Chapter 8

EU Falsified Medicines Directive: Requirements and Implications for Multi-Stakeholder Healthcare Delivery

By James A. Smith, B. Naughton, A. Kramm, Graham Smith, A. Ohanjanyan, Mark De Simone, Rob Horne and David A. Brindley

OBJECTIVES
- Introduce the problem of falsified medicines
- Define falsified and counterfeit medicines
- Define active substances and excipients
- Identify requirements for different stakeholders in the medicines supply chain arising from the FMD
- Discuss challenges in implementing FMD requirements
- Identify relevant existing EU initiatives
- Provide a list of third countries
- Outline expected timelines for implementation of the FMD
- Evaluate potential developments in detecting and managing falsified diagnostics

DIRECTIVES, REGULATIONS AND GUIDELINES COVERED IN THIS CHAPTER
- Commission Implementing Regulation (EU) No 699/2014 of 24 June 2014 on the design of the common logo to identify persons offering medicinal products for sale at a distance to the public and the technical, electronic and cryptographic requirements for verification of its authenticity

Introduction
Falsified medicines, as defined by the European Medicines Agency (EMA), “are fake medicines that pass themselves off as real, authorised medicines.” Such medicines pose a significant public health risk as they may lack active ingredients, contain dangerous contents, contain incorrect doses, or be inappropriately labelled. According to the World Health Organisation (WHO), “Spurious/Falsely-Labelled/Falsified/Counterfeit (SFFC)” medicines comprise up to 1% of market value in the developed world, with the global figure rising to 10% of a pharmaceuticals market worth, more than $300 billion (US) per year. Remarkably, efforts
### Figure 8-1. Comparison of EU FMD and Other Countries’ Falsified Medicines’ Legislation

<table>
<thead>
<tr>
<th>Year</th>
<th>EU</th>
<th>USA/Worldwide</th>
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<tbody>
<tr>
<td>1998</td>
<td>An EU Green Paper on Counterfeiting in the Single Market studies the pharma industry</td>
<td>Prescription Drug Marketing Act provides a legal basis for combating fake medicines</td>
</tr>
<tr>
<td>2000</td>
<td>In Italy, the “Bollini” Law requires drugs to be tracked to the point of sale using two bar codes</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>New laws in Greece and Belgium compel drug manufacturers to adopt mass serialisation</td>
<td></td>
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<tr>
<td>2006</td>
<td>European Commission warns about fake drugs on the Internet and issues resolution on Counterfeited medicines</td>
<td>FDA’s Counterfeit Drug Taskforce sets a framework for rollout of an ePedigree scheme by 2007</td>
</tr>
<tr>
<td>2007</td>
<td>Industry associations such as EFPIA look for standardisation and the adoption of second technology</td>
<td>Despite assurances, market players make slow progress toward deploying tracking technology</td>
</tr>
<tr>
<td>2008</td>
<td>European Commission launches a public consultation on anti-counterfeiting measures</td>
<td>Pfizer works on a proprietary mass serialisation system, while EPC looks for an industry standard</td>
</tr>
<tr>
<td>2008</td>
<td>Responses to the public consultation are made public</td>
<td>WHO launches the International Medical Products Anti-Counterfeiting Taskforce (IMPACT)</td>
</tr>
<tr>
<td>2011</td>
<td>Commission Implementing Decision of 23 January 2013 on the assessment of a third country’s regulatory framework</td>
<td>California also extends the deadline for roll-out of its state level scheme from 2007 to 2011</td>
</tr>
<tr>
<td>2013</td>
<td>New EU legislation becomes applicable</td>
<td>FDA looks at technologies for the ID, validation, track and trace and authentication of prescription drugs</td>
</tr>
<tr>
<td>2014</td>
<td>Good Manufacturing and Distribution Practices (GMP and GDP) are to be adopted</td>
<td>Switzerland, Israel, Australia, Singapore, Brazil and Japan are adopted as third countries</td>
</tr>
<tr>
<td>2014</td>
<td>Common logo design for legally-operating online-websites is implemented</td>
<td>US and New Zealand are adopted as third countries</td>
</tr>
<tr>
<td>2014</td>
<td>Safety features: unique serial number specifications and verification system are implemented</td>
<td></td>
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</table>
EU Falsified Medicines Directive: Requirements and Implications for Multi-Stakeholder Healthcare Delivery

Table 8-1. Definitions of Key Terms in this Chapter

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Source</th>
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<tbody>
<tr>
<td>Spurious/Falsely-Labelled/Falsified/Counterfeit (SFFC) Medicines</td>
<td>Medicines deliberately and fraudulently mislabelled with respect to identity and/or source.</td>
<td>World Health Organisation¹</td>
</tr>
<tr>
<td>Falsified Medicine</td>
<td>Any medicinal product with a false representation of: (a) its identity, including its packaging and labelling, its name or its composition regarding any of the ingredients, including excipients and 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 records and documents relating to distribution channels used.</td>
<td>Falsified Medicines Directive²</td>
</tr>
<tr>
<td>Counterfeit Medicine</td>
<td>Any medicinal product that does not comply with intellectual property rights and/or infringes on trademark law.</td>
<td>European Medicines Agency³</td>
</tr>
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1. WHO, Medicines spurious/falsely-labelled/falsified/counterfeit (SFFC) medicines (http://www.who.int/mediacentre/factsheets/fs275/en/)

Pioneering attempts to address this important global health issue, the European Parliament and Council of the European Union adopted the Falsified Medicines Directive (FMD), Directive 2011/62/EU³ and delegated acts and regulations.⁴ Adoption of the FMD has been described as the single largest change in the pharmaceutical industry in the last 40 years,⁵ and resulted from recognition of the issue’s significance⁶ (Figure 8-1). This chapter provides a comprehensive overview of this significant policy, outlines anticipated requirements and means of execution, and discusses implications for multiple stakeholders involved in healthcare delivery.

Defining Falsified Medicines
Understanding the meaning of “falsified medicines” is critical to understanding the FMD’s scope. The terms “counterfeit” and “falsified” medicine often are confused and applied incorrectly; counterfeit medicines “do not comply with intellectual property rights or infringe trademark law,” whereas falsified medicines are “fake medicines designed to mimic real medicines.”⁷ This difference and the need for explicit definitions is emphasised by the European Medicines Agency (EMA).⁸ The FMD defines falsified medicinal products as:

“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.”

Note: the definition “does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights.” Confusingly, although the two terms clearly are distinct, SFFC medicines often are referred to collectively as “counterfeits,” and those producing falsified medicines may be termed “counterfeiters” (e.g., WHO).⁹,¹⁰

Greater nomenclature clarity and consistency would be useful. Within WHO Member States, there is little consensus in defining counterfeit and falsified drugs,¹¹ creating considerable difficulty in global discussions. The EU has attempted to standardise the terminology, and the authors recommend the definitions used herein (Table 8-1) be adopted worldwide to facilitate standardisation in both discussion and policy.

Problem Scope
SFFC medicines are not a new concept; however, the advent of the Internet and e-pharmacies has augmented their threat. SFFC medicines’ appearance in international commerce was mentioned first in 1985 at the WHO Conference of Experts on Rational Drug Use in Nairobi, Kenya.¹²,¹³ Increasing international trade and the increase in online pharmaceutical sales has facilitated entry of SFFC medicines into the complex supply chain,¹⁴ eventually leading WHO to establish the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) in 2006.¹⁵ More than...
50% of medicines purchased online from illegal sites, which do not reveal their physical addresses, have been found to be SFFC medicines. However, SFFC medicines also may reach patients via the legal supply chain (Figure 8-2). SFFC medicines often are perceived as a problem largely affecting less economically developed countries and high-cost drugs (e.g., the 1985 WHO Conference Report suggested only high-cost drugs were affected). However, the problem actually affects high- and low-cost products, including branded and generic drugs in more- and less-economically developed countries (Table 8-2). For example, falsified vials of the relatively high-cost breast cancer drug Herceptin were confirmed in Germany and suspected in Finland, Austria and Sweden, following their theft in Italy. In France in 2013, 1.2 million doses of the common drug aspirin were seized.

To attempt to address the problem of falsified medicines, the EU adopted the FMD in 2011.

Falsified Medicines Directive

Aims and Scope

The FMD amended Directive 2001/83/EC on the Community code related to medicinal products for human use and aims to tighten medicinal product distribution chain control and protect consumers from falsified medicines. FMD addresses problems arising from the medicines supply chain’s increasing complexity, with the Internet being one of the biggest threats. Controls and checks throughout the supply chain are to be strengthened, including active substances (sometimes also called active pharmaceutical ingredients (APIs)) sourced from non-EU countries and the point at which patients receive medication from a pharmacist or delivery via the internet.

Similar to other recently introduced legislation in the EU, such as ATMP Regulation (Regulation (EC) No 1394/2007), one of the FMD’s central aims is harmonisation of falsified medicines regulation across the EU. Delegated acts ensure each Member State implements them uniformly, ensuring consistency throughout the EU. The directive also emphasises falsified medicines are a global problem, and in the interests of global health, cooperation with international bodies is essential with regard to falsified medicines.

Requirements

The FMD introduces new requirements for various stakeholders in medical supply chains, who can be categorised broadly as manufacturers, brokers, wholesalers and retailers. These requirements are outlined in Table 8-3. Introducing safety features—mandatory tamper-evident seals and unique pack identification—on packaging will provide assurance of medicines’ authenticity. The FMD substantially changes the European framework for the supply of medicines, and also will include businesses traditionally not regulated directly: medicinal product brokers, who do not handle products physically. Further, it provides definitions for active substances and excipients (Table 8-4), and introduces Good Manufacturing Practice (GMP) guidelines for active substances.
Not all medicines will be subject to the FMD’s rules. The directive states prescription medicines must bear the safety features mentioned above, whereas those not subject to prescription shall be exempt from the requirements. There are exceptions: if risk assessment excludes them, prescription medicines will not require safety features and, conversely, nonprescription medicines deemed particularly vulnerable to falsification will require the features. Risk assessment to determine exceptions should include considerations of price, sales volume, previous cases of falsification in the EU or third countries, implications of falsification for public health and severity of the condition to be treated. Any excepted medicines must be listed in a delegated act.

**Directive Implementation**

Perhaps the most significant regulation imposed in the FMD is the requirement for new safety features for medicinal product packaging: to verify whether the packaging has been tampered with (‘tamper-evidence’), and verify the product’s authenticity and identify an individual product pack (‘unique identifier’). In a concept paper released for public consultation in 2011, the European Commission outlined expected requirements for these features. For tamper-evidence, the technical specification choice is left to the manufacturer and specific guidance is not given. However, for the unique identifier, specific technical guidance is provided: the only way to uniquely identify a pack is to label it with a randomised serialisation number affixed to the package by a carrier holding the number. This carrier most likely will be a 2-D barcode, although radio-frequency identification also has been proposed. The serialisation number then is checked against its entry in the repositories system, which verifies its authenticity.

For this system to be successful, a reliable verification system must be in place. Since randomised numbers could...
Table 8-3. Different Medicinal Product Supply Chain Stakeholder Requirements Under the FMD

<table>
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<tr>
<th>Stakeholder</th>
<th>Requirements/Relevant Legislation</th>
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| Multiple                                         | • Packagers, repackagers, wholesale distributors, pharmacies/retailers and possibly others must be able to verify the medicinal product’s authenticity, uniquely identify individual packs and maintain a repository system in which to store identification data. They must be able to determine whether the outer packaging has been tampered with.  
• Active substance importers, manufacturers and distributors established in the EU must register their activity with the Competent Authority of the Member State in which they are established.  
• Each Member State must ensure the import of active substances from outside the EU, intended for use in the manufacture of a medicinal product, is accompanied by a written confirmation from the Competent Authority of the non-EU country stating standards of manufacture at the active substance manufacturing site are equivalent to EU requirements.  
• The Competent Authority of the Member State shall ensure legal requirements for manufacturers are met by inspection of facilities, which may be unannounced. Manufacturers and wholesale distributors are subject to repeated inspections. |
| Manufacturer                                      | • Any actor in the supply chain that packages medicinal products must hold a manufacturing authorisation.  
• Manufacturing authorisation holders who are not the original manufacturers must only remove, replace or cover the original safety features under strict conditions; if the product is repackaged, safety features must be replaced by equivalent safety features.  
• Manufacturers must inform the Competent Authority and marketing authorisation holder immediately should the manufacturer obtain information that medicinal products (manufactured under the scope of the manufacturing authorisation) may be falsified, regardless of whether those products are being distributed through the legitimate supply chain or by illegal means.  
• Active substance manufacturers should be subject to inspections on the basis of risk-analysis, as well as on the grounds of suspected noncompliance.  
• Regardless of whether an active substance is manufactured inside or outside the EU, its manufacture should be subject to Good Manufacturing Practice. A legally binding act regarding GMP for active substances has been introduced. |
| Broker                                           | • Introduction of the brokering concept for finished medicinal products and provision of a new definition for brokering: “All activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, including physical handling and consisting of negotiating independently and on behalf of another legal or natural person.”  
• Brokers must register with the Competent Authority of the EEA Member State in which they are established. |
| Wholesaler Distributors                           | • Wholesale distributors should verify their supplying wholesale distributors are holders of a wholesale distribution authorisation.  
• A person exporting medicinal products from the EU, including those with the sole purpose of exporting medicinal products, are considered wholesale distributors and are, as such, subject to relevant provisions and Good Distribution Practices.  
• A list of wholesale distributors complying with EU regulations based on inspection by a Competent Authority in a Member State will be published in a database established at the EU level. |
| Retailers (Suppliers to the Public)               | • Companies selling medicines online to members of the public must be authorised and require a common logo to be displayed on their websites (Figure 8-3), which should be linked to the website of the Competent Authority for the country in which the retailer is established. Websites of all Member States and of the EMA should explain use of the logo, and all of those websites should be linked to provide comprehensive information to the public.  
• Member States are allowed discretion regarding conditions for the supply of medicines to the public on their territory.  
• Given risks of online retail, Member States may, in principle, restrict sale of medicinal products to pharmacists alone. However, these restrictions should not unduly restrict functioning of the internal market.  
• A list of compliant retailers selling medicinal products at a distance should be provided to the public by each Member State. |
| Community Pharmacies (Independent and Multiple)   | • Pharmacies will be required to authenticate medicines at the point of dispensing with an approved FMD-compliant authentication service to ensure medicines supplied are from legitimate sources with clear distribution histories.  
• In keeping with their role in the community as the medicines experts, they also will be responsible for providing patient advice concerning queries relating to falsified and counterfeit medicines. |
| Hospital Dispensaries/Pharmacies                  | • Hospital dispensaries may be given special dispensations in certain circumstances with regard to FMD compliance, but it generally is understood they, too, will be expected to comply with the majority of FMD requirements.  
• Hospital pharmacies may encounter problems with authentication of medicines issued within the hospital and returned to stock as some medication packs are used for multiple patients and, therefore, multiple pack authentications, which is a problem not experienced by community pharmacies. |
be reproduced easily, the serialisation number must be ‘checked in’ to a repositories system and after its final use, removed or ‘checked out’ of the system (Figure 8-3). Such a system would have various benefits, for example, allowing recall of medicines, safety messaging, notification of expired or suspicious medicine and information on previously dispensed medicine, all based on information stored in the serial number and/or verification system.

In addition to those covered in Table 8-3 and made explicit in FMD, the introduction of unique product identifiers may elicit new stakeholders in the medicinal product supply chain: those who establish and maintain the verification systems and repositories. Several organisations are beginning to address unique identifier requirements, and some existed prior to FMD’s publication (Table 8-5). Such organisations will need to comply with several requirements specified in the FMD; notably, safeguards protecting personal and commercially sensitive information should be in place and the FMD applies without prejudice to Directive 95/46/EC on protecting individuals with regard to processing personal data and the free movement of such data.24

Third Countries

Under the FMD, countries outside the EU are obliged to provide written confirmation active substances exported from their country adhere to Good Manufacturing Practice (GMP) standards equivalent to those in the EU. Third countries can be added to a ‘white-list’ if the country’s “regulatory framework applicable to active substances exported to the Union and the respective control and enforcement activities ensure a level of protection of public health equivalent to the [EU].”25 So far, Australia, Switzerland, Japan, the US, Brazil and Israel have been added to the list, and other countries are at various stages in the process (Table 8-6). In particular, the assessment will take into account:

1. GMP rules in the country
2. regularity of GMP compliance inspections
3. effectiveness of GMP enforcement
4. regularity and rapidity of provision of information regarding noncompliant active substance production26

With this legislation, the EU aims to protect its Member States, but also supports recognising equivalent scientifically based standards worldwide, helping protect the public better and provide a greater level of protection on a wider international scale.

GMP for Active Substances

Commission delegated Regulation (EU) No 1252/2014 supplements Directive 2001/83/EC of the European Parliament and the Council with regard to principles and guidelines of GMP for active substances for medicinal products for human use.27 Continuing with one of the FMD’s central aims, the regulation strives to promote use of harmonised standards at a global level; therefore, developing guidelines aligning with those established by the International Conference on Harmonisation (ICH).

Broadly summarising the regulation:

Figure 8-3. An Example of the Common Logo Online Retailers of Medicines Must Display

The flag corresponds to the Member State in which the retailer is registered. Only EU Member State national flags are allowed, as well as those of Norway, Iceland and Lichtenstein. By clicking on the image, the purchaser is directed to the entry of the retailer on the national list. Commission implementing regulation (EU No 699/2014 details the requirements for the logo. (Image Source: http://ec.europa.eu/health/human-use/eu-logo/index_en.htm )
Table 8-5. EU Initiatives Relevant to the FMD

<table>
<thead>
<tr>
<th>European Stakeholder Model</th>
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<tr>
<td>European Stakeholder Model (ESM) is a partnership of organisations involved in the pharmaceutical supply chain, overseen by a not-for-profit stakeholder organisation called the European Medicines Verification Organisation (EMVO). The ESM’s aim is to develop a safe, cost-effective and partnership-based pan-European medicines verification system using 2-D barcodes to address FMD needs. ESM partners are establishing a coding and serialisation system to be implemented by Europe’s research-based manufacturers, licensed parallel distribution companies, wholesalers and pharmacists. Their approach was tested at a national level in Sweden.</td>
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<table>
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<tr>
<th>eTACT: Anti-Counterfeiting Traceability Service for Medicines</th>
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<tr>
<td>eTACT is the European Directorate for the Quality of Medicines and Healthcare (EDQM) anti-counterfeiting traceability service for medicines. The project has been developed in parallel to the FMD and is part of the Council of Europe’s global strategy to combat SFFC medicines. eTACT’s aim is to ensure traceability of individual packs of medicines using mass serialisation. Similar to safety features introduced by the FMD (mandatory seals and unique pack identification), it is based on the principle of generating a Unique Medicine Identifier (UMI) at the manufacturing stage. UMI allows traceability and verification by different stakeholders in the legal supply chain. It is designed in accordance with the FMD’s requirements and its future delegated acts.</td>
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<tr>
<th>ASOP EU</th>
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<tr>
<td>Alliance for Safe Online Pharmacy (ASOP EU) comprises patient organisations, Internet intermediaries, healthcare providers, pharmaceutical companies and supply chain stakeholders united in a campaign to make the Internet a safer place to obtain medicines. It aims to become a trusted partner of the authorities in combatting the illegal sale of medicines online.</td>
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</table>

- Personnel and equipment in the manufacturing area’s vicinity must be sanitary.
- To prevent cross-contamination when producing active substances harmful to human health, those substances should be manufactured only in separate areas; for active substances with potential to be harmful to human health due to potency, toxicity or infectiveness, risk assessment must be undertaken to evaluate the potential need for separate production areas.
- Detailed written records of production processes must be kept, and any changes affecting the active substance’s quality should be communicated to manufacturers using the active substance.
- Procedures must be in place allowing product recall and investigation of concerns over active substance quality.
- If the manufacture of any part of an active substance is entrusted to another party, responsibilities of the other party in terms of GMP quality compliance must be clarified in writing.
- GMP must be applied to the repackaging and relabelling process.

Safety features introduced require substantial medicinal product packaging manufacturing process adaptations. As such, the FMD stated the timeline for implementing provisions relevant to safety features must be sufficiently long to allow manufacturers to adapt their manufacturing processes effectively. Some Member States already have authentication or verification systems in place and will be given additional time to adapt to the harmonised EU system. Several EU initiatives have emerged or exist already with relevance to various FMD components, including the unique identifier and, more generally, combatting illegal drug sales via the Internet.

**Implications and Challenges**

Addressing falsified medicines ultimately requires global cooperation. The FMD recognises the need for concerted international effort against falsified medicines, particularly regarding Internet sales. As such, Member States and the European Commission are encouraging cooperation and supporting ongoing international efforts on falsified medicines. In line with this, and “to promote the use of harmonised standards at a global level,” delegated regulation regarding GMP for active substances adopted guidelines in agreement with those established by ICH. If other worldwide regulatory bodies act similarly and standardise terminology as suggested above, the battle against falsified medicines will be greatly accelerated and facilitated.

Despite these positive steps, many perceive FMD implementation as a challenge. Costs for affected actors in the medical product supply chain likely will be considerable, particularly regarding new safety feature requirements and accompanying systems; some have expressed concerns these costs will make some medicines unaffordable and could impact parallel trade negatively, particularly given they often are repackaged. Complex information transfer required
for FMD compliance will necessitate substantial changes to current system infrastructures, and ensuring these changes are harmonised throughout the EU will be essential to successful implementation.

This chapter has discussed implications for multiple stakeholders in the medicinal product supply chain affected by the FMD. However, ultimately, the most important stakeholder affected by the directive is the patient, and issues with costs of implementation likely will be outweighed by patient benefits. Beyond the clear benefits of reducing the prevalence of falsified medicines, there is considerable scope for wider reaching impact. In particular, adoption of unique identifiers and verification/repository systems could allow other health-related issues to be addressed: data generated could be used to measure and characterise patient behaviour with regard to medicine, aid communication between pharmacy and patient and allow development of tools to communicate with and support patients directly (Figure 8-3).

Although other legislation aims to combat trade of falsified medicines worldwide (e.g., the Drug Quality and Security Act, H.R. 3204 in the US), with the FMD, the EU is leading an ambitious attempt to develop a harmonised approach to tracking and labelling safe medicines and ensuring falsified medicines do not reach patients by authentication at the dispensing point. The FMD applies directly to the EU; however, by promoting standardisation more broadly, patients throughout the world may benefit. While inevitably introducing costs and challenges to the medicinal product supply chain, this historic regulation is an essential step toward a world free of falsified medicines, and should be perceived as such.

Ultimately, the problem of falsified medicines is a major risk to patient safety, damaging public trust in healthcare and the pharmaceutical industry—reducing revenue available to reinvest in R&D efforts to address unmet medical needs. While investment in requisite manufacturing and distribution infrastructure, particularly in primary and
secondary care pharmacies, initially may be burdensome, generation of primary benefits—reduction in falsified medicines and reimbursement fraud and tighter control of active pharmaceutical ingredients—likely will be swift. Secondary benefits including reduced dispensing errors, opportunity for patient engagement, providing information about medicines and supporting optimal adherence, electronic informed consent, real-time pharmacovigilance and business intelligence are tractable and impactful.

Preventing falsified medicines and realising the FMD’s secondary benefits are not just legal requirements; they are healthcare professionals’ responsibilities at all stages of the lifecycle to safeguard patient safety and improve patient outcomes.

**Potential Developments in Detection and Management of Falsified Medicines and Devices**

The FMD’s primary purpose is to identify and deter falsified medicines in today’s pharmacopeia, dominated by small molecules (high volume, low cost) and mAb biologics (high cost, low(ER) volume). However, a snapshot of contemporary basic science and clinical trial landscapes clearly indicates the future pharmacopeia is more complex, moving away from allogeneic small molecules to complex autologous therapeutics and combinational strategies, utilising therapeutics and devices (Figure 8-5). Consequently, guidance and regulation pertaining to falsified medicines and devices must adapt.

**Scope of Combination Therapies**

Combination therapies may be applied in a variety of approaches, including a small molecule being co-administered with a biologic; for example, anti-TNFs and Methotrexate. At the core of stratified and personalised medicine approaches is use of companion diagnostics to identify patients with a disease-specific genetic marker, which indicates a high likelihood of efficacy arising from application of a specific therapeutic. Finally, and more futuristically, combinational approaches include de-cellularised...
xeno-derived and/or cadaveric scaffolds to which human cells are engrafted in tissue engineered approaches; and gene modified autologous immunotherapies. All permutations of combinational therapies have major implications for effective implementation of the the FMD.

Companion Diagnostics

Companion diagnostics, applied with a (biological) therapeutic, are increasingly common feature of medical practice and biopharmaceutical company clinical trial pipelines. Presently, only the therapeutic component of the treatment will be protected against SFFC by FMD-mandated safety features. However, there is an incentive to falsify the companion diagnostic—which can command a high reimbursement level akin to some high-cost small molecules—both to generate direct revenue from the counterfeit diagnostic, but also potentially by generating a deliberate false positive to stimulate sales of legitimate and/or counterfeit therapeutics. Therefore, while discussions pertaining to potential legislation to identify and control falsified devices are on-going among international regulators, positive synergies between the FMD and the forthcoming EU Falsified Device Directive (EU FDD) should not be overlooked, nor should potential complexity in their parallel implementation and enforcement.

References

Chapter 8


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