Expanding Markets:

Where Next? A Regional Regulatory Roundup

Globalisation and growing pushes to standardise submission requirements and formats internationally continue to open up new markets for life sciences companies, yet for now, there remain significant differences in requirements between regions and individual nations. With that in mind, Kimty Bui-Van of ProductLife Group assesses current regulatory climates in four markets with strategic appeal: Benelux, the Baltics, Canada, and South Africa.

The Benelux Countries: Belgium, the Netherlands, and Luxembourg

At the heart of Benelux and as the home of the *de facto* capital of the European Union, Belgium is an important regulatory hub, an open environment that adheres closely to European legislation.

The ease of communication and the professionalism of the Belgian authorities have made Belgium a popular destination for clinical trials. According to pharma.be data, some 35,250 people were employed in the Belgian pharmaceutical sector in 2016. And thanks to a regulatory framework that supports research, 15 companies have headquarters in Belgium, and there are 14 R&D facilities, 32 production sites, 12 universities and research centres, 14 bioincubators, and seven academic hospitals.[1]

Market Differentiators

One of Belgium's defining features is its language diversity. Along with French, Dutch, and German, English is spoken widely, making it easy to support all European countries from Belgium while maintaining strong communication with HQ. More often than not, Belgian teams manage regulatory filings on behalf of Luxembourg and the Netherlands.

Market Complexities

The biggest difficulty companies face in Belgium is the need to have a single responsible person for pharmaceutical information about products marketed locally. The role is crucial — and demanding. It involves ensuring that all medicinal product advertising conforms to laws and regulations. For every change in product information, the responsible person must sign a declaration confirming any translations are correct and consistent. The person is also responsible for medical sample management.

The responsible person must be a physician or pharmacist approved by the Ministry of Health, must have at least one year of experience in pharmaceutical information, and must fulfil local qualifications even if not based in Belgium. The person has to have official backup because if the person is away, the agency must be notified.

Since the requirement was introduced in 1984, just 1100 people have been authorised in the role – typically those nearing retirement and comfortable with the role's significant responsibility. Global companies sometimes delay consideration of the requirement for a local responsible person until late in the submission process, which can be a significant oversight given the scarcity of qualified people.

Why Belgium or Benelux?

In general, Belgium is one of the most straightforward markets in which to base European operations. As a multilingual country that is strategically positioned geographically and with its well-established and transparent regulatory environment, Belgium serves as a progressive hub for European submission management.

The Baltics: Lithuania, Latvia, and Estonia

Since joining the European Union, Lithuania, Latvia, and Estonia have adopted relevant European Union legislation; and companies preparing local submissions must have authorisation from the local authority (each country has its own) or from the European Medicines Agency (EMA), depending on the type of registration.

The respective national authorities cooperate readily, and they liaise closely with EMA, the European Directorate for the Quality of Medicines & HealthCare, and other international organisations. In Latvia, the State Agency of Medicines assesses medicines before issuing market authorisations. Estonia also has a State Agency of Medicines. And Lithuania's regulatory body is called the State Medicines Control Agency.

With a combined population of around 6.3 million — 2.9 million in Lithuania, 2 million in Latvia, and 1.3 million in Estonia — the Baltic region is not known as a significant producer of pharmaceuticals. Latvia has the strongest pharmaceutical industry among them, with production estimated at €120 million, but the region has a long way to go to catch up to other European markets.

Market Differentiators

EU legislation requires that a marketing authorisation holder reside in the European Union. None of the Baltic countries requires the presence of a regulatory person, nor must there be a native speaker within each country to work with authorities; and authorities tend to communicate in English. It is advisable to have a native speaker for translations of summaries of product characteristics and packaging materials, however, and to provide advice on product implementation.

When a company receives approval for a new variation, the product must be implemented within one year, so having someone in country to monitor the environment and provide information about changes can be invaluable.

Market Complexities

The Baltic region has seen a marked decline in mortality rates in the past 15 years, yet the rates remain high compared with many other

European countries. For instance, Latvia's premature death rate per 100,000 people is 400 compared with Spain's 142. That presents particular healthcare challenges. But all three countries have recorded pharmaceutical market growth, with promising potential for innovative life sciences companies. In Estonia, improved reference pricing systems have led to a shift in spending — from older medicines to more-expensive innovative medicines[2].

Why the Baltics

Unlike more-complex European markets, the Baltics are relatively easy to manage from a distance. Their regulatory authorities are easy to communicate with and open to discussion. Dossier submission can be managed electronically via the Common European Submission Portal (or Platform) (CESP), though for Latvia, a signed paper application form, a cover letter, and proof of payment are required via courier or post in parallel with the CESP submission.

South Africa

As the gateway to the African continent, South Africa is an important pharmaceutical market, though its regulatory regime remains in a state of flux.

In June 2017, the government introduced the Medicines and Related Substances Amendment Act and is establishing the new South African Health Products Regulatory Authority (SAHPRA) to oversee medical devices and medicinal products. SAHPRA will replace the Medicines Control Council, but its full scope will be implemented over two years.

These are the latest in a series of steps to shake up the regulatory environment. Such steps have also included a move away from the old Medicine Registration Form format to the Common Technical document (CTD), which has been mandatory since 2016. South Africa is also an observer of the International Council for Harmonisation's (ICH's) guidelines and to a large extent follows European Union guidelines for the submission of marketing applications.

Market Differentiators

The South African regulatory environment is stringent. Regulators carefully assess every submission and expect companies to strictly adhere to CTD guidelines. And firms submitting marketing authorisation applications in South Africa must be locally-based pharmaceutical companies.

Each company must also have a responsible person in the form of a pharmacist registered with the South African Pharmacy Council. The person must ensure adherence to laws related to medicine control and is accountable for all technical and regulatory issues involving a company's products in South Africa. The responsible person has wide-reaching legal and regulatory responsibilities as well by being responsible for quality aspects related to releases of products onto the market, and for ensuring that all standard operating procedures are in place, that the site master files get compiled, that dossiers are compliant, that pharmacovigilance requirements are being met, and that marketing material is compliant with regulations.

Despite its 11 official languages, South Africa currently requires labelling in only English and Afrikaans, but there has been discussion as to whether the patient information leaflet should be made available in other languages.

South African – based pharmaceutical companies, subsidiaries, and consultants commonly handle submissions for other African countries, including Botswana, Ghana, Kenya, Mauritius, Namibia, Tanzania, and Uganda. Each country has its own regulatory nuances, requiring experts with relevant knowledge and good working relationships with in-country agents to ensure local compliance.

Market Complexities

Even though old dossiers can remain in their existing Medicine Registration Form format, if a chemistry, manufacturing, and control variation is submitted, the company must convert the entire submission to CTD and submit a fully updated Module 3. Although this involves a lot of work, many old dossiers contain only scant information, so an update is necessary.

Perhaps the most significant challenge for companies, though, is the national agency's regulatory backlog: the approval process currently takes around five years. One cause of this was a sudden influx of generic applications in response to price control measures. In addition, the government's focus on certain diseases that affect a large proportion of the population — such as HIV and tuberculosis — resulted in an increase in associated product applications. More recently, it was decided to do away with fast-track evaluation, too, to ensure all products get evaluated equally.

In 2015, South Africa initiated an electronic CTD (eCTD) pilot involving 18 products, which provided good insights into the eCTD process for both companies and regulators and helped speed the review process for at least some of those products. Even though eCTD applications are now accepted for both new chemical entities and generic applications, the time frame for compulsory submission in eCTD format has not yet been set.

Why South Africa?

As a pharmaceutical market, South Africa is the largest in sub-Saharan Africa – valued at €2.52 billion – and is expected to grow at a compound annual rate of 7.4% from 2014 to 2019, according to data from IMS Health (renamed IQVIA in 2017).

From a regulatory point of view, the market follows ICH guidelines similar to European Union requirements. The use of South Africa as a base for building regulatory submissions for other African countries is also highly appealing.

Canada

As a member of the International Council for Harmonisation, Canada takes a regulatory approach familiar to most global companies. The approach is similar to Europe's, although Health Canada has implemented certain country-specific regulations.

Canada requires that a physical entity (directly owned or otherwise) be in the country for a drug establishment licence. Companies that have experience with the European eCTD or even US sub-

mission requirements should find preparing an eCTD for Canada relatively straightforward. The United States and Canada have established a Regulatory Cooperation Council Pharmaceutical and Biological Products working group to enhance regulatory harmonisation between the two countries.[3]

The pharmaceutical industry in Canada employs around 27,000 people directly and more than 100,000 people indirectly and is growing at a compound annual rate of 2.2%, according to government sources. Most pharma companies are clustered in Toronto, Montreal, and Vancouver.

Market Differentiators

Among the Canada-specific regulatory requirements is the product monograph, which is akin to the EMA's summary of product characteristics and which documents non-promotional information about a drug, including its properties, claims, indications, and conditions of use.

Health Canada introduced plain-language labelling requirements in 2014 to ensure that patient materials are easy to understand. Another consideration is a requirement to publish a product monograph and all labelling in both English and Canadian French, which differs slightly from European French.

Although it is not a legal requirement to have someone on the ground in Canada to handle submissions, local knowledge, the ability to liaise with the health authorities, and a one-on-one relationship with the client are invaluable.

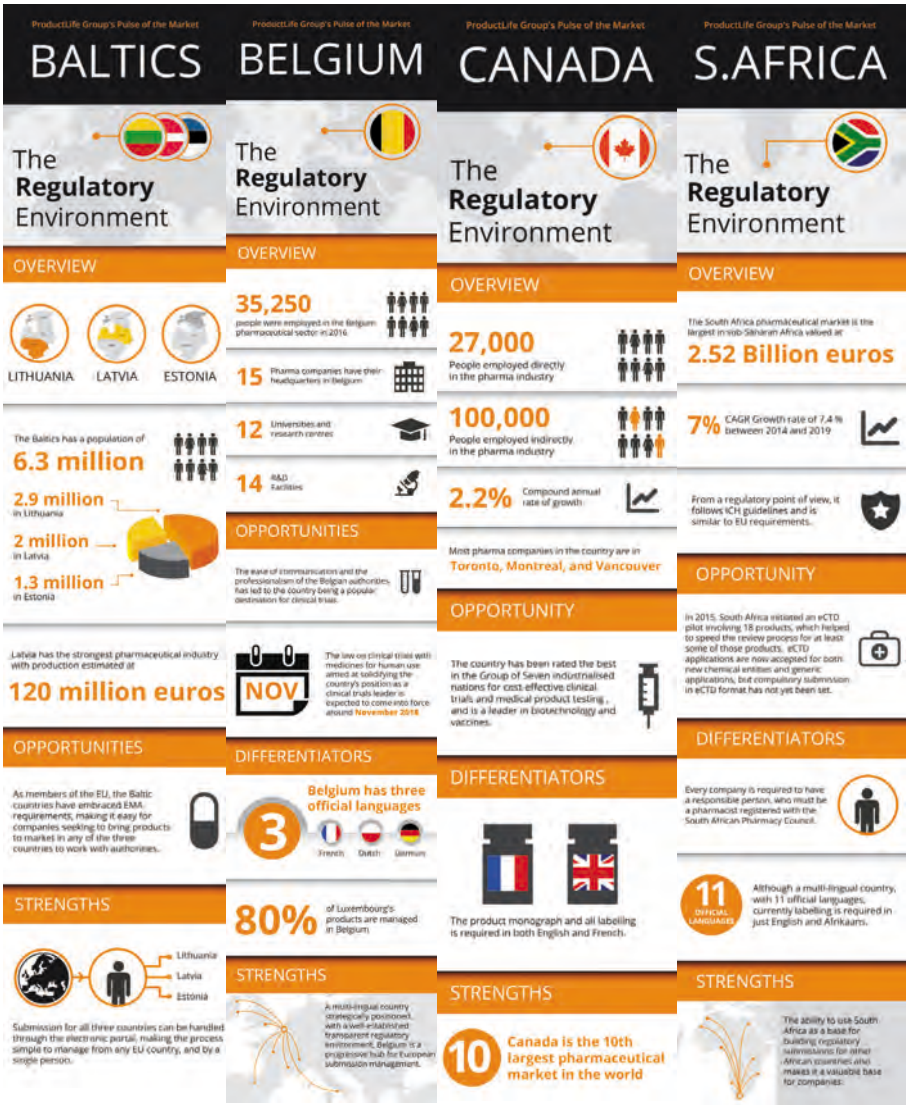
Market Complexities

As a straightforward and transparent market, Canada poses few specific regulatory complexities for companies. However, understanding the local environment and developing a rapport with the local authority are important to avoid delays to market given that, unlike in Europe, there is no predefined time limit in Canada for the question-and-answer review period.

Why Canada?

Canada is the 10th-largest pharmaceutical market in the world. It has also been rated the best in the Group of Seven industrialised nations for cost-effective clinical trials and medical product testing.[4] And it is a leader in biotechnology and vaccines. Given its similarities to both the United States and Europe with regard to regulatory requirements, Canada raises few hurdles for companies – and presents many advantages.

As global opportunities expand and barriers to market entry diminish, we can expect to see more pharmaceutical organisations broadening their outlooks as they pursue new growth in 2018 and beyond. As long as they approach the new frontiers with their eyes open and key preparations made, the gains could be substantial.



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