EXECUTIVE SUMMARY

THE COMPLIANCE LANDSCAPE OF HANDLING PHARMA PRODUCTS IN EUROPE AND THE UK

The safety compliance surrounding the manufacture, import, sale and distribution of human medicines and active ingredients is covered by a number of legal instruments for which licences to operate are required. This document is a high-level summary of each.

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THE AUTHORISATIONS

Marketing Authorisation Holder (MAH)

When granted a finished dosage form (FDF) product license based on a dossier of essential data you become a Marketing Authorisation Holder (MAH). Being an MAH comes with a series of strict obligations. All facilities, service providers, contract manufacturing sites and suppliers must be audited despite location. Importing carries additional requirements including product re-testing. The product dossier must always be kept up to date. Product and active ingredient manufacturing facilities need to be EU GMP compliant. Annual quality reports are needed for each MA and technical agreements with all providers. Patient safety (pharmacovigilance) is critical. Labelling requires detailed attention and can often be overlooked.

Wholesale Distribution License (WDA)

Once a product is in its finished form as described in the approved Marketing Authorisation the WDA then applies. Any movements of products, transportation, product verification and storage need to be managed in compliance with the regulations. A Responsible Person (RP) is required to oversee all activities and they need to approve the movement, import or export of any products into and out of each country. The RP must be an integral part of the business operations. The RP is named in the WDA and approved by the regulator. Import from the EU would need to have a named RPi, Responsible Person for Import, this involves further checks on released product by an EU QP.

Export is the RPs job, and all distribution.

Special approval is needed for controlled drugs. Specials approval for FDF and Named Patient are handled under the WDA. The overarching principles of Good Distribution Practice (GDP) strictly apply.

Manufacturer Importation Authorisation (MIA)

Products made within the EU/UK territory have to comply with EU GMP and MA compliance within the production location, the QP locally has the obligation to check the records permitting the product to be released for sale in the market or exported. Where a product is produced outside the UK/EU the MAH has to apply for a manufacturers import authorisation. The MAH also has the obligation to ensure that the imported product complies with all applicable EU/UK Human Medicines directives. This involves the QP who ensures that the API and Dosage form facilities comply with the EU regulations have GMP certification and have been audited for compliance. The products need to be quality control tested in the UK/EU, before being released for sale and the QP must ensure the results are matching the MA, compliance is critical. The QP is named in the MIA and each product MA. Special approval is needed for controlled drugs.

PRACTICES

(current) Good Manufacturing Practice (c.GMP)

This is the EU Directive that governs the controlled manufacturing, handling, testing and packaging of API, FDF and QC testing of products. GMP is the critical step of making the final product in compliance with the regulations, consistently the same way strictly following what is in the MA and Dossier. Such facilities are inspected by the authorities to ensure compliance, followed by a fresh GMP certificate being issued (as MAH this is needed in the QMS) and the MAH is also obligated to audit the same facilities every 2-3 years to ensure their own product are compliance. (no one auditor can uncover all deficiencies). An MAH becomes inoperative if any GMP certificate is out of date for a product.

Good Distribution Practice (GDP)

All and any movements of human medicine FDF products from anywhere in the world to the sales location in the EU/UK or when exported to anywhere in the world needs to be undertaken in compliance with the regulations as does their onward movement to end customers in the supply chain. The Falsified Medicines legislation needs to be complied with which means knowing the routing of all movements, auditing the parties handling the products, assessing and knowing if there are risks involved. This mapping step needs to be documented and managed. The same applies to API (soon to medical devices) and also applies to export. Approved suppliers/providers must have been audited to prove adherence to GDP standards, and a Health Authority GDP certificate is preferable for freight partners, there must always be a Technical Agreement in place defining responsibilities between parties. All customers must have “know your customer” process completed and evidence of their licenses to operate. Special approval is needed for controlled drugs.

Active Pharmaceutical Ingredient License (APIA)

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APIs made within the EU/UK territory have to comply with EU GMP within the production location, the QP locally has the obligation to check the records permitting the product to be released for sale in the market or exported. Where a product is manufactured outside the UK/EU the obligation is to ensure that the imported product complies with all applicable EU/UK Human Medicines directives. API facilities need to comply with the EU GMP regulations and must supply a GMP document from their local authority stating they are manufacturing to UK/EU GMP standards. All the principles of GDP also need to be complied with. Detailed records of API, source and customer are audited by the Regulator, each API needs to be approved by the Regulator. Special approval is needed for controlled drugs and will be added to the API licence. Each API will need to state where it comes from, EU/EEA or that is imported from outside the EEA, what it will be used for once in the territory, distribution or export and what type of products it will be used in. If it is imported from outside the EEA the manufacturing site will need to be named in the licence. The License from the EU regulator will need to define agent/broker, distributor or direct seller. Without such a license no product can be sold, moved, brokered or distributed.

APPROVALS

Specials Approval

Where a product does not have an MA in the UK/EU and a pharmacy has scripts from authorised doctors then under a WDA Special FDF products can be imported with regulator approval. Specials can be manufactured under a specials manufacturing license or pharmacy compounding licence in the UK/EU for the country concerned. Where the API being imported the importer must have APIA. Specials are regarded as an exception to the MA rule and that such specials should become MAs as soon as practical; however, this move is not being policed yet. The RP is responsible for managing. This is a complex area and great care is required

Named Patient Approval

Where a pharmacy has script for a product not licensed in the country of the patient but there is an MA in another country where the MAH is under the banner of an SRA (Significant Regulatory Authority) then under the WDA one-time product can be imported. The process is strictly import for the one script only, no anticipated stocking is permitted under the legislation. The RP is responsible for managing.

RESPONSIBILITIES

Qualified Person for Pharmacovigilance (QPPV)

The QPPV is the suitably qualified person, along with the QP and RP, seeks to ensure licensed human medical products do not compromise the health of patients. Pharmacovigilance has its own SOP's; some integrated with the QMS. The QPPV has oversight of all safety to health aspects of a product. This is initially wrapped up in a Risk Management Plan (RMP). The QPPV manages adverse side effects, assesses the implications and recommends remedial actions, they have a medical advisor on call 24:7 to take calls from practitioners about the products and they work closely with the QP and RP on compliance. Underestimate PV and the authorities can withdraw marketing authorisations and fine the MAH.

The Responsible Person (RP)

This role is one of total compliance of all products moved under the WDA/GDP (export) The RP has detailed knowledge of the business operations and plans, controlled drugs, APIs, Specials imported, Named Patient and oversight approval of all new finished dose form and API products. The RP is also responsible for ensuring all movements comply with the WDA approval, this includes temperature controlled movements. They must have suitable training, not be involved in any commercial decision making capacity and domicile in the country of operation.

The Responsible Person Import (RPi)

This new requirement is still evolving following Brexit. The essential draft legislation being adopted is that product made and released by an EU QP in the EU under EU GMP must be checked before it can be sold in the UK and if made in the UK checked by the first receiving member state. The aim of the RPi is to be a mix of RP and QP based on the range of documents that need to be checked. Once the product is approved for movement the WDA applies. The RPi will be approved by the regulator and added to an approved lists of RPi's. Only an RPi on this list can be nominated to be added to the WDA, new products cannot be brought into the UK from an EEA member state and sold without an RPi being approved on the WDA. Previously imported products from the EU have a 2 year grace period from 01/01/2020 to name the RPi, however it is expected that these checks are performed.

The Qualified Person (QP)

The QP must have suitable training, experienced in the product types being manufactured and must be members of at least one recognised professional science bodies (e.g., royal society of chemistry or pharmacy.) The QP signs formal documents confirming that API and FDF facilities are GMP compliant and that when releasing product for sale in the EU/UK that it meets the requirements in the dossier and complies with the human medicines' legislation. (It is a criminal offence if proved wrong). The QP has detailed knowledge of the business operations and plans. The QP cannot be involved in any commercial decision-making capacity and must be domicile in the country of operation. The QP is named in the MIA and each MA. It is generally recognised that a QP must take care how many products they can safely manage.

IMPORTANT EXPERTISE

Auditing

This is the systematic assessment that a facility meets all the needed criteria to maintain compliance with the applicable legislation. It is a detailed and intense inspection often with pre-questionnaires and requires certain expert experience. It is imperative and explicit in the Regulations that all suppliers involved in the WDA, MIA, GDP, API and QC tested are proven to be compliant. All must also have technical agreements.

Quality Management System (QMS)

The QMS is the hub of compliance for every aspect of operations in Pharma in Europe and the United Kingdom. The principles of QMS are known globally, however each must be tailored to meet the needs of a business. Being in compliance means having a fully functioning Quality Management Systems with a suite of Standard Operating Procedures, accurate record keeping, traceability of products at all times, undertaking risk analyses, noting that the regulatory authorities will undertake periodic inspections at least every three years. Any changes whatsoever need to be fully documented and implemented in a controlled fashion. Exporting from the EU/UK needs to be handled in the same controlled way. The falsified medicines act, product route mapping, knowing the entire supply chain are essential and temperature control are added essentials. The size and scope of the QMS relates directly to the number of licenses above, the number of products and the nature of the business.

Outsourcing part or all of these obligations is feasible with suitable Technical Agreements however Director obligations remain.