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The Relevance of the Guidelines on Good Distribution Practice (GDP) in the World of International Clinical Trials

The successful execution of international clinical trials requires the involvement of service providers adhering to a wide range of regulatory guidelines and industry standards including the Good Clinical Practice (GCP), the Good Manufacturing Practice (GMP) or the Good Laboratory Practice (GLP). Companies following the guidelines of Good Distribution Practice (GDP) are also involved in ensuring that the logistics and quality assurance requirements of the products used in clinical trials are duly met. The article aspires to highlight the different aspects of Good Distribution Practice (GDP) that are relevant to the sector of clinical trial management. It also aims to identify those professional characteristics that sponsors, and contract research organisations (CRO-s) should look for in a potential service provider within the realm of pharmaceutical wholesaling and distribution services.

Diversity of Professional Standards

International clinical trials involve a wide range of stakeholders and service providers including pharmaceutical manufacturers, contract research organisations (CROs), laboratories, public and private healthcare institutions, IT solution providers, regulatory agencies, and pharmaceutical wholesalers to name a few. All these different parties must adhere to the certain regulatory rules and regulations that directly derive from guidelines that govern the operational and quality standards based on which their activities must be executed:

- **The Guidelines on Good Manufacturing Practice (GMP)** describe the minimum standards that a medicines manufacturer must meet in their production processes. The GMP guidelines concentrate on areas, such as manufacturing standards, releasing, or licensing procedures.

- **The Guidelines on Good Laboratory Practice (GLP)** define the requirements of quality systems under which non-clinical health and environmental safety studies are executed. The GLP guidelines focus on how such studies are planned, performed, monitored, recorded, reported, and archived.

- **The Guidelines on Good Clinical Practice (GCP)** identify the ethical and quality standards based on which clinical trials that involve the participation of human subjects should be conducted. The GCP guidelines specify the required processes for duly designing, organising, recording and reporting trials while protecting the rights, safety and wellbeing of trial subjects and preserving the credibility and robustness of the collected trial data.

Apart from these principal regulatory guidelines, additional standards also exist, which are less widely known and are not necessarily codified so formally in legislation on European or national levels. These additional standards do however have a substantial impact on all the primary guidelines relevant in the pharmaceutical sector (GMP, GLP, GCP, etc.) and do constitute the basis for industry best practices for all parties involved in the manufacturing and distribution of pharmaceutical products, or the conduct of international clinical trials. Some of the most defining additional standards are the following:

- **The Guidelines on Good Documentation Practice (GDocP)** establish the standards for the full lifecycle of the formal documentation process in any operational settings. The GDocP guidelines outline how formal documents should be created, approved, modified, maintained, and archived.

- **The Guidelines on Good Pharmacovigilance Practice (GVP)** include measures to facilitate the due performance of pharmacovigilance activities in the entire supply chain of pharmaceutical products and with the participation of all stakeholders within all member states of the European Union.

- **The Guidelines in Good Storage Practice (GSP)** lay down the principles based on which pharmaceutical products should be stored and handled while in storage. The GSP guidelines cover the due requirements for infrastructure, equipment, personnel, documentation, and operations.

Guidelines for Pharmaceutical Wholesale Distributors

Along with the GMP, GLP and GCP guidelines, the Guidelines on Good Distribution Practice (GDP) are one of the most important regulatory standards within the pharmaceutical sector. Formally, they are enshrined in the Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use (2013/C 343/01) of the European Commission. The GDP guidelines determine the minimum standards that a wholesale distributor must meet to ensure that the quality and integrity of medicines is maintained throughout the entire supply chain from the manufacturer till the site of dispensation (e.g., pharmacy, private or public healthcare institution, etc.). Wholesale Distribution Authorization (WDA) holders should in all cases be strictly adhering to the GDP guidelines but there are other regulatory requirements (e.g., the Falsified Medicines Directive and Delegated Regulation) with which they should align their processes as well.

In general, the GDP guidelines identify the requirements for the infrastructure, the quality systems, the operational processes, and the personnel of wholesale distributors. The GDP guidelines include specific sections on all elements that could be relevant to the operations of wholesalers. These include the following topics:

- the composition of due quality systems,
- principles of documentation practices,
- the management of outsourced activities,
- the role of management review in quality assurance processes,
- quality risk management,
- requirements and training of personnel,
- requirements of physical premises including temperature monitoring and controlling systems,
- requirements of equipment including calibration, maintenance, etc.,
- qualification of suppliers and customers,
- management of falsified products, product recalls, returned products and complaints,

- receipt, storage, picking, packing, supply, and destruction of products,
- requirements for the transportation of products.

The Role of GDP Certified Service Providers in Clinical Trials

Service providers adhering to the GDP guidelines and equipped with a WDA play a substantial but often forgotten role in the world of clinical research. GDP certified pharmaceutical wholesale distributors are responsible for a wide range of services required for the successful execution of clinical trials. These services include the procurement, storage, picking and packing of a wide range of products as well as their scheduled delivery to clinical trial sites. Wholesalers are also frequently entrusted with the task of collecting unused products from investigatory sites and ensuring their proper destruction. In principle, it is the role of pharmaceutical wholesale distributors to guarantee the uninterrupted, safe, transparent, and well documented supply chain of rescue medicines, comparators and all types of ancillary products needed to duly execute the planned trial protocols.

The contribution of WDA holders can also be crucial when it comes to quickly reacting to and solving unexpected challenges, such as the sudden occurrence of product shortages. In these situations, a seasoned pharmaceutical wholesaler can quickly leverage its regulatory know-how and connections with the national competent authorities in the concerned markets and acquire the necessary import permits to replace the products impacted by the shortage situation. In addition, a skilled service provider can quickly mobilise its network of international partners and ensure a timely procurement of the appropriate quantities from products that could potentially serve as due substitutes. An experienced wholesaling operator should be well aware of the documentary requirements of such import transactions and be well versed in all the additional processes that such transactions entail (e.g., lead times for delivery, customs clearance, international logistics, etc.).

Criteria to Select a GDP Certified Service Provider

Selecting a GDP certified service provider and WDA holder to fulfil all supply related and logistic requirements concerning the different types of products needed in a clinical trial can be a formidable challenge. To ensure that all the above-described standard tasks and responsibilities are carried out with utmost efficiency, operational expertise in various types of related activities and a solid relationship capital with suppliers and regulatory bodies are required. An ideal wholesaling partner entrusted with the entire supply chain of a clinical trials must be well versed in all the applying regulatory and industry standards (GMP, GDP and GCP); must have a widescale enough local and international network of suppliers to secure a stable supply of products even in case of shortages; and should maintain direct lines of communication to marketing authorisation holders to guarantee the availability of the required quality assurance related documentation as well as competitive prices. The following six points aim to identify those professional characteristics that sponsors and CRO-s should look for in a potential service provider within the realm of pharmaceutical wholesaling and distribution services:

1. Demonstrating regulatory expertise within the context of clinical trials is key to ensuring logistics support compliant with all the relevant rules and regulations which sponsor and CRO initiated activities need to adhere to. Naturally, such regulatory expertise should include the implementation of the GCP standards to all services performed in relation to a clinical trial as well as a clear understanding of the additional needs (e.g., specific documentation protocols) of clients. Sponsors and CRO-s should select pharmaceutical wholesale distributors with a substantial enough sectoral know-how and robust enough quality system that could withstand a potential external inspection by a national competent authority or an internal audit by the sponsors or CRO-s themselves.

2. Maintaining a good relationship with regulatory agencies can play a major role especially when the transactions between the entrusted pharmaceutical wholesale distributor and the sponsors or CRO-s require frequent interaction with national competent authorities. These occasions might include situations where products needed for a clinical trial are subject to the issuance of imports permits on behalf of the national regulatory agency. Pre-existing communication channels to the main regulatory body and experience with various application protocols concerning import permits might be extremely useful particularly when the scope of products supplied to a specific clinical trial includes controlled drugs as well. Also, a good working relationship with the authorities is a definite advantage, when unexpected shortage situations critically threaten the continuity of a clinical trial. In those instances, pharmaceutical wholesalers must act quickly to resolve the impeding supply situation to which a preceding dialogue with the regulatory bodies is indispensable.

3. Fostering a good relationship with marketing authorisation holders is vital for various reasons. From a GDP compliance point of view, sourcing products for clinical trials via the shortest possible supply chain is crucial. The longer such chain is, the higher the risk becomes in terms of unexpected events (e.g., deviations) taking place during storage, handing and transportation. Also, sourcing products via pharmaceutical wholesalers in direct contact with marketing authorisation holders provides a competitive advantage in terms of cost efficiency as prices do not escalate given the limited number of participants in the supply chain. Finally, when a direct channel to marketing authorisation holders exists through a single service provider, essential product documentation, such as Certificates of Analysis (COA) or Certificates of Conformance (COC), can be easily obtained. The same applies to more specific quality assurance related information, such as stability data needed to evaluate temperature deviations.

4. Cultivating a wide network of international suppliers might prove relevant especially when the uninterrupted supply of products required for a clinical trial can only be achieved via different import mechanisms. In such cases, it is of paramount importance to choose a service provider who is well embedded in the global supply chain of pharmaceutical products. A pharmaceutical wholesaler with a wide network of international suppliers that consists of manufacturers, marketing authorisation holders and other wholesalers can much more efficiently leverage its international relationship capital than service providers focused exclusively on their local markets. Also, wholesalers with an international edge are most probably better experienced with all aspects of import mechanisms including the application processes for permits, the procedures of international transportation or the requirements of custom clearance.

5. Maintaining a comprehensive scope of logistics operation could be a major advantage that a GDP certified wholesaler can provide to a sponsor or CRO responsible for organising a large scale, multi-centre clinical trial. Working with a local wholesaler who is already involved in the provision of goods to the healthcare institutions acting as investigatory sites in the clinical trial in question makes deliveries more efficient and economical. Also, given the selected wholesaler's know how in terms of the

infrastructure layout, access or product receipt protocols of such healthcare institutions, potential mistakes concerning the delivery processes (e.g., delivery documentation not administered properly, products not delivered to the exact location or specified personnel, temperature deviations experienced during the handover process, etc.) can be minimised.

6. Offering manufacturing services required by clinical trials can be the cherry on top of the service cake offered by an ideal service provider. Naturally, manufacturing activities can only be carried out when the selected wholesaling partner also holds a manufacturing authorisation and adheres to the Guidelines on Good Manufacturing Practice (GMP). Additional activities carried out based on a GMP authorisation can include the storage, handling, and delivery of investigational medicinal products to clinical investigatory sites; or the labelling or packaging of any products as required by the regulations and specified in the clinical trial application dossier.

Conclusion

Regulatory guidelines and the involvement of service providers who strictly adhere to them play an important role within the world of international clinical research. Uniformity and standardisation are key principles to be uphold by all means in the context of services rendered and processes followed in case of clinical trials. Hence, sponsors and CRO-s must leave no stones unturned to ensure that they work with partners who are fully compliant with the guidelines relevant to their own activities, let those be the guidelines on Good Manufacturing Practice, Good Laboratory Practice or Good Clinical Practice.

Pharmaceutical wholesalers supplying products to clinical trials must abide by the guidelines on Good Distribution Practice. Such guidelines are complex and reflect on the wide scope of services typically rendered by pharmaceutical wholesalers to sponsors and CRO-s when it comes to physically storing, handling and delivering products to investigatory sites. The guidelines also include instructions on other tasks that could potentially arise during the administration of a clinical trial, such as arranging the destruction of unused products or the potential importation of products in case of shortages.

Sponsors and CRO-s have their work cut out in terms of finding a GDP certified pharmaceutical wholesale distributor who can serve as a reliable and professional partner to fully support their clinical trial operations. The ideal attributes of such service providers can be easily identified as listed earlier in the article. Sponsors and CRO-s should look out for organisations that can boast of having a well-established network of suppliers and wholesalers locally and internationally; a direct line of communication with the national competent authority; an existing know-how and regulatory understanding about the specific requirements of clinical trials; and a complex enough operational service portfolio.

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