were identified (Direct Exportation, National Market Direct delivery and indirect delivery) and tools were successfully used to map each of the identified supply chain.

Using the tools suggested by the ICQ Q9, some major risk factors were identified, analyzed and evaluated. Consequently, an overall risk of counterfeiting was defined for every supply chain.

Using retrospective analysis tools, some potential root causes were identified and measures were suggested to mitigate the risks by elimination or control of the root causes.

With the eventual implementation of this measures, the risk of counterfeiting will for sure diminish opening doors to not only the better understanding of the process but for future risk mitigation actions that will lead to an increasingly secure supply chain.

Overall, it can be concluded that given the problem of counterfeiting becoming more real with every passing day, the pharmaceutical organizations have to take measures to secure their products, the organizations image, and most importantly the safety of the patients.

This can be done by following, with given adaptations, the principles provided by ICH Q9 and a wise choice of anti-counterfeiting systems and procedures.

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