Abstract

Since publication of the falsified medicines directive (FMD) in 2011 and the subsequent delegated regulation (DR) in February 2016 there has been much discussion surrounding the level of FMD compliance required by secondary care institutions. Due to the heterogeneous nature of the secondary care drug distribution cycle the FMD allows certain dispensations for 'Healthcare institutions', this manuscript reviews the FMD and delegated regulation in an effort to understand and explain these dispensations and the true impact of the FMD on secondary care in an effort to address common misconceptions amongst stakeholders.

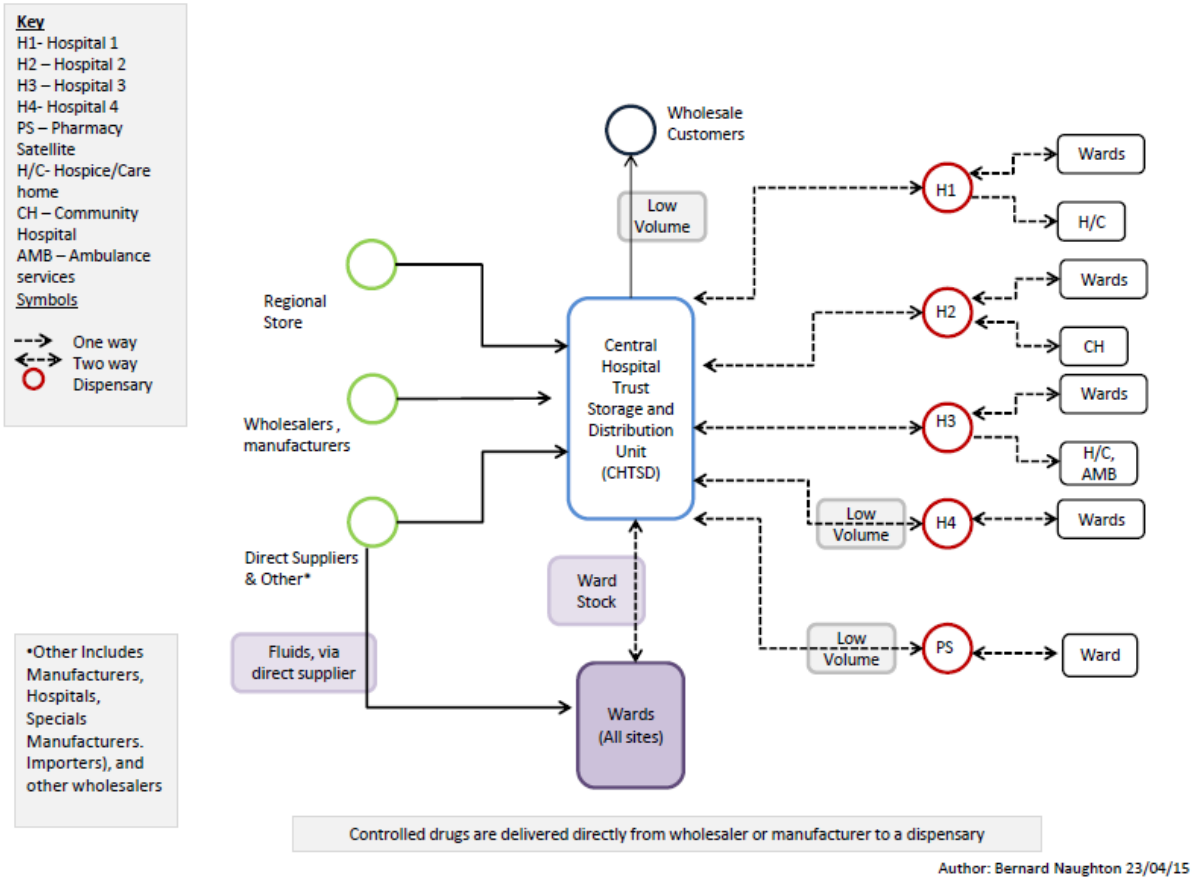
Introduction:

The Falsified Medicines Directive (FMD) aims to protect European citizens from the dangers of falsified medicines; an international public health issue [1]. A falsified medicine as defined by UK law is any medicinal product with a false representation of '(a) its identity, including its packaging and labelling, its name or its composition (other than any unintentional quality defect) as regards any of its 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' [2].The five core principles of the FMD include product serialisation with 2D data-matrix barcodes at manufacture, tamper evident seals for all products governed by the FMD, the majority of prescription only medicines and a minority of high risk over the counter medicines covered by the FMD, the responsibility of manufacturers for the cost of a medicines authentication service and compliance by all European pharmacies [1,3-6]. The authentication of medicine occurring at pharmacy or 'healthcare institution' level with a risk based verification at wholesale level aims to prevent falsified medicines from reaching vulnerable patients.

Criticality of EU FMD Compliance in Secondary Care

The FMD is a vital safety tool for secondary care and compliance for all secondary care supply chain protagonists is mandatory – subject to a small number of modifications versus primary care authentication. The rationale for this is axiomatic, if hospitals were exempt from the FMD this may create a scenario where medicines dispensed in secondary care posed more risk than those supplied in the community. Such a scenario would generate 'weak points' in the dispensing system placing vulnerable secondary care patients at risk.

In order to understand the importance of authentication in secondary care, it is crucial to first understand the drug distribution cycle within the National Health Service of any given state. Using the United Kingdom (UK) and the National Health Service (NHS) as an example (Figure 1.0) it is clear that the movement of drugs from the manufacturer to the hospital ward and corresponding patients is heterogeneous within individual hospital sites and internationally.



[7]Figure 1.0: An Exemplar UK (NHS) Drug Distribution Cycle

Sources estimate that a drug can travel through as many as 20 to 30 exchanges between supply chain and clinical stakeholders in European markets before reaching the desired patient[7], making drug tracing challenging. Furthermore, many NHS trusts return unused medicines dispensed to hospital wards back into stock in an effort to control drug expenditure. Although this is a crucial move to manage finances and

[1] This schematic largely represents the drug distribution cycle within the NHS; however certain NHS trusts may operate in variance dependant on the services they provide.

maintain the high level of healthcare that the UK has become accustomed to, this practice further complicates the drug distribution cycle in secondary care.

The complexity of the drug distribution cycle within the NHS also poses challenges vis-á -vis most large NHS trusts hold a wholesaler dealing license which permits each trust to routinely supply medicines to institutions such as community hospitals, hospices and the ambulance service not to mention the supply of scarce time critical medicines to other hospitals and community pharmacies in urgent circumstances.

These practices coupled with multiple drug entry points, via wholesalers, direct manufacturers and other suppliers creates an entirely necessary yet convoluted drug distribution chain which promotes the entry of illegitimate medicines. Such a distribution cycle is unparalleled in the primary care setting and creates an incredibly porous system with limited transparency [7].

Mandatory EU FMD Secondary Care Requirements

The FMD contains a number of points critical to secondary care hospital work processes.

Wholesaling Pharmacy Distribution Units

As highlighted previously many NHS organisations have wholesaler dealer licences and as such would be obliged to comply with FMD regulations in terms of wholesale supply. According to Article 23 of the Delegated Regulation (DR) [6] this means that a Central Hospital Trust Storage and Distribution Unit (CHTSD) with a wholesalers license must authenticate medicines before supply to certain persons or institutions, in a hospital setting this would more frequently be paramedics and emergency medical practitioners, universities, prisons, hospices and nursing homes but not to other healthcare institutions such as hospitals.

Misconceptions: The Hospital Dispensation to Decommission

The DR published in February 2016 describes most stakeholders as supportive of checking the unique identifier at the end of the supply chain, namely at community and hospital pharmacy level [6]. Despite this support there is a special dispensation for "*specific institutions*" (point 23) [6], which could remove the obligation of verification of the safety features in order to ensure that the verification measures on those parties 'is proportionate' [6]. This phrase has caused widespread confusion and has led many to believe that hospitals are exempt from the FMD legislation.

Point 23 of the DR [5] states that:

'It should be possible for the Member States to exempt specific institutions or persons authorised or entitled to supply medicinal products to the public from the obligation of verification of the safety features in order to accommodate the particular characteristics of the supply chain in their territory and ensure that the impact of the verification measures on those parties is proportionate.'

The DR states that 'specific institutions' may be exempt from authentication which does not necessarily equate to 'healthcare institutions' which specifically means a hospital, in- or out-patient clinic, or health centre (Point 2)[6].

Article 26 'derogations from Article 25' helps to further clarify this point, stating: '*Persons authorised or entitled to supply medicinal products to the public who do not operate within a healthcare institution or within a pharmacy are exempted from the obligation to verify the safety features and decommission the unique identifier of medicinal products where that obligation has been placed on wholesalers by national legislation in accordance with Article 23'*[6].

Truths: Healthcare Institution Decommissioning Exemption.

Within Article 26 (derogations to article 25) [6], the DR sets criteria below, which, if met, would remove the requirements for healthcare institutions to authenticate (decommission).

'(a) The person authorised or entitled to supply medicinal products to the public obtain the medicinal product bearing the unique identifier through a wholesaler belonging to the same legal entity as the healthcare institution;'

In terms of the secondary care environment this would relate to the CHTSU (figure1.0) with a wholesale dealers licence operating within the trust and therefore part of the same legal entity.

(b) The verification and decommissioning of the unique identifier is performed by the wholesaler that supplies the product to the healthcare institution;

In the case of secondary care the 'Wholesaler' would be the CHTSU which would be responsible for authenticating or decommissioning the product before it is delivered to a specific hospital with the NHS trust in question.

(c) No sale of the medicinal product takes place between the wholesaler supplying the product and that healthcare institution;

The CHTSD ('wholesaler') cannot sell authenticated or decommissioned products to a hospital within its own trust .The CHTSD is permitted to 'supply' but not 'sell' a decommissioned product to a hospital within the same legal entity i.e. a hospital within the same trust.

(d) The medicinal product is supplied to the public within that healthcare institution. [6.]

The decommissioned medicine would have to then be supplied to a patient in a hospital that is part of the same legal entity of the wholesaler (pharmacy distribution unit). This would disqualify any medicines decommissioned by pharmacy distribution from being sold to other legal entities such as other hospitals, community hospitals, prisons or the ambulance service etc. via a wholesaler dealer's licence.

In order to qualify for an exemption to decommissioning a trust would have to receive its medicines via a pharmacy distribution unit type department as per Figure 1.0, and such a unit would have to hold a wholesalers licence and form part of the same legal entity. As most NHS Trusts work via a pharmacy distribution unit, and many have a wholesale licence, this would be possible. However, for all intents and purposes this is the same as the rule which allows decommissioning before the point of supply to the patient. The practice of decommissioning by the pharmacy distribution unit or wholesale level adds an extra step at the 'goods in' stage with no added clinical value. Information regarding expiry dates, recall status and suspicious medicines is absolutely dynamic and to revert to a system in which medicines are decommissioned at the 'goods in " stage totally detracts from the core principle of the FMD that '*Persons authorised or entitled to supply medicinal products to the public should verify the authenticity and decommission a unique identifier at the time the medicinal product is supplied to the public so to access the most up-to-date information concerning the product and avoid that products which are expired, recalled, withdrawn or indicated as stolen are supplied to the public.'* point 24 [6].

Decommissioning before the point of supply to the patient

The DR states that within the 'Healthcare institution' medicines may be verified before the point of supply to the public:

'*In order to avoid an excessive impact on the daily operations of healthcare institutions, it should be possible for the Member States to allow persons authorised or entitled to supply medicinal products to the public operating within healthcare institutions to perform the verification of the authenticity and the*

decommissioning of a unique EN 10 EN identifier earlier than the time the medicinal products is supplied to the public, or exempt them from this obligation, subject to certain conditions' point 25 (page 9).

This is an exception to the rule that '*Persons authorised or entitled to supply medicinal products to the public should verify the authenticity and decommission a unique identifier at the time the medicinal product is supplied to the public*' (Article 25 point 2).

If a healthcare institution does decide to decommission a medicine before the point of supply to a patient this can only occur *'provided that no sale of the medicinal product takes place between the delivery of the product to the healthcare institution and the supplying of it to the public'*, this action revokes the suitability of such medicines for wholesale supply, having an enormous impact on the hospital wholesale business. To promote intra-trust and inter-trust movement of medicines it would make clear financial sense to decommission only at the point of supply to a patient, i.e. in the pharmacy for a patient specific supply, or at ward level by a nurse ensuring safety at the most crucial point and allowing flexibility for trusts to continue wholesale trading as usual.

'The Ten Day Rule'

For the purposes of practicality the DR has permitted organisations or persons such as wholesalers, manufacturers or pharmacies to revert the status of a drug previously decommissioned if the conditions from Article 13 (point1) [6] below, are fulfilled:

'(a) the person performing the reverting operation is covered by the same authorisation or entitlement and operates in the same premises as the person that decommissioned the unique identifier;

(b) the reverting of the status takes place not more than ten days after the unique identifier was decommissioned;

(c) the pack of medicinal product has not expired;

(d) the pack of medicinal product has not been registered in the repositories system as recalled, withdrawn, intended for destruction or stolen and the person performing the reverting operation does not have knowledge that the pack is stolen;

(e) the medicinal product has not been supplied to the public.[5].

The opportunity to reverse the decommission process facilitates the correction of decommissioning errors, with a 10 day window to perform this reversion which means that any medicine that decommissioned over 10 days previous would not be suitable for sale.

Article 13 (point1)[6]

'Medicinal products bearing a unique identifier which cannot be reverted to an active status because the conditions set out in paragraph 1 are not fulfilled shall not be returned to saleable stock.[6]*'*.

Where to Authenticate in Hospital

The Point of Supply: At the Bedside

The DR demonstrates (point 24)[6] that the verification of a product is not only for the purposes of establishing authenticity but also to inform the operator whether a product is expired, recalled, withdrawn or indicated as stolen using up to date information. It may take many months and in some circumstances years between a hospital receiving a medicine and delivering it to a patient, in this time a medicine may have expired, been recalled, or queries may have been raised as to its source. Therefore in order to best utilise this dynamic information, it is of utmost importance to authenticate medicines as close to the patient as possible. In terms of take away prescriptions, the most effective place to authenticate would be at the point of dispensing; in terms of an in-patient supply the safest place to authenticate would be at ward level before administration to the patient. This would provide a safety net for busy nursing staff and would work especially well with e-prescribing systems. Authentication could verify with the electronic prescribing system that the medicine selected matched that prescribed and that the medicine was not expired, recalled, with suspicious background or withdrawn.

Whether it is a pharmacist in a dispensary or a nurse on ward level each member of staff must physically pick up each medicine container and check that they have selected the correct product. This checking process includes the checking of the contents of the container, the drug name, drug form and the expiry date of the product. Authentication or decommissioning at this stage would add 250millisecond (the accepted FMD authentication speed) [1]. In fact, with the inclusion of tamper evident packaging, the FMD regulations will provide improved efficiency to current practise.

Medicines authentication services have the capability also to provide educational material when certain medicines are scanned which would be of great benefit in secondary care. This application could provide an

onscreen injectable monograph to help nurses in the administration of intra venous drugs or provide key points to pharmacists counselling on rarely dispensed drugs saving time associated with using paper based information. In future years it may be possible to link individual patient data to specific drug scans which would allow clinicians to compare medicines adherence in primary and secondary care linking disease control to adherence habits. The opportunity to educate further and to research patient behaviour would only be possible if medicines were decommissioned at the point of supply.

Authentication at 'Goods in'

To authenticate at 'goods in' would remove all requirements for pharmacists and nurses to scan medicines at the point of supply and allow this directive to be implemented without an impact on front line services. However, medicines that were in date, not recalled or appeared un-suspicious at goods in, may prove to be dangerous between the time they are decommissioned and the point of supply to the patient. The repercussions for supplying an expired, recalled medicine can be catastrophic and every effort should be made to ensure the most up to date information is used when deciding to administer a medication.

Authenticating at the goods in stage would place the onus on distribution staff and would act as an entirely new step in the goods in process. There have been discussions surrounding the aggregation of 2D data matrix codes to permit the decommissioning of multiple packs at once. The creation of aggregated codes will be set up to benefit large pharmaceutical wholesalers and is unlikely to deliver the same benefits to a CHTSU, due to lower ordering numbers. It is not always the case that medicines are delivered to hospitals in complete parcels, which would require the decommissioning of each individual medicine packets, a practice that would likely require the creation of further posts and financial outlays in an already financially constrained health care system. Unlike authentication at the point of supply, where useful up to date information regarding the drugs status (expired, recalled, suspicious, product shortage, reimbursement status, scientific pop up advice) decommissioning at the 'goods in' stage offers little or no advantage to distribution staff. With no incentive to decommission, it is feared that decommissioning rates by distribution staff would be far from complete.

There are a number of safety issues associated with decommissioning at the 'goods in' stage in terms of rare and time critical medicines. A hospital may be in possession of a critical medicine, however due to its decommission over 10 days previously the new law would not facilitate its wholesale supply to another trust in an emergency situation, putting patients lives at risk. The decommissioning products at the point of supply would alleviate this issue. The alternatives would be to create a dual stream system where a certain

percentage of medicines were decommissioned at goods in and others decommissioned at the point of supply to the patient or a 'specific institution'. A system of this would be possible but could prove difficult to manage and may reduce confidence in the entire authentication or decommissioning process.

When deciding on the optimum point to decommission it is also important to consider other secondary care medicine nuances such as robotic dispensing, ward based dispensing, split packs, satellite pharmacies, aseptic production and ward stock supply before deciding on the optimum point to authenticate.

Conclusion

The deadline for full FMD implementation and hospital compliance is 2019 (first quarter), a deadline which puts pressure on key stakeholders and decision makers within hospitals to prepare. The FMD contains a number of 'healthcare institution' or hospital references and despite confusion amongst some stakeholders it is clear that *hospitals are not exempt from the FMD*. The dispensations that have been made are pragmatic; but minor conferring hospitals the option to authenticate or decommission at either the goods in stage or the point of supply to the patient.

To authenticate at the point of supply to the patient is the FMD's raison d'être, 'accessing the most up to date information concerning the product' [5] and avoids dangerous medicines reaching the public, not to mention the potential additional benefits such as medicines adherence research, safety in medicines administration, staff and patient education; an incentive for the authenticating healthcare professional. To decommission at the goods in stage provides no incentive to the staff carrying out the task and undermines the ethos of the FMD, encourages a scenario where information regarding expiry, recalled status and suspicion comes to light only after the dangerous medicine is authenticated and administered to the patient.

Contribution Statement:

All authors contributed to the manuscript. BDN wrote the manuscript.

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