



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.

Resumo

O fenómeno global da falsificação de medicamentos está a aumentar com cada vez mais medicamentos a serem alvos da contrafação.

Desta forma, em Julho de 2011, a UE adoptou uma nova Directiva sobre a falsificação de medicamentos para uso humano como forma de fortalecer a protecção aos pacientes e utentes.

Esta directiva tem como objectivo prevenir a entrada de medicamentos falsificados nas cadeias de medicamentos legais e consequentemente a exposição dos mesmos aos pacientes. Introduce medidas de controlo e segurança harmonizadas com implementação transversal a toda a cadeia de medicamentos, tal como a obrigação de implementação de sistemas de segurança nos medicamentos.

A Directiva entrou em vigor a 21 de Julho de 2011 sendo que os Estados Membros tiveram de começar a implementar estas medidas em Janeiro de 2013.

As cadeias de distribuição da Indústria farmacêutica são naturalmente complexas e adicionalmente, existe potencialmente o aumento de custos relacionado com a implementação de um dispositivo anti-contrafação. Desta forma, este problema não poderá ser abordado exclusivamente de uma única forma. A melhor forma para uma organização abordar esta problemática é através da adopção de uma abordagem por Gestão de Risco.

Este tese apresenta um método de implementação de Gestão de Risco nas cadeias do medicamento (da OM Pharma, mais especificamente).

Baseia-se no modelo proposto pela ICH Q9[1] fazendo uso das ferramentas da qualidade mais básicas, para uma primeira iteração (tal como sugerido pela ICH Q9).

Este modelo permite fazer a identificação e análise dos potenciais riscos de contrafação das 3 principais cadeias de medicamentos da OM Pharma e apresenta soluções para aumentar o seu grau de protecção e segurança.

Tal é materializado através da implementação de dispositivos anti-contrafação escolhidos por um método que tem em consideração e relaciona o risco global de contrafação, o potencial para causar dano e os eventuais custos do processo de implementação dos dispositivos anti-contrafação.

Palavras-chave: Gestão de Risco, Anti-contrafação, falsificação, medicamentos, cadeia de distribuição

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Abbreviations

Abbreviations	Description
ALARA	As Low As Reasonably Achievable
ALARP	As Low As Reasonably Possible
API	Active Pharmaceutical Ingredient
ASAE	Autoridade de Segurança Alimentar e Económica
CAPA	Corrective Action, Preventive Action
CCP	Critical Control Point
CoA	Certificate of Analysis
EEA	European Economic Area
EU	European Union
FEFO	First Expired- First Out
FIFO	First in- First Out
FMEA	Failure Modes Effect Analysis
FMECA	Failure Modes Effect and Criticality Analysis
FTA	Fault Tree Analysis
GDP	Good Distribution Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HACCP	Hazard Analysis and Critical Control Points
HAZOP	Hazard Operability Analysis
ICDRA	International Conferences of Drug Regulatory Authorities
ICH	Internation Conference for Harmonization
IMPACT	International Medical Products Anti-counterfeiting Taskforce
INFARMED I.P.	Autoridade Nacional do Medicamento e Produtos de Saúde Instituição Pública
IR	Infra-red
ISO	International Organization for Standartization
IT	Information Technology
KPI	Key Performance Indicator
MAH	Marketing Authorization Holder
OVD	Optically Variable Devices
PHA	Preliminary Hazard Analysis
PT	Portugal
QA	Quality Assurance
QP	Qualified Person
RCA	Root Cause Analysis
RFID	Radio frequency identity
RPN	Risk Priority Number

SFAIRP	So Far As Is Reasonably Practicable
SOP	Standard Operating Procedure
UN	United Nations
UV	Ultra-violet
WHO	World Health Organization

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.

2. Legal / Regulatory background

2.1 Historical reference

The existence and dissemination of counterfeited medicines was first addressed, at an international level, back in 1985 at the Conference of Experts on the Rational Use of Drugs in Nairobi[5]. This conference resulted in the suggestion that the World Health Organization (WHO), alongside with other international nongovernmental agencies, should assess the feasibility of creating an organism that would collect data and inform governments about the nature and extend of counterfeiting. It wasn't until 1988 that the pharmaceutical world saw the primordial's of legal/ regulatory measures against counterfeited medicines, with the adoption of the resolution WHA41.16[6], which requested the Director-General of WHO to initiate programmes for the prevention and detection of the export, import and smuggling of falsely labelled, counterfeited or substandard pharmaceutical preparations, and to cooperate with the Secretary General of the UN in case provisions of the international drug treaties are violated[7]. Then, in 1992 WHO organized the first international meeting on counterfeit medicines in Geneva with the participation of great number of highly prestigious institutions (Interpol, World Customs Organization , International Narcotics Control Board, International Federation of Pharmaceutical Manufacturers and Associations, International Organization of Consumer Unions, and the International Pharmaceutical Federation), being most important outcome the definition of counterfeit medicine: "is one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient (inadequate quantities of) active ingredient(s) or with fake packaging." [8]

Given the unfortunate, but expected, success of the counterfeit drugs market, in 1994, the WHO adopted the resolution WHA47.13 which requested the Director-General of WHO to assist Member States in their efforts to ensure that available medicines were of good quality, and in combating the use of counterfeit drugs.[6]

The need for greater international cooperation in combating counterfeit medical products has been reiterated through resolutions WHA52.19 (1999), WHA57.14 (2004) as well as the "Guidelines for the Development of Measures to Combat Counterfeit Drugs" (1999). From 1994 to 2004 many ICDRAs (International Conferences of Drug Regulatory Authorities) request WHO to assist Member States to adopt measures to combat counterfeit medicines circulating and, in Madrid (2004), ICDRA requested WHO to work on a draft international convention on counterfeit medicines.[7] Nevertheless up until 2006 the member states wouldn't reach an agreement on an international convention on counterfeit medicines. In February 2006 at the Rome conference, it was recommended that an international taskforce should be established. This action culminated in the creation of the International Medical Products Anti-counterfeiting Taskforce (IMPACT). This taskforce "is a voluntary grouping of governments, organisations, institutions, agencies and associations from developing and developed

countries aimed at sharing expertise, identifying problems, seeking solutions, coordinating activities and working towards the common goal of fighting counterfeit medical products. IMPACT aims at ensuring appropriate regional representation, including in particular from developing countries.”[9]

In 2007 at the IMPACT general meeting in Lisbon, a new document was endorsed: “Principles and Elements for National Legislation against Counterfeit Medical Products”. This document focused on the public and personal health implications in relation to counterfeit medical products that need to be appropriately addressed in legislation.[10]

In 2008, a group of specialists of the boards of Pharmaceutical Industries contributed to the further development of previous document, proposing through a new document, some modifications to the directive 2001/83/EC that establishes the community code in relation to the medicines of human use. This new document was presented to public consultation and more than 100 European institutions gave their say and proposed modifications. No opinions were disregarded and the document was transformed into a formal proposal for modification of the directive 2001/83/EC.

In 2009, a setback was seen, when the European Social and Economic Committee issued its formal opinion where it was expressed that the actions expressed themselves in the document weren't enough. It should also be taken into account the legal consequences for counterfeiting acts, the protection of intellectual property, customs monitoring and international cooperation. Later, it was realized that the problem of identification and traceability of the medicines was underestimated and some measures were proposed to avoid any legal/regulatory gaps on this subject.

Interestingly enough, one of the driving forces that lead to the creation of IMPACT was the increasing international trade of pharmaceuticals and sales via the internet had, and have, further facilitated the entry of counterfeit products into the supply chain. This concern was also expressed later in 2009, by several Health Ministers of Countries belonging to the EU during the Employment, Social Policy, Health and Social Affairs Council. It was suggested that some measures had to be taken in relation to the control of the origin and route of the raw materials used in the manufacture of medicines because frequently the raw materials are imported from outside the EU thus representing an additional threat to the quality and safety of the marketed medicines.

All these entities collaborated on further changing this new document, that would change the directive 2001/83/EC, and finally in 2011 the European Parliament adopts the new legislation, that now should be transposed to the National Law of each member state.

2.2 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 (serialisation):** 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. [11]

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 an 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 than 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.

3. Portuguese Medicine Counterfeit Overview

In Portugal the authority responsible for the verification and control of the medicines and health products is INFARMED I.P. For that reason, it is stated on the Portuguese Law the legal obligations of this Institution. More precisely, on the Decree-Law 269/2007 it is clearly stated that INFARMED I.P. is obligated to verify and monitor the marketing and usage of medicines and that must proceed to the apprehension of the medicines whenever the public health might be compromised.[12]

Within the INFARMED I.P. exists a department dedicated to fighting and counterfeiting of medicines called "Célula 3C - Célula de Combate à Contrafacção" (3C Cell). This department promotes the exchange of information at national and international level and elaborates and maintains a risk analysis plan of which a "Whatchlist", of all the found counterfeited medicines, is part off.[13]

INFARMED I.P. also has a very important relation / partnership with the Customs Authorities. This is done in order to promote a better, more efficient and swift detection of potential entrance of counterfeited medicines.

Besides this continuous monitoring of the customs, INFARMED I.P., Portuguese Customs and ASAE (Autoridade de Segurança Alimentar e Económica) also participate in international special joint operations for fighting counterfeited medicines.

One international joint operation in particular, called PANGEA, identifies targets that promote the introduction and/ or distribution of medicines on the illegal supply chain, via sex-shops, p.e. or direct acquire via illegal websites.[14]

The results of these Operations in Portugal are summed as follows:

2009 - Pangea II:

- 239 postal orders were verified
- 48 of those postal orders were apprehended
- These materialized in 1075 units of counterfeited medicines.

2010 - Pangea III:

- 2296 postal orders were verified
- 40 of those postal orders were apprehended.
- These materialized in 5445 units of counterfeited medicines.

2011 - Pangea IV:

- 4217 postal orders were verified
- 54 of those postal orders were apprehended.
- These materialized in 2866 units of counterfeited medicines.

2012 - Pangea V:

- 3835 postal orders were verified
- 41 of those postal orders were apprehended.
- These materialized in 33685 units of counterfeited medicines.
- Totaling about 100000 €.

The last PANGEA operation (VI) occurred between the 18th and the 25th of June of 2013 and more than 100 countries participated. It was coordinated by INTERPOL with the help of WCO (World Customs Organization).

In Portugal the results were as follows:

- 3323 postal orders were verified
- 40 of those postal orders were apprehended.
- These materialized in 13600 units of counterfeited medicines.
- Totaling about 55000 €.

In result of INFARMED I.P. and Portuguese Customs on this kind of operation and others similar, it is concluded that, despite the alerts, Portuguese continue to gravely compromise their health, specially by acquiring medicines through the internet of off illegal websites.

It is demonstrated that it is necessary to continue with the public alerts and the action of cooperation, both at international and national level in order to fight these illegal situation that jeopardize the public health.[15]

4. 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 [16]:

1. Overt, or visible features;
2. Covert, or hidden features;
3. Forensic techniques;
4. Serialization/ Track and trace.[16, 17]

4.1 Overt (visible) features

These features are intended to allow the end user to verify the authenticity of a pack. They are fairly noticeable visible although expensive and/ or difficult to reproduce adding significant cost that can consequently restrict supply chain availability and often require a level of awareness by the end users to be effective. When applying such features, one must not consider only the direct costs of the features themselves, but also the requirements of an intensive boost in the supply chain. Using these methods will imply the creation of handling and disposal procedures to avoid unauthorized diversion. Additionally they must be applied in such manner that they cannot be removed or reused without causing any kind of damage to the pack – otherwise they could be recycled with fake content giving them a false impression of authenticity.

The following features are most commonly used/ available:

- a. Holograms

Holograms are the result of a photographic technique that records the light scattered from an object, and then presents it in a way that appears three-dimensional.

This is one of the most recognizable features as it has been used for several years on the protection of credit cards.



Figure 1 - Typical credit card hologram [29]

These kinds of holograms, commonly called “rainbow holograms” and differ from the other types because their 3D effect is revealed under white light (sun light) rather than a laser.

Holograms and other similar optically variable devices (OVD) are often incorporated in other devices, such as tamper evident or as a integral part of the primary pack (blister foil p.e.), in order to enhance their overall effectiveness.

They can also be incorporated also into tear bands in overwrap films, or as threads embedded into paper substrates. [16, 17]

b. Optically Variable Devices (OVD). [16, 17]

These features are very similar to holograms (but generally without the 3D illusion) and also commonly recognizable by the end user (used widely on banknotes), involving image flips and transitions including colour transformations or monochromatic contrasts.

They are made generically of a transparent film that acts as an image carrier, plus a reflective backing layer (normally a thin layer of aluminium).



Figure 2 - Example of and OVD [30]

Some modifications can be made in order to provide extra security. These include a partial removal (chemical removal) of the reflective layer – that provide an intricate and difficult to mimic outline – and / or making the reflective layer so thin that it appears as a clear film with a ghost like effect. These modifications however are more restricted, thus increasing the security of the product but also comprising an additional cost.[18]

c. Colour shifting inks and films [16-18]

These features can show positive changes in colour according to the angle of view and can be effective when used as an overt graphic element, or incorporated into a security seal.

Colour shifting pigments are finely ground metallic laminates that need to be laid down an thick opaque film to achieve the optical effect, and are there fore better suited for printing techniques such as gravure and screen printing rather than lithography printing. Their security value lies in the specificity and dynamics of colour change, combined with the difficulty and expense involved in the manufacture. They are not widely available, being limited to only a few ink specialist manufacturers. Their identification may involve forensic examination, such as microscopy, and embeded taggants (chemical or physical marker added to materials to allow various forms of testing - generally consist of microscopic particles built up in many layers, which are made of different materials).

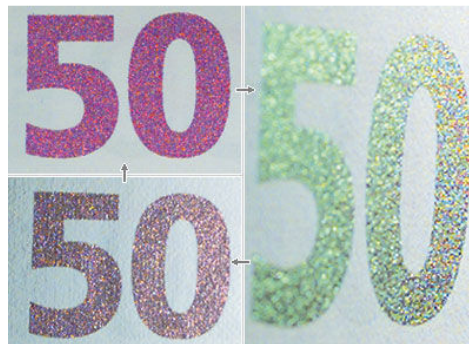


Figure 3 - Example of colour shifting pigments [31]

Colour shifting films have been used for security applications, involving multi-layerdecomposition of thin films to build up a structure with unique diffractive properties, and vibrant colour transitions. They can be applied as security seals or tamper evident labels.

d. Security graphics [16-18]

Fine line colour printing incorporating a range of overt or covert elements such as guilloches (engraving technique in which a very precise intricate repetitive pattern or design is mechanically engraved into an underlying material with fine detail), line modulation or line emboss. They may be used as a background in a discrete zone such as an overprint area, or as complete pack graphics, and can be printed by normal offset

lithography or, for increase security, by intaglio printing (printing technique in which the image is incised into a surface, and the incised line or sunken area holds the ink that transfers to the paper by pressure – normally a cylinder). Security can be further enhanced by incorporation of a range of covert design elements, such as microtext and latent images (based on the Kipp effect, made with the help of intaglio printing, the image is "hidden" in the areas of the same tone and it's built of raised parallel lines, which are perpendicular to the raised lines of the background. When you rotate such area with the light reflecting from it, at certain angles you will see the picture appearing and then changing into negative).

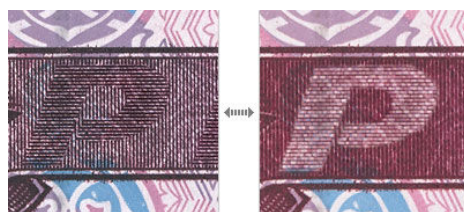


Figure 4 - Example of a latent image [31]

e. Sequential product numbering [16, 17]

Unique sequential numbering for each pack or label in a batch can make counterfeits easier to detect in the supply chain. When printed visibly it provides a semi-overt means of authentication by reference to a secure database, because duplicates or invalid numbers will be rejected. The main disadvantages of sequential numbering are that the sequence is easily predictable and therefore easily replicated and also it would required the end users to have some means of access to the information of the database. A more secure option of this kind would be serialization by means of a pseudo-random non-repeating sequence.

f. On-product marking [16, 17]

These kinds of technologies allow for special images or codes to be placed on conventional oral dosage forms. These overt technologies can be difficult to replicate and offer security at pill level which is effective even if the product is separated from the original package.

4.2 Covert, or hidden features

The objective of these features is to allow the product/ brand owner to identify a counterfeit product. The general public is not (and may not) be aware of their presence nor have the means to verify them. A covert feature should not be easy to detect and/or copy without specialist knowledge, and their details must be controlled on a "need to know" basis. If these features

become known they are immediately compromised and will lose some if not all of their security value. [16, 17]

a. Invisible printing

Using special inks, invisible markings can be printed on almost any substrate, and which only appear under certain conditions, such as via UV or IR illumination. They can be formulated to show different colours with illumination at different wavelengths.

For security reasons there is very little information disclosed on the composition of these inks and their respective manufacturing process.

b. Embedded image [16, 17]

An invisible image can be embedded within the pack graphics which can only be seen using a special filter, and cannot be reproduced by normal scanning methods.

Then effects can be quiet dramatic and yet remain hidden.

c. Digital watermarkings [16, 17]

“Invisible” data can be digitally encoded within graphics elements and verified by means of a reader and special software. The data can be captured using a webcam, mobile phone or any other scanning equipment, but the digital information is not visible to the human eye, and attempts to duplicate it will be detected by virtue of the degradation of the embedded data.

d. Hidden marks and printing [16, 17]

Special marks and printing can be uniquely applied in such way that escapes attention and are not easy to copy. They comprise an inherent uniqueness and their effectiveness depends on a combination of secrecy and subtlety.

e. Anti-copy or anti-scan design [16, 17]

Fine line background patterns appear as uniform tones, but when scanned or copied reveal a latent image which was not previously visible. Commonly used on secure documents to prevent photocopying, they can be applied to product packaging as a background tint.

f. Substrates [16-18]

There are many ways of incorporating covert markers within a substrate, such as visible or UV fluorescing fibers, or chemical reagents in carton board or paper. Watermarks can be embedded in leaflet paper, or metallic threads interwoven in the base material, possibly including an overt OVD feature. These require a dedicated supply source and large volume of production, which, if affordable, can be a very effective option.

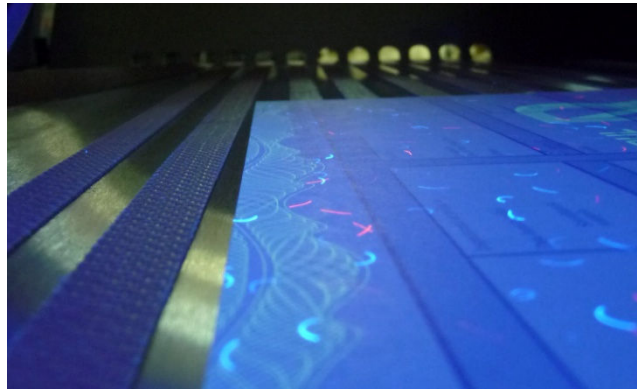


Figure 5 - Example of UV fluorescing fibers [32]

g. Odour [16, 17]

Micro-encapsulated distinctive odours can be applied as an additive to an ink or a coating to provide a novel covert or semi-overt feature.

4.3 Forensic techniques

There is a wide range of high-technology solutions which require laboratory testing or dedicated field test kits to scientifically prove authenticity. These are strictly a sub-set of covert technologies, but the difference relies in the scientific methodology required for authentication.

a. Chemical taggants [16, 17, 19]

These consist in trace chemicals which can only be detected by highly specific reagent systems not normally detected by conventional analysis.

b. Biological taggants [16, 17, 19]

Similar to the chemical taggant but makes use of a biological marker that can be incorporated at extremely low levels (parts per million or even lower) in product formulations or coatings, or invisibly applied to packaging components. At such low levels they are undetectable by normal analytical methods, and require highly specific “lock and key” reagent kits to authenticate.

c. DNA taggants [16, 17, 19]

Highly specific DNA “lock and key” reagent systems can be applied to packaging by a variety of printing methods. They require a “mirror image” recombinant strand to effect the pairing, and this reaction is detectable by a dedicated device. Security is further assured by hiding the marker and reagent pair in a matrix of random DNA strands, but the test is tuned to work only with one recombinant pair.

d. Isotope ratios [16, 17, 19]

Naturally occurring isotopes can be highly characteristic of the source of a compound, and accurately determined by laser fluorescence and magnetic resonance techniques. These can provide a fingerprint of one or more of the product constituents, or alternatively a specific marker can be added with its own unique signature. Detection requires highly specialized laboratory equipment.

e. Micro-taggants [16, 17, 19]

Micro-taggants are microscopic particles containing coded information to uniquely identify each variant by examination under a microscope. This may take the form of alphanumeric data depicted on small flakes or threads, or of fragments of multicoloured multilayered laminates with a signature colour combination. These can be embedded into adhesives, or directly applied to packaging components as spots or threads.

4.4 Serialization/ Track and trace

A number of track and trace applications are under development for the pharmaceutical sector, although the principles have been established for many years in other contexts. These involve assigning a unique identity to each stock unit during manufacture, which then remains with it through the supply chain until its consumption. These identities normally include details of the product name and strength, and the batch number and expiry date – although in principle it may simple take the form of a unique pack coding which enables access to the same information held on a secure database. [16, 17]

These serve a number of distinct functions:

- i. Tracking an item through the supply chain, to each point where there is the facility for data capture;
- ii. Providing traceability on the history of any item, subject to limitation of number of control points;

- iii. Enable authentication of the data at any time, and by implication, of the pack or unit in which it is applied.

The most obvious benefits are in the supply logistics, where greater transparency of inventories and demand patterns can lead to efficiency improvements and cost reductions. Another benefit is the ability to identify a product up to the time of dispensing to a patient, enabling the elimination of medication errors and the ability to speedily recall defective batches. The ability to tightly control and authenticate all the product through the supply chain greatly reduces the possibility for counterfeit, stolen or diverted product to entering the distribution system without being detected.

It should also be noted that track and trace tags or labels may not necessarily be applied at the unit pack level, but may be restricted to whole cases or even pallets – therefore affording the logistics benefits but not all the safety and security gains.

- a. Serialisation [16, 17]

In itself the track and trace may not be immune to copying or falsification, but its security is greatly increased by the inclusion of a unique and apparently random serialisation, or non-sequential numbering, ideally at individual item level. If the serialisation was sequential, then the level of security would be very low as the sequence is predictable, whereas random serialisation using a highly secure algorithm or method of encryption overcomes this problem. Individual pack may still be copied but the database will identify duplicates or invalid serials, as well as those which have been expired or cancelled, or appear in the wrong market, or with invalid product details.

Where secure serialisation is applied visibly to a pack, then it may be authenticated by customers via telephone or internet link to the database. One issue to be resolved is ownership, management of and access to the database, to ensure that the information readily accessible and yet secure against compromise.

- b. Barcodes [16, 17, 20]

These are high-density linear or 2D bar codes incorporating product identity down to unit pack level, which are scanned and referenced to the central database. One popular implementation is the 2D Datamatrix code, and other possibilities include PDF417 codes (are stacked linear barcode symbol format - PDF stands for Portable Data File and the 417 signifies that each pattern in the code consists of 4 bars and spaces, and that each pattern is 17 units long). A 2D typical code can be typically 1cm square or smaller and yet contains up to 1 Kb of data with some “redundancy” or error correction. Where space is no limitation, linear barcodes can also be used. The codes are printable by online methods including inkjet or digital printing, allowing direct computer control and transfer of records to the central database. Hierarchical systems are whereby the label on a shipping case is inextricably linked to the identities of all its contents, and this can further extend up the

chain to pallet labels, thereby overcoming the necessity for line of site scanning through the supply chain.

c. Radio frequency identity (RFID) tagging [2, 16, 17]

An RFID tag comprises of an antenna with a microchip at its centre. This contains item-specific and batch information which can be interrogated at a distance, without requiring line of sight (unlike barcodes). The radio frequency used determines the range and sensitivity, but no single specification suits all applications. Some systems are able to pick up multiple records for a mixture of different products, but there are some issues around orientation of the tags and absorbance of the radio signals by liquids and foils. One clear advantage of RFID is that it has the potential to be fully automated in warehouses and even through to pharmacies, without requiring manual intervention.

Specifications for equipment and data standards are being developed. The cost of tags remains a significant barrier to individual pack application as does the availability of the application and verification equipment if it is to be implemented at pharmacy level.

Robustness of the tags during application and handling through to end of life is another issue, as trials to date indicate a significant failure rate. However there is optimism that a printed version may be developed. Privacy issues and susceptibility to deliberate adulteration must also be addressed prior to widespread implementation.

d. Unique surface marking or topography [16, 17]

There are several methods for applying a pseudo-random image to each item in a batch, such as a pattern of lines or dots in one area of the carton, and then scanning the signature into the batch database via secure algorithms, for later authentication. Alternatively, the pack surface provides a unique fingerprint when scanned by a dedicated laser device, which enables each pack to be registered into the database at batch manufacture, and which is impossible to replicate or falsify.

As can be seen above there is a huge 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.

All of the above shown examples have pros and cons which will be briefly summarized below.

As for the overt options, they represent an attempt to put authentication into the hands 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. [16, 17]

5. Supply Chain Control and Risk Management

5.1 General Considerations

Supply chain in its essence is a system of organizations, people, activities, information and resources involved in moving a product from supplier to customer as simply illustrated in the chart below (figure 6).

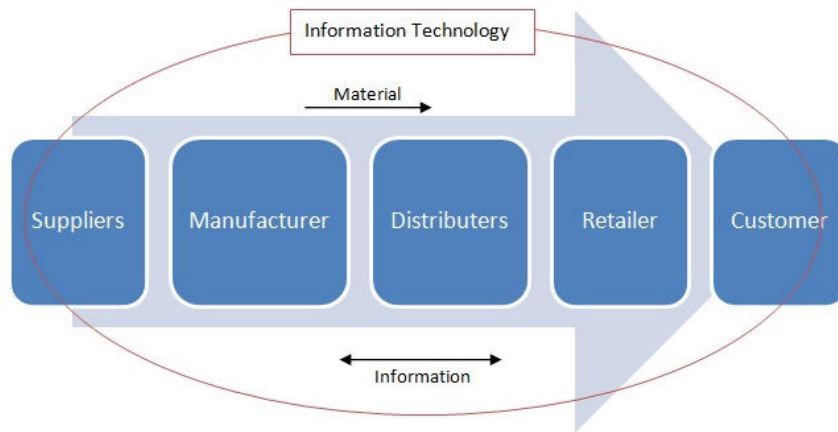


Figure 6 - Basic Supply Chain Flow [33]

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 as the next figure (figure 7) demonstrates.

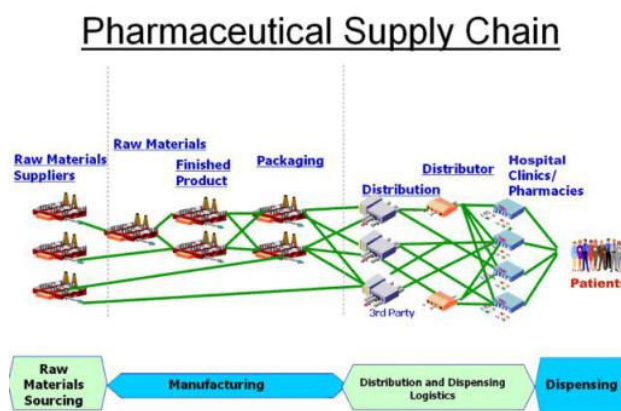


Figure 7 - Scheme of a typical pharmaceutical supply chain [34]

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 economical 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.

As previously stated and also 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, 22]

While these are some of the activities that one must take into account or implement on the road to a secure supply chain, as it will be further explained, they will not be limited to these previous examples. Nonetheless, the development of this work, had as a base, the Quality Risk Management model detailed in the ICH Q9 (as shown below in figure 8), 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]

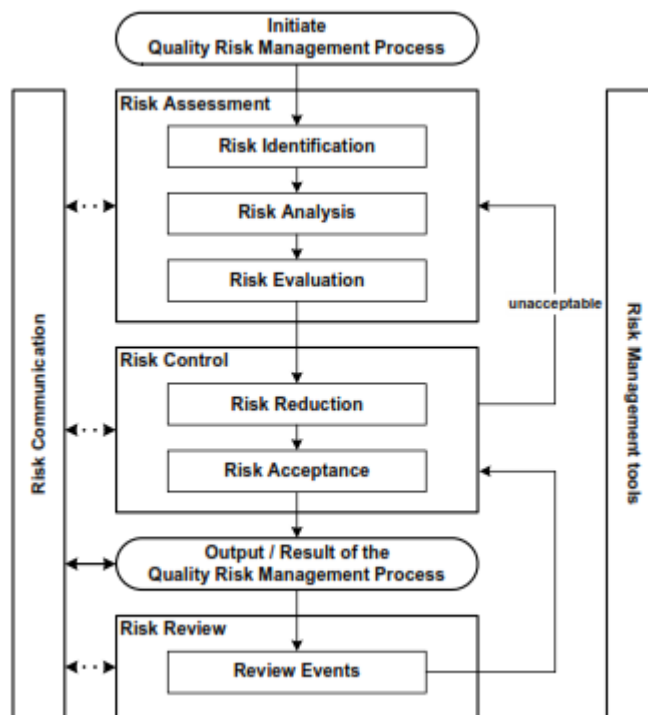


Figure 8 - ICH Q9 Quality Risk Management Model [1]

This process, as proposed by ICH Q9, will be further discussed and detailed on the next point “Risk management Process” as a process to integrate and control all the aspects of risk that may or may not reveal themselves throughout the supply chain.

As a note, it is important to refer that the risk management activities should provide a systematic, effective and efficient way by which risk management can be embedded and maintained throughout the organisation. These activities should comprise, at least, the following steps:

- Planning
- Implementation and maintenance
- Monitoring, reviewing and continual improvement
- Reporting

It should be clear by now that this is a very dynamic and ongoing process about anticipating hazards and controlling risk through a continuous of risk awareness, reduction and / or acceptance, and review. [23]

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.

To better represent the presence of possible hazards across the supply chain and their potential for damage, the next figure (figure 9) illustrates the typical pharmaceutical supply chain based on tiers, where suppliers are the starting point at the far end, and still present a potential threat.

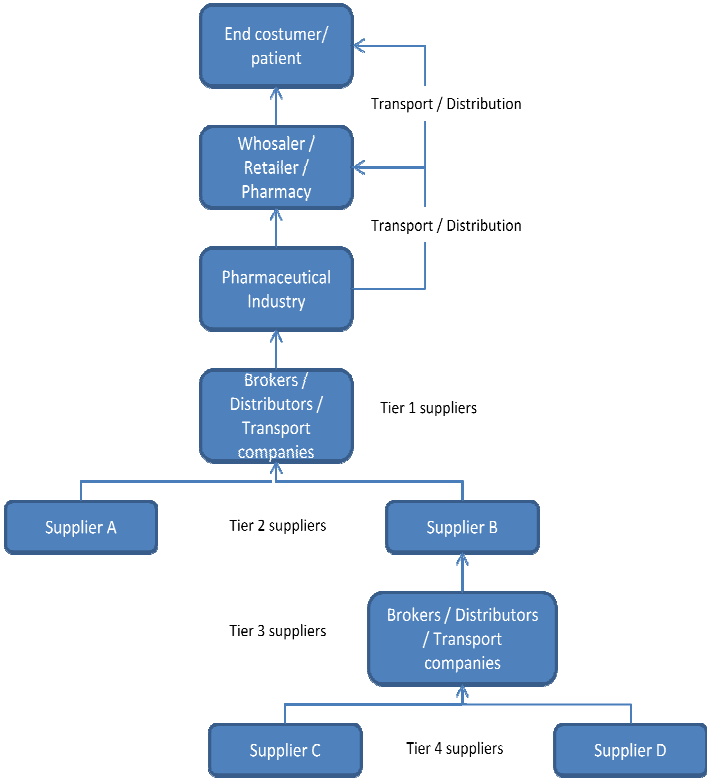


Figure 9 - Example of Pharmaceutical Supply Chain based on tiers

The more complex the supply chain, the more difficult it is to control, and the greater the risk of a supply chain impact on the quality of the end product. This figure also illustrates the high importance of the suppliers and their impact on the supply chain, and why they should be the primary focus of work when trying to take control over the supply chain. Therefore it is in the best interest of all involved parties that hazards are identified and the resultant risks are managed throughout every tier of the supply chain. Needless to point out that exceptional communication between all parties is required to do this effectively.[24]

For the accountable organization and their respective suppliers to manage risk effectively, it is also of the utmost 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 hazards are shown on the next table (table 1). It is worth noting that external hazards are identifiable and possibly controllable through careful planning and action whilst internal risks can be managed, mitigated or even eliminated. [24]

External hazards	Internal hazards
<ul style="list-style-type: none"> • Increase / decrease in demand 	<ul style="list-style-type: none"> • Non-conformity
<ul style="list-style-type: none"> • Political climate / instability 	<ul style="list-style-type: none"> • Rejection of a batch / Product recall

<ul style="list-style-type: none"> • Legal status (regulatory restrictions in individual markets and of supplier) 	<ul style="list-style-type: none"> • Capacity / resource issues
<ul style="list-style-type: none"> • Counterfeit / fraud 	<ul style="list-style-type: none"> • Reduced inventory
<ul style="list-style-type: none"> • Materials, product, service supply interruption 	<ul style="list-style-type: none"> • Single sourcing versus dual / multiple sourcing
<ul style="list-style-type: none"> • Termination of material or services 	<ul style="list-style-type: none"> • Inadequate supplier selection / qualification process
<ul style="list-style-type: none"> • Uncontrolled variation in materials 	<ul style="list-style-type: none"> • Longer / more complex supply chains
<ul style="list-style-type: none"> • Unexpected contaminants in supplied product 	<ul style="list-style-type: none"> • Non-conformance with contracts / agreements
<ul style="list-style-type: none"> • Deliberate or accidental adulteration 	<ul style="list-style-type: none"> • Staying with poorly performing supplier & not progressing improvement or exit strategy
<ul style="list-style-type: none"> • Unknown or poorly controlled use of brokers / agents 	<ul style="list-style-type: none"> • Inadequate communication
<ul style="list-style-type: none"> • Distribution / transportation / storage events 	<ul style="list-style-type: none"> • Transportation / storage events
<ul style="list-style-type: none"> • Inadequate communication 	<ul style="list-style-type: none"> • Personnel / organizational changes
<ul style="list-style-type: none"> • Lack of adequate documentation control 	<ul style="list-style-type: none"> • Lack of adequate documentation control
<ul style="list-style-type: none"> • Complex processes 	<ul style="list-style-type: none"> • Increasing process variability

Table 1- Examples of External and Internal Hazards

From this table, one should refer to the importance of the internal risk of inadequate supplier selection / qualification process. Information about potential suppliers should be used to determine additional potential supply and business risks and include the following:

- Financial viability of supplier;
- Continuity of supply;
- Liability;
- Amount of work awarded to supplier in view of the supplier's overall capacity;
- Technical capability;
- Distribution and transportation considerations;
- Agents and brokers (potential for agents and brokers to change source of supply);
- Capital investment needed;
- Single source suppliers (vulnerability);
- Supplier company legal status (licensing);
- Disaster / contingency plan for supply;
- Adequate management of the suppliers;
- Culture of continuous improvement.

The procuring department / organization is responsible by communicating and agreeing the product requirements with the supplier. It may request the previous described data and / or sample of product in order that the potential supplier can demonstrate the ability to meet the specified requirements. When defining the initial supplier arrangements, the relevant information should be communicated for consideration. The organization should ensure that the relevant people are involved in specifying, reviewing and evaluating information and should include, technical and quality representatives.

Risk management is an effective means of identifying the necessary controls required. To do this requires knowledge of the complete supply chain and all organizations involved within it. Then the activities of the organizations in the supply chain should be reviewed to identify what is critical to the product and what could go wrong.

The following lists some items that should be considered during sourcing and supply chain review:

- Knowledge of the complete supply chain and all organisations within it
- Change control and notification from suppliers
- Supplier audits or technical visits (note that this requirement should be included in any agreement for a critical supplier)
- Control of second or further tier suppliers via specifications or agreements
- Sampling / testing / verification
- Certificates of Analysis (CoA's) / conformity
- Formal requirements (e.g. specific certificates, contracts / technical agreements, etc)
- Methods for measuring performance
- Correction, reworking, investigations
- Batch / Lot sizes
- Inventory control (e.g. First-in-first-out (FIFO), First-expired-first-out (FEFO), time limit / target)
- Traceability (process, product, equipment, operators)
- Document / sample retention periods
- Protection of intellectual property

The organization should seek to continually improve the quality and delivery of the products based on periodic supplier performance evaluation, feedback and consideration of cost. It is important to continually review and strengthen relationships with suppliers, while balancing the short and long term objectives. Risk management activities provide, or at least should tend to provide, a basis for sharing identified hazards and mitigating the risks resulting from those hazards throughout the product or supplier lifecycle. It also should demonstrate that all parties are taking or keen to evolve into a responsible approach ensuring product quality and safety and security of supply. Investors and assessor / auditors expect organizations to be able to demonstrate that they manage their supply chains effectively and risk management provides the means to do this.[22, 24]

5.2 Risk Management Process

As previously stated, over the next points, it will be explained the process of Risk Management according to what is suggested by the ICH Q9 (please refer to figure 8 for process overview).

5.2.1 Risk management team and responsibilities

For the product / process being assessed it is critical that the different field experts are consulted / involved to ensure accurate and complete data / information. It is recommended that the risk management process is 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).

It is common and preferred to develop a matrix to identify the roles of the personnel associated with the risk management process at the beginning in so that responsibilities throughout the process are clear.[22, 24]

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.

5.2.2 Risk Assessment

Risk assessment is defined as:

“A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with the exposure to those hazards.”[1]

The very first step (step 0) of the process according to the flowchart (figure 8) 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. It is possible to define “profiles” of the supply chain so that every profile will cover several products that follow the same supply chain.

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.

As it will be seen, every step of the risk management process, involves generically inputs and outputs that will ultimately act as a guide to which step to take next.[1, 23, 25]

5.2.2.1 Risk identification[1, 23-25]

Risk identification is defined as:

“The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description”.[1]

Risk can be defined as:

“The combination of the probability of occurrence of harm (hazard) and the severity of that harm”,

and thus it can be simply represented by the following expression:

Risk = Severity of Harm x Probability of occurrence

It is important to carefully plan this Risk identification stage as it will be the foundation and will provide the outputs for the next stages / steps. For the identification of risk itself it will be considered the potential hazards as outputs. These will be duly scrutinized later on during the stages of Analysis and Evaluation.

Inputs

When assessing which risks should be considered as inputs at this stage, there are several points that must be verified / analysed:

- All supplier in the whole supply chain;
- Material / product / service being supplied;
- The structure of the supply chain and the links between the parties involved (i.e., suppliers of suppliers, transporters, etc);

- Current security of the supply chain;
- Internal processes (production processes and supplier management processes – including qualification process);

The data gathering should be as exhaustive as possible which in turn can complicate this stage given the fact the data can be present as quantitative (easily understood and workable) and qualitative (working history, supplier experience, etc).

When considering the risks, it must be achieved a balance between the importance given to the quantitative data and the qualitative one. Often the qualitative (and more subjective) information is given less importance or not considered as equal in comparison to the quantitative data leading to some information being disregarded leaving the overall assessment with major gaps.

This is the step where the answer “What can go wrong” must be answered, thus there is no room for unfilled blanks. To overcome this, it is recommended that a mapping of the process is done. It helps the visualization of the process and therefore the discovery of the hidden / outthought risks.

It is at this stage that a multidisciplinary team is involved in order to provide information to support the Risk Identification. Since the risks are transverse to the different departments

It is at this stage that the involvement of the multidisciplinary team is most noticeable. Since the risks inherent to a supply chain are dealt across an entire organization, at different levels and with different points of view, it is important that there are present people who have the necessary skills, expertise and sensitivity to identify the potential hazards, possibly unlooked by personnel working in other areas.

For example:

1. Quality Assurance may be able to help identify potential through the knowledge gained from:

- Known deviations / non-conformities;
- Complaints;
- Internal/ external audits;

2. Production / Maintenance / Warehouse:

- People;
- Premises;
- Utilities;
- Equipment;
- Production process itself (such as opportunities for cross-contamination, etc)

3. Logistics

- Transportation;
- Agents and brokers;
- Services;
- Supplier performance / attributes.

4. Financial

- Business stability / continuity;

5. Management and other areas

- Management review;
- Knowledge of the public domain (e.g. news, regulatory actions, legislation);
- Organization strategy
- Capacity increase / decrease vs capability;
- Etc.

Outputs

The outputs of the risk assessment are going to be all the known and potential sources of hazards and their associated risks. It is important to refer that despite how exhaustively the inputs were made, because process are in constant change, there is no assurance that all hazards are identified at any given time. Also it should be referred that these changes can influence the outcome and will implicate, naturally, a later review and reassessment.

To better summarize the different potential risks identified at this point, one can consider the following categories:

- Product quality risks
- Business risks
- Raw material risks
- Machinery / equipment risks
- Personnel risks

5.2.2.2 Risk Analysis[1, 23-25]

Risk analysis can be defined as:

“The estimation of the risk associated with the identified hazards”[1]

The risk analysis is the next logical step. If on the risk identification, the output was a list of all sources of hazards and their potential risk, on this stage, these risks will be dissected and an attempt to calculate the level of the severity of harm, probability of occurrence, and detection will be made.

Inputs

Naturally, the inputs of the risk analysis are the outputs of risk identification, i.e., the list of sources of hazards and their potential risk. It is relevant to note at this point that, some the inputs data has to be processed by means of risk tools. There are some risk tools that require hard data to be used, thus whenever possible, a way to transform soft data into hard data must be found. One way to do this is by attributing a comparative scoring system to the qualitative inputs. Naturally, quantitative data is considered more reliable and easier to work with but, because complete and trustworthy hard data is difficult to get, especially when an organization has little or no experience on any particular tools, it is

often recommended that it is a good start to work with more qualitative or semi-quantitative tools and work the way up to a quantitative tool after several full cycles of risk management. When opting for this approach, by every completed cycle of risk management, more knowledge and experience is gained, improving the confidence of the risk estimation and consequently, more value is added to each output every time.

For the process itself, it is worth referring that is a matter of the multidisciplinary team assessing the identified risks, using the preferably the same risk tool (when possible), and attribute a ranking or scores for each risk, following the guidance of the chosen risk tool.

Outputs

The outputs of this stage are a complete list of the risks analysed duly ranked according to the chosen procedure /risk tool.

5.2.2.3 Risk Evaluation[1, 23-25]

Risk evaluation is defined as:

“The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.”[1]

This is the process where the information from Risk analysis is organized and a level of tolerable risk is defined against which the risk analysis output can be compared. When completed, this will ease the decision making process of the next stages of Risk Reduction and Risk Acceptance.

Inputs

Just as for the previous steps, the inputs of Risk evaluation are the outputs of risk analysis. At this stage we have a ranked list of the identified potential risks. Before starting the process of evaluation itself, it is mandatory that a tolerance level is set allowing the comparison of the Risk Analysis output.

The level of tolerable risk depends on the nature of the product and on the criticality of its application. The simplest way of setting the level of tolerance is to organize the list of risks by value and use a Pareto analysis, selecting the top 20 or 25% and cover the 80 or 75% of the issues.

The process is simple, once the risk is sorted in order of descending value of risk, and the level of tolerable risk is set, the output of the Risk analysis is reviewed against the level of tolerance. The results are as simple as higher than or acceptable. Note that this procedure should be documented and duly communicated to the necessary people.

The outputs from risk analysis that are acceptable can go forward as residual risks for the Risk acceptance stage. The ones that are above the agreed level of tolerance are to be identified for Risk Reduction.

Outputs

The output consists of 2 data sets, above and below the level of tolerance. This data can either advance to the Risk Reduction or Risk Acceptance.

5.2.3 Risk Control

Risk control is defined as:

“Actions implementing risk management decisions” [1]

Just as the definition states, 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, 23-25]

5.2.3.1 Risk Reduction

Risk reduction can be defined as:

“Actions taken to lessen the probability of occurrence of harm and the severity of that harm”[1]

This stage then focuses for control and / or avoidance of risks that were previously identified as above the tolerance level.

Inputs

The inputs for Risk reduction and Risk Acceptance are the two lists previously made (Risks above and below the tolerance level).

The process begins with two major decisions:

1. Does the organization require every risk to be controlled?
2. Is it technically, safely or economically viable to work on reducing every risk identified?

Before making these decisions, or answering both answers, the organization must acknowledge that there are many actions that can be taken to reduce or even eliminate the risks previously identified. Nonetheless not all of these actions can be implemented within the expected / needed timeframe or are even economically and/ or technically viable. This means that the possible actions to implement have to be broadly discussed as one action might be preferable to other and these may reduce the

risk to different levels. Items to be taken into consideration when assessing the possible actions to develop may include: the available resources; capability; policy.

When making the decision to which actions to implement, the team must also consider the possible impact on the Risk Management process itself. An action can create a new risk or just replace one risk for another of a different nature.

Outputs

The outputs are the decisions and actions that were agreed to be implemented in regards to mitigating or eliminating the identified risks. At this point it is also useful define an implementation strategy and timeframe.

Below are listed some of actions that can be used to reduce the risk in the supply chain:

- Map the supply chain providing visibility of controls;
- Develop and implement a robust supplier qualification process;
- Establish a supply contract;
- Implement a Quality Agreement or a Technical Agreement;
- Verify and ensure that suppliers are proactive in managing risks;
- Identify, select and qualify alternative suppliers, preferably that do not share the same risks;
- Identify, select a different supplier within an effective timeframe, should the current supplier fail to meet the current defined acceptance standards;
- Audits;
- Etc.

5.2.3.2 Risk Acceptance

Risk acceptance is defined as:

“The decision to accept the risk” [1]

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.

Inputs

The inputs, are the outputs of the previous step, i.e., the risk evaluation must have been done and the list of the risks above the tolerable level should have been through the risk reduction phase. The inputs are the same list of risks now duly mitigated.

This a step of decision making, where the organization must review the risks and access whether to agree or not in continuing to operate without any further risk reduction. The conditions under which a positive decision should be made are If the risk was below the tolerable level of acceptance (before or after the risk mitigation) and/ or if the risk cannot be reduced at this moment.

Output

The output is a list of the accepted risks that should be formally approved and duly communicated to the interested parties.

5.2.4 Risk communication

Risk communication is defined as:

“The sharing of information about risk and risk management between the decision maker and other stakeholders”. [1]

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, 23-25]

Besides ensuring a proper understanding of the project, there are other beneficial results consequent of proper communication practices. These include but are not limited to:

- Time saving;
- Lesser communication errors;
- Consistence information sharing;
- Better reaction to changes.

When implementing a proper communication method, it should be defined all the parties involved in the process with whom communication will be established (p.e.: suppliers; different departments within the company; consultants; regulatory authorities, etc).

In terms of the communication that may have to be done regarding the risk management process, it might be related to the timeline/ urgencies, existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risk to quality.

The communication procedures should be standardized so that it is easy to understand the nature of the information being delivered and also, there should be established an agreed level of detail of the information provided. It should be just enough for an understanding of the situation allowing an easy informed decision.

Naturally, throughout the entire process, a great deal of information will be exchanged between many different parties. Nevertheless, there are some key points that should be identified as of mandatory communication. All parties should be aware of these points and comply with them:

- Unexpected developments;
- Routine developments – usually at milestone stages, or whenever previously defined;
- Whenever a periodic review takes place.

It also recommended defining how the information is transmitted. For routine developments, a more informal (such as e-mail) method might be acceptable. For key decisions, there should be a formal communication.

5.2.5 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”. [1]

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, 23-25]

Inputs

The base input shall be the original (or previous) assessment. The remaining inputs are all the new data gathered since then. These may include:

- Monitoring information
- Every event and changes that took place:
 - Inspections / audits;

- Case studies;
- Management reviews;
- Etc.

These changes or events have then to be scrutinized and a level of significance must be attributed and a reassessment made and presented to the decision makers. Appropriate measurement tools should be established to continue monitoring the performance and feedback on this process.

Outputs

The outputs of this process may vary and are not the end of the process.

A review outcome may well be that no action is required, as all risks are known and under control and the next review must be scheduled or new onsets for reviewing discussed and agreed. New risks may be identified that require immediate reassessment and action. It can also happen that no new risk is identified but an event with significant impact occurred that rendered invalid the original assessment resulting in a new Risk Assessment “cycle” for that particular supplier / product.

5.3 Risk Management Tools

While describing the basics of Risk Management, on which this work was based on, the term tool was repeated several times. In this chapter, because some of these tools are also used in this work (with or without modifications) it will be made a brief description of the most commonly available and their best usages. [1, 22-26]

The tools described in this chapter 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, 22-26]

5.3.1 Tools used for Risk Assessment

For better systematization, this will be divided in tools used for Risk Identification, Risk Analysis and Risk Evaluation. [1, 22-26]

5.3.1.1 Risk Identification Tools

Brainstorming

Brainstorming is a widely known and used technique whenever you have a team or a group of people working in ways to find solutions to a problem. It works on the principle of quality by quantity.

It is an extremely simple method that requires almost no resources (apart from human) and generates quantities of data fairly fast. When this is used by a multidisciplinary team, as suggested, this method can also cover and identify areas not considered at first sight. Unfortunately, because it relies on quantity it also produces a lot of information that has to be discarded later.

As the brainstorming progresses, a list of ideas (identified hazards / Risks) will grow it is often common to group the ideas under a similar classification for simplification purposes.

The output will be exactly the list of ideas duly organized that can be subject to the later steps or Risk Assessment.

Check Sheets

Check sheets are a very commonly used tool mainly to collect or confirm information from a process. The information gathered can be quantitative or qualitative but is done in a well organized manner and can also be used as an input for other tools. Although well organized, the check sheet can present some disadvantages, mainly due to the fact that it relies on people for data collection and because it involves a prior knowledge of the process in order to create a good sheet and thus it mainly becomes limited by default and miss relevant data.

Flowcharts and Process Mapping

Flowcharts are also a very known tool that is used to mapping the individual steps of a process according to the order of occurrence. By using arrows to connect the boxes (representatives of the steps) a flowchart indicates the direction of the process, the information / action flow. It is a very useful tool to systematize a process and give a clear overview aiding the identification of potential issues, hazards, defects, restrictions, etc. However much like the check sheet it requires a previous knowledge of the process in order to be fully dissected, which can again render it limited if applied to a complex external process, where not all data is available / known.

Process mapping is very similar in concept to a flowchart, however, this uses geometric shapes (standardized) to represent actions or stages. These actions / stages can include decision steps, start and end points of processes, documentation steps, etc. It has some advantages over the flowcharting because it can enable interactions, flow of material, people and services to be characterized and visualized.

Cause and Effect / Fishbone Diagrams

Fishbone diagrams, also known as cause and effect diagrams or Ishikawa diagrams, are used in this context to identify hazards / risks associated with an event.

It is a fairly simple method that requires almost no resources and very effective in identifying not only the associated risks but also possible knowledge gaps. It is also very helpful in terms of classification and aggregation of similar ideas into groups.

Although a truly systematic and useful tool it has some limitations, especially because it requires a process to be well defined active participants have to have an exhaustive knowledge of the process being dissected. It also generates a great amount of data, especially where processes are complex and long which can be counterproductive.

It's called fishbone diagram because its construction resembles the anatomy of a fish.

The first step is to make a box (fish's head) that contains the subject under examination (for example the Risk Question). To the left, the spine should start to appear with the bones coming off it. This represents the categories (for example Materials, Equipment, Procedures, Processes, Suppliers, etc). For every category it should emerge secondary bones that represent each identified risk (see figure 10).

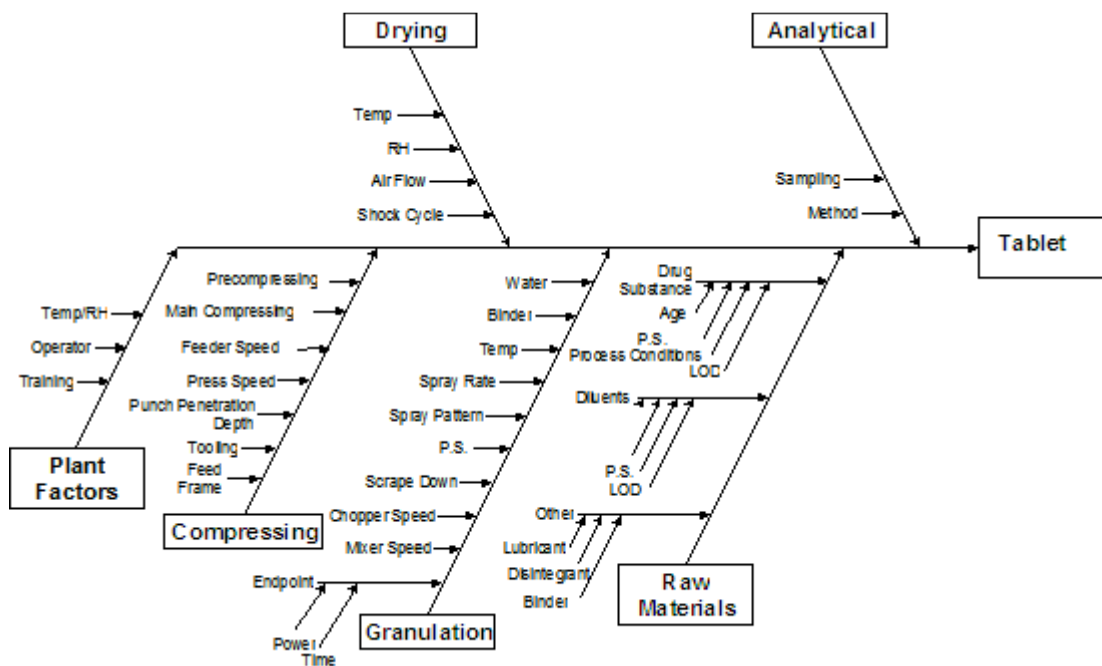


Figure 10 - Example of a Ishikawa Diagram [35]

This will act not only as a organized listing of the found hazards but also as a verification that all found risks are related specifically to the Risk Question. The number of secondary bones of a subcategory are also representative of the contribution to the overall risk of the category in question.

Hazard Operability Analysis (HAZOP) [1, 22-27]

HAZOP is a tool to be used under the assumption that events and hazards that generate risks are caused by deviations from the already established operations. The essence of the Hazop analysis approach is to review process drawings and/or procedures in a series of meetings, during which a multi-disciplinary team uses a prescribed protocol to methodically evaluate the significance of deviations from the normal design intention. This can be considered on its own as very similar to the Risk Management processes, including some of its previously described stages and making use also of some identification tools. Thus it can be used as an overall Risk Management tool for initial implementation.

It has the advantage of capturing and retaining knowledge of a company's product and/or process while providing assurance against error repetition. It is possible with this method to handle significant amounts of data and can be used even when hazards and their associated risks and consequences are difficult to compare using only a single tool.

It is a tool mainly used for processes and equipment thus if it is to be used for having in mind a different scope, it will require many modifications that can diminish its effectiveness.

It also has the disadvantage of not being capable of generating quantitative data rather relying on key words and it requires a combination with a hazard analysis tool and for that it will also gain its limitations.

Essentially, the HAZOP examination procedure systematically questions every part of a process or operation to discover qualitatively how deviations from normal operation can occur and whether further protective measures, altered operating procedures or design changes are required. The examination procedure uses a full description of the process and systematically questions every part of it to discover how deviations from the intention of the design can occur and determine whether these deviations can give rise to hazards. The questioning is sequentially focused around a number of guide words which are derived from method study techniques. The guide words ensure that the questions posed to test the integrity of each part of the design will explore every conceivable way in which operation could deviate from the design intention.

The main elements under consideration are:

- Intention
- Deviation
- Causes
- Consequences:
 - Hazards
 - Operating difficulties
- Safeguards
- Corrective actions

The logical sequence of steps in conducting a HAZOP are:

1. Collect all applicable documents and drawings;
2. Break the process into sections
3. Prepare a list of all the parameters and operations
4. Create a list of deviations for each section
5. List and record consequences for each deviation
6. List and record consequences for each cause
7. List and record safeguards or controls that may prevent either the cause or the consequence
8. List and future actions or recommendations that should be implemented

5.3.1.2 Risk Analysis Tools [1, 22-26]

This point will describe the most used tools useful for assessing the identified risks for their level of impact at the Risk Analysis stage of the Risk management process.

There are some very basic tools such as:

- control charts
- pareto charts
- risk ranking / filtering

There are some more complex tools such as:

- Fault Tree Analysis (FTA)
- Preliminary Hazard Analysis (PHA)
- Hazard Analysis and Critical Control Points (HACCP)
- Failure Modes Effect Analysis (FMEA)
- Failure Modes Effect and Criticality Analysis (FMECA)

All these tools require input of data, fortunately they provide solutions for input of hard quantitative data and also soft more subjective data. With this range of tool to be used, the selection of the most suitable one comes down to using what is the most adequate for the specific task and also the competency of the user.

The 3 basic elements of Risk Analysis are:

- Severity of event
- Frequency of occurrence
- Detectability of risk

It should be noted that not all tools account for the detectability of the risk. This is why these can be frequently combined, in order to cover more ground as possible.

For better organization of this part, the description will start for the previously stated simple tools and afterwards, the more complex tools.

Simple tools [22, 24, 26]

Control Charts

Control charts are simple charts used to determine if a process is in a state of statistical control or not.

The most used / known chart is the Shewhart Chart, that allows special cause variation to be differentiated from common cause variation and can aid prediction of the future state of the process.

This tool requires some degree of training but afterwards it is a quite simple method to master and use specially using modern statistical software able to work the input data and presenting a chart in a matter of seconds. It is also very useful for determining trends, patterns or states of control causing a high visual impact.

It is however a method based in statistics and therefore can only be applied to processes that comply with a normal statistical model or follow a normal distribution. It is able to reveal the potential cause of variation but it's not possible to identify its root cause needing an additional tool for Risk Assessment to be completed.

Pareto Charts

The Pareto principle states that for many events, approximately 80% of the effects com from 20% of the causes (reason why it is also known as the 80-20 rule).

The Pareto chart is usually represented as a graphic containing a bar chart and a line chart in one diagram (see picture 11)

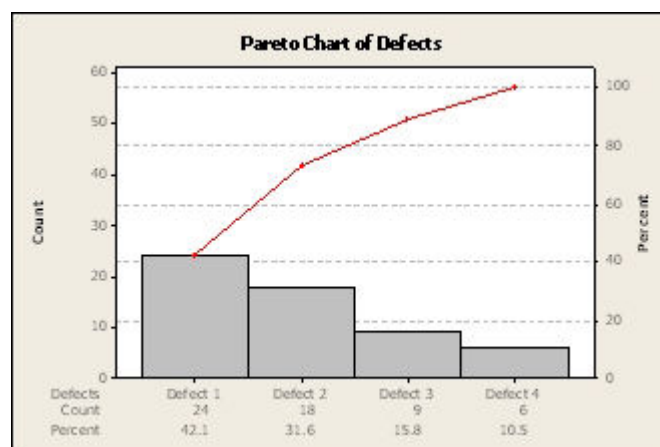


Figure 11 - Example of a Pareto Chart [36]

It is a reasonably simple method to use requiring very few resources especially because it does not require state of the art statistical software to create one. It is easy to understand causing a high visual impact aiding minimising effort for maximization of benefit.

It is nonetheless also a statistical method and therefore as also some disadvantages typical of these methods such as requiring additional tools of risk assessment and being limited to use where individual factors are significant or evenly frequent. It also does not reflect the consequence unless some sort of factoring or weighting is applied and duly validated.

As can be seen from the example chart, the left hand vertical axis represents a parameter of frequency for the subject being analysed. The vertical right hand axis represents the cumulative percentage of the occurrences of that parameter. The horizontal axis represents the categories of the parameter under analysis and represents each in a form of bar in decreasing order of values.

Risk Ranking and Filtering

This is a method used to compare risks and involves evaluation of multiple quantitative and qualitative factors for each identified risk leading to a two-dimensional (in the simplest forms) diagram of probability of occurrence against the severity of the consequences if it occurred. It is quite simple to used causing a high visual impact and allowing the easy ranking of risks against their outcomes leading to a view of the risk as High, Medium or Low. It has also the advantage of being based on principles of cause and effect allowing the use of soft data, which is something that a purely statistical tool cannot (as seen before).

It has however some disadvantages that cannot be overlooked, such as the detection of risk has to be built in (as it assumes that all risks are detectable events) and all consequences have to be fully recognized.

It works by assigning values to probability of occurrence and severity of the outcome. For example (see picture 12 for better understanding), a risk that is present but highly unlikely to occur has a low probability rendering it a score of C. The consequences of this risk should also be taken into account should it become a reality (i.e. the severity). If the consequences were severe in effect then this would be assigned a severity of high with a score of 1, which would translate in Medium Risk.

		Consequences		
		Minor 3	Moderate 2	Major 1
Likelihood	Probable A	Yellow	Red	Red
	Possible B	Green	Yellow	Red
	Improbable C	Green	Green	Yellow

Key	Green Low Risk	Yellow Medium Risk	Red High Risk
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Figure 12 - Example of Risk vs Consequence Matrix [37]

More complex models can be used for better ranking or discrimination. This matrix is used for every event and afterwards, it can be combined with a Pareto chart, p.e., for the next stage of decision making / risk evaluation.

Complex Tools [22, 24, 26]

Preliminary Hazard Analysis (PHA)

This tool analysis is based on applying prior experience or knowledge of hazard to identify future hazards, hazardous situation. This can be used for product, process and even facility design. This can be used in early development of a project where there is little information on detail is available.

Preliminary hazard analysis is a semi-quantitative analysis that is performed to identify all potential hazards and accidental events that may lead to an accident, Rank the identified accidental events according to their Severity and Identify required hazard controls and follow-up actions.

Although it is a very useful tool it can present some disadvantages such as requiring additional follow-up and not measuring levels of detection of an event.

Similarly to Risk Ranking tool, this tool works by assigning values to probability of occurrence when rated against its severity and if the consequences are negligible then the rating is that of a low risk.

These ratings can then be integrated into a second table, and hazards with their current or future risk controls identified (see figure 13 for example of PHA matrix).

System:		Operating mode:			Analyst:		
Ref.	Hazard	Accidental event (what, where, when)	Probable causes	Contingencies/ Preventive actions	Prob.	Sev.	Comments

Figure 13 - Example of PHA matrix[38]

Fault Tree Analysis

It is a deductive procedure used to determine the root causes of an assumed failure or problem that could cause undesired events (referred to as top events) at the system level.

The deductive analysis begins with a general conclusion, then attempts to determine the specific causes of the conclusion by constructing a logic diagram called a fault tree.

The main purpose of the fault tree analysis is to help identify potential causes of failures before the failures actually occur. It can also be used to evaluate the probability of the top event using analytical or statistical methods.

It can be conducted by taking the following steps:

- Define the undesired event to analyse
- Obtain an understanding of the system / process
- Construct the fault tree
- Analyse the fault tree – determine what hazards have a direct or indirect effect on the outcome of the system / process and which hazards / risks need most focus.

It has the advantage of being a tool that uses systematic logical gates (and/ or) to identify multiple events leading to an end result and identify common cause effects with resulting safeguards against the same mistakes.

It can be however a very time consuming tool depending on the complexity of the system being analysed requiring a significant level of expertise and the results depend also on the training of the analyst.

Hazard Analysis and Critical Control Points (HACCP) [1, 22-24, 26]

HACCP is a systematic preventive approach to food safety and pharmaceutical safety that addresses physical, chemical, and biological hazards as a means of prevention rather than finished product inspection.

HACCP is used in the food industry to identify potential food safety hazards, so that key actions, known as Critical Control Points (CCPs) can be taken to reduce or eliminate the risk of the hazards being realised. The system is used at all stages of food production and preparation processes including packaging, distribution, etc.

The HACCP is based on Seven Principles

- **Conduct a hazard analysis.**

The organisation determines the hazards and the preventive measures are identified and applied to control these hazards. A hazard is defined as the potential to harm the consumer or danger to the product. Hazard analysis identifies which hazards are such that elimination or reduction to acceptance levels is essential.

- **Identify critical control points.**

A CCP is a point, step, or procedure in process at which control can be applied and, as a result, a hazard can be prevented, eliminated, or reduced to an acceptable level.

- **Establish critical limits for each critical control point.**

A critical limit is the maximum or minimum value to which a hazard must be controlled at a critical control point to prevent, eliminate, or reduce to an acceptable level.

- **Establish critical control point monitoring requirements.**

Monitoring activities are necessary to ensure that the process is under control at each critical control point. Each monitoring procedure and its frequency may be listed in the HACCP plan.

- **Establish corrective actions.**

These are actions to be taken when monitoring indicates a deviation from an established critical limit. The final rule requires an organisation's HACCP plan to identify the corrective actions to be taken if a critical limit is not met..

- **Establish record keeping procedures.**

The HACCP regulation requires that all organisations maintain certain documents, including its hazard analysis and written HACCP plan, and records documenting the monitoring of critical control points, critical limits, verification activities, and the handling of processing deviations.

- **Establish procedures for ensuring the HACCP system is working as intended.**

Validation ensures that the organisations do what they were designed to do; that is, they are successful in ensuring the production of safe product. Organisations will be required to validate their own HACCP plans.

Failure Mode and Effects Analysis (FMEA)[1, 22, 24-26]

The goal of FMEA is to align the risks as closely as possible with its source. This enables the determination of the root cause of the risk, and allows the selection of ways to detect the occurrence of a particular failure and/ or to find options to prevent or Mitigate the effects of a particular failure.

Good FMEA methodology allows for the identification and documentation of potential failures of a system and their resulting effects. It also allows for the assessment of the potential failure to determine actions that would reduce severity, reduce occurrence, and increase detection.

During FMEA, all steps are analyzed for potential failure opportunities. The ultimate effect to product quality or patient safety and/or efficacy as a result of each potential failure opportunity is then quantified and then adjusted based on capabilities to detect or mitigate, to reach a final assigned score of risk.

The risk for each failure is often times entered into a risk score matrix which enables easy determination of the priority and/or level of attention required to be applied to each step based on its total risk priority number (RPN). The outcome of the FMEA is a list of recommendations to reduce overall risk to an acceptable level, and can be used as a source for designing a control strategy (see picture 14 for example).

Potential Failure Modes and Effects Analysis															
System _____					FMEA Revision _____										
Subsystem _____					FMEA Prepared By _____										
Part Number _____					FMEA Date _____										
Designer _____					FMEA Revision Date _____										
Item/ Function	Potential Failure Modes	Failure Mode Effects	S E V	Potential Failure Causes	P F	Current Controls	D E T	R P N	Actions Req'd	Owner/ Target Date	Actions Taken	S E V 2	P F 2	D E T 2	R P N 2

Figure 14 - Typical FMEA table [39]

Failure Mode, Effects and Criticality Analysis (FMECA) [1, 22, 24-26]

FMECA complements FMEA by incorporating the degree of criticality to the severity of the consequences and the respective probability / detectability of each consequence.

5.3.1.3 Risk Evaluation Tools [24]

The tools used for Risk Evaluation enable data to provide for a positive or negative decision. These tools will generate a level of risk which require evaluation for the risk acceptance decision and establish the criteria why a risk is deemed acceptable or not. They may also establish the residual risk level.

There are fewer tools available for Risk Evaluation than for the other steps of the risk assessment and for this step they focus primarily on justifying the level below which little or no actions are appropriate. However it is always advisable, if resources allow, to take (or try to) simple, often low cost steps to reduce identified residual risks until they become negligible.

These tools can be:

- Carrot diagrams
- ALARA & ALARP

Carrot Diagrams

Carrot Diagrams, has the name clearly states, are a form of diagrams where the risks are dispose from higher to lower, according to regions defined by their tolerability, on a diagram.

The higher risks are the ones that need immediate reduction and the lower risks, displayed at the bottom are considered by default acceptable. The risks displayed in the middle of the diagram, i.e. the tolerable region will be the scrutinized and decisions made in order to either take action and reduce them or lower them to acceptable, with no further action necessary.

For better understanding, please refer to figure 15 (below).

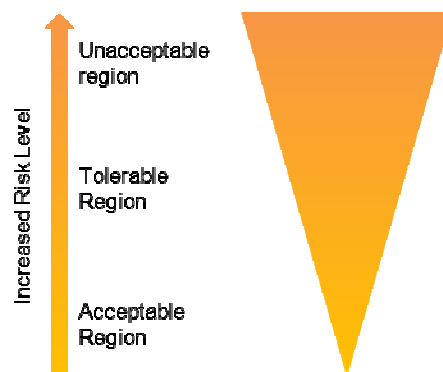


Figure 15 - Example of Carrot Diagram

ALARA and ALARP[24]

The ALARA (As Low As Reasonably Achievable) principle (also known as ALARP – As Low As Reasonably Practical) is that the residual risk shall be as low as reasonably practicable. It has particular connotations as a route to reduce risks SFAIRP (so far as is reasonably practicable).

For a risk to be ALARP it must be possible to demonstrate that the cost involved in reducing the risk further would be grossly disproportionate to the benefit gained. The ALARP principle arises from the

fact that infinite time, effort and money could be spent on the attempt of reducing a risk to zero. It should not be understood as simply a quantitative measure of benefit against detriment. It is more a best common practice of judgement of the balance of risk and societal benefit.

In determining that a risk has been reduced to ALARP, an assessment of the risk to be avoided should be carried out and compared with the actions involved in taking measures to avoid that risk totally.

Risk Threshold examples:

- High – risk should be reduced if possible or avoided;
- Intermediate – reduce risk to ALARP;
- Low – reduce risk according to ALARP principles considering cost versus benefit criteria or determine if it is an acceptable risk;

- Trivial – generally acceptable level of risk with no action required.

5.3.2 Risk Control Tools

As previously stated, the Risk Control phase comprises the Risk Reduction and the Risk Acceptance phase. It is worth noting that although a risk can be low enough to be accepted without undergoing any risk reduction action, it is a good practice that an Organization tries maximize risk benefit by reducing the risk to a minimum.

5.3.2.1 Risk Reduction Tools[22, 24, 26]

This point will describe the tools that can be used with effectiveness when assessing what action shall be taken in order to reduce the probability of occurrence or severity of a risk.

At this point, the risks are duly identified and thus it makes sense to use tools that can have into account the past, in a sense of retrospective investigation.

Some of the tools include:

- Root cause analysis (RCA)
- Corrective Action, Preventive Action (CAPA)
- The 4 T's
- Risk Avoidance strategy

Root Cause Analysis (RCA)

Root cause analysis is a problem solving process for conducting an investigation into an identified incident, problem, concern or non-conformity.

Root cause analysis is a completely separate process to incident management and immediate corrective action, although they are often completed in close proximity.

Root cause analysis requires the investigator(s) to look beyond the solution to the immediate problem and understand the fundamental or underlying cause(s) of the situation and put them right, thereby

preventing re-occurrence of the same issue. This may involve the identification and management of processes, procedures, activities, inactivity, behaviours or conditions.

Basic steps to application of root cause analysis irrespective of the tool used are as follows:

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

Corrective Action, Preventive Action

Corrective action and preventive action are improvements to an organization's processes taken to eliminate causes of non-conformities or other undesirable situations. It focuses on the systematic investigation of the root causes of non-conformities in an attempt to prevent their recurrence (for corrective action) or to prevent occurrence (for preventive action).

Corrective actions are implemented in response to customer complaints, undesired levels of internal nonconformity, nonconformities identified during an internal audit or adverse or unstable trends in product and process monitoring such as would be identified by SPC. Preventive actions are implemented in response to the identification of potential sources of non-conformity.

To ensure that corrective and preventive actions are effective, the systematic investigation of the root causes of failure is pivotal. CAPA is part of the overall quality management system (QMS).

In terms of Risk Reduction CAPA is a process that compliments other techniques such as Root Cause Analysis. In order to utilise CAPA for Risk Reduction these basic steps should be followed:

1. define the risk to be reduced = output of Risk Evaluation or the RCA
2. define the appropriate action i.e. correction, corrective action, preventative action
3. document the CAPA to be taken including, the responsible person(s) and the timeline for completion
4. implement the CAPA
5. document and observe the effect of the CAPA implemented
6. review and repeat as required

It is the goal of an organization that once CAPA process is implemented, the actions to develop are increasingly of preventive nature rather than corrective.

The 4 T's

The 4 T's stand for:

- **Treat** a risk to prevent it occurring or reduce its potential impact.
 - have processes in place that improve the control effectiveness;
 - the amount of effort to control risk should be proportional to the significance of the risk.

- **Transfer** the risk to someone else
 - risk financing, insurance, contracting out, etc;
 - some of the impact of the risk is transferred, not the responsibility that the business has for managing the risk.
- **Terminate** the risk – i.e. stop doing whatever it is that is exposing the business to the risk.
- **Tolerate** the risk after deciding that the risk has been reduced to an acceptable level.

Risk Avoidance Strategy

A risk management technique that seeks to eliminate any possibility of risk through hazard prevention, or the discontinuation of activities determined to entail any level of risk. Often used in extreme situations where the risk exposure creates an extraordinary liability potential.

Every risk avoided in this way is a loss in potential gain in terms of business, profit, end-user benefit and / or customer satisfaction. Risk avoidance is a practical and sometimes only viable approach to risk reduction. However it should be applied cautiously to ensure the benefit outweighs any alternatives.

5.3.2.2 Risk Acceptance Tools[24]

Risk acceptance decisions are performed by the responsible and accountable persons that should be defined at the start of the Risk Management process.

There are no specific risk acceptance tools to help the decision makers with a way to provide an accurate decision. The risk evaluation is always connected to risk acceptance, therefore it should be noted that “no go” is always an safe answer should there be any doubts at this point, causing a return to perform or improve risk reduction.

5.3.3 Risk Communication Tools

The method of communication depends upon what is being exchanged and the importance of the information regardless whether it is related to risk or other management activities.

The communication can be made through:

- **Contracts:**
 - The most formal method is a business contract however this is normally the method of communicating legal and basic business expectations.
- **Letter / Memo:**
 - A formal communication normally reserved for agreeing or approving actions and expectations. It may contain formal certificates, specifications, processes and other technical information.
- **E-mail:**

- These may contain electronic copies of draft documents and scanned agreements, technical information, certificates, etc, that may be used for agreeing, requesting or discussing information.
- **Telephone:**
 - Informal communication useful for discussing ideas, arrangements, informal agreement, etc.
- **Fax:**
 - Normally considered as formal as a letter but its use is being replaced by the use of e-mail.
- **Internet:**
 - This is a way of advertising and a source of information however care should taken to verify information freely available in this way.
- **Face to face meetings:**
 - To exchange ideas, presentations, carry out audits and come up with assignments, actions and agreements. Agreements and actions should formally recorded in minutes or a letter.
- **Presentations:**
 - Including graphs, mapping and plans that may be shared to show general proposals and action points but these reflect the author(s) ideas and situation progress. This is a common and visually effective way of quickly getting essential points across to explain a situation or proposal for a wider, possibly less knowledgeable, audience or to get outline management approval. These do not normally include detailed plans.
- **Reports:**
 - Reports are formal records which have been authorised and can be circulated both internally and externally. These can summarise the Risk Management activities performed and highlight decisions taken (mitigation, acceptance and actions to acknowledge or respond to risks can be included). [24]

5.3.4 Risk Review Tools

These tools are used to measure the success of the Risk Management process. Naturally tools able to provide a measure as an outcome are preferably used. [24]

There are two tools widely used for Risk Review:

- Key Performance Indicators
- Benchmarking

Key Performance Indicators (KPI)

Key performance indicators are quantifiable measurements, agreed to beforehand, that reflect the critical success factors of an organization. They will differ depending on the organization.

Whatever Key Performance Indicators are selected, they must reflect the organization's goals, they must be key to its success, and they must be quantifiable (measurable). KPI's usually are long-term considerations. The definition of what they are and how they are measured do not change often. The goals for a particular KPI may change as the organization's goals change, or as it gets closer to achieving a goal.

Benchmarking

Process of comparing one's business processes and performance metrics to industry bests or best practices from other industries. Dimensions typically measured are quality, time and cost. In the process of best practice benchmarking, management identifies the best firms in their industry, or in another industry where similar processes exist, and compares the results and processes of those studied (the "targets") to one's own results and processes. In this way, they learn how well the targets perform and, more importantly, the business processes that explain why these firms are successful.

Benchmarking is used to measure performance using a specific resulting in a metric of performance that is then compared to others.

Benchmarking usually involves:

- regular comparison of functions / processes with best practice examples
- the identification of gaps in performance
- exploring new ways of improving how things are done
- introducing and using the improved processes
- monitoring and reviewing of processes, measuring progress and beneficial outcomes

6. OM PHARMA, SA, Overview and Work Context

6.1 Introduction

OM Pharma is a pharmaceutical company integrated within the Galenica Group. It is an internationally active company that researches, develops, manufactures and commercializes pharmaceutical products all over the world.

The company's vision is to strive for excellence in our fields of expertise to make a true difference in patients' lives.

Its values are[28]:

- **Communication:**
 - Communicate openly and honestly, appreciate diversity of thought and action.
- **Teamwork:**
 - Trust, share and challenge each other, be accountable and enjoy working together.
- **Leadership:**
 - Demonstrate expertise and enthusiasm, delegate and empower, offer challenges and rewards and make sound professional decisions.
- **Innovation:**
 - Encourage innovation, assess potential and deliver creative solutions.
- **Ethics:**
 - Beyond compliance, practice a culture of integrity and high quality, respect the needs of all stakeholders.
- **Results:**
 - Drive to achieve results, action and positive achievement of agreed goals with a sense of urgency and simplicity, and use our resources in a sustainable way.

OM Pharma has two sites, one in Geneva (Head Quarters) and one in Lisbon.

The Lisbon site is located in Amadora making it strategically located near all major routes to efficiently and timely have access to both receive and deliver products. This site comprises of the manufacturing facilities (including warehouse) and the administration/ office facilities where all the other business related departments are located, such as:

- Management
- Industrial (Comprised by Production, Logistics, Engineering & Maintenance and Warehouse)
- Quality (Assurance and Control)
- Regulatory Affairs

- Legal and Human Resources
- Medical Affairs
- Financial
- Safety and Environment
- Marketing and Sales (Comprising Marketing, Sales and Customer Support)
- IT

Comprising a total of around 80 employees working permanently at this site.

OM Pharma has at its disposal both the equipment, knowledge and support to manufacture, store and deliver solid, liquid and semi-solid pharmaceutical forms in compliance with all current GMP's, GLP's and GDP's.

Part of the production performed at OM Pharma in Portugal are products of its own brand being the most known Aero-OM® line and Broncho Vaxom® line. The great majority of the production done at this site is to satisfy its major client, the Galenica Group itself, of which OM Pharma is a part of (as previously stated).

The development of this work was motivated by the new Regulations of the EU materialized by the DIRECTIVE 2011/62/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 8 June 2011 within the scope of the Industrial Department more precisely the Service of Logistics and Supply Chain.

The Logistics and Supply Chain Service, has under its responsibility the work related to Production Planning, Logistics, Purchases and Procurement, thus making it the service with the first hand involvement/ impact in the work herein described.

6.2 OM Pharma (PT) Supply Chains Overview

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 it is possible to group them into the following categories:

- **Export:**
 - Direct delivery
- **National Market:**
 - Direct delivery
 - Indirect delivery

In regards to the **Direct Exports** supply chain, it can be described as follows (refer to figure 16):

Raw materials are sent by the supplier (broker or manufacturer) through 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).

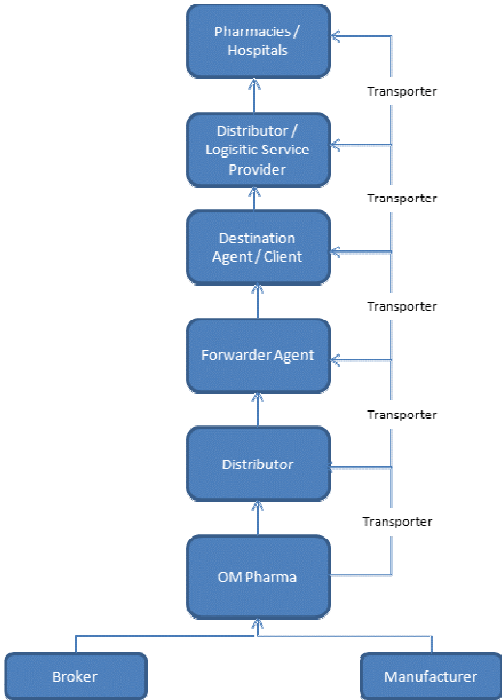


Figure 16 - Direct Export Supply Chain

Regarding the **Direct Delivery** to the National market the supply chain is as follows (please refer to figure 17):

Raw materials are sent by the suppliers (Broker or manufacturer) through 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).

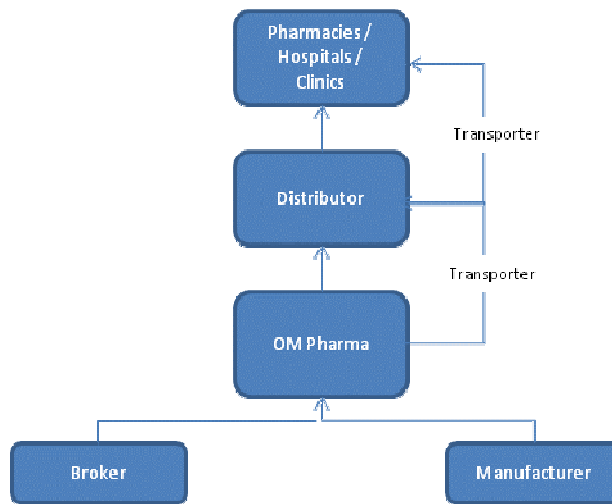


Figure 17 National Market Direct Delivery Supply Chain

As for the **Indirect Delivery** to the National market the supply chain is as follows (please refer to figure 18):

Raw materials are sent by the suppliers (Broker or manufacturer) through 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 then sells the product directly to the end client (Pharmacies / Hospitals / Clinics).

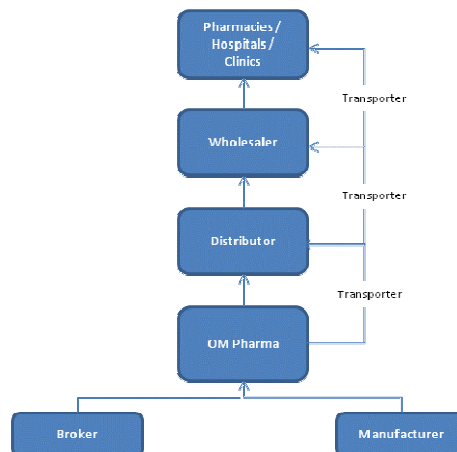


Figure 18 - National Market Indirect Delivery Supply Chain

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 through 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.

6.3 Risk Management Implementation

At this point, the initial exercise of characterization of the supply chains is performed. All key players are identified as well as their activities.

6.3.1 Risk Assessment

According to what is proposed by ICH Q9, the next logical step is the Risk Assessment, which will be made to all 3 identified supply chains.

Note that the first step of Risk Assessment is Risk Identification. In order not to go out of scope of the title of this work, the main risk being considered is in regards to the potential counterfeiting of any of OM Pharma's products and how choosing and applying an anti-counterfeiting device can or cannot be an asset to enhancing the supply chains robustness.

6.3.2 Risk Identification

Therefore, the risk identification will be made in terms of what are the risks of a product being counterfeited in one of the supply chains.

For this step, the tools used were essentially the flowcharts of the supply chains and brainstorming.

Direct Export supply chain identified hazards:

- Cartoons and literature suppliers do not destroy properly the remaining (lightly damaged 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 damaged 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 damaged 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)

6.3.3 Risk Analysis

Now that some of the hazards are identified, the proceeding stage is risk analysis. This will be done using a Risk Ranking tool such as a matrix of probability of risk versus severity of risk.

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

Direct Export 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. After which, an arithmetic sum was made to establish the overall risk value of counterfeiting happening within a certain supply chain.

The matrix used is the following (figure 19):

Increasing probability of an error or failure ↑	High	3	6	9
	Medium	2	4	6
	Low	1	2	3
		Low	Medium	High
	Increasing severity of consequences as a result of an error or failure →			

Figure 19 - Risk Analysis matrix [24]

The results are as follows:

Direct Export supply chain (please refer to figure 20):

- Cartoons and literature suppliers do not destroy properly the remaining (lightly damage and / or reusable product) of a production –**3 (green circle)**
- If an anti-counterfeiting device (covert) is already in place, the information is leaked and becomes of general knowledge:
 - At supplier - **4 (red circle)**
 - At OM Pharma –**2 (orange circle)**
- Complex supply chain with multiple agents involved including different transporters and distributors –**9 (Blue circle)**

- Product is being delivered to countries with different rules and health authority systems – 9 (blue circle)

Increasing probability of an error or failure ↑	High	3	6	9
	Medium	2	4	6
	Low	1	2	3
		Low	Medium	High
Increasing severity of consequences as a result of an error or failure →				

Figure 20 - Result Direct Export Supply Chain

Total Score: 27

National Market Direct Delivery supply chain (please refer to figure 21):

- Cartoons and literature suppliers do not destroy properly the remaining (lightly damage and / or reusable product) of a production - 3
- If an anti-counterfeiting device (covert) is already in place, the information is leaked and becomes of general knowledge:
 - At supplier - 4
 - At OM Pharma) – 2

Increasing probability of an error or failure ↑	High	3	6	9
	Medium	2	4	6
	Low	1	2	3
		Low	Medium	High
Increasing severity of consequences as a result of an error or failure →				

Figure 21 - Results National Market Direct Delivery supply chain

Total Score: 9

National Market Indirect Delivery supply chain (please refer to figure 22):

- Cartoons and literature suppliers do not destroy properly the remaining (lightly damage and / or reusable product) of a production –3 (green circle)
- If an anti-counterfeiting device (covert) is already in place, the information is leaked and becomes of general knowledge:

- At supplier - **4 (red circle)**
- At OM Pharma) – **2 (orange circle)**
- Slightly complex supply chain (more transporters / handling) –**3 (black circle)**

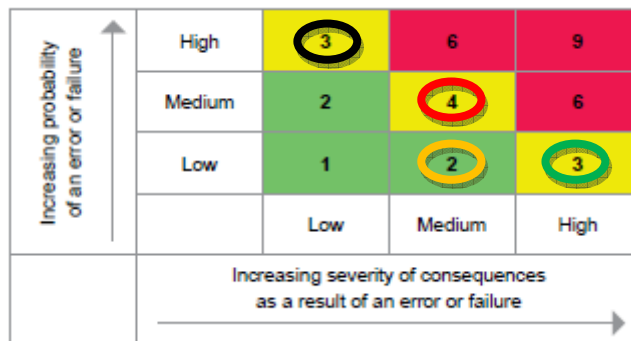


Figure 22 - Results National Market Indirect Delivery supply chain

Total Score: 12

This means that the overall risk of counterfeiting in each supply chain is:

- Direct Export supply chain – **27**
- National Market Direct Delivery supply chain – **9**
- National Market Indirect Delivery supply chain – **12**

As a preliminary discussion, we can verify that there is a clear difference in the overall risk between the export supply chains and the national supply chains. This is mainly due to the fact that the export supply chains are considerably more complex than the national supply chains and the more parties involved, the less control the company has over the security of the supply chain and consequently over the integrity of the product. This is not taking into consideration (for simplicity sake) other factors such as the nature of the product and the desirability to counterfeit, etc.

6.3.4 Risk Evaluation

For this stage, the carrot diagram was used.

The results were as follow (please refer to figure 23):

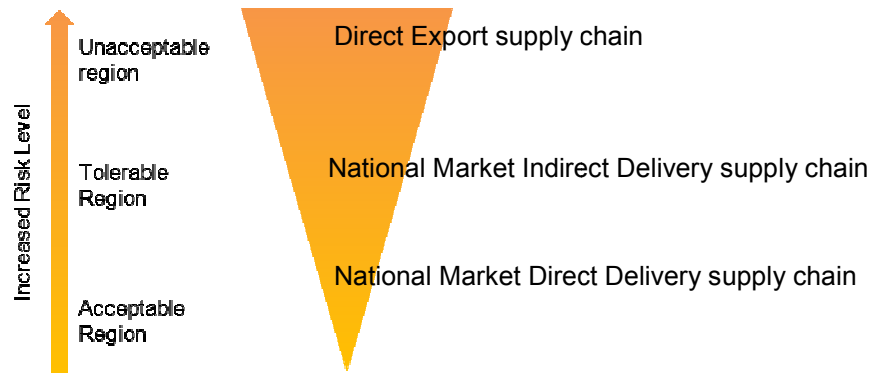


Figure 23 - Results of Carrot Diagram

The supply chains concerning the export 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.

6.3.5 Risk Control

6.3.5.1 Risk Reduction

At this stage, the Root Cause Analysis 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.

Results were as follows:

Direct Export supply chain

1. Define the risk to be reduced:
 - Overall counterfeiting risk on this supply chain.
2. Define potential root causes for this risk to occur:
 - Potential human error or lack of agreement with suppliers for proper destination of the remaining of production of secondary packaging material

- Lack of explicit SOP defining who should know about the implementation of anti-counterfeiting devices
 - To many players involved in the supply chain
 - Lack of proper anti-counterfeiting device that can overcome the problem of dealing with the introduction of products in different countries with different health authorities.
3. Define which root causes if removed will prevent or reduce the risk
 - Potential human error or lack of agreement with suppliers for proper destination of the remaining of production of secondary packaging material
 - Lack of explicit SOP defining who should know about the implementation of anti-counterfeiting devices
 - To many players involved in the supply chain
 - Lack of proper anti-counterfeiting device that can overcome the problem of dealing with the introduction of products in different countries with different health authorities.
 4. implement risk reduction measures = address the root causes
 - Establish an agreement with suppliers regarding the handling / disposal of material
 - Prepare and implement a SOP regarding the implementation of Anti-counterfeiting devices.
 - Try to exclude some non-essential parties from the supply chain or establish an agreement across the supply chain regarding the use of different transporters, or establish requisites for the use of transportation services (such as security details, routes to cover, number and place of product grouping, etc).
 - Select and choose a proper anti-counterfeiting device.
 5. document & observe the effect of implementing the Risk Reduction measures
 6. review and repeat as required

National Market Indirect Delivery supply chain

The same as for the Direct Delivery supply chain.

Although this was the result of a simple but realistic exercise, with only a few of many identifiable risks of 3 supply chains, it's evident there are some risks that can be easily mitigated, such as the development and implementation of SOPs and the establishment of agreements with supplier and service providers, other due to the nature of the business are not easily removable or even mitigated.

We can include in this the number of players involved, especially when it comes to exports.

6.3.5.2 Selection of Anti-counterfeiting System

One way of addressing this issue, and what motivated the preparation of this work, is by assessing the need to select and implement an anti-counterfeiting system that provides easy way of proving tampering with the product is so unique that acts as a dissuading agent for the counterfeiters or even being so well covert that it works as a forensic measure.

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 24) 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.

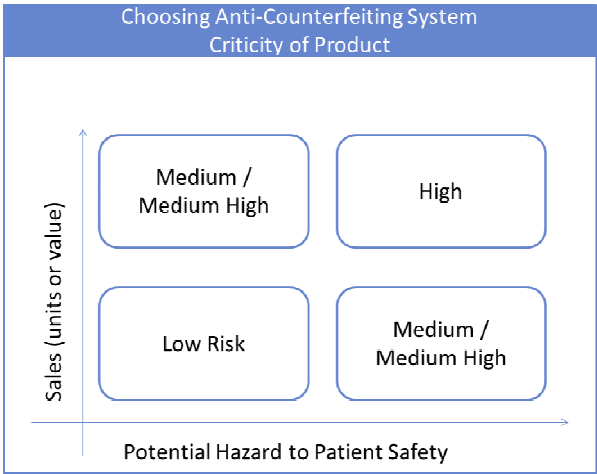


Figure 24 - Criticality level Matrix

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 25).

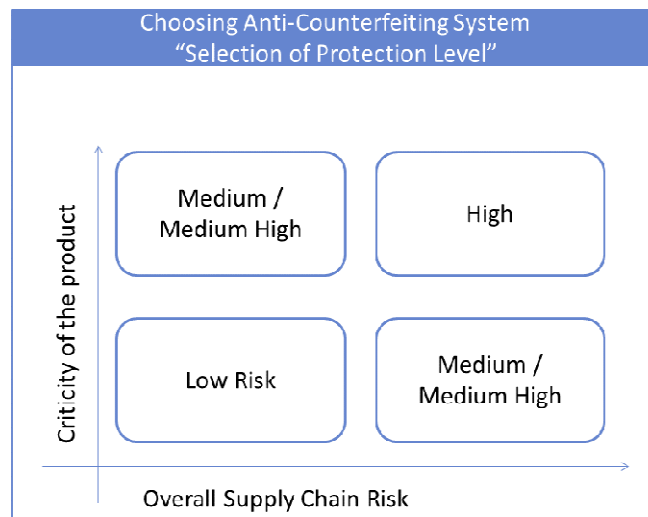


Figure 25 - Selection of Protection Level Matrix

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

There is no specific tool or method to ease 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.

Before exemplifying the choice of an anti-counterfeiting system it will be addressed the reality of what choices the pharmaceutical organizations in Portugal have at their disposal.

As described previously, on the technology review, although there are many technologies that can be used for anti-counterfeiting system in a pharmaceutical product the average pharmaceutical organization, i.e., without in-house development, is forced to consume what the suppliers have to offer.

Most of the systems are used on the secondary or tertiary packaging and are provided by the Cartoons and leaflets supplier, suppliers of PVC and PVC/ PVDC and other films, some plastic manufacturing companies, some more specialized tertiary packaging companies.

The great majority of these anti-counterfeiting systems are:

- Holograms (generic or personalized)
- Special UV / IR reactive inks
- Special color shifting pigments
- Micro-impession

- Special cutters
- RFID
- All sorts of tamper evident
- Codification / Serialization by some sort of code (bar code, data matrix, random algorithms, etc).

What this means is that because almost every organization has access to the most common / most widely spread anti-counterfeiting systems / technologies, either a combination of this systems has to be performed, or procedures and /or agreements must be prepared and signed, in order to protect the confidential nature of the an implemented anti-counterfeiting system.

As an example we will consider a product that has an overall annual sale of 455000 units divided by these four supply chains, as follows:

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

For direct export the criticality results are Medium High – coloured with green circle (please refer to figure 26). It has a high value of annual sales but the product has a low risk of causing potential harm to a patient.

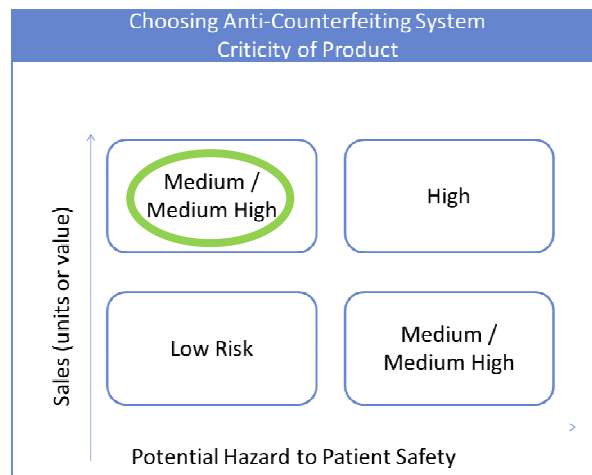


Figure 26 - Criticality of Product Direct Export

This output will now be taken into account for the selection of protection level as follows (please refer to figure 27):

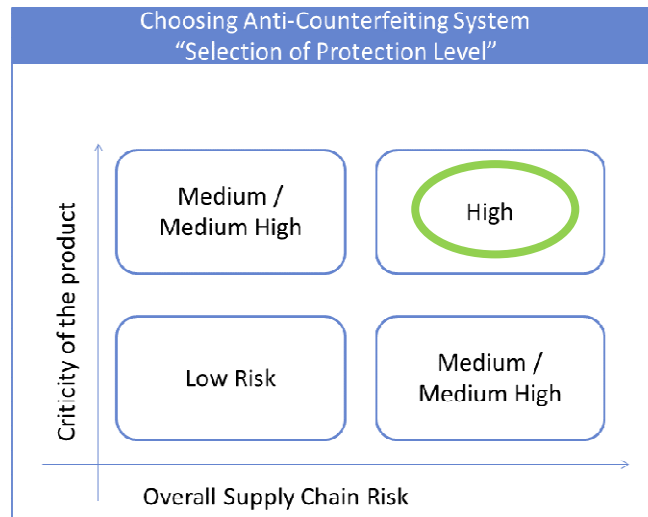


Figure 27 - Selection of Protection Level Direct Export

Since the criticality result was medium high and the overall supply chain risk was high, the selection of protection level is **high**.

For **National Market Indirect delivery** the criticality results are Medium High – coloured with green circle (please refer to figure 28). It has a High value of annual sales but the product has a low risk of causing potential harm to a patient.

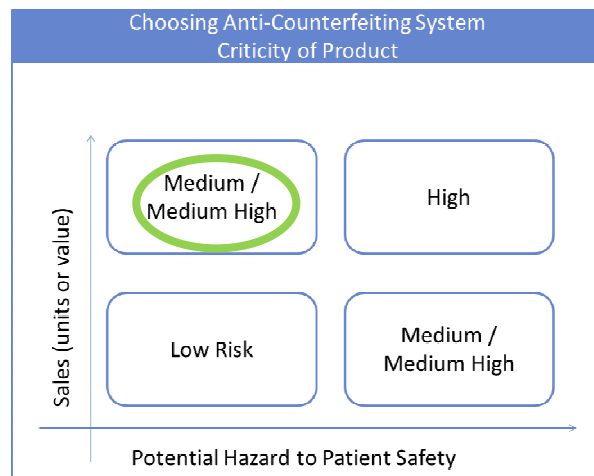


Figure 28 - Criticality of Product National Market Indirect Delivery

This output will now be taken into account for the selection of protection level as follows (please refer to figure 29):

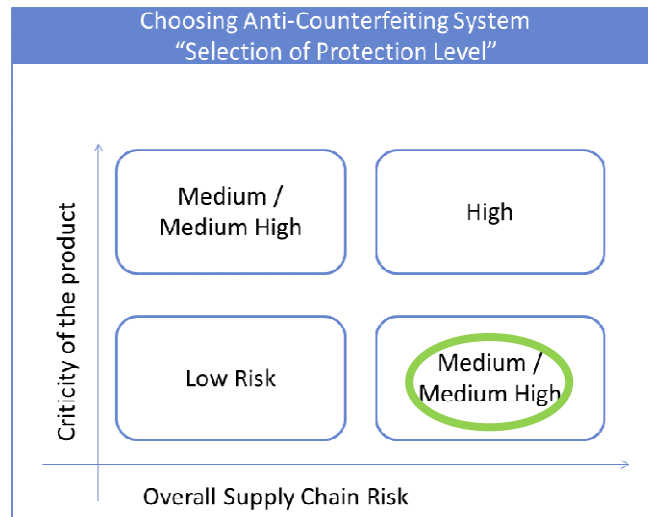


Figure 29–Selection of Protection level National Market Indirect Delivery

Since the criticality result was medium high but the overall supply chain risk was medium, the selection of protection level is **Medium (green circle)**.

For **National Market Direct Delivery** the criticality results are **Low** – coloured with green circle (please refer to figure 30). It has a low value of annual sales and the product has a low risk of causing potential harm to a patient.

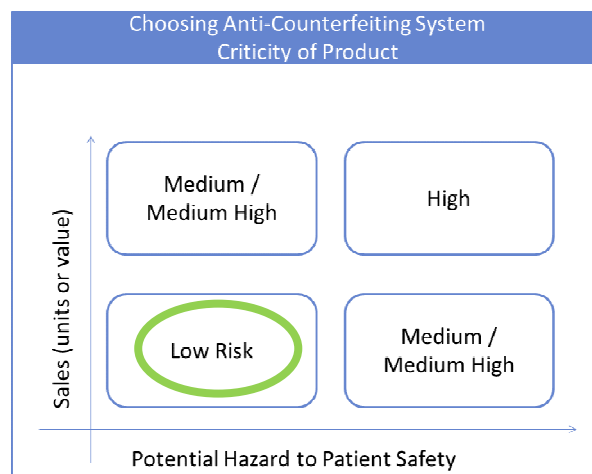


Figure 30– Criticality of Product National Market Indirect Delivery

This output will now be taken into account for the selection of protection level as follows (please refer to figure 31):

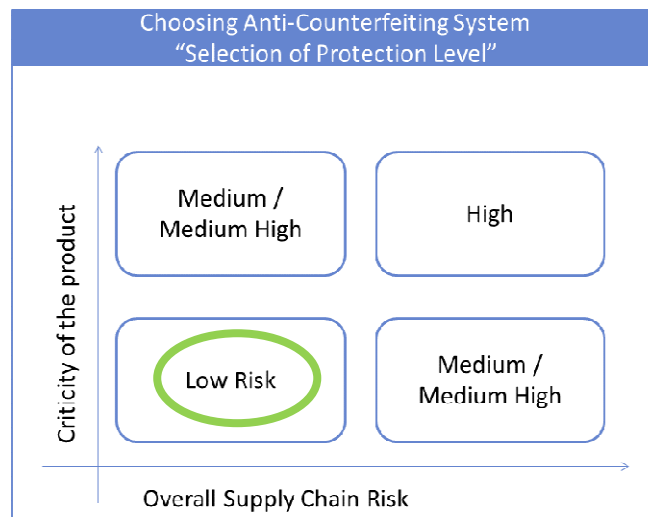


Figure 31 - Selection of Protection Level National Market Indirect Delivery

Since the criticality result was low but the overall supply chain risk was low, the selection of protection level is **Low (green circle)**.

Below, the sum up of the results of the level of protection that the anti-counterfeiting system should have:

- Direct Export: **High**
- National Market Indirect Delivery: **Medium**
- National Market Direct Delivery: **Low**

At this point the final step is for the decision makers to verify the suggested level of protection that must be conferred to the pharmaceutical form and decide whether the costs involved in implementing a certain anti-counterfeiting system outweigh the benefits provided by its protection.

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 Export:
 - Tamper evident secondary packaging with serialization to provide total traceability to the product combined with a personalized hologram and a micro-impresion.
 - Alternatively a combination of virtually costless anti-counterfeiting systems such as serialization, micro-impresion, tamper evident and special unique cutters.
- National Market Indirect Delivery:
 - Tamper evident secondary packaging with unique cutters, micro-impresion and serialization.

- National Market Direct Delivery:
 - Tamper evident secondary packaging, micro-impression and serialization.

The 5th step using RCA would be documenting all the process and observe the effects of the implementation of the measures.

After this is done, the team should review the impact of the measures applied to the reduction of risk.

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 export) and acceptable levels (National Market Indirect delivery).

The last step of risk control is the Risk acceptance.

6.3.6 Risk Acceptance

On this step 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.

6.3.7 Risk Communication

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.

6.3.8 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 reviewed.

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

7. Future Developments

Within the scope of the new Directive it is expected that all medicines subject to prescription should bear at least serialization and tamper evident systems (as a traceability and anti-counterfeiting features, respectively).

This will naturally be implemented in all of OM Pharma products that are subject to prescription in order to comply with the aspects determined by the Law.

After the completion of this thesis, it is recommended that this model is taken into consideration by the decision makers and that the implementation of additional features is reviewed using this risk management approach.

On this note, it is recommended by the author that for the products of the 3 supply chains herein considered, a standard pack of anti-counterfeiting devices is applied as follows:

Export Supply Chain:

- Products with higher price / or narrow therapeutic margin:
 - Serialization
 - Tamper evident
 - Invisible UV / IR reacting inks
 - Holograms
 - Unique cutters

- Products with lower price / or broader therapeutic margin:
 - Serialization
 - Tamper evident
 - Unique cutters
 - Invisible UV / IR reacting inks

National Market Indirect Delivery:

- Products with higher price / or narrow therapeutic margin:
 - Serialization
 - Tamper evident
 - Invisible UV / IR reacting inks
 - Unique cutters

- Products with lower price / or broader therapeutic margin:
 - Serialization
 - Tamper evident

- Unique cutters

National Market Direct Delivery:

- Products with higher price / or narrow therapeutic margin:
 - Serialization
 - Tamper evident
 - Unique cutters
- Products with lower price / or broader therapeutic margin:
 - Serialization
 - Tamper evident

Although for the National Market Direct Delivery supply chain (because it has the lowest risk of the 3 supply chains), only the systems mandatory by law are to be applied at first, the products / supply chain should not be excluded from this model, meaning that a future review could indicate the need to apply further anti-counterfeiting devices. Nevertheless, being the supply chain with the lowest risk, it is recommended that systems virtually costless should be applied first and only afterwards (if deemed necessary) more devices should be applied.

In regards to the implementation of anti-counterfeiting devices that involve higher costs (Holograms, especial inks, unique cutters), only the decision makers have the power to decide on how much the company is willing to lower its profit margin. Nevertheless it is reasonable that, for start, no more than 1-2% of the total cost of the product should be spent on such devices, and if necessary, gradually increase this margin.

A procedure should be developed and implemented clearly defining a rotatory use / change of the anti-counterfeiting systems chosen. This will act as a further enhancer of the security of the product and supply chain.

8. Conclusions

The new DIRECTIVE 2011/62/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 8 June 2011 enters 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 implicate 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 Export, 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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