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Partnering to Advance Human Health

Article

EU market challenges

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Although the European market is approximately 50% smaller than the United States in terms of land mass, the population of Europe is approximately 50% larger and this presents a huge market opportunity.

At our company, we have witnessed a steady increase in the number of US companies taking advantage of EU market opportunities, particularly for niche biopharmaceutical and orphan drug products. In return, this has increased the outsourcing requirements for country-specific packaging and temperature-sensitive distribution services. To meet this demand, we have increased investment in client-dedicated cold and frozen storage and developed a late-stage customisation suite for country-specific packaging. In addition to this, we have seen further growth across services in pharmaceutical development, commercial manufacture and packaging. Client requirements for customised solutions for biopharmaceutical packaging and distribution, as well as traditional toll manufacture of solid oral dosage forms (branded and generic) are also on the increase.

The challenges of the EU marketplace

The key challenges for a company launching drug product in the European marketplace can be summarised in three simple categories:

1. Regulatory and quality differentiations

Europe has different regulatory and quality requirements compared with the United States. For instance, all products manufactured outside of Europe must undergo EU import testing according to Directive 2001 / 83 / EC Article 51 to ensure they are compliant with the specifications outlined in the marketing authorization application (MAA). Within Europe, all drug products must be released onto the market by the Qualified Person (QP) to confirm that the product is fit for purpose and has been processed to cGMP standards. These two requirements are unique to Europe, which is why client companies need to ensure they select a CMO with quality resources, regulatory knowledge and experience in this region.

2. Impact of multiple languages on packaging requirements

One of the biggest challenges when entering the European market is the multitude of languages, which results in a large number of associated country-specific pack formats. Within the 28 member states of the EU, there are 150 regional and minority languages, of which 23 are recognised working languages. Labelling and packaging must be in the member state language, requiring design, generation and management of all packaging components, e.g. labels, Patient Information Leaflets (PILs) and cartons, for example.

For our clients, regional (multilingual) packs coupled with the application of blue box (country-specific detail) at our late-stage labelling operation have proved a success. Applying country-specific blue box information to the packaging commits a unit of drug product to that particular market. Partnering with CMOs that provide late-stage customisation enables pharmaceutical companies to benefit from flexible stock utilisation. This results in the ability to be responsive to fluctuations in various market demands, as well as eliminate excess storage of stock.

3. Complexity of the supply chain throughout the EU

Another challenge faced by client companies is defining their distribution strategy and associated product requirements throughout the distribution process. When distributing products to target markets, the drug product will face varying temperature ranges and transit times, so careful consideration needs to be given to product packaging and distribution configurations.

Variations in country requirements for anti-counterfeiting measures also adds to supply chain complexity. For example, the French market requires drug products to have a 2D matrix barcode, incorporating the CIP code and batch and expiry details. Meanwhile in Turkey, each individual saleable unit of drug product must also have a unique serial number, printed both in human readable format and incorporated in a 2D code.

Common pitfalls

For a US company, the MAA submission strategy in Europe can present challenges in itself because of the different filing routes (centralised and decentralised), and the various options and constraints that must be considered depending on the type of product and therapeutic indication.

One of the most common pitfalls of companies moving into the EU from the US is the assumption that complying with FDA requirements will automatically lead to European product approval. This is often not the case. Given the fact that the EU is a far larger market than the US in terms of population, it is worth considering a development programme that meets the combined needs of both regions.

The most cost-efficient approach to drug development is to consider multi-regional or global regulatory requirements as early as possible, thus preventing the need for several development programmes to be initiated to comply with separate regional regulatory requirements. The key to successful global drug development is to seek endorsement and buy-in on the key aspects of pharmaceutical and non-clinical drugdevelopment, particularly on the acceptability of clinical trial designs for pivotal studies from the key regulatory authorities. Normally, the main aspects of clinical development packages and pivotal registration trials that need to be aligned are in the areas of clinical endpoints, trial duration, choice of patient population and the selection of active comparators. These deliberations may be met with differing opinions between FDA and EU regulatory authorities, with difficult choices having to bemade at the time of protocol finalisation. Knowing the differences up front can help avoid unpleasant surprises at the product approval stage and more importantly, make all the difference to the type of approach that is taken when seeking scientific advice from regulatory authorities.

Securing the supply chain

Importation of the drug product

As previously discussed, all pharmaceutical products manufactured outside of Europe must be analysed in line with the specification outlined in the product's MAA upon entry into the EU. In addition, depending on the composition of the pharmaceutical drug product, importation duties and taxes can vary significantly and add to the overall supply chain cost. By assessing the drug product and the manufacturing processes of the product, it may be possible to apply a specific customs procedure to minimise, or even eradicate, duties payable. For example, we have used this approach for a number of high-value biologic APIs being shipped into Europe by US clients.

Securing the supply chain and ensuring tracability

With the increasing problem of counterfeit, misbranded, adulterated and diverted drugs entering the supply chain, it is essential to ensure full traceability of the drug product. This is achieved by seeking advice on the country-specific requirements and then implementing an anti-counterfeiting strategy, such as serialisation or 2D matrix barcodes. For example, it is useful for service providers to be able to apply and verify 2D codes to packs, including on-line verification of 2D code quality (ISO / IEC15415) standard and content. At our company, we can receive and / or generate serial numbers and apply these within the code and verify online. This includes aggregation to shipper and pallet level and the management of the data and collation thereof for supply to the client.

Distribution strategies for the drug product

Traditionally, client companies would have their drug product manufactured at a CMO and then the finished goods would be shipped to a wholesaler for storage and distribution. To mitigate risk, cost and shortening of the supply chain, many client companies are now using CMOs that provide third party logistics services to reach their target market end users. When deciding upon a distribution strategy, the CMO, in conjunction with the client company, must conduct a distribution risk assessment that considers factors such as product value, transit times to target markets and temperature requirements. Results from the risk assessment should then be written into the distribution instructions to ensure consistency and repeatability in all activities for every product dispatched.

To ensure all drug products reach the end user in optimum condition, the CMO should conduct a full validation of shipping and packaging configurations. For example, our validation and logistics teams work with the client company, the packaging supplier and distribution partners to design a customised configuration for the drug product being shipped.

We also develop and execute a full validation program to ensure the solution is fit for purpose. This can be extended to include route qualifications where 'dummy' shipments can be made to test the performance of the system in transit. Additionally, it is helpful to find a service provider that can identify paperwork requirements in relation to import, export and customs documentation early in the project to ensure there will be no delays at shipment.

Finally, one of the most important aspects of successfully launching a drug product into the European marketplace is, quite simply, good project management. Having a detailed, realistic project plan and an experienced and dedicated product supply manager are the keys to success.

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