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Medical Device White Paper Series

The convergence of the pharmaceutical and medical devices industries

Navigating the innovations and EU regulations

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Introduction

The medical device and pharmaceutical industries each share in a mission to improve health outcomes, from prevention to intervention. As a result of this shared mission, integration and overlap between these two industries has been taking place for decades. Established opportunities at the interface of these two industries stem from biological and chemical innovations meeting other advances in science and engineering. Blurring the line between these two industries even further is the growing influence of data science in medicine. Applications in software engineering are altering the patient experience and facilitating a personalized experience tailored to an individual's health needs. One example are closed loop systems that enable diabetics to monitor and maintain glucose levels. Opportunities to embed technology in the pursuit of better-health outcomes pervade every medical discipline and area of health practice from daily monitoring to compliance. Research and Markets forecasts global drug-device combination product market size will reach Euro 46.02 or USD 177.7 billion by 2024, at a growth rate of 7.9% each year.[1]

By working to clarify guidance on the quality requirements for device-drug combination products, the European Commission and regulators such as the European Medicines Agency (EMA) are responding to the need for coordinated regulation to encourage innovation and facilitate new combination products reaching the market while ensuring public safety. The EMA Strategy[2] to 2025 is a good starting point to introduce the state of the industry.

As innovation and complexity of products increase at the interface of the pharmaceutical and medical device industry so do the regulations. For medical devices the introduction of the European Medical Device Regulation (MDR) (Regulation (EU) 2017/745)[3] is set to take effect on May 26, 2021. This regulation also amends 2001/83/EC, the medicinal product directive for the regulation of medicines.[4] Coordinated with the EU MDR, EU Regulation 2017/746 of the European Parliament and of the Council on in vitro diagnostic medical devices (IVDR) entered into force on 25 May 2017,[5] replacing the EU's previous Directive on in vitro diagnostic medical devices (98/79/EC).[6] The IVDR has a transition period of five years and will fully apply from 26 May 2022.

The IVDR will replace the original EU Directive on in vitro diagnostic medical devices and require a significant number of manufacturers certify their products using a notified body. The regulatory routes, within the European framework, to be taken for the various combination products described in this paper are discussed below.

[1] https://www.researchandmarkets.com/reports/4656191/drug-device-combination-products-market-by accessed 26 March 2021
[2] https://www.ema.europa.eu/en/news/launch-public-consultation-joint-network-strategy-2025 accessed 26 March 2021
[3] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745 accessed 06 April 2021
[4] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf accessed 06 April 2021
[5] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746 accessed 06 April 2021
[6] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A31998L0079 accessed 06 April 2021

An overview of drug-device combination products in the EU

For the purpose of this white paper, drug-device combination products are therapeutic and diagnostic products that may combine medicinal products, including biological products, with a medical device. From a regulatory perspective, the intermixing of device technologies and pharmaceutical innovation associated with combination products requires greater coordination and communication between the various stakeholders.

An important point to note is that in the EU, unlike the USA, there is no single definition of a combination product in the legal framework of either medicinal products or medical devices. EU products combining a medical device and medicinal product are either regulated as a medicinal product or a medical device with the primary mode of action governing the regulatory pathway. Over the course of this white paper, the different categories of combination products within the EU will be described along with the regulatory pathways designed to ensure they are safe and perform as intended. In Europe, the agencies involved in these assessments include the EMA, the national competent authorities for the medicinal product part and the Notified Bodies for the device part. A Notified Body is an organization designated by the EU Commission to assess the conformity of medical devices before being placed on the market. A summary of product categories and regulatory agencies is given in Table 1.

Table 1

Product Category	Examples	Regulatory agency	Outcome
Integral Drug Device Combinations	pMDI inhaler Pre-filled syringe	EMA or medicines Competent Authority (NB input may be required).	Marketing Authorization (with Notified Body Opinion)
Non-integral Drug Device Combinations	Dry powder inhaler co-packed with medicine capsules Syringe co-packed with vial of medicinal product	EMA or medicines Competent Authority for the medicinal product. Notified body for the delivery device.	Marketing Authorization for the medicinal product. CE certificate for the delivery device.
Devices with ancillary medicinal substance	Drug eluting stent Dressing with antibiotic	Notified body who will consult with a Competent Authority for the medicinal aspects	CE certificate (with consultation report from Competent Authority)
Devices intended to administer medicines	**Syringe pump** **Ventilator**	Notified Body	CE Certificate

With the introduction in the EU of the Medical Device Regulation (MDR) and the *in vitro* Diagnostic Regulation (IVDR), regulatory complexity has increased in line with the growing complexity of combination products.

In 2019 the EMA published draft guidelines on quality requirements for medical devices in human medicines specific to drug-device combinations. The guidelines were a response to a growing number of requests for advice, cover the main aspects of the quality requirements. Among the key challenges in developing drug-device combination therapies are those associated with addressing human factors studies and studies in representative user populations. These are particularly pertinent to patient-administered drug-device combinations. New requirements for post-market surveillance also present an important consideration for developers as they prepare applications.

The regulatory framework for medical devices incorporating medicinal substances as an 'integral part' is described in Article 1(8) of MDR[7]:

1. Where the action of the medicinal substance is ancillary, the product is regulated as a **medical device** and must be CE marked. As the action of the medicinal product is considered ancillary, a scientific opinion must be provided from a medicines authority before a notified body can issue a certificate for the combined product.Although the majority of digital trends are being driven and implemented in the developed world, developing economies will be further left behind if they cannot progress in areas that will benefit them.

2. Where the action of the medicinal substance is principal, the combination product is regulated under the **medicinal products** framework. In this case, the relevant general safety and performance requirements (GSPR) of the MDR apply to the device part.

The regulatory framework for administration devices is described in Article 1(9) MDR[8]:

a) If the administration device is marketed as a single integral product intended exclusively for use in the given combination and is not reusable, the combination product is regulated under the **medicinal products** framework. In this case, the relevant GSPR requirements of the MDR apply to the device part.

b) In all other cases, the administration device is regulated under the **medical device** framework. When the medical device is not physically combined with the medicinal product the device will need to be CE marked. The (separate) medicinal product must be licensed for use under the medicinal product directives.

c) Different types of combination product have different regulatory requirements. The combination type and requirements are discussed in more detail below.

For all the above, adhering to the foundations of effective combination product development is essential to meet regulatory requirements. Those foundations rest on the integration of quality by design, design controls, human factors, risk management and standards. While developers may be accustomed to considering the suitability of the device for drug delivery, the intended use, product configuration, intended user(s), risks and controls; mapping a cascade of controls and sharing information about each GSPR through the product lifecycle is an added dimension of complexity. Effective purchasing controls and supplier quality agreements are another critical tenet in a successful strategy for control of combination products.

The combination product category encompasses a wide variety of products. Changes in EU policy seek to introduce greater transparency to the process and encourage combination product developers to engage in early dialogue with the pertinent regulatory agencies. For example, one category of combination product to consider is known as Drug/ Device Combinations or DDCs, although this is not a regulatory term. In the EU, combination products that are integral, exclusively for use and not reusable, can be considered DDCs and their regulation now described in Article 117 of the MDR[9]. If the device is intended to administer a medicinal product and the product is placed on the market in such a way that it forms a single integral product intended exclusively for one-time use in the given combination, that single integral product is governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable.[10] [11] In that case, the relevant GSPRs set out in Annex I to this Regulation apply as far as the safety and performance of the device part of the single integral product are concerned.

[7] https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745 accessed 06 April 2021
[8] *Ibid.*
[9] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
[10] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf accessed 06 April 2021
[11] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf accessed 06 April 2021

Article 117 of the MDR also introduced additional requirements for the manufacturers of such combinations in requiring the involvement of a Notified Body in the process to provide an opinion on the conformity of the device aspects against MDR Annex I, GSPRs, in the cases where the device itself has not been CE marked in its own right.[12] The examples above cover some of the products that can be considered combination products. In the sections below categories of products combining pharmaceutical and medical device technologies are described. For each category laid out below a corresponding section outlines the EU regulatory approach.

Drug / Device Combination Product Examples

A prominent example of DDCs is the pressurized metered dose inhaler (pMDI). A pMDI is a pressurised device that propels the medicine into a patient's lungs using a propellant spray. These are the most widely used delivery system for the treatment of lung diseases such as asthma and chronic obstructive pulmonary disease. The first boot-shaped inhaler was introduced in 1956. Since then, the two market leaders have updated designs to enable the delivery of dry powdered drugs (Stein, 2017) and combinations of more than one drug from a single inhaler have been introduced. Due to significant corporate investment, this ubiquitous plastic drug delivery device continues to undergo updates. These updates to the device are aimed at improving patient compliance, and therefore improve treatment outcomes. Newer models are introducing intelligent control and the collection of data as the patient uses the device, and alerts patients to when they need to replace the device. This can range from a simple dose counter on the device to a more complex, application-enabled solution.

In the context of DDCs, it is important to note in pMDIs the drug is integral to the device and the device, once all the doses have been used, is not reusable. There are inhalers available on the market that may be reusable, and others where the medicinal component may be prescribed or sold separately. These variations fall into a different combination category and are described in more detail later.

Another common example of integral, exclusively for use, non-reusable DDCs are pre-filled syringes and autoinjectors. Prefilled syringes contain injectable drugs such as vaccines, blood stimulants, therapeutic proteins, erythropoietins, and interferons. Autoinjector devices are designed to overcome the hesitation associated with self-administration. These devices are often spring-loaded syringes that make it easier for patients to administer an accurate dose of medication. Mitigating the risk of a severe allergic response with an adrenalin injection suits an auto injector device.

A growing demand to increase patient convenience and to improve healthcare cost management achieved through self-administration of drug therapies is fueling demand for these types of products (Bittner, 2018). Diabetes and other chronic conditions serve as a point of focus for the hybridization of device and pharmaceuticals combined in the interest of eliminating needles from the daily routine (see case study below).

The integration of the pharmaceutical and device often manifests as a large pharmaceutical company licensing a technology from a smaller company or academic group. Additional opportunities are opening up as more antibody therapies to treat chronic diseases enter the market. Antibodies are large molecules and administration to the body requires an injection. Companies developing these therapies are looking to academic and industrial innovations to help make their therapy convenient and safe for the patient. The convenience of self-administration for the growing number of antibody therapies serves as one of the drivers for optimistic forecasts on growth in combination products.

The introduction of needle-free injection technologies (NFIT) for administering insulin seemingly marked a welcome alternative to daily injections for patients. However, in the past the market has shown reluctance to take up products of this nature, largely based on cost concerns. The rapidity at which the latest approaches can deliver therapies is a key improvement over previous generations. Therefore, an emerging generation of NFIT approaches are taking aim at insulin delivery, as well as providing a convenient way to deliver newer therapies for other chronic diseases.

[12] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745

Needle-free injection systems can be used to introduce liquid formulations of drugs as well as vaccines in the form of solid particle dosage. These can encompass a vast range of drug delivery systems that transfer drugs through the skin employing a range of physical forces: electromagnetic, laser-induced shock waves, pressure by gas or electrophoresis. Jet injection, currently the most popular approach, uses pressure. The formulation of the drug and even the materials used to create the device are additional variables in the development of these systems (Dev Ravi A, 2015). The next generation of needle-free drug delivery for the growing number of chronic antibody therapeutics adds a digital dimension to the elimination of needles.1 One innovative approach introduces a computer-controlled closed-loop system that senses pressure and adjusts the speed of a jet stream of drug to optimize delivery. The device delivers the drug in a jet stream of liquid as thin as a strand of hair.

Transdermal delivery is another alternative to hypodermic injection. Transdermal drug delivery also offers greater convenience relative to controlled-release, and starts to address the low oral bioavailability of many drugs (Prausnitz MR, 2008). Previously, a limited number of drugs were amenable to administration by this route, however, advances in the understanding of the outer layer of skin, known as the *stratum corneum*, have facilitated the development of a new generation of transdermal delivery systems poised to make significant impact on drug delivery. Chemical enhancers and iontophoresis previously expanded delivery capabilities for small molecules, and newer technologies have been developed to deliver macromolecules and vaccines.

The same processing techniques used for manufacturing microelectronic chips, known as microfabrication, offer another alternative for creating novel drug delivery platforms. Academic research groups and early stage startup companies are engineering microchip systems to store a number of drugs and control the timing and rate of their release. Devices supporting the customized release (i.e. fixed dose, pulsatile or continuous) of a wide variety of drugs may one day be safely implanted inside the body. These reservoir-based microelectromechanical systems or MEMS-based devices have the potential to revolutionize drug delivery (Stevenson CL, 2012). These innovations are a great example of the expanding product landscape, and show the need for development of regulatory expertise to keep pace with cutting-edge science and to ensure patient safety.

Drug delivery is an area where the pharmaceutical and device companies have decade of cross-development. Additional examples of drug delivery devices pushing the envelope of what is possible include sustained and controlled transdermal delivery technology, and fiber-based technology for implantable devices. This includes targeted penetration matrix technology for non-invasive delivery and location-specific nanomachines.

As can be seen in the examples above, with the integration of new technology these devices become more complex, and the corresponding regulatory framework is advancing to match these innovations.

Case study: From insulin pumps to the artificial pancreas: Devices for diabetics evolve to increase patient autonomy

At the core of all therapeutic advances achieved for Type-1 diabetes, insulin remains the pillar of treatment. Long-acting and rapid-acting insulin formulations help patients to maintain steady-state glucose levels, which is the primary function of long acting insulins, and prevent dangerous blood glucose spikes after meals, which is done by rapid-acting insulins. Given the complexity of hormonal systems, achieving the desired homeostatic balance allows room for other therapeutic interventions. The most recently approved class of diabetes drugs is the sodium–glucose cotransporter 2 (SGLT2) inhibitors. These inhibitors act on the kidney to promote urinary glucose excretion. The potential benefit of adding an SGLT2-inhibitor is they address common side effects of insulin therapy such as glycaemic variability, weight gain, or hypoglycemia (Evans M, 2020). However, this new drug class comes with long list of side effects. Therefore these benefits need to be assessed against the risks. Challenges remain relative to the integration of this class of drugs in the context of precision medicine. Still elusive is the well-defined criteria that enables physicians to prescribe SGLT2 inhibitors to patients likely to derive the greatest benefit and least likely to experience serious harm.

Insulin therapy has advanced from traditional needle and syringe administration to pre-filled pens or pens with cartridges. The former would be an integral drug device combination. The latter, more common for chronic conditions, require the 'pen' delivering device to be CE marked for administration of the medicinal product insulin.

An evolving area of delivery include portable devices called insulin pumps. A catheter placed under the skin continuously delivers calibrated amounts of rapid or short-acting insulin. For people living with Type 1 Diabetes, and some with Type 2, insulin pump therapy or continuous subcutaneous insulin infusion (CSII) therapy provides an alternative to administering multiple insulin injections each day. Also, pumps deliver insulin much more precisely when compared to a pen or syringe. By increasing a person's ability to closely control blood glucose levels and maintain levels within a normal range, the user is more likely to avoid hypoglycaemia and other complications associated with Type 1 Diabetes. These advantages, and the evolution of smaller, more portable devices have made insulin pumps an increasingly common treatment.

Insulin pumps deliver short-acting insulin every few minutes, 24 hours a day, and the user changes the catheter every 2 or 3 days. A background level or basal insulin is programmed to address the individual needs of the user and the user presses a button to deliver a bolus of insulin in response to food consumption or to bring down a high blood glucose level. Two types of insulin pump devices are currently on the market: a 'tethered' pump which is worn in a pocket or clipped to a belt and uses a fine tube to connect to the catheter, and a micro-pump which is attached to the skin with a very short tube. On the market, tethered pumps are more popular than patch pumps, however rising technological advancement and adoption of insulin pumps over traditional methods are driving increased demand for both types of devices. For most insulin pumps, a separate device measures blood glucose.

Continuous glucose monitoring (CGM) technology monitors blood glucose and glucose delivery. These devices provide 24-hour tracking of blood glucose values; delivering exponentially more data compared to the intermittent data associated with glucose-meter testing approaches that have been around since the 1970s. More data better informs diabetes care decisions. These CGM systems involve multiple components, including a continuous insulin delivery device, a glucose sensor, an insulin-dosing decision algorithm, and the components necessary for device communication. Like insulin pumps, CGM's are inserted under the skin though into an area of fatty tissue. The glucose sensor is connected to a transmitter that sends information to a receiver or smartphone where the user can view their glucose level and chart its direction. Patient advocacy groups accelerated the introduction of remote monitoring into these devices, demonstrating the direct influence patient groups can have on device and pharmaceutical industry development.

[13] 39 Potential New Continuous Glucose Monitors for Diabetes, https://www.healthline.com/diabetesmine/39-new-cgms-for-diabetes

CGM devices require multiple calibrations throughout the day. However, physical pressure can attenuate the sensor signal, and medications can also interfere with the measurements. The next generation of CGM sensors are reported to be addressing these limitations. In 2019, both European and US regulators approved a small number of these devices, helping to make these monitors an integral part of insulin therapy. According to Healthline, close to 39 novel approaches are currently in development.[13] The next step in devices that assist diabetics with managing a continuous insulin regimen over the course of the day is sensor-augmented pump (SAP) therapy. Closed-loop systems compete with the utility of these systems. SAP therapy is not autonomous, whereas an artificial pancreas system (APS) is designed to mimic the pancreas, automatically adjusting insulin delivery in response to glucose. Achieving this autonomy is particularly important at night, when many people with type 1 diabetes experience potentially dangerous low blood glucose levels.

Also known as automated insulin delivery (AID), an APS adds an adaptive control algorithm – often personalized using body weight and/or total daily insulin dose and based on individual sensor glucose data – that automatically and continuously adjusts insulin delivery in response to sensor-detected glucose concentrations. Automated glucose monitoring is particularly beneficial to patients at night, when many people with type 1 diabetes experience potentially dangerous low blood glucose levels. Researchers and companies are employing at least three different approaches to achieving autonomous glucose control (Eleni B, 2018): hybrid (ie, different device makers) closed-loop systems, fully automated closed-loop systems, and dual-hormonal systems. Dual hormonal systems inhibit the glucose raising hormone glucagon as well as infuse insulin in response to glucose. All under development at various stages of clinical testing.

In 2018, a major device maker introduced the first APS to the market. Research indicates that many patients find the device difficult to use.[6] Concurrently, the relative slowness of the industry to offer a single closed-loop device created an opportunity for tech savvy diabetic patients to democratize access to this highly desirable advance in diabetes care. The three core technologies (algorithm, pump and sensor) have been available separately for decades. An open-source, DIY movement for building an APS from components found on the market emerged. One project, the Open Artificial Pancreas System project (#OpenAPS) is an open source and transparent effort to make safe and effective basic Artificial Pancreas System (APS) technology widely available. [https://openaps.org/what-is-openaps/]. Specifically, the open access platform enables anyone with compatible medical devices to build their own basic overnight closed loop APS system. The resources on the site are accessible to the public and device developers, but it should be noted that proper medical device practices and regulations should be followed.

In another hint at the shape of things to come, in early 2020 a clinical research team launched the world's first downloadable artificial pancreas app in the UK. Access to the app is through subscription and initially organised by a small number of UK diabetes clinics. People can access the app by confirming which clinic they attend. Currently the app is designed to interface with two specific pump and glucose monitor brands. The research group is aiming to make the app compatible with all devices.

A tablet or mobile phone app monitors the blood glucose and sends the data to an infusion pump. In addition to the therapeutic benefits of stable control patients, the application software frees up the patient from taking measurements and calculating doses throughout the day.

These novel devices all show the complexity of developments at the growing edge of the device and pharmaceutical industries. The regulatory pathway is determined by the configuration of the device. Whether the drug and device is integral; any active components in the system; any ancillary medicinal substances (for example, anti-inflammatory agent); software to control the device and apps for the patient or physician feedback, all these elements are covered under the MDR. It is important a Notified Body with appropriate scope and expertise is selected for the conformity of devices at the convergence of the pharmaceutical and medical device industry.

Device / Drug Combinations or Devices with Ancillary Medicinal Substances

In this section, the phrase 'device/ drug combinations' is used to discuss when the physical action of the device is the primary function of the product, which may be supported by an ancillary medicinal substance. A classic example at the intersection of the pharmaceutical and device area is the drug-eluting stent. A drug-eluting stent is placed into peripheral or coronary arteries narrowed by atherosclerosis or other vascular disorders. The stent expands the opening in the vessel whilst slowly releasing a drug to inhibit cell proliferation and to prevent restenosis after angioplasty. The health benefit of avoiding invasive cardiac bypass surgery introduced by the first generation of these devices was offset by an increased risk of late stent thrombosis. The pursuit to eliminate that risk led to an evolution in the development of coronary stents that would avoid both restenosis and thrombosis (Sheiban I, 2008). On the engineering side, developers focused on the conformation of metallic or resorbable structures, while striving for an adequate balance between trackability and radial force. Pharmaceutical-facing development focused on improving antiproliferative drugs and the polymers to control release and allow adequate endothelialisation and an optimal duration of the antiplatelet regimen. Due to the associated risks, experts and databases are still tracking long-term outcomes associated with first and second-generation drug eluting stents (Piccolo R, 2019).

Another example in this category are dressings containing antimicrobial agents. These dressings are used when wound healing may be impaired by the presence of an infection. Traditionally, dressings are combined with antiseptic agents; silver and iodine are the most common additives found. Most dressings with silver or other antimicrobial agents aim to provide a bacterial barrier and inactivate a wide range of wound related pathogens, preventing contamination in the wound bed and prolonging the life of the dressing. Importantly they are not a method of drug delivery and are not indicated in place of systemic antibiotics. The silver has an ancillary or supportive role and the main function of the dressing is to protect the wound during healing. If it were intended to treat infected wounds then the silver would be primary and it would be a drug device combination and regulated as a medicinal product (Simoes D, 2018). Devices such as these have been around for a long time; innovation in this area is more challenging from a regulatory perspective.

Nanomedicine, the application of nanotechnology to improving clinical outcomes, promises to vastly expand the utility of dressings in combatting infection and promoting wound-healing. Advances in the field now make it possible to engineer nanofibers that are structurally similar to the skin's extracellular matrix — a porous scaffold that provides structural support to the skin. The skin's extracellular matrix plays a key role in wound healing through its interactions with the immune system. Using electricity, both natural and synthetic polymers can be spun into a scaffold that mimics the matrix (Croitoru AM, 2020). Electrospinning is a versatile technique (Enizi AM, 2018). The nanofibrous scaffold created can be endowed with topographical and biochemical additions, thus providing an interchangeable system that can be applied to infection control and wound healing in an exponential number of ways.

To interfere with the progression of resistant and chronic infections, academic research groups (and very early stage start-up companies) have imbued scaffolds with anti-infective, antifouling, bactericidal, and antibiofilm properties (Ramasamy M, 2016). These properties are achieved by incorporating molecular nanoparticles that interfere with microbial metabolism or disrupt the cell wall. Nitric oxide-releasing nanoparticles, chitosan-containing nanoparticles, and metal-containing nanoparticles are some examples. Antifouling and antibiofilm properties are desirable because 80% of microbial resistant infections are associated with the formation of a biofilm. Also the simultaneous use of multiple-microbe-busting mechanisms, deter the development of resistance. These sterile dressings have demonstrated promise in addressing previously insurmountable wound healing challenges such as diabetic ulcers.

A key question for these novel devices is around the mechanism of action of these novel materials or substance. Are the properties the result of a pharmacological, metabolic or immunological action? If so, and if the action is ancillary those would be classed as devices with an ancillary medicinal substance.

Besides providing support for tissue repair, nanofibrous materials can also serve as delivery systems for drugs, proteins, growth factors, and other molecules. Nanostructured drug delivery systems include nanoparticles, micelles, nanoemulsions, and liposomes. In addition to antimicrobial activity, these nanoscale delivery systems have demonstrated several benefits for wound healing, including reduced cytotoxicity of drugs, administration of poorly water-soluble drugs, improved skin penetration, controlled release, stimulation of fibroblast proliferation, reduced inflammation and protection of drugs against light, temperature, enzymes or pH degradation (Albert T, 2017). Again, it is important to be clear about the intent of the dressing. If the primary intent is to deliver a medicinal product, it would be classed as an integral DDC. If the primary intent is to either protect the wound from infection, or to promote wound healing, and the secondary intent is antimicrobial, it may be classified as a device.

EU Regulation for Combination Products

Summary of Regulations for Drug Device Combinations

As described above, single integral, exclusively for use and non-reusable DDCs are regulated as medicines in the EU under 2001/83/EC.[14] The changes stem from Article 117 of the MDR which legally amends Annex I, Section 3.2 point 12 of the Medicinal Product Directive (MPD) (Directive 2001/83/EC) as follows:

'Where, in accordance with the second subparagraph of Article 1 (8) or the second subparagraph of Article 1 (9) of Regulation (EU) 2017/745 of the European Parliament and of the Council, a product is governed by this Directive, the marketing authorization dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant GSPRs set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a Notified Body allowing the manufacturer to affix a CE marking to the medical device'.

The EMA and National Competent Authorities require that the marketing authorization applications include a CE certificate or declaration of conformity for the device or, in certain cases, an opinion from a Notified Body (NB) on the conformity of the device. With the introduction of the MDR, a Notified Body provides a report to the manufacturer, detailing an opinion of the conformity of the device. A list of organizations receiving the EU's NB designation is to be included on the European Commission's New Approach Notified and Designated Organizations (NANDO) database. BSI was the first to be listed, and more have followed.

[14] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf Accessed 06 April 2021

[15] Quality requirements for drug-device combinations, European Medicines Agency. https://www.ema.europa.eu/en/quality-requirements-drug-device-combinations accessed 2 April 2021

[16] MDR Documentation Submissions, Best Practices Guidelines, BSI Group. https://www.bsigroup.com/meddev/LocalFiles/en-GB/Documents/BSI_Best_Practice_Guidelines.pdf

[17] Team-NB Position Paper on Documentation Requirements for Drug Device Combination Products Falling in the Scope of Article 117 of MDR 2017/745, Team-NB. https://www.team-nb.org/wp-content/uploads/2020/04/Team-NB_Position-Paper_on-Documentation-Requirements-Article117-V1.pdf

The introduction of a Notified Body Opinion (NBOp) is required with respect to conformity of the device part to MDR Annex I GSPRs. This brings new documentation requirements for the applicant both in terms of the Market Authorization Application (MAA) and the NBOp. Information on the device part in the CTD dossier is described in an EU Guidance document.[15] Requirements for the documentation to support a NBOp application are available from several sources. Section 4, Annex II of the MDR describes the data required for conformity assessment to the GSPRs and this is further expanded upon by BSI's documentation guideline.[16] The industry body for NBs, Team-NB, has also published a position paper on documentation requirements for Article 117 applications.[17] These sources all show that in order to demonstrate conformity and enable NBs to assess that conformity to the GSPRs, the data and solutions adopted, including demonstration of conformity with the relevant standards, all need to be provided for review. The outcome of an Article 117 assessment is a NBOp, which will take the form of a report detailing the device, the data reviewed and a summary of conformity for all the relevant GSPRs. The intention of the reports is to show the NCAs exactly what has been reviewed with respect to the device part of the DDC which will give them confidence in their conformity assessments and avoid duplication of review.

For non-integral drug-device combinations, the EMA expects the devices to be CE marked in accordance with incoming regulations. In some cases, the EMA may require additional information about the impact of the device on the quality, safety and efficacy of the medicinal product.

Summary of Regulations for Device Drug Combinations

Rule 14 of the MDR states:
All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma, as defined in point 10 of Article 1 of that Directive, and that has an action ancillary to that of the devices, are classified as class III.

All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma, as defined in point 10 of Article 1 of that Directive, and that has an action ancillary to that of the devices, are classified as class III.

In summary the device is regulated as a device and conformity to the MDR, in Europe, is required prior to placing on the market. For the ancillary medicinal substance there are additional requirements including an assessment by analogy with the MPD.[18] Therefore, in addition to fulfilling the requirements of the MDR, a medicinal dossier describing the medicinal substance, incorporation and testing in the device, and both clinical and non-clinical safety information is required. To align with the MPD this dossier should be in CTD (Common Technical Document) format. To accompany the dossier, the notified body will provide a usefulness report describing the risk and benefit of adding the medicinal substance to the device. Approval and certification of the device under the MDR can only occur with a positive opinion on the risk and benefits of the ancillary medicine. The consultation process is mandated as 210 days in the MDR, and follows the assessment process for medicinal products under 2001/83/EC.[19]

Any changes to the ancillary medicinal substance, for example in manufacture or testing, or any changes to the incorporation into the device, such as changes to stability or to indications of the device drug combination, may require a supplementary consultation with the CA involved in the original consultation. This will broadly follow the variation procedure and a timetable of 60 days is mandated for these changes.

[18] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf accessed 02 April 2021

[19] ibid

Summary of Regulations for Drug Delivery Devices

For devices for the delivery of medicines, but not integral or exclusively for use, the regulatory pathway is conformity assessment according to the MDR in Europe. If the device is an active device (one that uses stored energy) then Rule 12 will apply. The intended use of the devices is in combination with a medicinal product. As the device and the drug are assessed separately in this scenario, it is important the intended use is considered during certification of the device part to ensure any medicines recommended for use through the Instructions for Use or marketing materials are licensed for that use. A device cannot promote the use of a medicine 'off label'. This is captured in GSPR 10.3 which states:
If the devices are intended to administer medicinal products they shall be designed and manufactured in such a way as to be compatible with the medicinal products concerned in accordance with the provisions and restrictions governing those medicinal products and that the performance of both the medicinal products and of the devices is maintained in accordance with their respective indications and intended use.

As device manufacturers innovate with methods of drug delivery, they need to be aware of the regulatory status of the medicine they intend to deliver. A medicine that has been licensed using a conventional delivery method will not necessarily be licensed for use with a new delivery device if that device impacts the pharmacokinetics of the drug in question. For further information please refer to GSPR 10.3 in the MDR.

Other Post-Market Considerations

Companies developing any type of combination products need to address the challenges associated with establishing proactive post-market surveillance as part of the quality requirements recently introduced by the EMA. when submitting an application for all combination device types discussed, complying with post-marketing safety reporting rules is an important strategic consideration. Companies need to prepare a post-market surveillance plan when submitting an application, because relying on the spontaneous reporting of complaints and incidents will eventually not be an acceptable approach to post-market adverse event monitoring. In Annex XIV of the MDR for devices, the EU has strengthened regulations around post-market risk evaluation of medical devices. The post-market requirements of that legislation apply to drug device combinations regulated under the medicinal product directives. Devices and device parts that are CE marked need to comply with the relevant European device legislation.

According to the MDR, the Post-Market Surveillance Plan will have to define the process for proactively collecting, recording, and investigating complaints and reports from healthcare professionals, patients, and users on events suspected to be related to a medical device, "with the aim of confirming the safety and performance throughout the expected lifetime of the device, of ensuring the continued acceptability of identified risks and of detecting emerging risks on the basis of factual evidence." The need is for the system to allow for early detection in medical devices of possible malfunctions, complications or both that may occur only after years or even decades of usage, and the implementation of appropriate risk minimization measures. That means developers will need to consider the risks from all angles (e.g., materials, human factors) for the entire lifecycle of the product. For devices at the interface between device and drug the need for post-market is just as important. Analysis of any reports will require a collaborative effort to ensure the right experts are involved and the data attributed to the parts of the system of concern.

A recent example of this relates to potential longer-term safety concerns raised about the use of paclitaxel-containing devices in the treatment of femoropopliteal artery occlusive disease in a meta-analysis of summary-level data (Kastanos K, 2018). The meta-analysis suggested potential safety concerns with paclitaxel containing balloons and stents versus non-medicated variants. It is not the purpose of this white paper to examine this paper specifically, but it demonstrates the need to have a cross-function team to understand the impact of these data on the certified device. Are the effects related to the drug component, the stents used, the patient group or clinical practice these devices are used in? The interaction of drug and device experts persists from development to manufacture and through to post-market analysis.

Future Challenges

Other innovations, such as sensors and bluetooth enabled apps, may further blur the line between device and medicine, and present new challenges associated with adhering to regulatory oversight. One company has created tablets that dissolve in the stomach and produce a small signal that is picked up by a sensor worn on the body (Patel P, 2017). The data is then relayed to a smartphone app, confirming that the patient has taken their medication as directed, something that could be useful in addition treatment or any illness where patient compliance is key to successful outcomes.

Additionally, pharmaceutical companies are actively exploring the use of digital apps that enable the large-scale collection of data directly from patients. Academic research groups and companies are taking up an open-source app (Empowering Researchers, Doctors and You) that allows people to use their iOS devices and apps to join medical studies and send data to researchers. In an effort to ease patient recruitment and reduce costs, most large pharmaceutical companies are looking to digital technology to open clinical trials up to more patients via remote monitoring technology. The COVID-19 pandemic has motivated a more ubiquitous embrace of remote technologies that can facilitate the continuation of clinical trials.

The Digital Medicine Society (DiMe) has launched the Library of Digital Endpoints, focused on industry-sponsored studies of new medical products or new applications of existing medical products that provides a comprehensive overview of how remote monitoring is being used in clinical trials.[20] Some examples might include a PKG wearable device, or a mobile health technology that provides continuous, objective, ambulatory assessment of the symptoms of Parkinson's Disease such as tremor, bradykinesia, dyskinesia, and daytime somnolence.

Increasingly, the Internet of Things is finding its way to helping the pharmaceutical industry and healthcare providers to improve care by monitoring patients more closely and promoting patient compliance. Successful medical device and pharmaceutical companies are engineering simulation and connected patient modeling to develop systems that ensure high reliability and provide data privacy. While developing these technologies may be a challenge, further success rests with finding designs that ensure patients use medical devices correctly, and that both data and the patient are kept safe from cyberthreats.

Conclusion

As technology advances and the intersection of medical device and medicinal product becomes more pronounced, regulation becomes more of a challenge for manufacturers and legislators. Recent regulations have been introduced to help manage this intersection and, where possible, to future proof as the state-of-the-art changes. The integration of software and other innovations, such as those associated with nanotechnology, present the industry and its regulators with the challenge of keeping the public safe while navigating unchartered territory. Working with industry, regulators have attempted to provide a roadmap for keeping the public safe without stifling the promise of new approaches to human health. With the harmonization of regulations, the future of individual patients promises to improve as the application of new technologies advances and the intersection of pharmaceuticals and medical devices continues to flourish.

[20] https://www.dimesociety.org/communication-education/library-of-digital-endpoints/ accessed 07 April 2021

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