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INJECTABLE COMBINATION PRODUCTS:

Industry Insights On The Challenges Of Meeting A Growing Global Need

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Pharmaceutical Services

INJECTABLE COMBINATION PRODUCTS:

Industry Insights On The Challenges Of Meeting A Growing Global Need

Companies are increasingly looking for innovative ways to combine medicinal products with self-injectable devices, commonly known as combination products, in a quest for more user-friendly drug delivery solutions that lower health care expenses. As a result, novel injectable combination drug and biological products – offering promising treatment avenues, added patient convenience, cost savings, and importantly the chance to move health care to homes from hospitals – are fast becoming integral to product development. The global injectable drug delivery market, including intravenous administration, in fact, is seen in coming years eclipsing oral delivery as the most valuable route for administering drugs.[1,2]

Driving the injectable combination drug products market has been the explosion in the incidence of chronic diseases globally – the Centers for Disease Control and Prevention estimates 60% of people in the US suffer from at least one chronic ailment – and the need for repeat dosing to treat these illnesses along with the trend toward home injection treatment.[3] North America, due to a rapidly aging population and rising prevalence of chronic disease, is the largest market, followed by Europe and Asia Pacific, where demand is being fuelled by a fast-growing patient population and rising affluence.

At the same time, biosimilar versions of blockbuster biologics are coming to market as the patents on branded products expire. That trend is driving innovation in the injectable combination drug product market. With multiple biosimilars competing for patients once served by a single branded biologic, companies are turning to device

technology to differentiate their products in competitive niches.

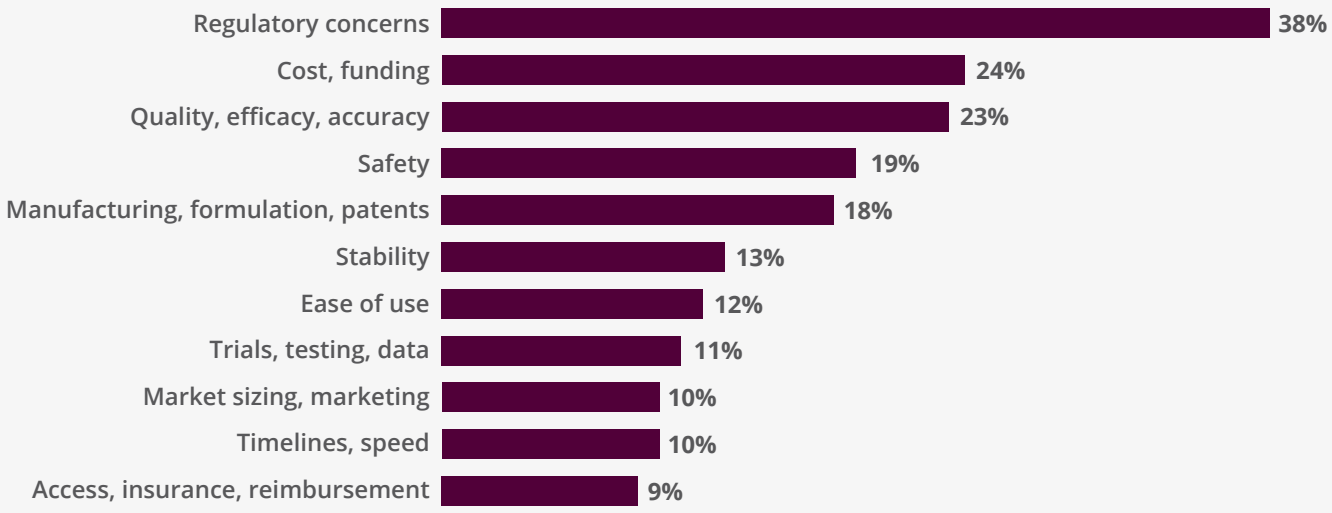
To gain further insight into challenges the industry faces in developing and marketing such products, between March and June 2020 Informa Pharma Intelligence and Owen Mumford Pharmaceutical Services surveyed nearly 200 pharmaceutical executives of whom almost 60% occupied director-level or more senior posts and close to three-quarters held jobs involving global responsibilities.

Injectable combination drug products are already helping patients suffering from cancer, heart disease, multiple sclerosis, rheumatoid arthritis, diabetes, and other serious conditions. To bring more combination products to market, companies need to follow a rigorous regulatory approval process which differ from market to market.

Of respondents, 38% identified regulatory concerns as the chief obstacle in getting to market patient-centric injectable combination products, which are segmented into categories such as autoimmune, hormonal, orphan, and oncology. Concerns about regulatory approval may reflect the elaborate regulatory hurdles involved in winning approval for the actual drug (active pharmaceutical ingredients or APIs) as well as the additional complexities of obtaining approval of the combination product – the device and the drug. The characteristics of the latest drugs being developed, especially the plethora of biologics that cannot be delivered orally and involve bigger volumes and higher viscosities, mean that the modes of action of drug-device combination products are becoming ever more sophisticated and yet simplicity and ease of use for patients is still a key requirement. As new product technologies emerge, regulations, guidelines, and standards are also evolving in each market, making it tough for companies to keep abreast of the rules. *(See Figure 1)*

Just under half of respondents strongly supported a dedicated regulatory approval pathway for

Figure 1: Key Challenges in Developing & Marketing Combination Products



Question: What are your top three key challenges when developing a combination product (device and drug) for injection, and bringing it to market?

Base: All respondents; up to three responses permitted (n=162).

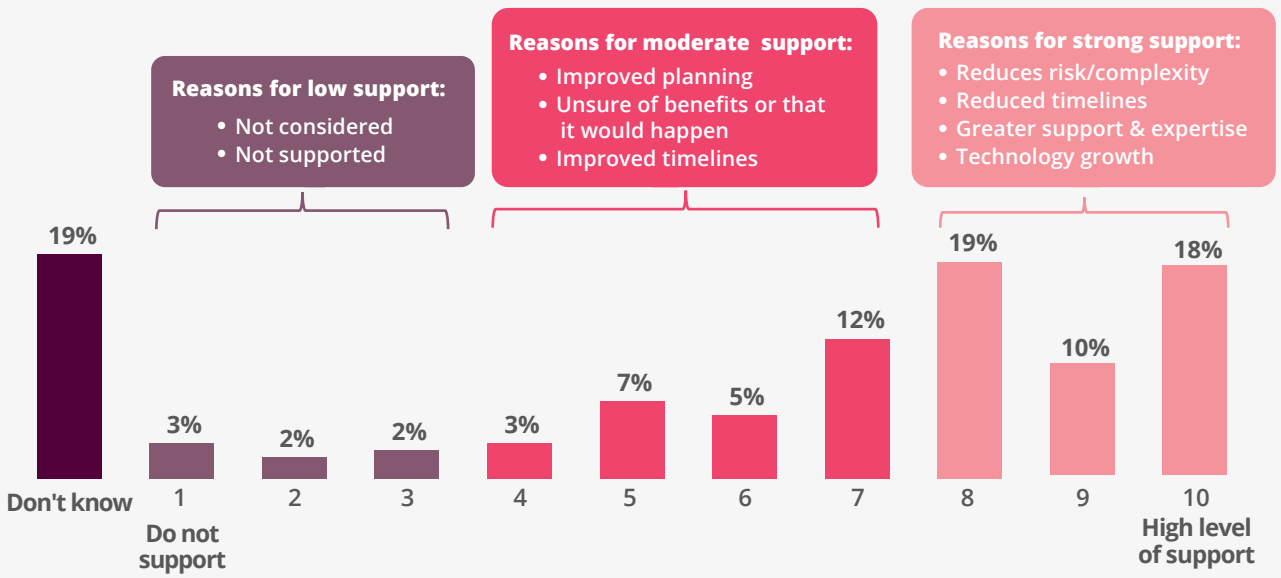
combination products such as that offered by the US Food and Drug Administration, saying it would reduce timelines, risk, and complexity. In comments accompanying their replies, respondents mentioned as hurdles the regulatory landscape's ever-growing complexity, the challenges of meeting safety regulations, the absence of regulatory precedents for certain products, as well as the lack of global regulatory harmonization on requirements for injection systems and combination product definitions.

The US FDA, for instance, defines a combination product as two or more different products: a drug and a device; a biologic and a device; or a drug, a biologic and a device. At the European level, a product is either a medical device or a medicinal product. If the device contains a medicinal product whose action is ancillary to the medical device, the product is regulated as a medical device. But if the device is intended to support the medicinal product, the product is classed as a medicinal product. "If [the regulatory pathways were] harmonized with FDA, [it] would be advantageous," said one respondent. *(See Figure 2)*

Another 24% of respondents said cost and funding concerns loomed as the biggest hurdles to developing and marketing combination products. Quality, efficacy, and accuracy were identified by 23%. Companies must make significant outlays in R&D, facilities, equipment, process controls, compliance, and other areas to meet regulatory standards for these combination products, and there are many pitfalls beyond the drug itself that can arise during the development-through-lifecycle process.

Although drug development focuses on the drug candidate, interaction with other parts of a combination product such as the primary container and the actual delivery device (e.g safety syringe or autoinjector) components must be demonstrated to prove the joint product's

Figure 2: Dedicated Regulatory Approval Pathways



Question: To what degree do you support dedicated regulatory approval pathways for combination products, such as that which exists with the FDA?

Base: All respondents (n=166).

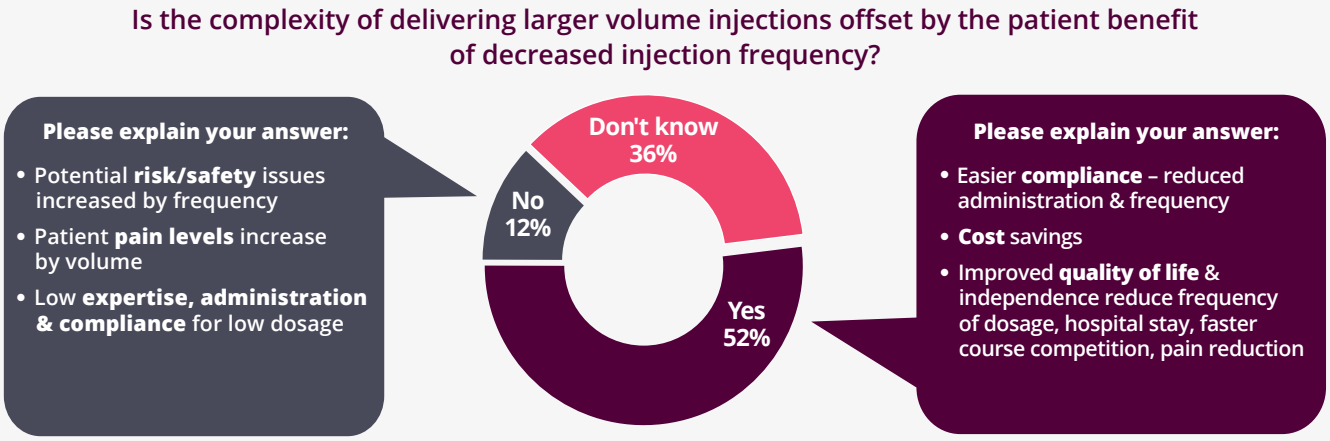
safety and effectiveness. While each generation of products confers new benefits, each also poses technical hurdles and risks not just in the product development but also in the scale up for manufacturing at capacity. Hence the need for a design for manufacturing and automation (DfM and DfA) approach early in the development of these type of products.

Some 52% of participants held the view that the benefits of fewer injections, better compliance, cost savings, and improved quality of life offset the complexities of delivering larger volume injections, such as overcoming potential pain at the injection site and risk/safety issues. "The patient experience is our main focus so if we can make and design a more comfortable streamlined device that delivers a larger volume less often [it] would benefit the patient," one respondent said. "Any time you can decrease frequency of administration it is an advantage worth pursuing within reasonable means. Complexity should not be an a priori deterrent," said another survey participant. Over a third of respondents said they didn't have an opinion on the subject, whereas 12% said that any benefits from delivering larger volume injections were outweighed by risks and safety issues. "The efficacy/safety of the volume to be administered should not be offset by patient convenience," commented a respondent. *(See Figure 3)*

On subcutaneous injection, some 44% of respondents said there was a strong need for devices delivering more than 2mL volumes to decrease injection frequency and make it easier for people to administer the drugs themselves. Historically, the delivery method for small-molecule drugs to treat chronic diseases was of little concern, as many of these medicines could be administered orally. But newer drugs being developed, especially in biologics are not suitable for oral administration and often need to be delivered subcutaneously, sometimes in higher volumes than a standard 1mL prefilled syringe can handle, hence the emergence of 2.25mL syringes and associated delivery devices And right now, the majority of available treatment options require frequent dosing and involve repeated hospital visits.

Over the past few decades, a number of companies have developed advanced therapeutic delivery

Figure 3: Larger Volume Injections: Complexity vs. Decreased Frequency



Question: Do you believe the complexity of delivering larger volume injections is offset by the patient benefit of decreased frequency of administration?

Base: All respondents (n=178).

solutions such as autoinjectors, pen injectors, and prefilled syringes to overcome the challenges associated with the administration of both conventional and novel drug/therapy molecules. Prefilled syringes and autoinjectors are designed to administer small drug volumes (equal to or below 2mL) in under 15 seconds. But wearable injectors can administer larger volumes (more than 2mL) of drug subcutaneously over an extended period, allowing highly concentrated drugs to be diluted into larger volumes and administered over longer periods without saturating the subcutaneous space. But even though the need for safe, easy to use larger-volume wearable injectors is growing, particularly in diabetes management, only 40% of respondents reported their companies were "actively" developing on-body injection devices for higher-volume subcutaneous administration.

Of those firms developing wearables, 46% reported new chemical entities and lifecycle management were the biggest drivers. In addition, the lifecycle management of an injectable drug-device product spans the entire period from research to manufacturing and clinical development through to post-approval surveillance.

Drilling down into the numbers, 35% of respondents reported a strong focus and investment when asked to what extent their companies were exploring formulation options that would permit a switch from intravenous to subcutaneous therapies. Only 18% reported little or no focus and investment. This move from IV to subcutaneous would seem to reflect a desire to produce formulations that have the ability to be self-administered by the patient and where possible reduce the need for treatment in acute care settings to reduce health care expenditure. Further, 35% said their firms were highly likely to consider using excipients with biologics to improve subcutaneous absorption and dispersion, whereas

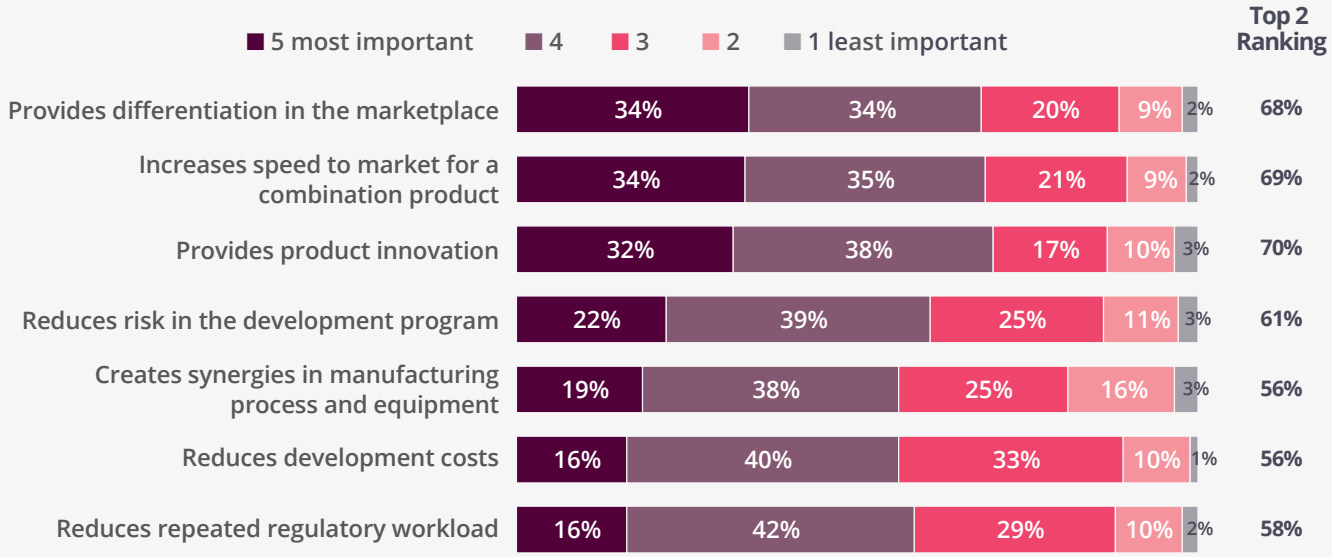
44%

of respondents said there was a strong need for devices delivering more than 2mL volumes to decrease injection frequency and make it easier for people to administer the drugs themselves.

11% of respondents said their firms were highly unlikely to do so.

When considering the benefits of introducing injectable drug-delivery combination platform devices, increasing speed to market and providing differentiation in the marketplace were the two most important features for respondents. Providing product innovation was cited as another key advantage. Summing up the wish list of many respondents for a combination product, one survey participant commented that they would want it to be "intuitive to use, easy to execute successful delivery each time, non-re-usable, less expensive

Figure 4: Important Features for Combination Product Platform Device



Question: On a scale of 1 to 5, how important are the following features when introducing of a platform device for combination products? (Please assign a value from 1 to 5 for each feature, where 1 is the least important and 5 is the most important)?

Base: All respondents (n=173).

than current market offerings and [have a] strong international IP [intellectual property] portfolio utilizing CIPs [cleaning in place] to build out a successively progressive product line." *(See Figure 4)*

The survey findings also highlighted strong industry interest in connected products, which are seen encouraging adherence to treatment therapies while reducing the risk of medication errors.

Almost 50% believed the need for connected products permitting data transfer should be decided on a case-by-case basis, whereas 35% thought they were relevant only to certain markets. Some 23% felt all new combination devices should incorporate data connectivity, whereas a mere 3% believed such products were completely unnecessary. The mixed survey findings on the need for smart devices may reflect that the link between compliance and improved outcomes still needs robust proof. Advocates of smart devices say they can enhance patients' adherence to treatment, provide reminders and training to the user, and adherence/non-adherence data to payers, health care providers, regulatory authorities, and the pharmaceutical manufacturer. Benefits of connected injection devices for the pharmaceutical industry also include pre- and post-market clinical trial data, reimbursement evidence, adverse events data, and product and training improvements. Even so, improved patient outcomes, improved patient adherence, and demonstrated compliance to insurance payers for reimbursement were rated as the top three benefits of connected devices.

But uncertainty about regulatory approval for such connected devices surfaced again in the survey as central to the pharmaceutical industry's concerns, with 59% of respondents stating the primary challenge in developing smart devices was winning regulatory clearance. The electronics in these devices add additional complex layers of required regulatory compliance. One regulatory hurdle, for example, is gaining approval for the electronics in

Almost half of respondents said their firms were giving moderate to strong support to the exploration of alternatives to disposable devices.

these devices, which add extra layers of complexity to the process as well as required compliance with other regulations, for example, WEEE (Waste Electrical and Electronic Equipment Regulation). Ease of use, utilizing appropriate technology, and keeping a lid on costs were other key worries. The development of new technologies and connectivity of the devices also bring new challenges around data management and raise questions as to the protection of patient information, control over data integrity, and system cybersecurity.

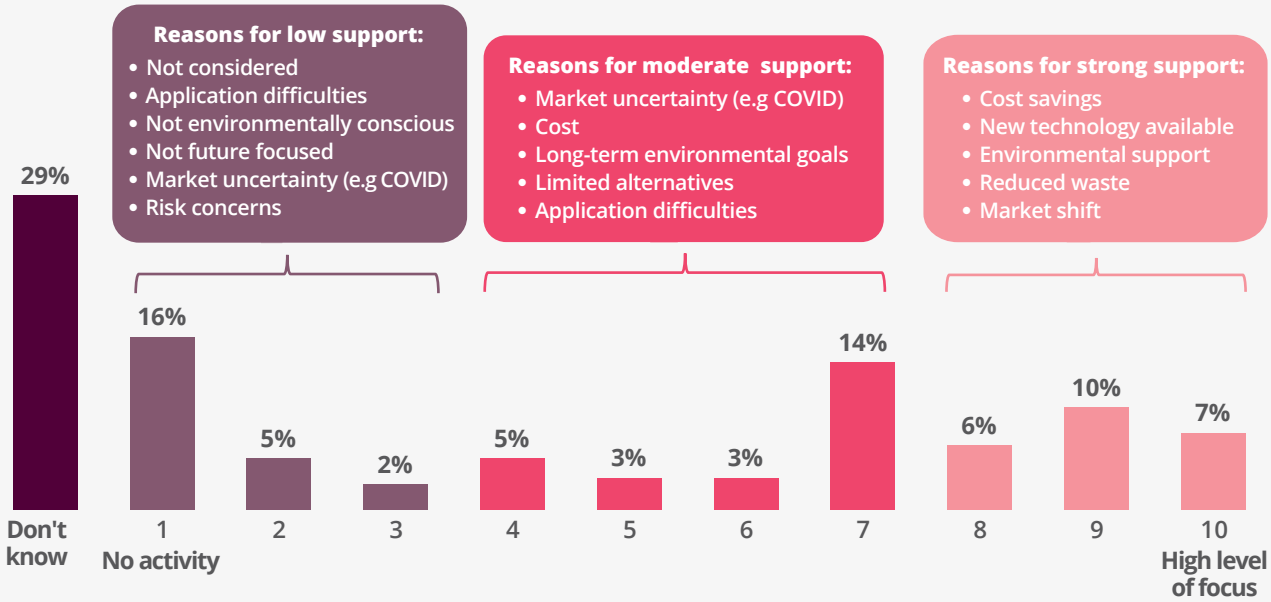
There are additional challenges associated with developing new connected technologies and assuring accurate dose delivery and drug compatibility with device components. These challenges may be even more formidable for combination injection products involving biologics.

On the environmental front, 23% of respondents said their companies were exploring alternatives to plastic disposable drug-delivery devices, despite plastics having only recently become a high-profile global pollution issue and the continued strong need for single-use injectable devices. They cited cost savings, environmental support and new technology as reasons for their companies' strong support. "This marketplace is naturally progressing toward the simplification of product design [e.g., Apple – intuitive, easy to use] and away from non-natural materials and hazardous waste disposal issues," one respondent said.

Almost half of respondents said their firms were giving moderate to strong support to the exploration of alternatives to disposable devices. Reasons cited for strong support for environmental actions were that their companies foresaw cost savings, market shifts and reduced waste. "As an R&D company we believe this space offers a tremendously 'wide and long' runway for a new line of cost-effective product offerings that are bold and exciting and that will support the purchasing argument for value and reimbursement," one respondent said. The support levels identified in the survey may have been higher still if the poll had been conducted prior to the pandemic. "Normally this would be at the core of our activities but due to COVID-19 our focus has shifted," another respondent said.

Some 29% said they didn't know their companies' environmental stance. A third of respondents said their firms had changed packaging or materials to be more sustainable. Almost half said their companies were working to achieve

Figure 5: Exploring Alternatives to Disposable Drug-Delivery Devices



Question: To what extent is your organization actively exploring alternatives to disposable (plastic) drug delivery devices?
Base: All respondents (n=167).

United Nations sustainable development goals. That figure jumped to 66% among big pharma companies. *(See Figure 5)*

With the survey showing injectable combination products are desirable from the perspectives of better quality of life, compliance, and outcomes, the industry appears to see such devices as the preferred route forward, offering a lower cost, more convenient method for dosing that accommodates patients, health care providers, and insurance payers. At the same time, it is evident that the regulatory approval process poses challenging and complex hurdles. Fast-changing global regulatory landscapes, regulation complexity, varied certification requirements, and a lack of international harmonization of standards make navigating the combination drug-device development pathway challenging and could hold back efforts to bring such products to market. However, the growing and increasingly competitive market for biologics and biosimilars along with the need to differentiate mean that combination products will continue to be a focus for drug delivery in the pharmaceutical industry.

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Owen Mumford Pharmaceutical Services specialises in the design, development and manufacture of injectable drug delivery systems for the pharmaceutical, biotech and generics industries. Our trusted devices are used daily in the delivery of various medications for a multitude of conditions across the globe.

Our offering includes single and multi-dose reusable and disposable auto-injectors, pens and syringes for subcutaneous and intramuscular administration. These innovative products are designed to meet the needs of both our pharmaceutical partners and their patients through simplicity, ease of use and improved safety and patient compliance.

With an established history of developing world-leading custom devices, we have now extended our capabilities to produce platform products. We pride ourselves on our expertise, support and personal offering; designing products with patient needs at the forefront of mind and to simplify our partners combination product development process. Therefore, reducing complexity and risk for the pharmaceutical and biotech industry.

Our products are supported by our services, and we work with our partners every step of the way, supporting and guiding from initial concept stage through to taking the solution to market.

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