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White Paper

Pre-approval Access

Regulatory Update 2020

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Pre-approval Access Regulatory Update 2020

Background

The regulations governing pre-approval access (early access, expanded access, compassionate use, named patient supply etc.) are constantly being updated by the respective country authorities. These changes are generally made in order to clarify the processes involved. Over the last 10 years, the majority of such changes have been positive, and intended to make the provision of medicines to patients in need more straight forward for the manufacturer and the treating physician.

There have been some recent notable announcements by some of the key commercial pharmaceutical markets regarding pre-approval access regulations. This White Paper is intended to provide an update on some of these changes, and also provide some information on some of the less high-profile pre-approval access countries.

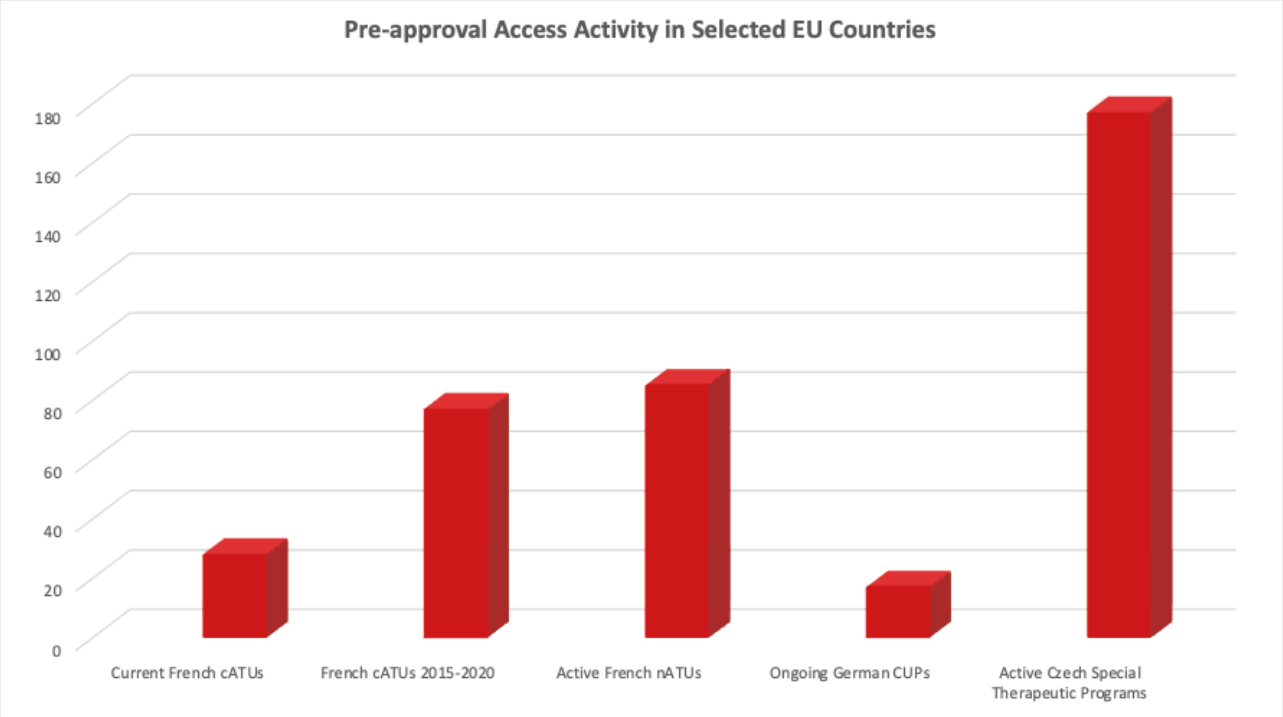

Table 1 Pre-approval Access Activity in Selected EU Countries.

France

For many years France has featured prominently in most companies' pre-approval access plans. A combination of a sizeable commercial market and clear, supportive regulations have been attractive to companies making their products available prior to commercial approval. However, spiraling costs (reimbursement of drugs under the ATU system now costing the French healthcare system >€1billion per year [1], a number of changes to the ATU system have been planned by the French authorities:

1. The recently-passed annual French Social Security Financing Law (LFSS) for 2020 [2] imposes new conditions for nominative ATUs (nATUs, or the individual patient regulatory route). From March 2021, the Ministry of Health (MoH) will unilaterally decide on the compensation for a medicine being made available via the ATU route. Manufacturers will still be able to set their own price initially, but if this price is lower than what is eventually set by the MoH, the manufacturer will have to repay the difference. This change is being made in response to the increasing budgetary demands being placed on the ANSM, specifically due to some high-cost medicines being made available (a notable example being charged at >€2million per injection). Manufacturers will still be free to set their own price in the cohort ATU (cATU), or group approach mechanism.

2. As of August 2019, ATUs can be granted for products undergoing indication expansions [3, 4], so it is possible to put in place an ATU for a product which is already commercially-available in France for a new, as yet unlicensed indication. It is also possible to run concurrent ATUs for the same product in different indications.

3. The Haute Autorité de Santé (HAS) has also announced that it intends to utilize data from the ATU system in a more structured manner and ensure that the data collected is available to HAS, and is used as part of the supportive evidence for that product [5].

These changes are significant, and how they will work in practice, together with their consequences, are not yet apparent, but it is likely that smaller biotech companies focused on rare diseases will not be willing to take the risk of having a price attributed to their medicine by the MoH, prior to a full marketing authorization submission. Such a pricing decision, based on a limited amount of data, has the potential to negatively impact the longer term reimbursement process both within France, and in other countries, as the price set in the ATU system in France is used as a reference price in many other countries.

There can be no argument against the HAS making changes to preserve the long-term viability of the French healthcare system, but some compensatory changes to the cATU route to offset the impact of the nATU changes would be welcome, such as removing completely, or reducing the responsibilities for an exploitant, which companies with no commercial presence in France find both costly and confusing. Currently the cATU route is typically invoked if patient numbers exceed approximately 25 (however it must be noted that this is not a legislated number). For a country the size of France, patient numbers, even for a rare disease, often exceed that. The cATU route is very much akin to the US Expanded Access pathway, and requires significant resource and investment, not least the requirement to subcontract an ‘exploitant’. For larger pharmaceutical companies, this does not present much of an obstacle, but for smaller companies, especially US biotech operating in the rare disease space with no commercial presence outside of the US and with promising Phase 2 or interim Phase 3 results, this is very challenging. Being forced to utilize the cATU route can be an insurmountable barrier. This means that many promising rare disease medicines will just not be made available to patients in France ahead of commercial approval in France.

Regarding data capture in the ATU system and HAS' utilization of it, there can be little argument against demonstrating that a medicine being used prior to approval is effective, especially if it is being charged for. Quite how this data capture will be enforced, and how this data will be used is yet unclear. Recent interactions with pharmaceutical companies has revealed some reticence about mandatory data capture, due to concerns that the patient population in the pre-approval setting is inherently sicker than the clinical trial population, and that outcomes data may not be as strong as the clinical trial data. However, it is hoped that any assessment made from pre-approval data will take this fundamental aspect of pre-approval provision into account.

Germany

Recently a group of German Health Insurance Funds wrote a letter to the German Health minister, setting out their concerns about a very high value medicine being made available pre-approval in Germany [6]. Although, pre-first approval provision in Germany must be free-of-charge, their concerns were that there was a campaign to pressurize the German authorities to reimburse the medicine at the company's desired price, driven by patient/parent pressure to maintain uninterrupted access from the pre-approval provision. The authors of the letter called on the German government to restrict compassionate use only to circumstances where there is an immediate danger to life, and asserted that the current activities risked jeopardizing pricing negotiations in general.

There have been other examples of such practices, notably a high-value rare disease medicine made available prior to approval in Belgium, and efforts to influence the media to argue for continued treatment and reimbursement at the manufacturers desired reimbursement price.

Like France, Germany is a key country for companies making their medicines available prior to approval. Like France, the German authorities have been amenable to such provision. But, like France now, recent overtly commercial practices within pre-approval access risk jeopardizing many thousands of patients. Whilst, like France, it is difficult to contest the reasoning behind the objections of the signatories, it is to be hoped that any changes implemented will measured and not impact the vast majority of well-intentioned, ethical pre-approval access in Germany, which benefits not only patients and manufacturers, but the Health Insurance Funds too, by providing medicines at no cost for a period before approval, with the consequent benefit on patients and caregivers.

Southern and Eastern Europe

Southern and Eastern European countries comprise a substantial proportion of the European population, but these countries are rarely included in pre-approval access programs. The reasons for this are many, but include; they are often not considered core commercial countries, their regulatory pathways are perceived as being less clear than other countries and there is a belief that they have less capacity to pay for pre-approval medicines. This results in a clear inequity, whereby patients in Germany may be receiving a promising medicine free-of-charge via the Compassionate Use pathway, whilst patients in neighboring countries such as Poland and Czech Republic, due to these perceptions, will not be able to access those medicines, and may have to wait many years for the product to be approved and reimbursed in their country. It must be noted that the Czech Republic does have legislation which allows the free-of-charge provision of unlicensed medicines via a group approach similar to that of Germany, however this is under-utilized by pharma in comparison.

But, demand for pre-approval access to medicines in these countries is significant. In 2017 there were over 10,000 applications in Hungary for Named Patient (pre-approval) access to medicines [7]. In Slovakia, the pharmaceutical spending per capita is in line with the EU-28 average [8]. Hungary, Greece, the Czech Republic, Poland, Romania and Slovakia all have well-defined pre-approval access mechanisms (see graphic illustrating the number of ongoing Special Therapeutic Programs ongoing in the Czech Republic). Yet these countries are often excluded from 'European' pre-approval access programs. These countries should present no issue to companies making their medicines available prior to approval.

Pre-approval access is not equitable. Companies must balance the cost of provision against many factors. Smaller countries (whilst combined may constitute a significant patient population) are often lower down the list when it comes to commercialization, and hence pre-approval, priorities.

Given the clarity of the regulations, the combined size of the Southern and Eastern European markets (population in excess of 100million), it is recommended that these countries are considered within the scope of any 'European' pre-approval access program. Aside from the ethical considerations, there are clearly wider benefits here for companies willing to think outside of the EU5 or EU10.

China

Given the size of its population, China is frequently a country of interest to pharmaceutical companies considering pre-approval access for one of their assets. Historically, pre-approval access into China has been extremely difficult, and as a consequence, China rarely features in pre-approval access programs.

The Chinese Drug Administration Law does allow provincial governments to approve one-off imports of drugs for an urgent clinical need, but this process is rarely used, as meeting the urgent clinical need requirement is difficult. The Hainan Medical Tourism Zone is supporting pre-approval access to by allowing medical institutions within the Zone to apply to import unapproved medicines from countries outside China, for use within the Zone [9, 10, 11]. However, this is an exceptional example within China and there remains a lack of an overarching national regulation on pre-approval access in China.

In December 2017 the then Chinese State Food and Drug Administration (as it was) instituted a public consultation on *'Administrative Measures for Compassionate Use of Investigational Drugs ("Draft Compassionate Use Measures")'* in China. Since this consultation closed in January 2018 no announcements have been made providing an update on the outcome of the consultation. If the Chinese authorities do open such a regulatory pathway to international companies, then it will be one of the most significant changes in this space in the last 20 years.

Conclusions

For a number of years, it has been highlighted that one of the biggest threats to pre-approval access is the overtly commercial focus that some manufacturers place on such activities. Undoubtedly there can be commercial benefits from such activities, but the driving force behind pre-approval access needs to remain patient-centric and ethical.

The changes being introduced in France, and potentially in Germany, will result in fewer novel medicines being made available to patients. This is clearly bad news for patients and manufacturers alike. However, the agencies cannot be criticized for introducing such changes. As vendors in the pre-approval space, we have a duty to guide client companies not only through what is possible, but what is ethical. As such, compensatory mechanisms to support the ethical provision of pre-approval medicines, to enable access to potentially life-changing medicines to patients with no other treatment options would be welcome.

At the same time, the inclusion of Southern and Eastern European countries within pre-approval access should be considered more broadly. There is demand for access in these countries, the regulations exist to support pre-approval access and healthcare infrastructures in many of those countries support payment for access to novel medicines ahead of licensing.

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- 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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