

The new frontier of biopharmaceutical and medical device regulations

The past decade has seen an unprecedented level of regulatory change in Europe's biopharmaceutical and medical device industry. In this article, we highlight some notable regulatory initiatives that will impact industry over the coming years. We explore why these are being rolled out, what the impact on industry will be, where the potential challenges are and how value can be realized from these efforts.



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Driven by a concern for greater patient safety, a number of major regulatory initiatives have either commenced or are on the cusp of being rolled out. These changes have demanded action from industry and regulators, in addition to coordination with a range of stakeholders. Achieving and maintaining compliance is critical, as this will directly impact whether a product can remain on the market. However, moving to new regulatory standards is not without risk; remediation costs are high and may not have a positive return on investment. Consequently, organizations will have to make key strategic decisions on their portfolio, execution approach and market presence.

European Union Medical Device Regulation (EU MDR)

The European medical device market, the second largest in the world, was valued in 2015 at approximately €110b (US\$122b).¹ Medical devices and *in vitro* diagnostics have seen considerable innovations over the last 30 years. In part, this has been due to progress in engineering and manufacturing processes, the development of advanced polymers, and the application of computer technology to support device design and development. Additionally, advances in novel surgical and interventional techniques have further catalyzed rapid progress across the industry.

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Despite these advances, the regulatory framework governing devices and diagnostics in Europe (and the US) had not changed significantly since the mid-1990s. As such, product development had outpaced the governing principles that ensured safer products.

Underscoring the need for change were a number of scandals in Europe and the US, though with global implications:

▶ **June 1974: Dalkon shield recall^{2,3}**

The flawed design of the Dalkon shield contraceptive intrauterine device led to pelvic inflammatory disease and sepsis. Though it was believed that design faults were known to the company that manufactured and marketed the product, they were ignored. An estimated 21 fatalities were linked to the device, while as many as 200,000 suffered device-related injuries.

▶ **July 2011: vaginal mesh recall⁴**

The U.S. Food and Drug Administration (FDA) warned of serious complications associated with transvaginal surgical meshes for the treatment of incontinence or prolapse. By 2011, nearly 4,000 adverse events had been reported; causes ranged from the use of plastics not suitable for human implantation, erosion and breakup of the mesh (causing vaginal perforation), tissue entanglement and poor implantation by the clinician.⁵

▶ **June 2012: Poly Implant Prothèse (PIP) breast implant scandal⁶**

The French company PIP was discovered to have illegally sold breast implants made with low-cost industrial-grade, rather than medical-grade, silicone for nearly a decade. These implants were two to six times more likely to rupture or leak than other breast implants and had been linked to fatalities. Globally, an estimated 300,000 women were affected and were advised either to have the implants removed or, at the least, have periodic investigations to assess the risk of rupture.⁷

▶ **July 2012: U.S. FDA whistle-blower controversy⁸**

Through a series of leaks, a group of five FDA scientists claimed that the regulator had been knowingly approving devices that posed severe health risks without demanding better clinical evidence of product safety from manufacturers. The controversy came to a head when a wide-ranging surveillance program was discovered to have been requested by FDA bosses to monitor the activities of these whistle-blowers.

1. "The European Medical Technology industry in figures 2016," *MedTech Europe* website, <http://www.medtecheurope.org/node/946>, accessed 26 June 2017.

2. "The Dalkon Shield Disaster," *Washington Post* website, https://www.washingtonpost.com/archive/entertainment/books/1985/11/17/the-dalkon-shield-disaster/6c58f354-fa50-46e5-877a-10d96e1de610/?utm_term=.8301e1d31143, accessed 13 June 2017.

3. "The sad legacy of the Dalkon Shield," *The New York Times* website, <http://www.nytimes.com/1987/12/06/magazine/the-sad-legacy-of-the-dalkon-shield.html>, accessed 26 June 2017.

4. "Transvaginal mesh overview," Recall Report website, <https://www.recallreport.org/dangerous-drugs-products/transvaginal-mesh/>, accessed 13 June 2017.

5. "Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse, July 2011," FDA website, <https://www.fda.gov/downloads/medicaldevices/safety/alertsandnotices/ucm262760.pdf>, accessed 26 June 2017.

6. "The Safety of Poly Implant Prothèse (PIP) Silicone Breast Implants – Update of the Opinion of February 2012," European Commission, https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_043.pdf, accessed 13 June 2017.

7. "PIP breast implants: French court tells TUV to pay damages," BBC website, <http://www.bbc.co.uk/news/world-europe-38692678>, accessed 13 June 2017.

8. "Vast F.D.A. Effort Tracked E-Mails of Its Scientists," *New York Times* website, <http://www.nytimes.com/2012/07/15/us/fda-surveillance-of-scientists-spread-to-outside-critics.html>, accessed 13 June 2017.

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A critical concern for the medtech industry is the need to provide clinical evidence of product safety and efficacy.

In light of these concerns, and other incidents, the need to reform medical device regulation was highlighted. In June 2017, after five years of iteration and negotiation, the final versions of the revised EU MDR⁹ and *In Vitro* Diagnostic Regulation (IVDR)¹⁰ were formally published. Medtech companies now have a specified time within which to achieve compliance: by 2020 for medical devices and by 2022 for *in vitro* diagnostic products.

The new rules emphasize patient safety, demanding stricter requirements on the conformity assessment of products, coupled with post-market surveillance and documentation of the device's safety profile from a clinical standpoint. This is supplementary to any performance or expected side-effect details that might already be documented. Additionally, the new rules are anticipated to support cost-effective market access for products that are considered innovative.

A critical concern for the medtech industry that these regulations have raised is the need to provide clinical evidence of product safety and efficacy. This is a particular challenge for products deemed high risk, where the need for supporting data is considerable; the EU MDR categorizes these as Class III devices, e.g., long-term surgically invasive implanted devices. Naturally, notified bodies will exert most pressure on manufacturers of such devices to provide this evidence. The challenge is further compounded by the likelihood of the EU MDR demanding a product be reclassified in a higher risk category, thereby adding to the regulatory burden to which the manufacturer must adhere.

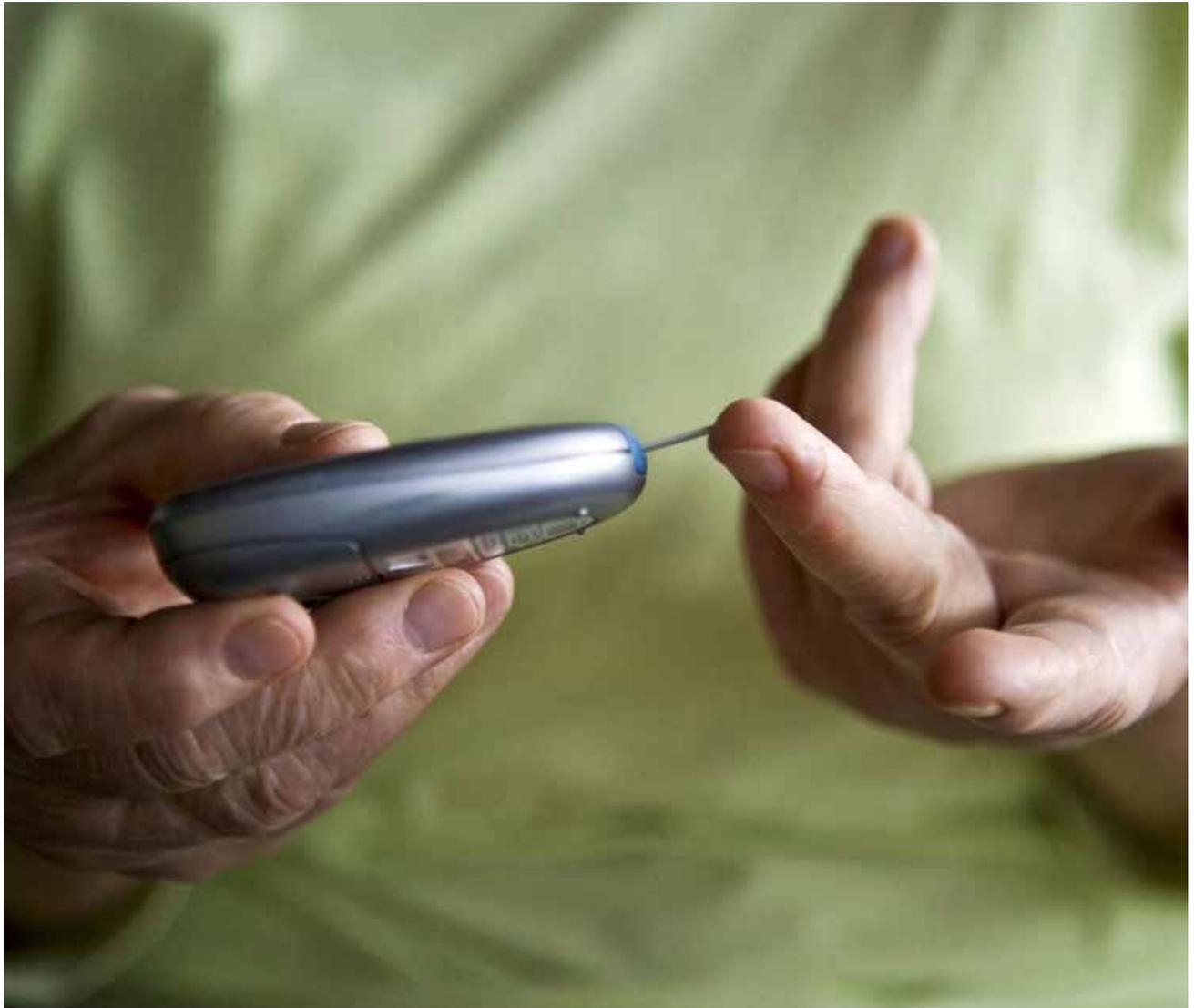
Portfolio size and diversity make it challenging to attribute a per-company cost of achieving EU MDR compliance. However, in 2013, the industry group Eucomed surveyed its members to estimate the pan-industry impact of the new regulations over the period leading up to 2020.¹¹ Investments of €7.5b (US\$8b) would be required to introduce relevant measures to ensure compliance (e.g., device identification, labeling improvements and clinical data collation). The additional cost to an SME of bringing a Class III device to market was estimated to be €17.5m (US\$19m).

As organizations weigh up the cost of compliance, strategic decisions may be required as to whether divesting a product line may be preferable to the potential considerable investment to maintain a product on the market.

Unique Device Identification (UDI) and GS1¹²

Traceability of medical devices throughout the supply chain lies at the heart of improving both patient safety and the reputation of the medical device industry more broadly. This demands the ability to define the provenance of a product and track its movement through each step of its journey: from the manufacturer through to any importing or distributing agent, downstream to the health care facility where the device is used and, finally, the patients themselves. Within the EU MDR there are requirements for UDI, which necessitates a globally accepted device coding standard to support unambiguous identification of a device. These identifiers are to be placed on device labels for use across a range of product management purposes; for example, reporting issues, recording inpatient records and regulatory documentation references. All stakeholders in the product supply chain are mandated to record product UDIs in an electronic manner.

The requirement for the European UDI System is based on guidance from the International Medical Device Regulators Forum (IMDRF) and is aligned to global harmonization efforts in conjunction with the U.S. FDA. Achieving the goal of a universal identifier requires a global labeling standard, and the chosen standard is GS1. This not-for-profit organization's barcoding platform has already supported a range of sectors and is fully compliant with UDI requirements: a system that encodes both device and



production identifiers, supplemented by a centralized database. Indeed, GS1 has been implemented for Class III medical devices in the US since 2014; in contrast, the lowest-risk devices (Class I) will require UDI-compliant product labeling by 2018.

The adoption of GS1-based UDI is explicitly focused on patient safety. However, the implicit corollary of this is the potential for cost savings to be realized by health care providers. For example, approximately 10% of inpatient stays in the UK are considered to be impacted by an error of some nature, such as incorrect allocation of products or procedures to a

patient, transcription errors and out-of-stock or expired products. Collectively, these incidents are estimated to cost the UK's NHS £2.5b (US\$3.2b) in extra hospital days and resource waste, all of which are preventable adverse events.¹³ It is anticipated that the application of a more robust electronic procurement and inventory tracking system, which UDI can provide, could contribute to procurement efficiencies of £1.5b (US\$1.9b), a more market-driven competitive tendering environment, associated operational gains and enhanced patient safety.¹⁴

9. Directive 2012/0266, final text of the medical devices regulation, <http://data.consilium.europa.eu/doc/document/ST-10728-2016-INIT/en/pdf>, accessed 26 June 2017.
10. Directive 2012/0267, final text of the EU in vitro diagnostic medical devices regulation, <http://data.consilium.europa.eu/doc/document/ST-10729-2016-INIT/en/pdf>, accessed 26 June 2017.
11. "Financial impact of the Revision of the EU Medical Devices Directives on European SMEs and industry," *Eucomed* website, <http://archive.eucomed.org/uploads/Modules/Publications/20130910-financial-impact-mdd-factsheet.pdf>, accessed 26 June 2017.
12. GS1 is a not-for-profit organization that develops and maintains global standards for business communication.
13. "Exploring the costs of unsafe care in the NHS: a report prepared for the Department of Health," *Frontier Economics* website, <https://www.frontier-economics.com/documents/2014/10/exploring-the-costs-of-unsafe-care-in-the-nhs-frontier-report-2-2-2-2.pdf>, accessed 26 June 2017.
14. "NHS eProcurement Strategy," Department of Health website, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/344574/NHS_eProcurement_Strategy.pdf, accessed 26 June 2017.

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The use of the GS1 standard is already being considered globally. As noted, the US has been using it since 2014. Meanwhile, Canada, Australia and New Zealand have all indicated that they are likely to implement GS1. In parallel, case studies have been developed to assess its application in France, the Netherlands, Sweden, Ireland and China. The NHS is planning for a nationwide adoption of GS1 by 2020. In the lead-up to this,

pilot activity called the Scan4Safety program is due to launch in late 2017; this will encompass a number of trusts across England with the goal of establishing procurement standards, commercial benchmarks and product traceability.¹⁵ Once fully rolled out across all NHS hospitals in England, by some estimates, potential annual savings could approach £6b (US\$7.6b) through improved inventory management and product allocation.¹⁶

15. NHS Scan4Safety website, <http://www.scan4safety.nhs.uk>, accessed 26 June 2017.
 16. "Review of Operational Productivity in NHS providers: an independent report for the Department of Health by Lord Carter of Coles," GS1 UK website, <https://www.gs1uk.org/-/media/documents/carterinterimreport.pdf>, accessed 26 June 2017.

Identification of Medicinal Products (IDMP)

Similar to the EU MDR, the IDMP standards aim to achieve safer medicinal products with defined accountability and traceability within the product supply chain. Specifically, IDMP represents a common global data standard to describe a medicinal product. These standards span a range of product information domains, such as its ingredients, the manufacturing processes (and manufacturers) used to bring it to market, details of its packaging, its regulated clinical applications and details of the marketing authorization holder.¹⁷

The concepts underpinning IDMP have been circulating the biopharmaceutical industry for at least 20 years. The first formalized attempt was Product Information Management (PIM) in Europe¹⁸ and Structured Product Labeling (SPL) in the US.¹⁹ In particular, PIM was championed by regulators and some pioneering industry players. However, without the necessary legislative backing, it failed²⁰ – despite the potential value it could have delivered, the demand for data collection was challenging to justify. In contrast, SPL has become established for the electronic submission of product information in the US market. In fact, its underlying data exchange standard, Health Level Seven International (HL7), will be co-opted by IDMP once it also launches.

Where PIM failed to take hold, the move toward standardizing medicinal product information is now being spearheaded by the need for better product safety.

As organizations weigh up the cost of compliance, strategic decisions may be required as to whether divesting a product line may be preferable to the potential considerable investment to maintain a product on the market.

A key strategic goal has been better product codification to help support safety monitoring across the region. The establishment of the centralized safety monitoring database, EudraVigilance by the European Medicines Agency (EMA), in 2005 was a step toward this ambition. In 2012, this platform received a major update with the implementation of the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD), which, for the first time, introduced a legal mandate for biopharmaceutical companies to submit product data to the centralized database. Concurrent with this, the International Organization for Standardization (ISO) had been developing a comprehensive product data model, described in a set of five ISO standards. These are collectively referred to as "IDMP," and contain within them the data model for how a medicinal product should be described and the approach to interchanging this between industry and regulators.

Originally, these standards were due to be enforced from July 2016. However, to help facilitate a smoother implementation for all impacted stakeholders, an iterative

approach is now planned; the first iteration is due for implementation in early 2019. A master data management approach will underlie the implementation strategy: the IDMP data standards will have a series of iterative implementations, which are themselves spread across four information domains spanning substances (S), products (P), organizations (O) and referentials²¹ (R), collectively referred to as the SPOR data services.²²

17. "Implementation of ISO IDMP standards," EMA website, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000645.jsp, accessed 26 June 2017.
18. "Submission of the dossier: update on electronic submissions and PIM," EMA website, http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/10/WC500004233.pdf, accessed 26 June 2017.
19. "Structured Product Labeling Overview," National Library of Medicine website, https://www.nlm.nih.gov/mesh/presentations/Smith_SPL_Overview.pptx, accessed 26 June 2017.
20. "European Medicines Agency closes PIM project," EMA website, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/03/news_detail_001233.jsp&mid=WC0b01ac058004d5c1, accessed 26 June 2017.
21. Referentials refer to lists of terms that are centrally controlled and applied uniformly to all products; for example, dosage forms, routes of administrations and units of measurement.
22. "Introduction to SPOR data services," EMA website, http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/08/WC500212059.pdf, accessed 26 June 2017.

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The key imperative of these regulatory activities, as well as other related efforts, is to be in the service of a better patient outcome and enhanced safety.

The standards themselves have been evolving with input from industry, regulators and vendors, and further revisions are expected. Moreover, the EMA has yet to release its implementation guidelines, which is critically linked to the timeline for implementation and subsequent enforcement; though these were expected in 2018, there is a likelihood that they may not be made available for a further year. There are some concerns across industry that IDMP in Europe may suffer a similar fate to PIM. However, there are some key differences in this case – most notably that IDMP is a global standard and other regulatory regions (the US, Switzerland, Canada and others) are already looking to implement IDMP despite the delays in Europe.

Timelines associated with IDMP have changed a number of times, which is not completely unexpected for what

will be a significant change activity for all stakeholders. For industry, this uncertainty has had an impact on change programs and allocation of resources. However, the scale of the challenge – from an information collation and curation activity through to its maintenance, management and submission – is such that an extended timeline will help to make programs more feasible and achieve compliance while realizing business benefit. Indeed, any effort founded upon robust, complete and compliant product data would be a key beneficiary of the dataset that IDMP will deliver. These include supply chain efficiency projects, product serialization, “good manufacturing practice” quality initiatives and more.

Moreover, a common data standard that promotes enterprise-wide data mastering, coupled with strong governance and quality measures, will increase data integrity by several orders of magnitude. This represents an opportunity to create operational efficiencies by harmonizing regulatory information management and enabling better control of information and an organization's portfolio more broadly. This value will increase further beyond 2020 as IDMP approaches its full implementation.

Planning for change

The key imperative of the strategic and operational regulatory activities described in this article – the EU MDR, UDI, GSI and IDMP – as well as other

related efforts, is to be in the service of a better patient outcome and enhanced safety. By instigating industry-wide transparency initiatives, medical devices and biopharmaceutical products reaching the market are anticipated to be of a higher quality and with a more controlled safety profile. Moreover, these efforts improve the risk and benefit evaluation of these products, supported by rapid communication of product information and their traceability through the supply chain. In totality, these facilitate a more patient-centric approach to product life cycle management, in addition to enhanced risk and vendor management.

For industry, the outcome is that significant investment of resources and budget will be needed over the next five years at least. Organizations, regardless of size, will have to review their portfolios carefully and assess the potential investment needed to remain compliant; those with a heterogeneous mix of medicines and medical devices will likely be the most impacted, but we would also foresee SMEs rationalizing their product mix to balance regulatory spend against commercial opportunity. It seems likely that executives will expect their teams to propose an integrated regulatory compliance program in order to maximize value; by integrating upfront, organizations will be able to make better use of scarce resources, while the regulatory landscape (both in Europe and the US) shifts into place.



Additional regulatory efforts

In addition to the regulatory activities described in this article, there are some other key initiatives that are due to occur in the next few years:

► **EU clinical trials regulation**

New regulations will come into effect in 2018, aimed at harmonizing the method for electronic assessment and supervision of clinical trials in the EU. This will create consistent rules for clinical trials conducted in the EU (Member States will remain responsible for trial authorization), coupled with publicly available information on these trials, which includes details of study conduct and results. The goal is to establish increased transparency while improving the safety of studies performed in the region. A key component of the regulation is the establishment of a centralized EU clinical trial portal and

database – the Common European Single Submission Portal (CESSP) – which will be managed by the EMA. This portal will support electronic application forms in the first instance, but will eventually integrate with IDMP data, which is currently anticipated to occur in 2020.

► **Product serialization**

To address the increasing concern of counterfeit medicines, product theft and reimbursement fraud, new regulations are due to come into effect in both Europe and the US. The EU Falsified Medicines Directive (FMD) is due to be implemented in early 2019, while the US Drug Supply Chain Security Act (DSCSA)

will be mandated from November 2017. These will make product serialization a legal requirement by demanding that product-marketing authorization holders add safety features to product packaging (i.e., 2-D bar codes, anti-tamper packaging and unique identifiers). Additionally, supporting infrastructure will be strengthened: establishing a common EU-wide logo to identify legal online pharmacies, more stringent control of active pharmaceutical ingredient (API) production and inspection, and stricter requirements for wholesale distributors to maintain records of sales and the associated product batch. ■