



Microstructure secured and self-verifying medicines SAVEmed

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1 Executive summary

Counterfeit medicines are a serious and fast expanding threat for the customer's health and the pharmaceutical manufacturers business. The aim of this research collaboration was to add anti-counterfeiting and track & trace technology to the product level that goes beyond the state-of-the-art security approach on the packaging level.

The project SAVEmed brought a solution for the counterfeit and the illegal re-import problem in the medical product market, thereby ensuring product pedigree and defending illegal re-packing.

In the SAVEmed project the direct marking of medical products with secure microstructures was realised by modifying the tools used to manufacture the products as well as the ones used for their packaging on the micron- and sub-micron level. The project aim was to transfer diffractive gratings, random microstructures, micro-barcodes and contrast generating micro-prisms into steel tooling. Moreover, algorithms enabling cross checking of the secure microstructures on the product (even through coatings) and on the package were developed to ensure the highest level of security possible. In SAVEmed this direct product marking approach was realized for pharmaceutical tablets, injection moulded pharma caps and laminated sterile pouches.

Nevertheless the approach is applicable to nearly all other types of medical products.

The strategies of criminal organisations were analysed and the technological development was adapted to counteract these strategies. Key advantage of the implementation of secure microstructures directly in or on the medical products themselves is that no chemical or biological additives and that no costly changes of production lines are needed. Thus no additional approvals from regulatory agencies are typically requested by using this approach.

This project ensured a correct balance of market-pull and technological push by including major actors in anti-counterfeit technology research, 3 SMEs, 2 large industries and pre-assembled end-users External Advisory Board.

2 Summary description of project context and objectives

2.1 Project context

Counterfeit medicinal products are a threat to the health and safety of patients around the world. They range from drugs with no active ingredients to those with dangerous impurities.

They can be copies of branded drugs, generic drugs or over-the-counter drugs as well as faked implants or diagnostic devices.

In SAVEmed self-verification security systems highly relevant for a secure track-and-trace system throughout the whole supply chain of a variety of medical products (e.g. solid dosage forms, pharmaceutical container, medical implants, and sterile pouches) were developed. The key of the system is that it can work independently of external databases. It enables the verification of the product's genuineness and its correct supply chain on-site at every step of this chain. However, the information can be stored in a database for track and trace purposes as well.

Key is the implementation of security microstructures directly in or on the medical product itself without any chemical or biological additives AND in or on the primary packages. This is achieved by micro-structuring the tools used to manufacture the medical products and the corresponding primary package on the micron –and sub-micron level. The approach is not limited to a certain type of medical products but can be applied to many different types. The implementation of these security structures does not modify the manufacturing process.

The already high level of security of such micro-structures can be distinctly increased by coupling these microstructures with readable micro-barcodes and other codes on the package of the medical products. A reader will detect the wrong supply chain without access to any external database, e.g. by reading the information of a 3D-datamatrix micro-barcode.

Algorithms (including privat-/ and public-key strategies) were developed, which enable cross checking of the secure microstructures on the product and on the package. This ensures the highest level of security possible.

In parallel the project realized an overt/visible self-verifying system based on contrast generating microstructures. E.g. lines of micro-prism on tablets and in the blister package of the tablet resulted in a Moiré pattern if the contrast the microstructures generate is large enough. This gives a tool to the end-customer to see that the product and the package belong together.

Throughout the project the strategies of criminal organisations will be analysed and the development was adapted to counteract these strategies. Information as the most common entry points of fakes or illegal re-imports in the supply chain; the concealment methods used; the strategies of complex criminal business networks behind internet sales, was used to build a self-verifying system that, from its very beginning, is conceived to react to organized crime's modus operandi.

2.2 Objectives:

1. Safer package-product system against counterfeiting

Today the protection against counterfeiting of pharmaceutical products such as solid dosage forms is achieved only by applying anti-counterfeiting technology to the packing. The idea of the SAVEmed collaboration was to extend this counterfeiting protection to the whole package-product system by applying redundant overt and covert microcodes and microstructures directly on the product and to combine them with coupled codes or structures on the primary and secondary package. This approach allows for an offline self-verification mechanism of the product-packaging system without any external database.

The identification of the genuine product can be achieved in different ways. Overt effects can be inspected by looking at the product and its packaging to observe e.g. Moiré patterns on a tablet that is revealed by the blister pack or diffractive effects.

Covert level microstructures and codes are recognized by verification devices (e.g. handheld pOCT reading devices).

2. Secure microstructures and the measurement principles

CSEM has know-how in the manufacturing of a variety of microstructure types. In this project we focused on diffraction gratings (linear or crossed), micro-barcodes and contrast generating micro-

prisms or -pyramids. All these structures were transferred into steel tools and used to manufacture medical products or packages of such products.

One challenge that was mastered in this project was to implement the different microstructures in the surface of curved hardened steel tools. Tablets are mostly round shaped and injection moulded or thermo-formed parts exist in many different shapes. Thus the implementation process must be very flexible regarding curvature and shape of the tool to be modified.

3. Cost effective production of steel tools with secure microstructures

Micro-structuring every production steel tool for a certain medical product as described before is a time consuming and costly process. Nevertheless it is a doable option, especially if only a few production tools are needed. A more cost efficient way to microstructure steel tools is to emboss the micro-barcodes or microstructures with a hardened master steel tool in the surface of secondary unhardened steel tools in a fast manner. This approach was developed within SAVEmed and increases the tool production speed and decreases production costs significantly.

Huge forces need to be controlled and high precision deformation of steel in the micrometer range were achieved. The embossed micro-structures in the secondary tools have to survive a hardening process with temperature above 1000°C.

4. Criminal strategies

Counterfeiting is an ever-growing and constantly evolving criminal activity.

Therefore, the development of a new anti-counterfeiting system may greatly benefit from a thorough examination of the criminal strategies used in the illicit supply chain. This research focused in particular on some aspects that may have a relevance for the technology itself. Among these of importance are indications as: the weakest points of the distribution chain, the concealment methods used, or the most common trafficking routes.

Fake medicines can, in fact, enter the licit supply chain at almost any step of the distribution chain. Lack of respect of commercial/distribution agreements with the manufacturers, distributors or wholesalers buying from unauthorized/not trustful sources, repackaging, parallel traders, each such case represents a possible entry point.

For this reason, a part of the research was dedicated to the identification of which information could complement the anti-counterfeiting technology. Information like: the country of destination, the “purpose” of the product’s shipping (charitable distribution to Africa for instance), and its “life” (expiry date or marking the product as hospital waste after its use) could be associated to a datamatrix or a simple barcode and would support an easier identification of counterfeit products shipping, preventing “diversion” and recycling of stolen or expired medicines. Further attention was also be given to the role of internet as a facilitating factor allowing the criminal organization to anonymously reach the patient and directly sell to her/him a counterfeit medicine.

In this regard, the role of the spammer as a possible “advertising department” of the criminal enterprise was analyzed as well as the business network that is behind the internet distribution.

One of the best ways in which law enforcers may easier recognize a counterfeit medicine and better tailor their investigations on specific products/routes, is thanks to the information provided by the private sector on their products and their distribution network. Companies and the information they own and provide to the law enforcers are of fundamental importance for the identification of counterfeit products in general and of counterfeit medicines in particular.

However there is still much room for improvement. For this reason, a specific part of the project was

dedicated to open a dialogue between producers and law enforcers to identify a mutually beneficial practice that may improve communication flow from producers to law enforcers. The direct involvement of the interested parties allowed for the creation of a shared approach that resulted in the creation of Good Communication Practice.

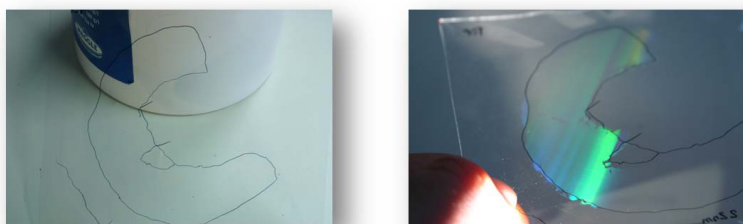
3 A description of the main S&T results/foregrounds

A master specification plan and research on strategies of criminal networks provided guidance and focus for the best possible solutions to combat the counterfeiting of pharmaceutical products. It was updated regularly to ensure that the input of the analysis of strategies of organized crime and of the advisory board was taken thoroughly into account in the ongoing research.

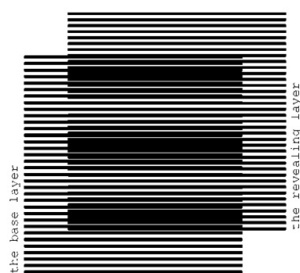
3.1 Period 1

In the first project period different microstructures were designed and tested, and steel tools were developed for flat and curved products. Methods and equipment for optical analysis of the microstructures were developed, and first tests for self-verifying systems with medical products and packaging were performed.

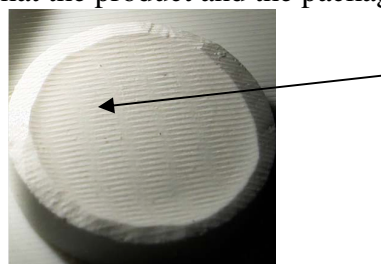
As one new effect we created partially hidden holograms in plastic film:



Furthermore, we developed microstructures with Moiré effects in order to enhance security by using two separate parts of the product. Moiré effects are based on interference patterns which are formed when two similar grids overlap each other



Structures could be printed on tablets and on the blister package of the tablet which resulted in a Moiré pattern, even though the contrast is not very strong yet. This gives a tool to the customer to see that the product and the package belong together.



Analysis of criminal strategies

We did a preliminary analysis of the supply chain for counterfeit medicines and the supply via internet sales. This led to initial recommendations for action strategies in these areas.

For example, one of the elements of the internet sales is the anonymity of the buyer and especially the seller. The anonymity makes it difficult or practically impossible for potential buyers to verify the authenticity of the offer on the internet. The consumers do not have the possibility to verify the authenticity of the website/pharmacy from which they would like to purchase. Therefore, it is necessary to have a verification tool inside/incorporated by the medicines. Only self-verification with the packaging gives the consumers the opportunity to check the authenticity of the product they bought.

3.2 Period 2

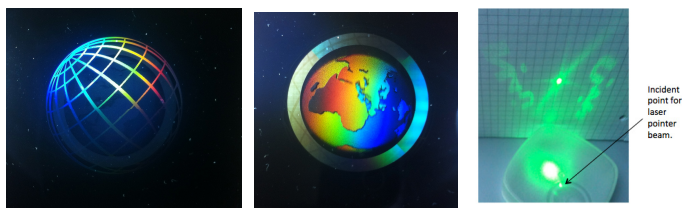
The objective for the second period was to provide the groundwork for the development of production processes that were to be implemented in the third project period. A master specification plan and research on strategies of criminal networks provided guidance and focus for the best possible solutions to combat the counterfeiting of pharmaceutical products.

Different microstructures were designed and tested, and microstructures were transferred in a hardened master steel tool with curved surface. Tests were carried out under production conditions and the verification tool was developed to read through blister packages.

Methods and equipment for optical analysis of the microstructures were developed, and tests for self-verifying systems with medical products and packaging were performed.

Based on the results of the first project period the following results were achieved during the second period.

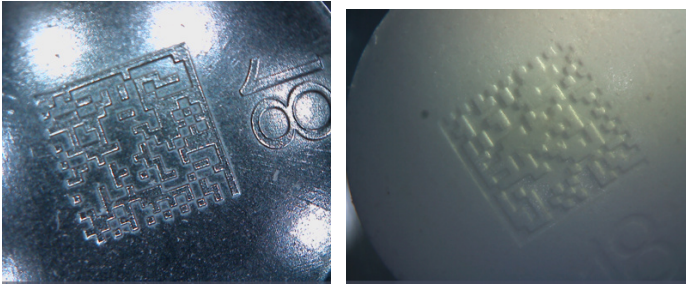
As one new optical effect we created partially hidden holograms:



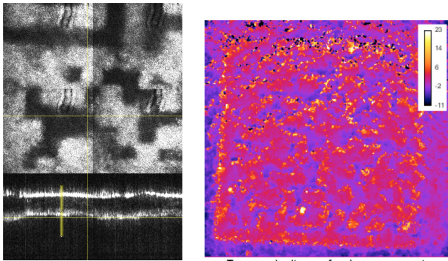
The pictures above show a hologram with continents based on light diffraction.

Different images can be seen at different viewing orientation (left and middle) and hidden details are visible at specific points using a laser pointer (picture on the right side). These structures can be created in steel tools and applied to various products like foils or injection molded caps.

Also microstructures can be impressed on pharma pills and the production parameters have been developed to ensure clear and distinct codes even after using the tools after many cycles.



Tablets are normally coated. Therefore the question arose if the code can be read below the tablet coating. Measurements done in the SAVEmed project show that it is possible to reliably read codes through clear coatings using an optical coherence tomography microscope (left).



In some cases the surface topology of an opaque coating can follow the microstructure of the code beneath in such a way that the code might be hidden to the human eye but readable by the pOCT (right).

Another area of research in SAVEmed is the encoding, writing, scanning and verification of datamatrix codes in the embossed or molded product. It has been shown that it is possible to read the code and decode the information from foils or tablets.

We did an analysis of the supply chain for counterfeit medicines and of the typical supply routes via the internet. This led to initial recommendations for action strategies in these areas.

Roundtable discussions between pharmaceutical companies and relevant authorities in selected EU countries were done, as part of pilot studies to improve communication between the different parties involved. Several pilot studies were started in period 2.

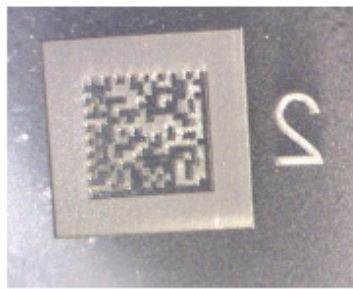
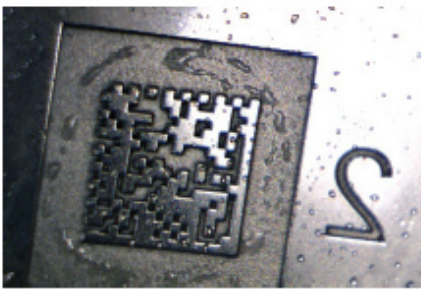
3.3 Period 3

The objective for the third project period was the testing of the tools under production conditions and to perform research on the influence of tablet coatings on microstructures on tablets. Furthermore, a handheld pOCT device was developed and a self verifying system was established.

Tablets were coated without destroying the microstructure (below). Even though the data matrix was hardly visible to the human eye, the scanner was still able to read the data matrix code.



In production conditions the tools did not show any significant wear after typical numbers of industrial production cycles



Code on stamp 2 before & after testing.

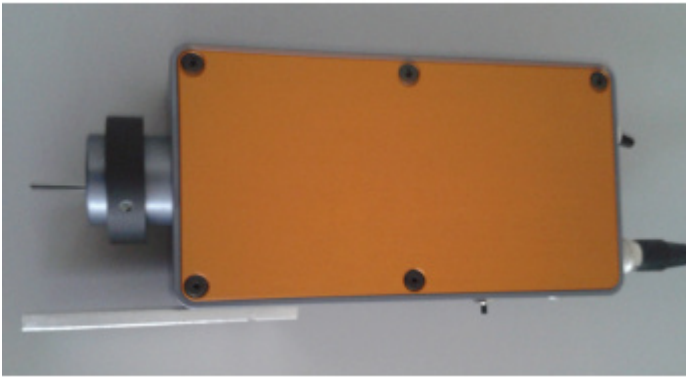


Code 2 at the end of the run (stamped on a hard tablet)

A complex hologram on an injection moulded cap still shows all features without any decrease of functionality in the overt and covert areas, even after having been used in 24/7 industrial production environments:



A Handheld pOCT Scanner was developed to read the tablets through a blister:



With regard to enhancing the communication between governments, customs and pharmaceutical companies the Good Communication Practices were tested in different countries and showed to be efficient.

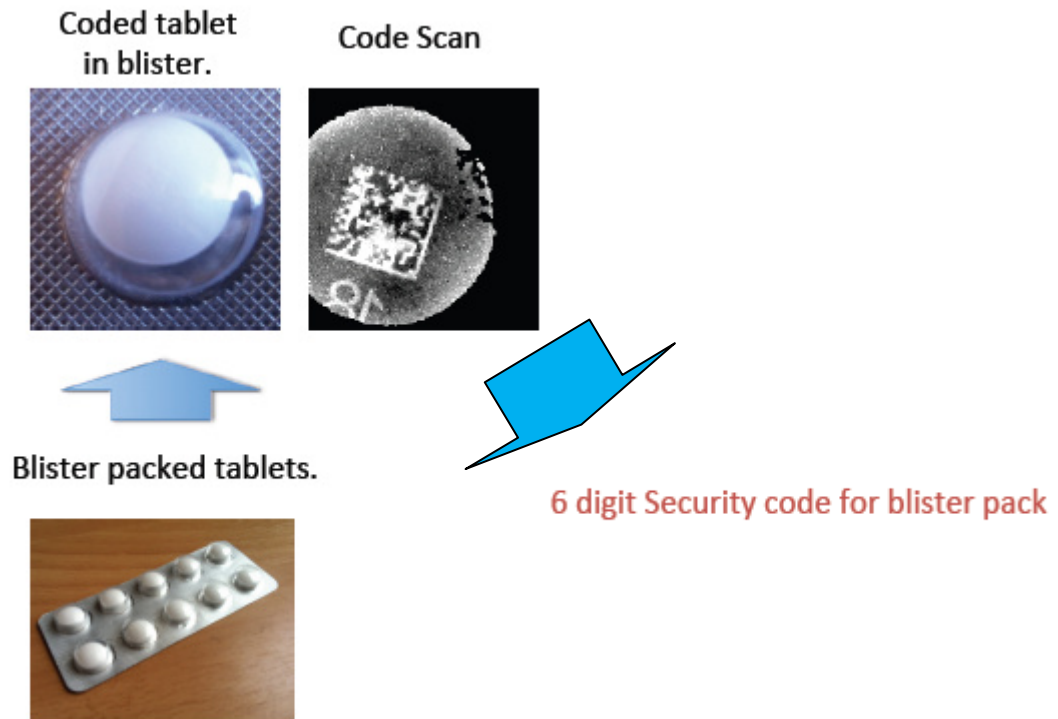
3.4 Objectives were met

1. Safer package-product system against counterfeiting

Two different package product systems have been developed in the SAVEmed project:

- a. The Moiree pattern where the micro-structure on the tablet and the microstructure on the blister combined create a certain pattern. However, this system only works with tablets which are not coated and has low visibility due to lack of contrast with white tablets.

- b. The second system shows the potential to be easily implemented: A data matrix code is stamped on a tablet which can be coated. The tablets are set in blisters and the codes are read through the blister creating an identifiable pattern which is encoded and the information is printed on the blister. The code on the blister can be read and verified against the data matrix codes on the tablets which can be read with a handheld pOCT device:



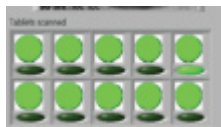
Read security code on blister:



Then read data matrix on tablets:



Software checks if the codes match:



2. Secure microstructures and the measurement principles

As was shown for period 1 and 2 several overt and covert microstructures have been developed and were applied to flat and curved surfaces.

3. Cost effective production of steel tools with secure microstructures

It was possible to emboss microstructures from a master steel tool into soft steel blanks, but the structures were lost during hardening.



4. Criminal strategies

Good communication practices were developed and successfully tested to enhance communication between the government, customs and pharmaceutical companies.

4 Potential impact and the main dissemination activities and exploitation of results

The SAVEmed project partners have very complementary background know-how which is indispensable for the exploitation of the results. Furthermore, the involvement of an External Advisory Board ensured proper technological progress and will help its introduction into the broader European medical and pharmaceutical markets.

4.1 SAVEmed impact

The main expected impact of the project results lies in the lowering of the number of counterfeit medicines and medical devices (by introducing the new security and identification features) and in improving the supply chain monitoring (by new tools developed). This will lead to increased security given to the European citizens regarding purchased medical products. The results of this project can boost the technological tool box of available anti-counterfeiting methods. An ultimate result of the

project should be renewed confidence in original products with all the resulting ethical and socio-economic impact.

Furthermore, the identification of counterfeit medicines is highly dependent on the collaboration of producers, and relying on the effectiveness of a pre-emptive approach also on the quality and quantity of information at the disposal of the law enforcers. SAVEmed's Good Communication Practice guidelines provide a set of tools for governments to use against counterfeiting of medicines and potentially other product categories.

4.1.1 Societal and economic impact of anti-counterfeit on medicals

Counterfeiting is a growing and increasingly dangerous phenomenon. The statistics of seizures confirm an existing and clear trend. Counterfeited and pirated articles threaten the health and safety of EU citizens, their jobs, community competitiveness, trade, and investment in research and innovation.

Concerning pharmaceuticals, reduced safety, quality, or efficacy can be life threatening. In this respect, pharmaceuticals are distinct from many other consumer products.

The most vulnerable drugs, medical devices, and pharmaceuticals are high technology products which require very specialized material systems and production procedures and huge investments in development and marketing. As these products usually have large sales margins and are distributed globally it is not surprising that medical devices manufacturers and pharmaceutical companies suffer from enormous losses due to counterfeiting. The problem has been attenuated by strongly increased sales over the internet, where everything from counterfeit Viagra to false glucose tests is readily available. Counterfeiting and tampering of products poses a danger to consumer safety and corporate revenues.

The amount of \$ 30 billion annually, representing 10% of all prescription drugs, is commonly accepted as a conservative estimation for counterfeit medical material. It is widely known that blockbuster drugs are among the prime counterfeiting targets; Counterfeit Viagra, Aricept, Norvasc (Pfizer) Procrit (Amgen) Levitra (Bayer) and Cialis (Lilly) are just a few of the commonly counterfeited products in circulation. Pfizer's annual Viagra turnover is about \$ 2 billion. The company has published that it is losing in the tens of millions of dollars annually because of counterfeit Viagra. Most drug manufacturers tend to downplay the problem because they fear negative consequences in the form of loss of consumer confidence. We believe that Pfizer's actual lost sales per annum are very likely over \$ 100 million. In a study where counterfeited erectogenics (e.g. Viagra®, Cialis® and Levitra®) were analyzed it was concluded that the copied drugs have become increasingly accurate in appearance.

Boxes and blister packs of Viagra®, Cialis® and Levitra® have become so well copied that consumers can no longer judge from their appearance whether the medicine is genuine or counterfeit.

With an increase in the utilization of medications and disposable devices, manufacturers as well as consumers are taking a closer look at the measures that can be undertaken to make these products safe. The growing fear of counterfeiting has gripped both industries alike.

Furthermore, medical devices and pharmaceutical markets are highly regulated and under greater pressure from regulators to introduce better traceability and labelling of products.

Maintaining transparency throughout the supply chain is essential not only to enhance product safety, but also to put a halt to existing malpractices such as pilfering, tampering, and counterfeiting.

Historically, protection against counterfeiting of medical products has relied on combining more or less happily different technologies and features on products and packages. Single companies

sell and sold their technology to a given customer (for example as a label) who then combined and applied one or several such features at their own discretion. The technologies between the different companies were not linked at all. Security companies sold single security features. With the advent of the internet and globalization, and the rising problem of re-imports however there has been a rethinking of this historical position and several security companies are currently attempting sell customized security concepts to their customers.

The increasing use of the internet to sell fakes (mainly medicines) and the fact that the high quality of fakes often makes identification impossible without technical expertise, increases the challenge customs services face.

4.1.2 Situation at the EU borders

Counterfeiting is a problem in all continents. Regions with seemingly low incident totals are not necessarily unaffected by or at a lower risk of pharmaceutical crime. Due to competing law enforcement priorities, lack of funding or inadequate regulatory structures, in certain regions of the world, counterfeit medicines often go undetected (certainly in the case of Africa where Interpol is extending its activity). It is also broadly accepted that counterfeit pharmaceuticals are often produced outside the EU and subsequently imported.

In 2008, during the action targeted to illegal medicines EU Customs seized over 32 million medicinal products being stopped by customs. The annual increase of identified counterfeit medicine articles is 118% between in 2008 and 51% in 2007. This number is in line with Industry estimation 20-100% grow if this illegal market annually. Such a significant increase makes this product category the most controversial one and resulted in urgency of many political activities in the EU and member states. More than 15 percent were suspected of infringing intellectual property rights (trademark, patent, or registered design).

Some 50% of all articles were intercepted in import procedures, 26% in transit and 21% on re-export. More than half of the articles suspected of trademark infringements were detained in import procedure, a quarter in transit procedures and the rest were detained during reexport procedures or were discovered in customs warehouses. Most articles were discovered by customs in air transport (more than 50%) and due to one large case, sea transport represented 36%. The main category of medicines is the so-called life style drugs (e.g. erectile dysfunction and weight loss medicine) but recently also more and more innovative and life-saving medicines (e.g. cancer, heart disease, psychiatric disorders, infections).

Moreover, the end-product drugs are not the only problem, but more than 25 million items containing drug precursors were also stopped, equating to the production of 25 million street doses with an estimated value of 50 million Euros.

4.1.3 EU and Member States activity

The European activities of the anti-counterfeit fight are lead by directorates of the European Commission and the. Particularly it is DG Enterprise and Industry, Directorate-General Taxation and Customs union (TAXUD) European Anti-Fraud Office (OLAF) and others (DG SANCO, COMP, INFSO, RELEX, JLS etc.).

As a recent action at EU-level, an amendment of the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use was announced in early 2008. The aim of this initiative is to address in

particular the risk of counterfeit medicines entering the legal supply chain of medicines in the EU. To protect EU citizens the safe supply of authentic and high quality medicines should be provided.

The proposed actions are:

- Identify more easily false representations of medicinal products in particular through safety features ensuring full traceability of each individual package of high-risk products.
- Improving the control at the EU external borders through which false medicinal products could enter; and
- Ensure that the active pharmaceutical ingredients are of high quality standard and not falsified.

As a consequence the public consultation has been launched and the Commission carried out a study to assess the economic, environmental and social impact of the proposals. Within Europe the standard system of 7-13 digits is not sufficient and easily faked, while the secret security features are usually discarded, removed, covered, generally “modified”. This modification is not illegal and therefore largely used. Community legislation on medicinal products placed on the EU market is based on Art. 95 EC Treaty.

4.2 Dissemination actions

4.2.1 Public Website

A public website showcasing the project’s activities is available at www.savemed.org. The website is being used as the main vehicle of dissemination and interaction with the public seeking information about the SAVEmed project and its activities.

4.2.2 Press Releases and publications

A press release about the project was issued in March 2012. It has been distributed via dissemination channels mainly in the German-language printed press.

The Consortium’s participation in HOMSEC 2013, upon invitation by DG ENTR, has led to the publication of an article about SAVEmed by the Chief Editor and Policy Analyst of Security Europe, a magazine produced in Brussels. This article was in fact published in Security Europe’s April 2013 edition.

Further publications were effected in the following media:

Moulded Holograms Tackle Product Security, European Plastics News, by David Eldridge, Sept 2013, p34.

<http://www.europeanplasticsnews.com/subscriber/featured2.html?cat=1&featuredid=3489>

Direkt gespritzte Hologramme schützen vor Produktpiraten, DeviceMed, Nov 2013.

<http://www.devicemed.de/fertigungseinrichtung-produktionstechnik/articles/423609/>

The SaveMed Project for Security Marking Pharmaceuticals, Authentication News, Oct/Nov 2013, p1 & 8.

4.2.3 Project Leaflet

A project leaflet highlighting SAVEmed results was published in autumn of 2013. The leaflet was used in the context of general marketing activities performed by the consortium members.

4.2.4 Newsletter

A regular SAVEmed newsletter was issued, presenting the project's progress to the "outside world". Its first edition was published in early 2012, and it has been disseminated to a wider audience, including providing it via the project website.

4.2.5 Publication of Papers in the context of conferences/workshops

Conferences and journals are an important pathway of disseminating scientific knowledge. Given the fact that SAVEmed is categorized as a security-relevant project by the European Commission, the SAVEmed consortium was striking an appropriate balance between publication and safeguarding critical information that may put consortium members in a unique position of collaborating successfully with e.g. law enforcement agencies and other stakeholders

4.2.6 Participation in trade fairs

The European Commission (Directorate General for Enterprise – DG ENTR.) extended an invitation to the project consortium to participate in the security technology fair HOMSEC 2013 in Madrid in March 2013.

Together with consortium member Klocke Holding, the coordinator visited the Compamed medical trade fair in Düsseldorf, Germany, held in late November 2013. Information about the SAVEmed project and its results was distributed to various potentially interested parties and was duly followed up during the final project year.

4.3 Exploitation of Results

Because of SAVEmed's security relevance, the European Commission has also made special clause 24 applicable to the SAVEmed Grant Agreement (GA).

Given the nature of SAVEmed as a security-relevant project, an effective protection and commercialization scheme for project results, as well as background, was always built on a combination of codified (published) IP and aspects that are being held by consortium partners as trade secrets. The consortium is well aware of these necessities and has implemented such management schemes before.

The exploitation of results has been described in detail in the Dissemination and Use Report.

4.4 Patents

Two beneficiaries have agreed to a joint patent application on some of the project aspects to be filed during August 2014
serial number: not yet available