Divided by a Common Language: PV Differences Between the UK and the US – Notes for Ambitious Biotechs

Small biotechs come under the same scrutiny as large pharma when it comes to pharmacovigilance. In this article non-executive advisors to Arriello, Eric Caugant in Paris and Judi Sills in New Jersey, outline key differences in requirements on either side of the Atlantic and provide some practical tips for biotechs looking to optimise their PV budgets.

In the modern market, small and nimble biotechs possess many great advantages in terms of their ability to bring new innovation to market quickly, unhindered by legacy ways of operating. Yet the smallest startups share the same obligations as large pharma companies when it comes to safety and pharmacovigilance, which means they are likely to face a steep learning curve.

It doesn't help that requirements vary from region to region, from authority to authority, around the world. Relying on an individual CRO partner to manage all PV requirements internationally may be appealing, but is a risky strategy – unless there is experienced CRO oversight to ensure that the regulatory requirements are met in all countries where a compound is studied and/or marketed. A far better approach is for biotech companies to grasp for themselves the complexity of the task they face.

Before going to market

Most pre-market PV requirements are the same across the European and US markets, in line with agreements and guidance on standardisation via the ICH – the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. But there are some small, noteworthy variations.

Companies tend to favour filing in the US first, because on top of the market's vast size the US benefits from being one country, governed by one main agency – the United States Food and Drug Administration (FDA). In Europe, marketing authorisation can take much longer because beyond the central European Medicines Agency (EMA) each EU member state has its own unique requirements to navigate.

Even at a central level, EMA submissions have a different look and format to US dossiers so require different handling. For instance the Summary of Product Characteristics (SmPC) and labelling in relation to side effects are not presented in the same way in Europe. Differences exist too between the risk management approaches – the FDA's Risk Evaluation and Mitigation Strategies (REMS) and EMA's Risk Management Plan (RMP) – one cannot be substituted for the other. Failure to factor in these differences could present an issue at the time of filing. In addition, national EU-specific requirements may be requested in certain countries, on top of the RMP EU requirements, even for centralised procedures.

Get any of this wrong, and companies risk their dossiers being rejected, or authorisation being delayed as requests for amendments or additional information go back and forth.

Keep it together

All of this means that biotechs need a clear strategy and timeline for how they will file to their target markets. Leaving Europe to one side until sales in the US are up and running is inadvisable, given the additional time that is likely to be required to prepare for EMA's differing requirements – and those of each EU country beyond that. And of course the UK must now be treated as its own market, following Brexit which means it is no longer under the jurisdiction of EMA.

It isn't just European information and formatting requirements that differ and are more involved than in the US. Standard operating procedures (SOPs)/process requirements can be more complex in Europe too.

Real-world monitoring

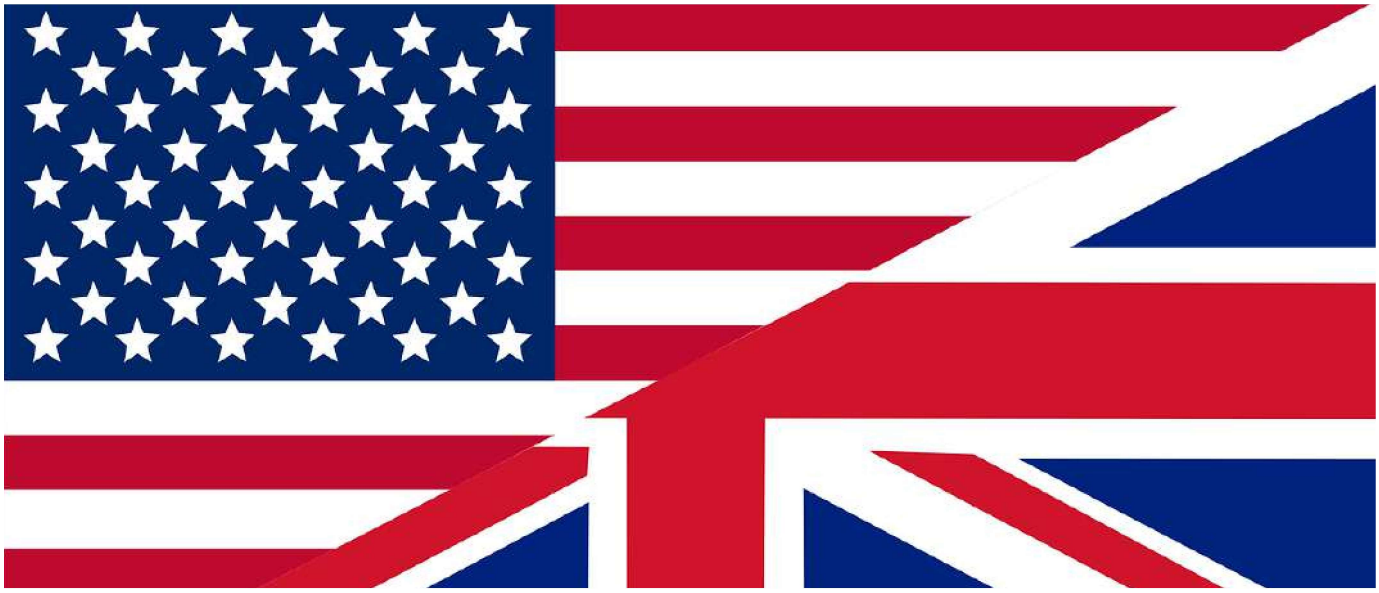
The post-marketing regulatory environment is highly regulated and inspection driven, and it is here that biotechs are likely to find the greatest challenges in managing their PV obligations. Here, the differences between US and European requirements differ more significantly.

In the early 2000s, Europe revised its post-marketing PV requirements, making these very clear and prescriptive. In the US, equivalent post-marketing safety requirements are considerably older and quite vague in their language, leaving much to interpretation. For post-marketing safety studies, for instance, Europe has done quite a nice job of breaking down the requirements for interventional versus non-interventional studies and what needs to be reported – or not – for each. In the US, companies tend to tread a much more cautious path, interpreting the requirements more conservatively because precise guidance is lacking.).

If studies are used to support a product claim, and the right data hasn't been collected in the right way for the given market, this could pose problems. So the different requirements do need to be well understood – and designed into post-marketing and market research studies – to avoid potential problems later.

Differences in definition

A further variable in all of this is that categorisation and treatment of different products types by the authorities can differ between regions. A 'device' or 'combination product' (device plus medicine) may carry different definitions and requirements from one region to another, for instance. Being aware of this, and building this into PV processes and planning, is another international regulatory imperative then.



Filling capability gaps

The challenge for biotechs is that, while these companies have extensive product expertise, this is not typically matched in understanding and expertise in PV requirements and process rigour. To mitigate safety compliance related risk, they need to fill that gap – both with the right knowledge and experience, and with skills in writing SOPs and setting up PV systems which, in Europe, must be in place from the time of filing for marketing authorisation (checks for which could be made during filing/pre-authorisation if the regulator feels in any doubt about a company's PV provisions).

Relying on a third-party safety services provider to take on this burden without in-house oversight is not a practical or advisable solution. This is not least because the marketing authorisation holder retains ultimate responsibility for PV compliance: it is they rather than the CRO (contracted partner) that will be liable if anything goes awry.

So, irrespective of the biotech's size and scale, the company will need to bring in someone experienced who understands PV and can keep a check on vendor quality – rather than simply send someone on a course.

Continuous tracking

Where biotechs have entered into distribution partnerships/relationships with other MAHs, there will be additional considerations - such as who will coordinate and be responsible for the PV requirements in a given market and how this will be written in any contracts. The MAH in the local country always is ultimately responsible for meeting PV requirements in that country. For PV, there is also the decision of who will be the global database holder (usually the company that developed the product and got it approved).

PV capabilities need to evolve, too – not just to keep pace with changes to regulatory requirements across the different markets, but also to stay on top of evolving channels and technologies when tracking safety signals. Where web sites and social media platforms create scope for market feedback, companies have an obligation to monitor and filter that content for potentially important real-world safety information, where digital media is considered to be company-sponsored (if it is owned, paid for and/or controlled by the MAH).

Meanwhile, the increase combination treatments involving drugs and devices may drive new rules which clarify how responsibility for adverse drug reactions is calculated and apportioned between those relative components. So this situation needs to be tracked, too.

Ultimately, setting aside a PV budget to develop the right internal knowledge and connect with appropriate external guidance will be essential for any biotech navigating all of this international complexity. It may seem a lot for a small emerging biotech to take on board, but lay the right foundations early on and there will be a world to play for.

Dr. Judith M. Sills

A non-executive director and advisor to Arriello, Dr. Judith M. Sills, Pharm.D. is president of JM Sills Consulting LLC, specialising in pharmacovigilance and benefit-risk management. She has over 30 years' experience in pharmacovigilance in the pharmaceutical industry, FDA, and consulting. Prior to establishing a consulting practice in 2018, she was VP and head of global pharmacovigilance at The Medicines Company. Judi has also held senior positions at Novartis, Warner-Lambert and The Degge Group.

Dr. Eric Caugant

Also, a non-executive director and advisor to Arriello, Dr. Eric Caugant has over 25 years' experience in pharmacovigilance, drug safety, risk management, and more broadly pharmaceutical medicine. In 2017, he founded Pharmacovigilance Systems Consulting (PhVSC). Prior to this, Eric held senior positions in various pharmaceutical and biotech companies including Alexion, Bayer Lilly and Wyeth as well as the French Ministry of Health.