The Falsified Medicines Directive
– What does it really mean for stakeholders?

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Abstract
The Falsified Medicines Directive (FMD, 2001/83/EC as amended to 2011/62/EU) and its Delegated Regulation EU 2016/161 sets out the overall requirements that manufacturers of human medicinal products must meet as part of their legal responsibility. These responsibilities also extend to wholesalers, dealers and parallel importers. While it is widely known that all of the aspects of the FMD will come into force by 9 February 2019, the preceding (and related) requirements that have either already been implemented, or are in the process of being implemented, are less well understood.

This article serves to provide an overview and history of the Directive as well as including its key requirements, and how these are being fulfilled by stakeholders and manufacturers. There is wide variability in the approaches being taken and the pace of progress, but one certainty remains; this Directive will be enforced for all manufacturers intending to supply human medicines into the EU.

Introduction
A falsified medicine is any medicine that is not manufactured by the approved manufacturer (the marketing authorisation holder – MAH), contains too much, too little, or no active ingredient, contains another/undeclared active ingredient, is past its expiry date, is deliberately mislabelled, has fake packaging, or is in some way not as the authorised manufacturer intended. All of these situations have a direct impact on patient safety and there have been many documented cases of harm (including death) caused through falsified medicines. While all of the information provided in this article is available through a number of channels including online, this article provides a collated summary to act as a point of reference.

This article is intended to provide an easy-to-follow overview of the background and history of the FMD before taking a closer look at the key elements. The operational implementation of the key elements is described in context of the overall output and effect on patient safety. Finally, this article provides a flavour of the current trends and potential risks and areas that are still unclear, and seeks to provide an expert narrative on the resolution of some of these areas.

Background and history
The multi-billion dollar trade in falsified medicines is well known and documented extensively. There have been many initiatives that have had varying degrees of success and global impact, but the risk to patients continues to drive regulatory authorities to develop and implement increasingly rigorous processes.

One of the most serious cases in Europe involved 72,000 packs containing 2.1 million doses with a retail value of £4.7 million. Affecting seven batches of three medicinal products, it resulted in four Class 1 recalls and the UK's Medicines and Healthcare products Regulatory Authority (MHRA) seizing 40,000 packs before they reached pharmacies. This operation was referred to as Operation Singapore as counterfeit products manufactured in Tianjin China were routed through Hong Kong and Singapore before being shipped to Belgium and then the UK; the flow of money was from the UK to China via Luxemburg and Mauritius.

Given the global nature and lucrative value of such counterfeits, there are already a variety of local and regional initiatives that have been developed and implemented to provide some level of assurance to patients and carers. These range from a relatively simple application of scratch codes by legitimate manufacturers that are scratched-off by customers to reveal a code that is texted to a central data centre to verify the product's provenance and authenticity. This system was launched in a number of African countries in 2009 and to date around 28 million verifications have taken place.

In the EU, Directive 2001/83/EC allows safety provisions to be enacted; amendments to Directive 2001/83/EC allowed the Falsified Medicines Directive 2011/62/EU to be defined with the key safety requirements. These safety features were delegated to be implemented nationally in the Delegated Regulation EU/2016/161 which will be implemented by 9 February 2019. The evolution and summary of these requirements is provided in Figure 1.

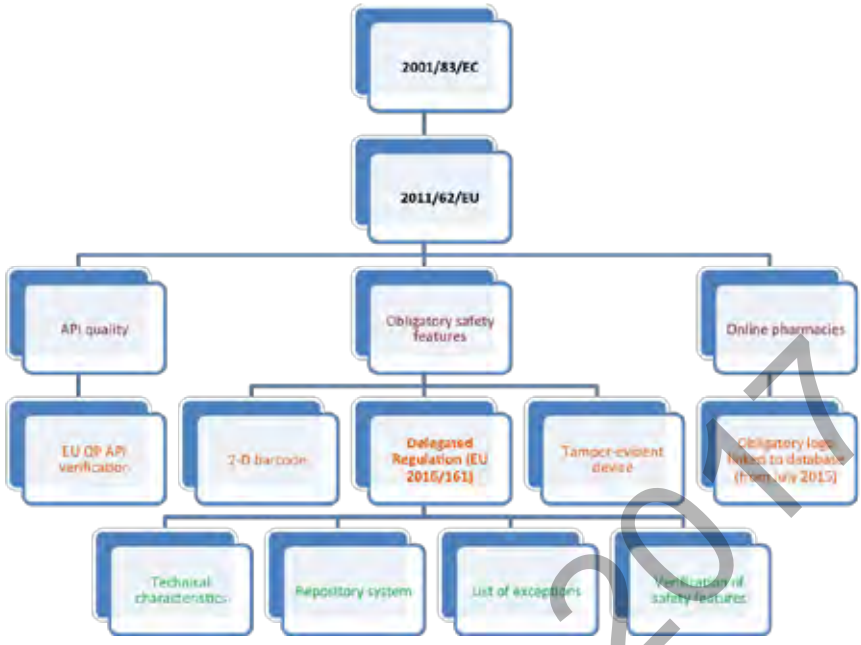
The main parts of the requirements and their implementation as part of the FMD are discussed in the following sections of this paper.

The key parts of the FMD
There are three main strands to Directive 2011/62/EU that are further defined under the obligatory safety features (under the Delegated Regulation EU/2016/161) and which form part of the national competent authorities' (NCAs) responsibilities for implementation.

Active pharmaceutical ingredients (API) quality. While the requirements for APIs have always been implicit for good manufacturing practice (GMP)-compliant manufacturers, the FMD has made the finished product releasing Qualified Person (QP) responsible for ensuring that APIs are manufactured within the principles of current GMP (cGMP). This requirement came into effect in July 2013. Its implementation has involved a wide range of activities that finished products manufacturers have undertaken, typically by outsourcing upstream QP activities; these include:

- Paper audit/assessment of API manufacturer's quality management systems (QMS)

Figure 1: Summary of the development of FMD legislation and requirements.



- Refinement of existing API manufacturer's QMS to align with QP requirements
- Provision of robust quality technical agreement (QTA)
- Provision of alternative API suppliers where available, and termination of supply from non-compliant suppliers.

The overall effect has been the implementation of robust, GMP-consistent supply chains for APIs manufactured outside the EU; the requirements under the FMD have been fulfilled.

Online pharmacies. The rapid growth in online pharmacies and the availability of prescription medicines was seen as a major risk factor to patient safety. Given the nature of the internet, this area is very difficult to regulate and while the trade in "unauthorised" medicines will continue, consumers (patients) are being encouraged to only purchase products that display the online pharmacy logo. The requirements to register online pharmacies to obtain a certified logo became obligatory from July 2015. Consumers are able to click on the approved online pharmacy logo that verifies that the merchant is registered with the NCA and complies with the requirements of FMD online sales. The logo has the wording: "Click to verify if this website is operating legally" for ease of use by potential purchasers. If the online pharmacy is an approved supplier, clicking will take users to a webpage which lists not only the name of the supplier but its full postal address and the website address(es) at which it is approved to sell medicines online.

Obligatory safety features (EU 2016/161). Two key safety features that are required as part of the FMD are a 2-D barcode and tamper-evident packaging. While the general minimal requirements are provided for in the FMD, the technical requirements that underpin these features have been delegated to Regulation EU 2016/161. These are discussed in further detail below.

- ***2-D barcode:*** A unique identifier (UI) in the form of a 2-D barcode as well as readable details of the batch number and expiry date must be included. While this is not its intended use, NCAs can decide whether this code will be used for reimbursement purposes.
- ***Tamper-evident device:*** Tamper-evident packaging is an obvious visual deterrent to any attempts to tamper with the container closure system. The requirements for tamper-evident packaging include solutions from label seals and tear-off strips to shrink-wrapping. Regardless of the option selected, each must be able to demonstrate that the container-closure system is as it was on leaving the manufacturing /QP release site and has not been tampered within the supply chain.

The specific safety feature requirements and their implementation are detailed in the Delegated Rule (EU 2016/161) to the FMD (EU Directive 2011/62/EU). These are summarised below.

- ***Technical characteristics:*** The 2-D barcode must be included on all secondary packaging; this must comply with the requirements of ISO 15495. In addition to the barcode, a readable 20 alphanumeric character code that includes the expiry date and batch number must be included. All new marketing authorisation applications (MAAs) filed after April 2016 must include a unique identifier. All existing / approved products have a 3 year transition period ending in February 2019. A serialised barcode will be required to be applied by parallel importers as part of their responsibilities under FMD.
- ***Verification of safety features:*** A system whereby the supply chain many be verified must be implemented for all products. While this does not need to be a full track-and-trace system, it should be risk-based and enable the verification of approved lots from the manufacturer to the pharmacy. This verification system relies on the verification of the tamper-evident device as well as the confirmation of provenance using the unique identifier. Parallel importers will have to ensure that relabelled blisters are packed into acceptable packs that do not compromise the integrity of the supply chain.
- ***Repository system:*** A controlled electronic repository forms the backbone and framework against which the other elements of the FMD are delivered. The repository must allow approved

manufacturers to upload details of unique identifiers that can be tracked and verified throughout the supply chain, and be decommissioned at the point of supply. The Delegated Rule allows stakeholders to establish and maintain this system; this is being undertaken by secureMed in the EU, which is under the supervision of competent authorities. The Blueprint system agreed by secureMed comprises a central EU hub linked to national/super-national repositories that will be interrogated by approved/verified users. NCAs will be responsible for issuing user licences for the repository.

- ***List of exceptions:*** As a general rule, all prescription products are subject to the FMD and all over-the-counter (OTC) products are exempt; there are however a number of exceptions to these rules. These include homeopathic medicines; medicinal gases; radionuclide generators and precursors; kits; advance therapy medicinal products (ATMPs); various solutions, media and extracts. Furthermore, a number of dispensers are also exempt from the FMD, including prisons, dentists, vets and opticians.

Limitations. One of the key limitations to the full implementation of the FMD is the delay in the selection of the Blueprint system that will provide the database structure and backbone to the electronic verification against the European Medicines Agency (EMA) and local hubs. At the time of writing, the anticipated decision by the MHRA was overdue by two months.

The current state of play

The key stakeholders have varying degrees of understanding and preparedness for implementation of the FMD. The typical activities that are required to be in place for successful deployment include:

- Manufacturing/packaging line upgrades (cost estimated by the MHRA to be around £150,000 per line)
- Access to and training in Blueprint software (estimated to be ranging £50,000 to £200,000+)
- Serialisation sequences (2-D barcodes)
- Tamper-evident packaging
- Updates/revisions to QMS
- Supply chain mapping
- Staff training.

Manufacturers and MAHs. Generally, manufacturers fall into one of two categories:

- ***Innovators:*** Innovators/original MA applicants and holders are generally well down the path in preparing to implement the requirements of the FMD. This group is typically seen as the most cash-rich in terms of their products and their exclusivity.
- ***Generics manufacturers:*** Generic pharmaceuticals manufacturers have a wider range if implementation positions, with larger manufacturers progressing at the same pace as the innovators. Smaller manufacturers appear to be seeking to "collaborate" with other smaller manufacturers and use trade bodies such as the British Generic Manufacturers Association (BGMA) to lobby regulators and decision-makers. Consequently, there are a considerable minority of smaller/national generics manufacturers that are starting to lag behind the implementation curve.

Wholesalers/distributors/brokers. This group of stakeholders is required to track the receipt and onward distribution of inventory and ensure the continued security of the supply chain. As these activities do not require any intervention with the product and product packs, this group will require access to the controlled repository and deployment of the Blueprint software. These stakeholders are therefore insulated against many of the more intricate requirements of the FMD.

Parallel importers. Parallel importers are perhaps one of the most contentious group of stakeholders in the deployment of the FMD, given that they are not MAHs but will undertake some manufacturing activities such as labelling and repacking. This group will be impacted by the requirements for the provision of 2-D barcodes, tamper-evident packaging, and access to the repository and software. A number of these stakeholders have considered the impact of the FMD and developed contingency plans to ensure their business is not impacted; the potential impact of the Brexit vote is of more concern given the potential risk to their supply chains.

Manufacturers – specials licence holders. The manufacturers of products with a "specials" licence are exempt from the requirements of the FMD. Nevertheless, there are a handful of Specials manufacturers that have sought to understand and implement some parts of the FMD legislation. This is commendable and should be encouraged for others.

Online pharmacies. The requirements for online pharmacies are already in force and implemented.

Risks

Any major programme that seeks to overhaul the arrangements for the supply of pharmaceutical products will involve a wide range of risks. The FMD is no different as its implementation will impact manufacturers, suppliers, brokers, distributors and patients. Despite the phased deployment of the FMD, tangible risks remain.

Clearly, one of the most obvious risks to the supply of drugs to the health service is if the requirements of the FMD are not met by stakeholders by the deadline of February 2019. The degree of impact will depend on the number of stakeholders and the number and types of product affected, and whether alternative treatments are available to switch patients.

From discussions with various stakeholders, it clear that the risks stem from factors outside their direct control. For example, delays in the identification of software solution providers and access to the secure databases carry significant risks in successful deployment. Equally important are cost considerations. The capital investment required for line upgrades as well as the cost to MAHs for the overall deployment and implementation of the FMD has prompted many to reconsider the cost of goods, and to lobby to prevent non-paying beneficiaries such as parallel importers to be denied access to the repository.

As the deployment activities continue, further discussions will no doubt ensure that will seek to tweak and amend the requirements, while the regulatory bodies continue to push back and stay aligned with the origins of the FMD.

Conclusions

The Falsified Medicines Directive (FMD, 2001/83/EC as amended to 2011/62/EU) and its Delegated Regulation EU 2016/161 will come into force in February 2019. This Directive represents a significant set of changes to the manufacture and supply of pharmaceutical products that have been subject to significant counterfeiting. The measures included within FMD will go a long way to assuring patient safety and product efficacy.

As would be expected in such a significant programme, there are still a number of areas of concern that could result in increased risks if they are not resolved in a timely manner. However, manufacturers and stakeholders have in the main responded positively and the majority have well-advanced plans for deployment by the deadline.