White Paper

Providing Access to Unlicensed Medicines

The Role of Pharmaceutical Manufacturers

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The Role of Pharmaceutical Manufacturers

What's driving demand for unlicensed medicines in non-launch or non-commercialised markets? And what are the challenges for the pharmaceutical manufacturer of not actively engaging in providing access?

Irrespective of the manufacturers stance, demand will still exist in unlicensed markets. Healthcare professionals and patients will look to source the drug elsewhere. Without a corporate solution in place, allowing controlled access, what are the risks being taken by the manufacturer?

Pharmaceutical manufacturers are asked regularly, if they can help provide access to one of their drugs into a country where it is not licensed. They often find it difficult though to be able to respond to these requests due to either procedural, practical, or organisational constraints. However, the issue cannot be ignored, and they have two choices:

- Allow International Pharmacies/3rd party suppliers to meet this demand (whilst legal, this poses risks and disadvantages to pharmaceutical manufacturers, patients, and HCPs)
- Consider implementing a corporate solution to allow access to their drugs in countries where they are not licensed or commercially available

Let's first examine what is driving the need to access medicines on an unlicensed basis.

Pharma's Portfolios & Pipelines: Most pharma companies are focused on developing and commercialising new chemical entities aimed at meeting high degrees of unmet medical need. It is these types of new drugs that are increasingly sought to be accessed on an unlicensed basis. Patients and their physicians who have exhausted licensed treatment options in their own country will be seeking access to these drugs.

The increasing focus on development of drugs for orphan and rare diseases is changing the commercialisation model. Even for the largest multi-national pharmaceutical companies with orphan and rare disease drugs there is limited commercial viability in launching in more than the largest 20-30 markets worldwide. Indeed, for smaller biopharmaceutical companies looking to commercialise their orphan and rare disease products themselves, there may only be a commercial focus on launching in 10-15 markets.

This leaves a huge access gap for physicians and their patients residing in smaller markets. They may never be able to access these drugs on a licensed, commercial basis. If no solution is put in place to allow them access by the drug originator, they will often seek to gain access through international pharmacy.

Informed Patients: Patients themselves are also driving the need for International Pharmacy. The internet has given patients across the world more access to information than they have ever had before. Patients and their families are researching their conditions and treatment options and will be acutely aware of drugs approved and available in other countries. They understand that these drugs may be a viable treatment option for them but are not available through a standard prescription route in their country. Very often, these patients seek to gain access to these drugs themselves or request their treating physician to prescribe the unlicensed drugs, which are then often sourced via International Pharmacy.

The internet has also brought patient organisations and communities across the globe much closer together, especially within orphan and rare disease areas. Patients are sharing experiences of different treatment regimens which are licensed and available in some countries, thus creating demand in other countries where the same treatment is not available.

Informed Physicians: The international medical community is increasingly more closely connected, with Key Opinion Leaders (KOLs) from across the world attending the major global medical congresses. Particularly in specialist areas such as oncology and orphan rare diseases, knowledge-sharing is recognised as an important part of improving treatment options for patients. A close network of peers mean KOLs are very aware of new drugs coming through clinical development, as well as drugs licensed and commercialised in other countries, but not available to their patients in their country. Again, this increases the need to turn to International Pharmacy to source drugs that may benefit their patients.

Market Access Challenges: Even for the largest pharmaceutical companies, a global launch of a new chemical entity can take dramatically longer than the initial launch in the priority markets. Increasingly, the USA is the priority market and the first to launch the majority of new products. In 2015, 31 of 44 new drugs were approved in USA first, 5 were approved in Japan first, and only 4 were approved in the EU first. This leads to a delay in access for new drugs across the world. Even with the European Union's Centralised Approval there are delays in true commercial availability due to local pricing and reimbursement and market access criteria that need to be met.

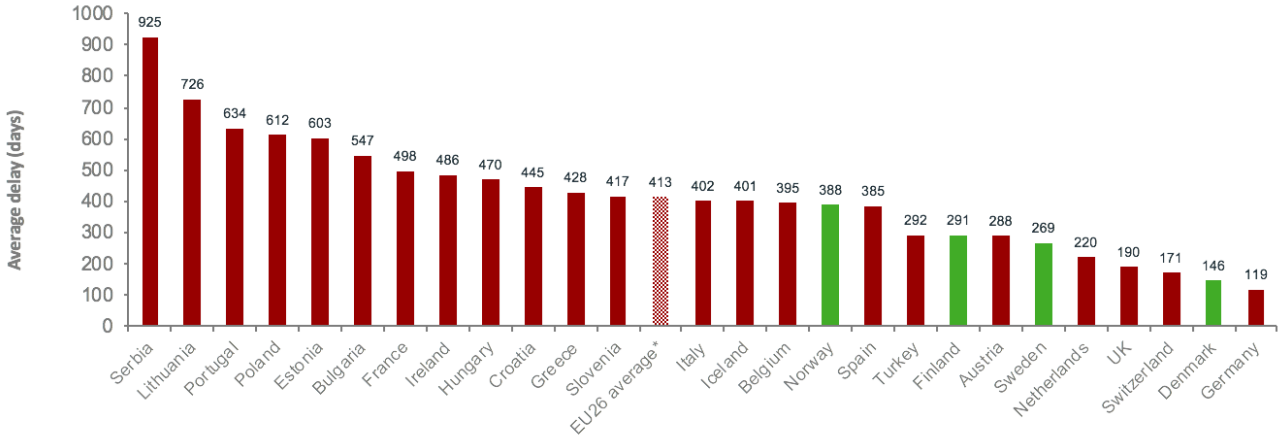

Fig 1. Average time between marketing authorisation and patient access, EFPIA Patients W.A.I.T. Indicator 2018 Survey, IQVIA, February 2019.

Regulations exist across the majority of countries which allow for the importation and use of an unlicensed medicine on an individual, "named patient", or case by case basis. This demand usually comes from the physician treating a patient, who in their clinical opinion would benefit from treatment with a drug which is not licensed in their country, above and beyond the drugs that are approved and commercially available in that specific country.

A pharmaceutical manufacturer deciding not to provide or enable access to a drug in markets where it is not licensed and commercially available does not reduce the demand: patients and healthcare professionals (HCPs) will turn to other organisations (wholesalers, distributors, and international pharmacies) to source the drug. This creates a commercial opportunity for individuals and organisations trading in unlicensed medicines.

International pharmacies can be both virtual (internet based) or local wholesale or pharmacy organisations selling unlicensed medicines to hospitals, pharmacies, medics, and in some cases patients directly.

Internet (Online) International Pharmacies:

There are numerous online internet pharmacies that have varying degrees of regulation controlling their activities. These are enabling patients or HCPs to order drugs online to be exported to the country where the patient is located, and often require a prescription to allow a product to be dispatched. There are limited controls on these types of online pharmacies, and governance by competent authorities is often limited.

Local or International Wholesale Organisations:

There are multiple international or local wholesalers who operate as International Pharmacies and can be split into three categories: global, regional, and single countries organisations. However, as mentioned previously there are a large

number of small, locally-based organisations that will trade in unlicensed medicines, often importing drugs as a response to specific demand from their customers. These smaller organisations either add this service of trading unlicensed medicines to traditional commercial pharmaceutical wholesale operations or will be sole-traders buying and selling unlicensed medicines to meet local demand.

There is a huge variation within these organisations, from very compliant, well-regulated and quality controlled global organisations, to local traders with questionable regard and appreciation for the standards required for the safe and compliant distribution of pharmaceuticals. Many will often seek to source drugs to sell on an unlicensed basis directly from the manufacturer in the country where they are licensed and commercially available. Often though, manufacturers are unwilling to sell drugs for export which leads International Pharmacies to source drugs through the wholesale, pharmacy, and retail environment in countries where they are licensed to then export for sale into unlicensed countries. The full supply chain history and pedigree of drugs sold by International Pharmacies is difficult to validate once drug is sourced from wholesale and pharmacy networks.

Pharmaceutical manufacturers risk a myriad of challenges if they allow others to provide their products without the manufacturer's direct involvement. Some of the risks to consider include:

Healthcare Professional (HCP) Engagement:

There will be no interaction between the manufacturer and the HCP. This can result in the following potential issues:

- No visibility as to who is prescribing the drug
- Inability to support the HCP with educational / administration information
- Loss of opportunity to build a direct relationship with the HCP
- The HCP will receive a pack of product only, often in a foreign language with no supporting information

Patient Safety & Pharmacovigilance:

With no interaction with the HCP, there will be no ability to influence or control the type of patients who receive the drug or make a decision as to whether the drug is a safe and appropriate treatment option for the patient. It will also not be possible to influence the indication the drug is used in, which line of treatment, in combination with which other therapies, or the dose used.

If the use of the drug in an inappropriate patient or inappropriate manner results in a safety event that is reported, all such events will need to be investigated by the company and will be added to the central file.

With no visibility of where and how drugs are being utilised, adverse events occurring as a result of a drug being used as an unlicensed medicine can often be unexpected and unusual in nature.

Financial:

The price charged to patients and HCPs by international pharmacies is often very inflated versus the normal commercial price. Where drugs have been passed through multiple wholesalers, all adding a margin to the drug, prices of drugs sold via an international pharmacy can be in excess of Wholesale Acquisition Cost (WAC)+ 100-300%.

There are significant financial gains to be made by international pharmacies in the export, import, and selling of unlicensed medicines. In this situation, it is often the patient or HCP that is being financially exploited and paying an over-inflated price for a drug which they desperately need.

Recent examples have highlighted drugs launched in the USA, but not in Europe and Rest of World at more than 100% mark-up on the USA Wholesaler Acquisition Cost (WAC) price. Whilst in this situation the manufacturer is not involved in the supply chain, there are potential reputational issues with their drugs being sold at highly inflated prices on an unlicensed basis.

Supply chain integrity:

Supply chain integrity and the risk of counterfeit medicines is one of the major risks for of sourcing drugs from international pharmacies. Whilst certainly the larger organisations operating as international pharmacies will have robust quality and compliance systems in place, there is a risk amongst smaller organisations of maintaining adequate supply chain integrity to ensure patient safety.

In any scenario with an extended supply chain, the risk of counterfeit medicines is increased. Unless drug is sourced by an international pharmacy directly from the manufacturer, there is a risk of counterfeits, and the greater the number of steps in the supply chain, the greater the risk. Smaller organisations trading in unlicensed medicines may have limited quality management systems in place, and limited concern for product integrity. This risk is compounded by the fact that the end user is sourcing a drug on an unlicensed basis that they are unlikely to be familiar with, and the drug will be a foreign territory pack which may be in a foreign language. Given the financial gains to be made in International Pharmacy and the often high value of drugs being sold through this mechanism, the risk of counterfeits entering the supply chain either knowingly or unknowingly is heightened.

In addition to the risk of counterfeits, there is also a risk to the maintenance of product quality. Storage and transportation conditions will be compliantly

managed by larger international pharmacy organisations. However, any supply chain with multiple links, where a drug passes through organisations with less robust quality management systems and where supply is potentially into countries with less strict controls, risks impacting the quality of the product that reaches the patient. So, even with genuine product being provided through International Pharmacy, there is an increased risk to the quality of the drug reaching the patient. This could impact patient safety or the efficacy of the drug.

Visibility:

Drug manufacturers have no visibility of where their drugs are being supplied by International Pharmacy, as commercial product is exported from launched countries and provided around the globe

This creates a number of potential challenges for the manufacturer:

- In the event of product recall, the product is likely to be untraceable
- Supply chain challenges, as in some launched countries, where a significant proportion of inventory may be being exported to International Pharmacy
- Inventory planning issues, which may cause drug shortages in markets from which product is exported
- Missed opportunity to understand unlicensed usage patterns and volumes
- Inability to identify KOLs in non-commercialized countries who are using the drug

There are clear benefits to Pharma of providing controlled access to their drugs on an unlicensed basis in countries where they are not licensed or commercially available:

- A moral and ethically positive solution for patients and HCPs often trying to overcome an unmet medical need
- Ability to have a direct relationship with HCPs
- Ability to educate HCPs and provide supporting information to assist in safe, appropriate administration and prescription of drugs
- Visibility of exactly where drugs are being used
- Protect patients and HCPs from risk of counterfeit medicines by supplying direct from manufacturer
- Control of supply chain to ensure quality of drug reaching patient
- Inventory planning and ability to ensure stock availability
- Offer drugs at a price more in line with the company's intentions
- Positive PR and reputational benefit to be meeting patient and HCP demand

Inceptua advise that companies develop a clear, publicly-visible corporate policy on access to drugs in countries where they are not licensed and commercially available. If the policy is to allow access, it is essential to provide a clear solution as

how patients and HCPs can access the drugs in an efficient, compliant manner. If the policy is not to provide access, it should be accepted that others will meet the need. Whatever the approach undertaken, the potential impact on reputation should be considered.

Inceptua can offer a number of solutions to support access to unlicensed medicines for pharmaceutical manufacturers, from consulting services to help formulate your access policy, to a range of distribution solutions where Inceptua will handle access to your product portfolio globally on an unlicensed basis in countries where they are not commercially available.

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