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I. Why EU legislation was implemented

Due to the very nature of the problem, counterfeit drugs are very difficult to detect and therefore accurate statistics as to the scale of the problem are difficult to attain. Contributing factors to this are a lack of regulation in many states throughout the world, little or no resources dedicated to detecting counterfeit drugs and the internet makes it much easier for criminals to target people who self-diagnose, prescribe and order drugs from their illicit websites.

EU legislation was implemented because a considerable increase in the scale and frequency of seized counterfeit pharmaceutical drugs for human use has been trending since 2005.
An impact assessment by the European Commission (ec.europa.eu, 2008:12) listed nine cases occurring in 2006/07, affecting thousands of patients and in one case, eighty one deaths may possibly have been caused. According to the same assessment, there was a 384% increase in seizures from 2005 to 2006 at EU customs borders, with almost three million medicinal articles seized in 2006 alone.

In 2006 WHO established its own task force called the International Medical Products Anti-Counterfeiting Task Force (IMPACT). Who.int. (2006). In 2009 this task force report that 20million tablets and sachets were seized throughout China and seven of its neighboring states. 33 people were arrested and 100 outlets closed. Who.int. (2016).

In 2014, two operations were launched by The World Customs Organization. Operation Pangea VII and Operation Biyela 2, Wcoomd.org. (2014).
Operation Pangea VII shut down thousands of illicit online pharmacies. 237 people were arrested and USD $31million of potentially falsified medicines were seized.
Operation Biyela 2, mobilized customs agencies in 14 sub Saharan African countries over a 10 day period, (May 26 – June 4'th), seizing 110 million pharmaceutical products, most of which originated from China and India.
Although particular shipments were targeted in this operation, if this amount of product is seized in just 10 days, what is the true scale of the problem over a year?

This is a major concern for the European Union and the rest of the world. A lot of generic drugs and starting materials are imported into Europe from Asia, India being a principle supplier.
It is therefore necessary for Europe to establish robust legislation to prevent entry of falsified medicines into the legal supply chain.

A. *Drivers for implementation*

Ultimately it is legislation that is the key driver and it has been fascinating to learn the amount of time and effort required to get legislation proposed, accepted and implemented through the European Parliament. Although greatly time consuming, the detail this particular legislation goes to is remarkable and is chronologically summarized on the following website ec.europa.eu. (2016). "*Falsified Medicines - Major Developments*."

The process of combating counterfeited medicines in the European States and promoting international efforts formally began in Sept 2006 when a joint motion resolution was passed by the European Parliament calling for various institutions, including the European Commission and Union to take action. Since that time much work was carried out by various institutions to culminate in legislation being passed in 2011 under European Directive 2011/62/EU, which amends Directive 2001/83/EC in regards entry into the legal supply chain of falsified medicines.

The directive introduced tougher rules in regulating the pharmaceutical supply chain and resulted in accompanying delegated regulation to the 2001/83/EC directive for each member state to enforce. In 2014 such regulation was introduced to amend good manufacturing practice for API substances. And in February 2016 regulation was introduced to make it a requirement to place safety features on the packaging of medicinal products for human use.

This regulation is signed into legislation at a national level by the health minister of each member state, which then requires the responsible departments and agencies to implement the regulatory requirements.

Citing Ireland as an example, the Health Products Regulatory Authority is at the forefront of driving and implementing the required changes, working closely with the Department of Health, European Medicines Agency, the European Commission and other stakeholders.

Announced by the Minister for Primary Care and Social Care, an example of one such implementation took place on the 24'th June 2015, where all legally operating pharmacies/retailers established in the EU will display a safety logo redirecting the consumer to a list of officially recognized retailers.

B. *Falsified V Counterfeit medicines*

World Health Organization. (2016) *"There is currently no universally agreed definition amongst Member States of what used to be widely known as 'Counterfeit medicine'. WHO will continue to use the term Substandard, Spurious, Falsely labelled, Falsified and Counterfeit (SSFFC) Medical product until a new definition is agreed."*

Many states have their own legal definition as to what counterfeit drugs are, mainly due to their existing legislations. There is a very strong need to agree on an international definition for the following reason.

"*The term counterfeit is now closely associated and legally defined within intellectual property legislation and concentrates on trademark protection, this has been perceived to have reduced the focus from what is first and foremost a public health issue*." World Health Organization. (2016).
Much existing legislation uses the word 'counterfeit' which refers to a trademark infringement and therefore existing legislation will cover this aspect of criminality and does not take into account and provide sanction for the following scenarios: wrong ingredients, without active ingredients, with insufficient (inadequate quantities of ingredient(s) or with fake packaging. For the above reason, the term 'Falsified Medicines' is introduced and defined in the Eur-lex.europa.eu. (2011:17).

Counterfeit Definition: Ema.europa.eu. (2016) "Counterfeit medicines are medicines that do not comply with intellectual-property rights or that infringe trademark law."

Falsified definition: (ec.europa.eu. 2011:17) "*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."

II. The main principles of the EU legislation

The legislation introduces safety features to appear on all outer packaging of medicinal products.

To introduce stronger methods of inspecting verifying and controlling manufacturers of starting material, through assessment by competent authorities in their respective state.

To hold all actors in the supply chain accountable for their activities, which now includes brokers.

To introduce a logo to be displayed on all websites authorized to sell medicinal products for human use. This provides consumers the opportunity to verify the supplier as having genuine authorization to sell.

A. *Importation of active substances*

The European Union must ensure that all active substances imported from third countries is manufactured and distributed to a quality level the same or exceeding that of the EU.

An imported product must be accompanied by a written confirmation from the delegated authority nominated by the non- EU state, reference article 46b, ec.europa.eu. (2012).

However, this rule is not applicable if the third state has been added to the EU list of approved states.
To achieve this, the competent authority within that state must inspect the site and approve it for a manufacturing authorization or a wholesale distribution authorization.

To attain either of these authorisations, the site will be subjected to an inspection following the guidelines for GMP & GDP as per EU Directive 2001/83/EU.

If it is determined the requesting site passes the EU equivalency test, it may be added to a list of approved manufacturing sites. Manufacturing authorization is granted for a period of up to 3 years but must be inspected before then in order to retain its authorisation.

Article 111, Directive 2001/83/EU, states that the competent authority of member states and third countries must perform inspections regularly. These inspections, if necessary, may be unannounced and an official laboratory be used for the purpose of testing samples obtained from the site under inspection.

B. *Good manufacturing practices (GMP) for active substances imported from outside the EU.*

Any actor in the supply chain that packages medicinal products must hold a manufacturing authorization. ec.europa.eu. (2011)

To prevent falsified product reaching the EU, the legislation requires verification that third country manufacturers are following good manufacturing practices as laid down in directive 2001/83/EU. This is achieved by competent authorities inspecting the manufacturing sites on a regular basis.

It increases the verification that equivalent good manufacturing practices are being adhered to by the manufacturer of medicinal substances in the third state.

C. *Good Distribution Practices (GDP)*

"*Persons procuring, holding, storing, supplying or exporting medicinal products are only entitled to pursue their activities if they meet the requirements for obtaining a wholesale distribution authorisation in accordance with Directive 2001/83/EC."* ec.europa.eu. (2011)

These actors must now inform the appropriate competent authorities of their activities when importing active substances and excipients from third countries.

Possession of a manufacturing authorisation entitles the holder to distribute its product also, but must do so in accordance with current GDP.

There are many actors in the supply chain and Directive 2001/83/EU covers many of these, but legislation laid down under directive 2011/62/EU will now cover brokers i.e. those persons who do not necessarily handle or store the product, but are involved in the purchase and selling of medicinal products.

D. *Safety features for medicinal products for human use*

Legislation released in 2011 provides for the introduction of two safety features which will be applied directly to the product.

A unique 2D code will be printed onto the packet of each medicinal product at the point of manufacture. This code will be registered in an approved repository, so that when scanned it will show up on the repository as approved or unapproved for sale. The product will be scanned at the point of sale to the public, thus ensuring its authenticity at the last point in the supply chain. The scan will also help to reduce the potential for issuing the wrong medicine by the pharmacy.

Size dependant, a 2D barcode can store a lot of information and according to ec.europa.eu. (2016) the unique identifier will contain “the product code, the national reimbursement and identification number, the batch number and expiry date.”

If the unique identifiers were incremented codes, falsifiers would not be long in being able to replicate these numbers and add major confusion to the supply chain. The Commission Delegated Regulation ec.europa.eu. (2016) makes provision for randomly generated codes according to international standards.

Another safety feature is a tamper proof seal, which will provide evidence of package having been opened. This can be checked throughout the supply chain and ultimately reassure the end user.
It would be difficult for producers of falsified medicines to reproduce such a feature, much like paper currency.

III. International efforts

Many international organisations contribute their efforts to combating falsified medicines. The issue extends across the end to end supply chain, crossing international borders and therefore affects many interest groups representing intellectual property, customs and excise,

pharmaceutical manufacturing, pharmaceutical retailing, domestic and international law enforcement agencies and so on.

The Pharmaceutical Industry Initiative to Combat Crime is an agreement between Interpol and 29 of the largest pharmaceutical companies in the world to help tackle the problem of falsified medicines. Launched in 2013 with funding of 4.5 million Euro over three years, it will help bolster current activities and help dismantle organised crime networks built around falsified medicines.
On the occasion of its tenth anniversary and in conjunction with An Garda Siochana and the Health Products Regulatory Authority of Ireland, Interpol held a Global Conference – Ten Years Combatting Pharmaceutical Crime – Review & Prospects. The event was hosted in Dublin, Ireland, over two days from 19-20 November 2014. It was attended by 180 different organisations ranging from national law enforcement and health regulatory agencies, pharmaceutical companies and non-government organisations.

In 2006, the World Health Organisation established an agency called the International Medical Products Anti-Counterfeiting Taskforce (IMPACT). The organization is a partnership between pharmaceutical associations, non-government agencies and international organisations.

The World Trade Organisation establishes trade agreements between countries and deals with disputes that arise over issues such as compulsory licensing. A government within a country may grant a license for the manufacture of a patented drug, without the consent of the owner. This is legal but under certain conditions only. Parallel importing of the drug from a country manufacturing under compulsory licence also raises its issues which and can be resolved through the WTO.

The Council of Europe Convention, Council of Europe. (2011), otherwise known as "*The "Medicrime convention", is the first international criminal law instrument to oblige States Parties to criminalise: the manufacturing of counterfeit medical products; supplying, offering to supply and trafficking in counterfeit medical products; the falsification of documents; the unauthorised manufacturing or supplying of medicinal products and the placing on the market of medical devices which do not comply with conformity requirements*."

It is very interesting to note that of the 26 countries that signed up to this treaty, only six have ratified and put it into force. This means that international law to criminalise the act of counterfeiting or producing falsified medicines or medical devices exists only between six countries.

The OECD produced a very comprehensive report in 2015 regarding a range of issues concerning illicit trade. "*Remarkably, the production of counterfeit medicines or medical products is not an international crime, and current definitions and laws are inconsistent. An international public health convention or treaty would greatly benefit law enforcement authorities in combating criminal networks and counterfeiting operations. The lack of consensus and a legally binding force inhibits true progress.*" OECD. (2015)

Considering the international scale of the problem, it would make sense that a fundamental effort in combatting the problem would be to criminalise it. The problem directly affects human life and is potentially causing deaths on a regular basis.

The Working Group of Enforcement Officers, set up by the Heads of Medicines Agency in 2007, purpose is to "*Promote liaison and co-operation between Member States and agencies with the purpose of sharing information."* Hma.eu. (2016). This group coordinates between the National Competent Authorities (NCA) of the member states and agencies. Their aim is to identify emerging threats to the existing legal supply chain and provide practical training in the illegal supply of falsified medicines. They set up the Rapid Alert system whereby a network of single points of contact (SPOC) can use the system to quickly and confidentially inform their counterparts to discoveries of medicines with undeclared content and to report large amounts of stolen medicines.

There are many other institutions that contribute at an international level. The Pharmaceutical Security Institute (PSI) is regarded to have some of the most reliable data available, though it is not made available to the public according to OECD. (2015). The International Pharmaceutical Federation (FIP) is the global federation of national associations. The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) represents research orientated manufacturers and associations across the globe.
There are many more that could be named but there is no singular entity that has official administration rights over the global spectrum of organisations.

IV. Assess if it has made an impact since its introduction in the EU

To asses a program for impact towards a worsening or improving situation, an agreed standard of measure (quantitative or qualitative) should ideally be in place before an objective assessment of a situation can be made.

On an international scale, these measures are not in place for falsified and counterfeit medicines. Whilst there are many estimates from different agencies, the true scale of the problem remains largely undefined.

WHO estimate the use of falsified medicines in developing countries to be 10-30% of all medicinal drugs used. Who.int. (2016).

An Interpol analytical report attempts to examine the scale of the problem in its report Interpol.int. (2014:7)"*Pharmaceutical Crime and Organized Criminal Groups."* which does not attempt to quantify the problem, but uses the number of media reports as an indicator as to the growing scale of the problem.
Again, this method is also unreliable as the media may have an increased interest in the problem due to awareness campaigns, but the increase of reported incidents may be due to an increase in detections and prosecutions.

The Pharmaceutical Security Institute does attempt to quantify the problem. Psi-inc.org. (2016). The website shows statistics relating to Trends, Geographic Distribution and Arrest Data. The data has been gathered for twelve consecutive years, but information as far back as 2010 is displayed only. According to the report by the OECD. (2015), this data is the most reliable available, but only available to members. The numbers remain relatively static from 2010 to 2014.

Seized counterfeit medicines at EU borders has increased 380% in 2006 compared to 2005, Director of Consumer Goods to the European Commission 2007, Georgette Lalis in her introductory speech at the WHO Impact Conference, ec.europa.eu. (2007)

V. Conclusion

It is not possible to say if the legislation has made an impact or not. It has been accepted there has been a sharp increase in the amount of pharmaceuticals detected since 2001, which indicates directive 2001/83/EU did not make an impact to the illegal supply chain. However, this legislation was very much targeted at the professional and legal side of the pharmaceutical supply chain and not developed as an instrument in response to falsified medicines.

It is too early to say what effect directive 2011/62/EU will have in the fight against falsified and counterfeit medicines.
On the face of it, this legislation makes very good practical sense and strengthens the legal supply chain considerably.
The four main pillars of the legislation have yet to be practically implemented. For example, Ireland has until 2019 before it must be fully compliant with the new safety features. Therefore it will be a number of years before it will be known, subjectively or otherwise, as to whether the legislative changes will make a difference.

References

- ec.europa.eu. (2008). *Impact Assessment*. [online] Available at: http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/counterfeit-ia_en.pdf [Accessed 15 Mar. 2016].
- ec.europa.eu. (2008). *SUMMARY OF RESPONSES TO THE PUBLIC CONSULTATION DOCUMENT*. [online] Available at: http://ec.europa.eu/health/files/counterf_par_trade/2008_06_19_summary_of_responses.pdf [Accessed 16 Mar. 2016].
- ec.europa.eu. (2011). *Directive 2011/62/EU*. [online] Available at: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf [Accessed 17 Mar. 2016].
- Who.int. (2006). *WHO | WHO launches taskforce to fight counterfeit drugs*. [online] Available at: http://www.who.int/bulletin/volumes/84/9/06-010906/en/ [Accessed 16 Mar. 2016].
- ec.europa.eu. (2016). *Falsified Medicines - Major Developments*. [online] Available at: http://ec.europa.eu/health/human-use/falsified_medicines/developments/index_en.htm [Accessed 16 Mar. 2016].
- World Health Organization. (2016). *Definitions of SSFFC Medical Products*. [online] Available at: http://www.who.int/medicines/regulation/ssffc/definitions/en/ [Accessed 17 Mar. 2016].
- Who.int. (2016). *WHO | Growing threat from counterfeit medicines*. [online] Available at: http://www.who.int/bulletin/volumes/88/4/10-020410/en/ [Accessed 17 Mar. 2016].
- Ema.europa.eu. (2016). *European Medicines Agency - Human regulatory - Falsified medicines*. [online] Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000186.jsp [Accessed 17 Mar. 2016].
- ec.europa.eu. (2012). *DIRECTIVE 2001/83/EC*. [online] Available at: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf [Accessed 18 Mar. 2016].
- ec.europa.eu. (2016). *Commission Delegated Regulation*. [online] Available at: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2016_161/reg_2016_161_en.pdf [Accessed 18 Mar. 2016].
- Wcoomd.org. (2014). *World Customs Organization*. [online] Available at: http://www.wcoomd.org/en/media/newsroom/2014/may/thousands-of-illicit-online-pharmacies-shut-down-in-global-operation-targeting-fake-medicines.aspx [Accessed 19 Mar. 2016].
- Wcoomd.org. (2014). *World Customs Organization*. [online] Available at: http://www.wcoomd.org/en/media/newsroom/2014/september/biyela.aspx [Accessed 19 Mar. 2016].
- Apps.who.int. (2016). *WHO | News*. [online] Available at: http://apps.who.int/impact/news/en/ [Accessed 19 Mar. 2016].

- Council of Europe. (2011). *Full list*. [online] Available at: http://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/211 [Accessed 19 Mar. 2016].
- OECD. (2015). *Illicit Trade: Converging Criminal Networks*. [online] Available at: http://www.oecd.org/gov/risk/illicit-trade-converging-criminal-networks.pdf [Accessed 19 Mar. 2016].
- Hma.eu. (2016). *Heads of Medicines Agencies: Working Group of Enforcement Officers*. [online] Available at: http://www.hma.eu/wgeo.html?&L=0 [Accessed 20 Mar. 2016].
- Psi-inc.org. (2016). *PSI-Inc.org*. [online] Available at: http://www.psi-inc.org/incidentTrends.cfm [Accessed 20 Mar. 2016].
- Interpol.int. (2014). *Pharmaceutical crime - INTERPOL*. [online] Available at: http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Pharmaceutical-crime [Accessed 20 Mar. 2016].
- ec.europa.eu. (2007). *Developing Effective Legislation to Combat Counterfeit Medical Products*. [online] Available at: http://ec.europa.eu/health/files/counterf_par_trade/conterfeit_doc/2008_04_presentation-counterfeit_en.pdf [Accessed 20 Mar. 2016].