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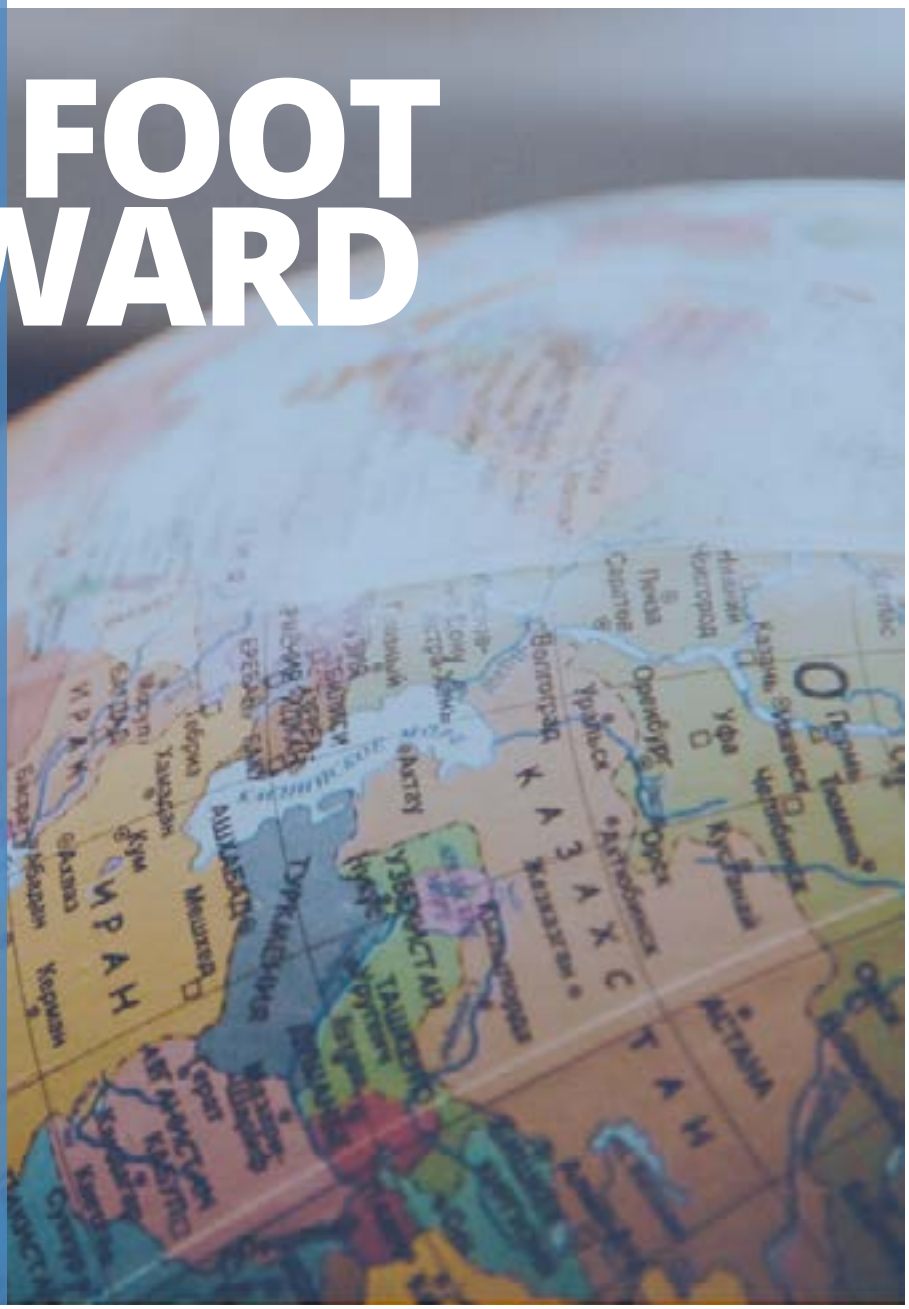

Which market to enter first?

Pros and cons of the regulatory scenario in key international markets (the UK, the US and Europe) within a changing regulatory environment.

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MANAGEMENT SUMMARY

In today's rapidly evolving landscape of healthcare and technology, navigating the realm of regulatory compliance for medical devices has become an increasingly complex endeavour. With advancements in medical technology, the development and deployment of innovative devices have brought forth immense opportunities for improving patient care and revolutionizing the healthcare industry. At the same time, however, major markets such as Europe and the UK are experiencing unprecedented regulatory shake-ups in the form of the introduction of the new EU MDR and IVDR and the Future UK Regulatory System.

These regulations aim to safeguard patient safety, ensure device effectiveness, and maintain ethical standards throughout the product lifecycle, from design and manufacturing to post-market surveillance. However, achieving regulatory compliance in this intricate landscape is no simple task. It requires a deep understanding of the evolving regulatory landscape, meticulous planning, robust quality management systems, and effective risk assessment strategies.

Manufacturers and stakeholders must navigate through a web of complex standards, guidelines, and country-specific regulations before they decide which markets will be the most profitable to enter and which ones they should tackle first, laying the groundworks for further expansion in the most time-efficient and cost-effective way possible. This whitepaper looks at three major markets for medical devices- the EU, the UK and the USA- highlighting some key considerations relating to entering each of these geographies "first" to help manufacturers make informed decisions and prepare for engaging with regulatory experts that can help them enter foreign markets successfully to expand the global presence of their products.

INTRODUCTION

The global medical devices market size was valued at $512.29 billion in 2022 & is projected to grow from $536.12 billion in 2023 to $799.67 billion by 2030, with a CAGR of 5.9% over the period[1]. Aging populations are driving an increase in incidence of chronic diseases which, combined with exciting new advances in technology ranging from AI to robotics are contributing to creating enthusiasm for new product development, research and development.

At the same time, however, medical device manufacturers are facing a time of unprecedented uncertainty in the global regulatory landscape, mainly driven by the changes revolutionising the EU and UK markets. First the introduction of the new EU MDR, with its protracted roll-out and delays to ensure suitable provisioning and to face the challenges imposed by the global pandemic, then Brexit, which effectively draws the UK out of the European regulatory environment and imposes the creation of new guidelines and regulations.

To add to this climate of uncertainty there have been various extensions for Medical Devices Regulation (EU) 2017/745 (MDR) and the In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746 (IVDR) implementation, with full compliance now set to come into force at end of 2027 for high-risk devices and at the end of 2028 for medium and certain lower risk devices. This is, however, an area with unique complexity with context specific issues relating for example to actions taken or inaction.

Whist full compliance requirements for some products may be delayed in the EU, critical elements of regulation have already been enforceable for some time. Specifically, PMS requirements under the MDR have in fact been applicable since 26th May 2021 for all medical devices sold into the EU, regardless of a device's MDR CE Marking status. Proactive PMS measures have been a requirement for IVDs since 26th May 2022, as outlined in the latest IMed Consultancy whitepaper "A perfect Time to perfect PMS".

Understandably, medical device manufacturers have embraced extensions, particularly as Notified Bodies are also under significant capacity pressure, but have also become somewhat confused as to which requirements are already enforceable and which they have more time to prepare for. Similarly, in the UK, the transition to the UK MDR is currently in a transition period and set for official implementation on 1st July 2024, but some requirements, such as the need to have a UKRP have been in force as of January 2021.

For businesses placing devices on the Northern Ireland market, where the EU MDR and EU IVDR have applied in Northern Ireland respectively since May 2021 and May 2022 there are several options for Northern Ireland compliance using either the UK or EU regulatory systems.

In this complex environment it is hardly surprising that medical device manufacturers with new devices or that want to expand into new territories are confused. Costs, timelines, shifting deadlines and potential extensions, these are all elements of uncertainty that make the decision regarding market entry, and particularly which market to enter first, highly complex.

This whitepaper draws on decades of experience across different geographies to outline the benefits and pitfalls of entering a range of markets “first”, to help medical device manufacturers make informed decisions on which markets offer the simplest, fastest or, indeed, most cost effective route to putting their devices on the market.

US FIRST

The U.S. medical device manufacturers market size was valued at USD 176.7 billion in 2020 and is anticipated to exhibit a compound annual growth rate (CAGR) of 5.0% over the forecast period, according to Grandview Research, with imaging diagnostics and orthopaedics leading the fray, making this a highly dynamic market.[2] It is not surprising therefore that many medical device manufacturers are keen to abandon their preconceptions over FDA strictures and initiate their market entry by launching on the US market first of all.

For the majority of medium risk devices the typical regulatory route is the submission of a 510 (k) registration. A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is as safe and effective as an already legally marketed device, and doesn't raise new questions on safety and effectiveness. A route for novel devices also exists, where the product is not able to demonstrate similarity to an existing legally marketed device which is called a De Novo submission.

Lower risk devices require registration and listing with FDA, but are often exempt from formal regulatory submission to FDA prior to being placed n the USA market.

Higher risk devices are usually considered via a pre-market approval (PMA) route, which is similar in approach and evidence requirements to UK and EU Class III medical device certification.

PROs & CONs

While the US is a tough market to enter first with a very innovative, high risk product, if there is an existing, similar product- an equivalent device with the same intended use- submission is vastly simplified.

While the device developer needs to ensure their QMS meets FDA requirements (21 CFR Part 820), overall regulatory approval fees are usually considerably lower than in the EU for product assessment. The device manufacturer will also need to undertake establishment registration and for non-US (foreign) manufacturers, arrange a US Agent (21 CFR Part 807).

If this is their own device, they will have access to all the information about the predicate, but if this is another manufacturer's device the information to which they have access is restricted to that in the public domain (e.g. the equivalent device 510(k) summary, manufacturer websites, publications, IFU, brochures and public complaints data.). It is unlikely there will be access to technical information.

The manufacturer must use their development documentation to support their argument of substantial equivalence when writing the 510(k) which needs to be carried out in line with publicly available FDA guidance. FDA will follow specific timings for response and in case of a positive outcome the manufacturer will receive a letter confirming that the device is indeed substantially equivalent. In addition to this, if the manufacturer is able to prove that the device is substantially equivalent a clinical investigation isn't always necessary when using the 510(k) submission route, helping to reduce time-to-market and overall costs.

Contrary to this, if the manufacturer receives a Not Substantially Equivalent (NSE) letter they will have to restart the process identifying either a new predicate device or a new submission type.

4 common causes for NSE letters:[3]

1. ***The manufacturer failed to verify that the predicate is a legally marketed device***

2. ***The manufacturer failed to evaluate the substantial equivalence of their device's intended use with the predicate.***

3. ***The manufacturer failed to convince the FDA that technological differences do not raise different questions of safety and effectiveness.***

4. ***The manufacturer failed to provide sufficient data*** **demonstrating substantial equivalence.**

Pre-Submission requests are a useful tool to help avoid falling into one of these 4 causes, allowing a discussion with the FDA in advance of the formal regulatory submission could be useful to avoid omissions in regulatory strategy which can be avoided through early FDA interaction. Specifically, a Pre-Sub request could verify with the FDA that the predicate is appropriate to use (point 1 and 2) and to understand any questions of safety and performance raised by technological differences (point 3). The manufacturer can also use the Pre-Sub to propose testing methods to demonstrate appropriate safety, performance and substantial equivalence (point 4). Without a doubt, if used correctly the Pre-Sub is a useful dialogue tool that can help avoid issues further along the approvals process, reducing unnecessary delays.

It is worth noting that the pre-sub is not restrictive, but the FDA will only address specific questions, so these need to be drafted correctly. In addition to this, guidance provided in a Pre-Sub response is not binding for the FDA but it is generally confirmed, unless the manufacturer has changed the device following the pre-submission and the changes affect the guidance provided by the FDA (e.g. a change to the intended use of the device).

The FDA have a very different way of operating to EU authorities, so understanding of FDA procedural and cultural expectations is important for successful interaction. While manufacturers who successfully find a suitable predicate will have a reasonably easy and pain-free experience, innovative devices may need to follow a more complex process, called De-Novo. The De-Novo process looks to qualify and classify a new product type, and determine the special controls necessary to demonstrate safety and performance. Following De-Novo approval, the new device can in fact become the predicate for future product submissions in the USA under the 510(k) route.

If the manufacturer cannot find a predicate, then it may be that there are no similar devices currently cleared in the US market. It may also simply be that there are similar devices, but the search terms used did not show any relevant results. Before proceeding down a more complex and expensive submission route, however, the manufacturer should consider enlisting the help of an expert consultant who can help with a search for a predicate device and what options exist for market access in the USA.

EUROPE FIRST

While the US is the biggest world market with 43,5% share of medical device sales, the European Union trade bloc follows with 24.5%, making this an appealing market to launch your medical device.[4] The top five biggest markets are Germany, France, the United Kingdom, Italy, and Spain. Medical technology offers solutions for many disease areas. On a worldwide perspective, in vitro diagnostics (IVD) is the largest sub-sector of devices, followed by cardiology. In fact, in addition to market size it's important to look at the clinical need the medical device is addressing and whether it is relevant to the target geography.

In the EU a medical device manufacturer of medium risk devices faces quite a complex and long journey towards approval, compared with entering the US market under 510(k). Specifically, in the EU the medical device manufacturer needs to build up a larger body of evidence and create a technical file dossier. They also need to find a Notified Body to certify their products, evaluate their QMS, review their technical documentation and particularly their clinical evidence.

Notified Body capacity issues are of particular concern with many close to reaching a bottleneck in their activities and not accepting new manufacturers, or requiring lengthy pre-assessment wait periods to begin the technical assessments needed for approval. The European Commission (EC) has taken new measures to relieve some of the pressure on Notified Bodies by reassessing the frequency of with which they have to face reassessment by Competent Authorities and the EC.[5]

The 38 existing Notified Bodies are responsible for having issued 1,990 of the 8,120 applications received as of October 2022 according to BSI, leaving a majority of devices still to transition to the EU MDR by 26th May 2024.[6] In particular, Notified Body bandwidth is occupied with this transition making it difficult for businesses wanting to propose product changes, reclassify devices and for businesses with new products looking for a NB willing to take them on.

PROs & CONs

In Europe, like elsewhere, the risk class of the device is going to determine how much financial and staff effort, as well as how much time is required to get the product onto the market. However, with the current climate of uncertainty and lack of NB bandwidth, more and more businesses are choosing not to be present or delay entry to the European Union market.

In addition to linguistic fragmentation that raises costs for labelling and marketing materials (often calling for specialist medical translators) there are also regional legislative differences within each country: example, Germany has very restrictive regulations about medical device pricing. Regional, provincial and other institutions may also have a say in pricing decisions depending on where the medical device is to be sold.

On the other hand, the EU commission has clearly acknowledged that there are issues and is working on addressing these to make the EU a more attractive market and ensure that patients are not put at risk by a lack of new, innovative and existing medical devices. As a result, there are various measures in the works to help make the transition from earlier regulation to the EU MDR/IVDR less complex. The recent extension of deadlines for implementation is one such measure for existing products certified to older regulations.

Deadline extensions to comply with MDR requirements:

Existing higher-risk devices (class III and certain class IIb implantables), such as pace-makers	*extended to 31 December 2027, subject to certain conditions (including requirements for post-market surveillance, quality management systems, and en-gagement with notified bodies)*
Medium and lower-risk de-vices (other class IIb devices, class IIa, class Im, Is and Ir devices), such as syringes	*extended to 31 December 2028, subject to certain conditions (including requirements for post-market surveillance, quality management systems, and en-gagement with notified bodies).*

At the same time, while access to EUDAMED is making more information available to businesses that want to innovate as well as the public, this also means that competitors are able to access more data relating to manufacturers devices.

It is also worth noting that although CE Marking may take more time and result a little more complex, the CE Mark is one of the certifications that is most widely accepted in other territories. It is often more powerful as a mark than FDA approval and is particularly effective in speeding up market access in the Middle East, Africa and ex Commonwealth nations. Manufacturers that want to scale up fast and export their products globally would therefore do well to consider gaining EU certification before any other.

UK FIRST

While a smaller market than the overall EU and US, the UK is a significant player in the global medical device market. Not only are there fewer language barriers for US manufacturers and indeed for many other producers that have adopted English as the lingua franca of commerce, but the appeal of the NHS which presents a "one provider/one payer" model, at least in perception, is significant. The 4 yearly tender framework offers a lot of potential to manufacturers that hope to interface with one single big buyer.

In addition to this, the UK is increasingly positioning itself as an ideal market for products that are novel and niche (in contrast with the EU where NBs are under pressure and not taking on new products, and with the US where routes to approval for innovative and high risk products are more complex). As published in the first ever Medical Technology Strategy plan in February 2023: *"MedTech is a vitally important industry for the UK economy, representing over half of all life sciences employment, with businesses situated across the UK and contributing billions of pounds to the economy. As a country we are known for world-leading scientific research and development capabilities, and the UK health and care system is globally recognised as a successful and trusted health system, making the UK a major player on the global healthcare stage."*[7]

The document confirms that: *"We must encourage ambitious, innovative research...helping secure the position of the UK as a global science superpower. Moving forwards, we have the opportunity to make the UK an even more attractive market for businesses by improving access, shaping our own regulatory framework, leading in research and development, and maintaining a strong international market presence."*[8] This is exciting breeding ground for innovation and for innovative new medical device manufacturers, and we see a particular focus on innovative software devices being high up the regulatory agenda – with the potential for new and quicker routes to market being proposed.

From a regulatory perspective, the transition to the new UK MDR is in full swing with deadlines to meet new requirements following on from each other faster than many medical device manufacturers realise. To accommodate the contrasting needs of driving revolutionary technologies, the UK is also considering accepting the approvals of other countries to speed up admissions.

Currently, however, the UK is still operating a more mature regulatory system than the EU MDR, where risk classes are generally lower, especially for AI and Software devices as well as certain IVD products. As a result this period of transition between the current UK regulations and the potential new UK regulatory system, is an ideal time to enter the market before the transition brings about more uncertainty and potential complexity.

CONCLUSIONS

There is of course no clear-cut answer for medical device manufacturers evaluating which market to enter first, but understanding the strengths and weaknesses of the regulatory systems currently active in these major markets can help frame the decision-making process. Without a doubt, device maturity, therapeutic area and classification will drive the selection of the market most likely to yield success, but venturing forth without experienced guidance and advice means taking unnecessary risks in what is currently a changing and complex regulatory landscape.

Securing the support of international regulatory experts will not only help navigate the complexities of specific markets, managing the expectations of their authorities efficiently and rapidly, but can help identify areas of overlap between the different geographies' requirements to help structure longer term expansion strategies.

Contact the team at IMed Consultancy for deeper insight into the UK, US and EU regulatory scenarios: hello@imedconsultancy.com or visit www.imedconsultancy.com

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