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White Paper

Expediting Access to Rare Disease Therapies in Europe

Exploring Multi-Stakeholder Approaches

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Globally there are approximately 7,000 known rare diseases. About 4,000 – 5,000 of those have no available therapies [1]. Consequently, there are many patients with a rare disease who are waiting for a new therapy to become available.

To compound this deficit in treatment options; patient need is further accentuated by the delays in obtaining a Marketing Authorisation. According to the latest European Federation of Pharmaceutical Industries and Associations (EFPIA) data (figure 1), the average time between marketing authorisation and patient access for an orphan drug varies from 113 days up to 1,141 days across Europe. In order to ensure patients in need can access new therapies as quickly as possible, it is critical that a multi-pathway, multi-stakeholder approach is taken.

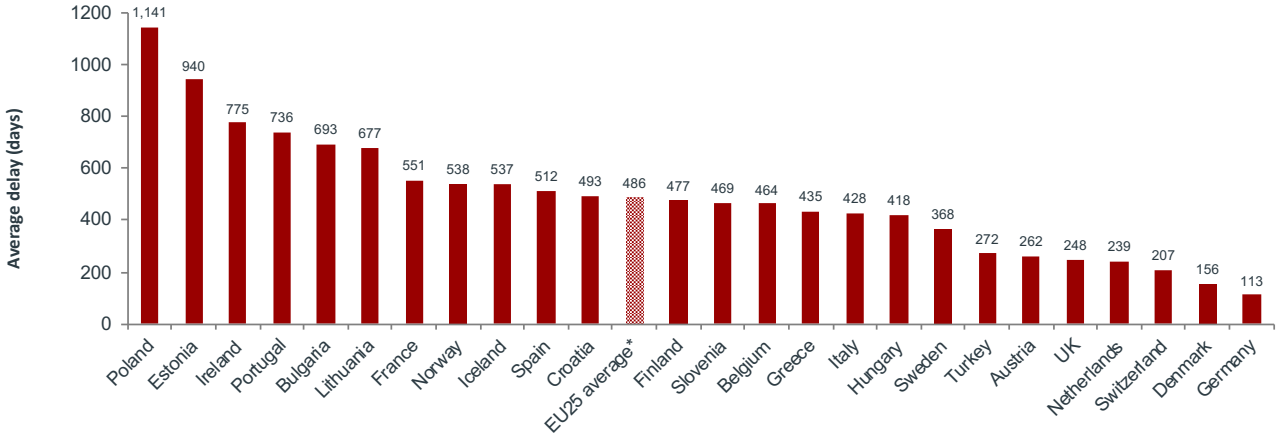

Figure 1: The average time between orphan drug marketing authorisation and patient access. [2]

In this white paper we explore the various pathways for pre-approval access before regulatory approval, data generation to support regulatory approval and the benefits of early engagement with key stakeholders to secure timely, sustainable access to patients in need.

Designed for success - a multi-stakeholder approach to clinical development

Planning for patient access for orphan drugs must start early in the life-cycle of the product, right at the time of clinical development.

Traditionally, drug development has operated in a siloed approach, whereby functions that are critical to the drugs success post phase three are missed from early consultations with research and development teams. Over the years, many companies have adopted a multi-stakeholder approach to drug development, involving other critical functions, such as regulatory, medical, commercial and patient access, and importantly, patient groups early in the development process. In addition, regulatory engagement opportunities such as PRIME (PRIority Medicines) [3] set up by the European Medicines Agency (EMA) and open to manufacturers and marketing-authorisation applicants to engage in early dialogue, helping to optimise clinical development plans and potentially speed up evaluation, thus allowing new therapies to reach patients in need earlier.

"*Through PRIME, we offer early and enhanced dialogue to enable the generation of better data and more robust evidence on a medicine's benefits and risks.*" Guido Rasi, EMA's Executive Director [4]

PRIME is relatively new, and it is proving popular especially with small and medium-sized enterprises (SMEs). Since its launch in March 2016 there have been 177 requests for entry into PRIME. The entry and review process is stringent. Consequently from 177 applicants only 36 medicines have been accepted for PRIME that are either rare diseases or paediatric treatments.

The scheme offers the following benefits:

- The appointment of a rapporteur from the Committee for Medicinal Products for Human Use (CHMP) or Committee for Medicines on Advanced Therapies (CAT) to help 'build knowledge ahead of a marketing-authorisation application'
- Organise a multidisciplinary meeting with the rapporteur for the medicine and appropriate chairs and experts from relevant EMA committees to provide "guidance on the overall development plan and regulatory strategy"
- Assign a dedicated contact point
- Provide scientific advice at key milestones which can include input from health technology assessment (HTA) bodies and patients.
- Confirm potential for accelerated assessment at time of the marketing authorisation application

In addition to planning suitable clinical trials, there has been a recent trend across large pharma to formally include pre-approval access planning in to the clinical development process. Increasingly, early access is seen as a key aspect of the commercialisation pathway of a drug. Typically, large pharma are making an assessment at the end of Phase II as to when and if early access will be granted to that medicine.

As part of the decision process to help a company decide where and what type of pre-approval access is applicable and available, some of the key questions (below) should be addressed in order to provide clarity as to whether pre-approval access is likely to achieve the intended objectives.

Key questions to address

- Is there a high unmet need?
- Have access requests been received which have been denied or not actioned?
- What is the expected future demand?
- What does the safety and efficacy profile look like at end of Phase II?
- Is there enough stock available to allow pre-approval access supply?
- What, if any, data collection is required?
- Have preparations been made to interact early with HTA bodies?
- What are the commercialisation priorities and are there any territories which require extended compassionate use support?

In summary, by engaging relevant stakeholders early in the clinical development process, it ensures that the therapy meets the expectation of the prescribers, patients and importantly, the payer budget holders, optimising the outcome of achieving sustainable access and enabling new therapies to reach patients in need earlier.

Navigating pre-approval pathways

Pre-approval access can be an incomprehensible list of laws, regulations, terminology and different pathways which vary by country, cost and complexity. At the European level there are two important Articles that provide the legal basis for compassionate use and the supply of unauthorised medicines:

- Directive 2001/83/EC, Article 5(1) [5]
- Regulation (EC) No 726/2004, Article 83 [6]

Each Member State has adopted the Articles into their own laws but it has not produced an EU-wide harmonised approach for compassionate use programs or individual named patient supply, but has instead resulted in multiple possible mechanisms.

The role of the EMA

The EMA can provide a recommendation on Compassionate Use [7]. Only the National Competent Authority of a Member State can make a request to the EMA to provide a recommendation and this is not open to manufacturers or marketing-authorisation applicants. On request by a Member State the CHMP provides an opinion on the administration, distribution and patients who would benefit from the use of specific medicines supplied within the framework of compassionate use. The CHMP opinion is non-binding on the Member States and does not provide any form of approval for unlicensed medicines.

The EMA compassionate use recommendation should not be confused with compassionate use programs or individual named patient supply that are governed by each Member State.

Since 2007 only five medicines have been reviewed at the request of three National Competent Authorities (Table 1).

Name of product	Requesting National Competent Authority	Opinion Date
Ledipasvir/Sofosbuvir	Ireland	20/02/2014
Daclatasvir,	Sweden	21/11/2013
Sofosbuvir Gilead	Sweden	24/10/2013
IV Zanamivir,	Sweden	18/02/2010
Tamiflu IV	Finland	20/01/2010

Table 1: Medicines that the EMA has reviewed for compassionate use

The role of the Member States – country specific access

Navigating the myriad of pre-approval access laws and guidance in each of the 28 Member States is the only way companies can provide medicines to patients outside a clinical trial on a pre-approval basis. The complexity of national requirements should not deter companies from providing pre-approval access to their medicines as the actual positives outweigh any perceived negatives.

- Patient access to treatment without the expense, the burdensome interventions or limitations of entry compared with supply through a clinical trial
- Demonstration of an ethical response to requests
- Provision of controlled and compliant access to medicine according agreed inclusion criteria
- Increases product experience of the product in a limited version of the 'real world'
- Potential to build or enhance relationships with potential Key Opinion Leaders (KOLs) and agencies

Country-specific access can be authorised either for a group of patients, referred to as a *compassionate use program*, or individually, referred to as *named patient supply*. Both of these pre-approval access approaches are coordinated and implemented by each Member State not the EMA. Each Member State has its own unique interpretation of the EU guidance on compassionate use, how best to implement a method which allows patient access, data collection, group or individual supply and at what stage in development this will be allowed (Table 2).

Member State	Access Pre-approval available routes		Access Post-approval available routes	
	Group Compassionate Use Program	Individual Named patient use	Group Compassionate Use Program	Individual Named patient use
Austria	✓	✓	X	✓
Czechia	✓	X	X	✓
France	✓	✓	✓	✓
Germany	✓	X	X	✓
Italy	✓	✓	X	✓
Poland	X	X	X	✓
Spain	✓	✓	✓	✓
Sweden	✓	✓	X	✓
UK	✓	✓	X	✓

Table 2: Examples of the different pre- and post-approval access programs in each Member State

It is important to note that Member States must notify the EMA when a compassionate use program is approved but that there is no requirement in the legislation for companies to inform the EMA if a product is being supplied by nationally-approved program or individual patient supply mechanism.

Timing

A key consideration for those considering early access pathways is one of timing. In the majority of European countries there is no restriction as to when in the development process pre-approval access can be provided. However, most competent authorities will expect there to be some safety and dosing data available for the product. The National Competent Authority, within each Member State, do not make any judgement as to the potential clinical benefit – this is left to the discretion of the prescribing physician.

In areas of high unmet need it is not uncommon to provide access during Phase II, but more commonly companies consider access once any ongoing, pivotal Phase III has completed enrolment. The decision as to when to allow access is best addressed on a product-by-product basis, due to the product-specific attributes such as potential benefit, unmet need, demand, availability of stock etc.

Charging and pricing

In the majority of European countries, it is possible to charge for a globally-unlicensed medicine through the formal early access mechanisms which exist. Once first approval has been attained (typically FDA) then it is possible to charge in all European countries. Unlike the US Expanded Access Program (EAP) system there is no requirement to reveal cost of goods or research and development costs, instead you are at liberty to charge what you hope your eventual list price will be.

However, where a product is charged-for under pre-approval access mechanism, uptake will be lower than if the product was provided free-of-charge, which may conflict with the commercial strategy of reaching as many patients as possible.

In some countries the price charged for under the pre-approval access mechanism will be used as a reference price, and as such any national/local reference pricing mechanisms should be considered when determining the pre-approval access supply price. Given these factors, we would recommended only to charge for the product once the anticipated list price has been defined.

Data

In recent years there has been a greater focus on outcomes data collection in the pre-approval access environment. Any real-world data (RWD) collection during pre-approval access should not be viewed as a substitute for clinical trial data. The scope and depth of data which can be collected means that any RWD should be considered as supplemental only.

That said, data collected during pre-approval access programs can provide insights into how the product works in a patient population more similar to the commercial patient population and can help feed in to planning for subsequent clinical trials.

Usage of RWD in HTA decision-making processes varies across Europe, but is still generally agreed to lack the robustness of controlled clinical trials. However, some HTA bodies do accept that in rare diseases, where patient numbers in a clinical trial are low, data collected through other mechanisms may be used for decision-making.

Marketing approval process out of sync with demand

In Europe, centralized EMA approval is only the beginning of a long process of in-country marketing authorisation applications and there can be delays of years between centralized approval and in-country commercial supply. During that time, especially in the rare disease environment, physicians and patients are aware of the fact that potentially beneficial medicines are available to patients in the US and in some other EU countries, whilst they may have many more months to wait before they can access the medicine via the commercial route. This inequity in access fosters a demand for early access to medicines through compliant pre-approval pathways.

Common concerns

Companies considering pre-approval access often raise concerns over the potential impact adverse events identified during pre-approval may have on subsequent marketing authorisations and product label. This concern is based on the fact that pre-approval access programs often have

broader inclusion criteria than clinical trials, meaning the patient population tends to be in a poorer health state than the clinical trial population. However, the regulators (notably the FDA issued guidance around this to reassure companies [8]) understand that the patient population in a pre-approval access program is inherently different from the clinical trial population and assess any reported adverse events in that context.
The possibility that pre-approval access risks cannibalising recruitment into ongoing EU clinical trials is another commonly-raised concern. In reality, pre-approval access programs can help bolster recruitment into clinical trials as physicians are always advised to enrol patients onto any in-country trial they may be eligible for, before considering them for pre-approval access.

In practical terms, these two concerns can be readily mitigated, and they should not deter companies from considering how pre-approval access in Europe can bring a range of benefits.

What is the impact of Phase III not meeting its endpoint?

If a company has opened a pre-approval access program prior to Phase III readout, and the final results of the Phase III are deemed not to have met the pre-defined endpoints, then typically the company will close the program. However, this is not necessarily a requirement. Pre-approval access mechanisms in some countries can continue to be utilized if Phase III fails. This will depend on many factors including but not limited to: ability/risks of transitioning patients, competent authority and physician clinical opinion in non-trial countries.

In some cases, physicians still seek access to a product that they believe is benefiting patients, despite apparent negative trial results. Where the decision is made to continue the clinical development of the asset, continuing to provide pre-approval access may facilitate the capture of real-world data whilst clinical development continues.

Critical Success Factors

- Plan collaboration and engagement as early as possible using all available mechanisms, building insights in to commercialisation strategies
- Include early access consideration and planning in the clinical development process
- Plan for all possible scenarios and ensure you have plans in place to mitigate any potential risks
- Be open, listen and understand the challenges each stakeholder is facing and build in to the commercialisation planning
- Be open to new approaches and willingness to take a longer-term view

References

1. www.orpha.net accessed February 2019
2. EFPIA Patients W.A.I.T. Indicator 2018 Survey, IQVIA, February 2019
3. www.ema.europa.eu/en/documents/report/prime-two-year-overview_en.pdf
4. https://www.ema.europa.eu/en/news/two-years-prime
5. Guideline On Compassionate Use Of Medicinal Products, Pursuant To Article 83 Of Regulation (EC) No 726/2004
6. www.ec.europa.eu/health//sites/health/files/files/eudralex/vol1/reg_2004_726/reg_2004_726_en.pdf
7. www.ema.europa.eu/en/humanregulatory/researchdevelopment/compassionate-use
8. Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers Guidance for Industry. FDA October 2017.

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We bring medicines to patients:

- Inceptua has leading expertise in the strategy, design, and operational implementation of pre-approval access programs making pharmaceutical products under clinical development available to patients as appropriate.
- We offer full pharmaceutical company capability to register and commercialize products through in-licensing and flexible partnerships
- We provide high quality clinical trial comparator sourcing and manufacturing services, with an agile global supply chain to ensure that products are correctly packaged, at the right location, exactly when needed

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