The Role of The Falsified Medicines Directive and Delegated Regulation in The Supply Chain of Clinical Trials

Companies providing clinical trial supply services to sponsors and contract research organisations (CROs) need to comply with a complex framework of regulatory requirements and industry standards. These include the obligations prescribed in the Falsified Medicines Directive (2011/62/EU) and Delegated Regulation (EU/2016/161) with regards to the verification and decommissioning of safety features on products provided for clinical trial purposes. But whose responsibility is it to perform such obligations among the various stakeholders in the clinical supply chain? What implications does FMD-awareness have in terms of compliantly administering clinical trials? And what benefits do FMD related processes offer to clinical trials?

Introduction of the FMD

To ensure that the integrity of the supply chain of pharmaceutical products remain intact in the European Union (EU), a series of regulatory measures have been adopted by the European institutions and the European Medicines Agency (EMA) in the last decade. The implementation of the Falsified Medicines Directive (2011/62/EU) and Delegated Regulation (EU/2016/161) were among the leading initiatives to prevent the entry of falsified medicinal products into the legal supply chain. These regulatory instruments led to the creation of the European Medicines Verification System (EMVS), an overarching, EU-wide IT infrastructure linking a series of national data depositories to a central EU hub. The directive and delegated regulation also introduced the mandatory placement of safety features – a unique identifier (UD) and an anti-tempering device (ATD) – on each box of prescription medicine produced after the implementation date.

In addition, the new regulatory framework obliges manufacturers, wholesalers, and persons authorised or entitled to supply medicinal products to the public (e.g., pharmacies) to perform certain tasks related to the safety features. Along the different phases of the pharmaceutical supply chain, the authenticity of the unique identifiers and the integrity of the anti-tampering devices are to be verified by the different stakeholders. Also, at certain stages of the distribution process and for specifically designed purposes, the unique identifiers are to be decommissioned and hence removed from commercial circulation. The Delegated Regulation unambiguously defines the responsibilities of each stakeholder with regards to when, how and why they must verify and decommission safety features. Instructions in the Delegated Regulation cover various contexts of distribution, such as when products are supplied to the public, exported outside of the EU, provided to the authorities as samples or subjected to further manufacturing processes for clinical trial purposes.

Implementation of the FMD

The implementation of the FMD upon its introduction proved to be a complicated process with many unforeseen challenges and an unexpectedly high level of non-compliance on behalf of stakeholders. The development of several national data-repository systems was not completed by the implementation date hence their integration to the central European database has been delayed. Manufacturers were substantially lagging behind with regards to some of their obligations, such as the timely uploading of unique identifiers to the appropriate data repositories or the appointment of their delegated wholesalers in the verification system. Pharmacies across Europe failed to acquire the IT tools, software systems and procedural know-how to fully comply with their responsibilities. These systemic failures led to a transitional stabilisation or grace period of the implementation that was characterised by an immense number of alerts in the system and a constant breach of the prescribed protocols with non-compliant stakeholders.

During the implementation process, a plethora of questions have been raised by all the different stakeholders. In many cases, even the regulatory authorities could not provide definitive answers in terms of how the regulatory rules and regulations are to be interpreted in real-life, operative scenarios. Early in the implementation process, the European Commission has started to compile a document with all the relevant questions submitted by the stakeholders and the answers provided by the Member State expert group on safety features. Nothing demonstrates more the uncertainty around the implementation than the fact that, as of November 2021, such document has undergone over more than 20 extensions and modifications and currently include approximately 120 questions.[2] To further exacerbate the situation, shortly after the implementation date of the system, the United Kingdom – a previous adaptor of the FMD regulatory framework and infrastructure – has withdrawn from the European Union.

Benefits, Tasks, and Risks for the Clinical Research Sector

The implementation of the FMD offers various benefits within the field of clinical research. An enhanced level of security with regards to the integrity of the supply chain of products used in clinical trials is certainly a benefit for the sector. In the past, several clinical trials have been negatively impacted when falsified products were identified in their supply chain hence a more transparent and rigorous verification system concerning the authenticity of the involved products is highly advantageous. In addition, combined with a thorough documentary check, the verification of the products used in clinical trials via the European Medicines Verification System also allows for more transparency relating to the distribution history of the involved products.

The implementation of the FMD also poses additional operative tasks and responsibilities during the organisational process of clinical trials. The classic clinical trial supply chain – primarily concerning the manufacturing and distribution of previously non-marketed investigational medicinal products (IMPs) – is outside the scope of

the FMD and the Delegated Regulation. However, when previously marketed, non-investigational medicinal products (NIMPs) are introduced in the clinical supply chain as comparators, rescue medicine or concomitant medications, the obligations of stakeholders prescribed by the FMD regulations do apply. FMD rules are also relevant when commercially marketed products with safety features are considered as IMPs in case they are being examined in different indication(s) than those included in their marketing authorisations. The types of tasks and the identity of the stakeholders who should carry them out depend on various factors, such as the extent of the manufacturing process (e.g., labelling) the products need to undergo before being introduced to the clinical supply chain.

Apart from the extra operational tasks of verifying and decommissioning unique identifiers as described above, the FMD implementation also introduced several additional administrative and compliance-related tasks with regards to the appropriate supervision of clinical trials. Sponsors or contract research organisations cannot afford to have non-compliant service providers in their supply chains let those be negligent wholesalers ignoring their verifications responsibilities, neglectful manufacturers omitting the step of decommissioning products before labelling them or irresponsible investigational sites where products are not decommissioned before they are administered to patients taking part in the clinical trials.

The price to pay in case of not properly executed FMD tasks is way too high. Products that are not duly verified can turn out to be recalled, withdrawn, indicated as stolen or flat out falsified with a false representation of their identity, composition, source, or history as defined in the guidelines on Good Distribution Practice of medicinal products for human use. Such scenarios can lead to the temporary suspension or ultimate cancelling of an entire clinical trial and might bring about additional legal consequences to the sponsor or the contract research organisation in charge of ensuring compliance with all regulatory requirements. The lack of proper verification protocols can also generate system alerts sent directly to the regulatory authorities, such as the alert for example that is raised when a clinical investigatory site intends to duly decommission the unique identifier of a product that is already marked as 'supplied to the public' in the medicines verification system. Such alert would automatically warrant unsolicited attention and a formal investigation on behalf of the regulatory authorities.

FMD Obligations of Manufacturers in the Clinical Supply Chain

The verification and decommissioning of the unique identifiers on products supplied for clinical trial purposes can be carried out in numerous stages of the distribution process and by different stakeholders. Manufacturers – as described in Article 16 of the Delegated Regulation[1] – must verify the unique identifiers before decommissioning them on packs to be repackaged or re-labelled for further use as authorised investigational or auxiliary medicinal products. When wholesalers provide commercial products to providers of clinical trial manufacturing services for labelling or repackaging, it is such manufacturing service providers' responsibility to decommission the unique identifiers of the products. When and how such decommissioning takes place depends on multiple factors since once a product is decommissioned for manufacturing processes (e.g., labelling) it cannot be returned to the supplying wholesaler and needs to be destroyed should it end up not being used in the trial for any reason.

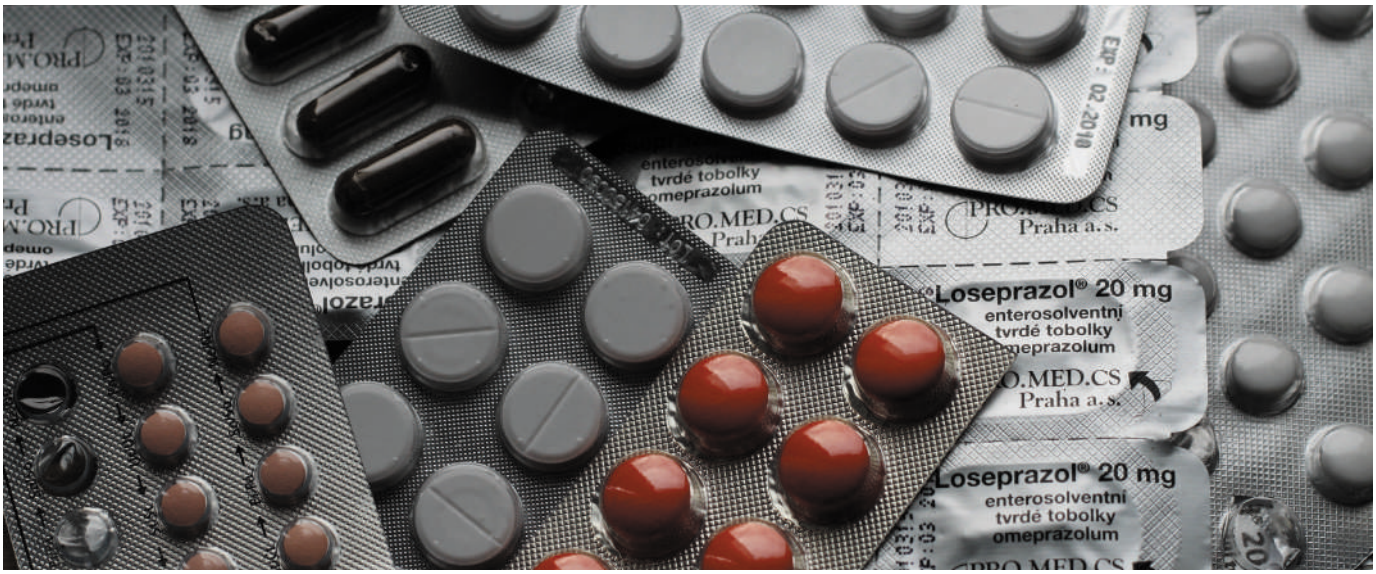
Once the unique identifiers of commercial products are decommissioned and the manufacturing processes have been concluded, manufacturers are not bound to apply new safety features to the repackaged or labelled products to be used exclusively in clinical trials. As mentioned earlier, this is because the scope of FMD does not cover the clinical trial supply chain including products not used in commercial circulation. The situation is different in other supply chain scenarios, such as parallel distribution, where the repackaged or labelled products re-enter commercial circulation. These repackaged or labelled products need to comply with all FMD requirements including the replacement of the old unique identifiers and anti-tampering devices with new ones.

Products manufactured for known use in a clinical trial – as described in Question 1.6 of the previously mentioned document maintained by the European Commission[2] – are excluded from the requirement of the FMD. These are products defined as investigational medicinal products (IMPs), manufactured in accordance with the original marketing authorisation but are specifically packaged for a clinical trial in a way that substantially differs from their commercial presentation. The manufacturer of such products would be required to hold a manufacturing and importation authorisation covering IMPs and the manufacturer should be named and authorised in the specific clinical trial application approved by the appropriate regulatory authority. Since these products are not required to carry any safety features; manufacturers have no verification or decommissioning tasks associated with them. Naturally, manufacturers could still opt for placing unique identifiers on these boxes for better transparency and traceability purposes but those are not to be included in and checked against the data repositories of the European Medicine Verification System.

FMD Obligations of Wholesalers in the Clinical Supply Chain

Wholesalers – as described in Article 20 of the Delegated Regulation[1] – are bound to verify unique identifiers of packs not sourced directly from manufacturers, marketing authorisation holders or their designated wholesalers to be later supplied for clinical trial purposes. Wholesalers are also obliged to verify products returned by pharmacies or other wholesalers. Such returned products are however preferred to be excluded from the clinical supply chain owing to the additional risk they represent. Since the verification of unique identifiers can be carried out voluntarily and at any times, prudent sponsors and contract research organisations are advised to request their wholesaling partners to verify every pack before being supplied. Verification by wholesalers should take place before goods are delivered to the investigatory sites where they are dispensed to patients or before they are delivered to the manufacturing entities responsible for further repackaging or labelling. Wholesalers providing commercially available non-investigatory medicinal products to clinical trials hold the key to ensuring that no falsified medicinal products are provided in the clinical supply chain and no alerts are raised in the medicines verification system that could jeopardise the continuity of the clinical trial.

Wholesalers in possession of a sole Wholesale Distribution Authorization (WDA) have limited options to decommission unique identifiers. The full range of decommissioning options available for wholesalers are described in Article 22 of the Delegated Regulation[1] and they do not involve the possibility of decommissioning for repacking or relabelling activities within the context of clinical trial supply. To acquire such decommissioning capabilities, a service provider must hold a manufacturing authorisation and operate according to the Guidelines on Good Manufacturing Practices (GMP). Also, as frequently misunderstood within the context of the clinical trial supply chain, wholesalers are not authorised to decommission the unique identifiers of commercial products delivered to clinical investigatory sites either. When supplying products to specific institutions that dispense them to the public (e.g., prisons, nursing homes, etc.) wholesalers might be able to decommission unique



identifiers as required by national authorities. Article 23 of the Delegated Regulation[1] lists all the different types of such specific institutions and reasons among which however clinical trial purposes are not included.

FMD Obligations of Pharmacies in the Clinical Supply Chain

Within the context of clinical trials, persons authorised or entitled to supply medicinal products to the public typically constitute of pharmacies located at the clinical investigatory sites where the clinical trials are conducted, and patients involved in the clinical trial receive treatment. The implementation of FMD has introduced an additional layer of complexity to dispensing products to patients under the purview of a clinical trial specifically when those products are commercially marketed and hence carry safety features. Article 25 of the Delegated Regulation[1] places a clear obligation on pharmacies to verify the safety features and decommission the unique identifier of medicinal products which they supply for subsequent use as authorised investigational medicinal products or authorised auxiliary medicinal products. It is very important to emphasise that omitting to decommission commercially marketed products used in clinical trials is an evident case of non-compliance with the applying regulatory rules and regulations and hence should be avoided by all means.

Conclusion

The regulatory framework and infrastructure implemented in the last couple of years in the EU have undoubtedly improved the safety of the supply chain for pharmaceutical products. A more transparent, more verifiable, and securer network of distribution for clinical trials supplies certainly benefits the sector of clinical research as well. The implementation of the regulatory framework has had its fair share of challenges owing to delays in infrastructure development, a lack of clarity about tasks in certain contexts (e.g., clinical trials, parallel distribution, etc.) as well as non-compliance of stakeholders with their transactional tasks and responsibilities. Ambiguity about FMD processes still prevail as certain political developments (e.g., Brexit) and the lack of enforcement of the rules on behalf of certain Member States still stand in the way of a fully harmonised European compliance.

Within the context of clinical trials, not all processes pertaining to the verification and decommissioning of unique identifiers have initially been fully understood. This was particularly the case with commercially marketed products carrying safety features that are supplied to patients involved in clinical trials as non-investigational medicinal products. However, three years after the implementation of the Delegated Regulation, the tasks and responsibilities of manufacturers, wholesalers and persons authorised or entitled to supply medicinal products to the public within the context of clinical trials have been distilled. Providers of clinical trials supply services now navigate the waters of FMD requirements with substantially more confidence. Compliance with FMD regulations must become a norm for sponsors and contract research organisations as the initially granted stabilisation or grace periods have ended and regulatory agencies are announcing focused FMD audits to come for all participants in the clinical supply chain.

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