



A long-term implantable sensor. Trelleborg is a full-service supplier of finished medical devices involving silicone-API processing, assembly of sensor and insertion device, ready-to-use package, and sterilization. (Credit: Shutterstock)

3 Areas of Innovation for Combination Medical Products

Wearable smart pump systems with highest precision microcomponents produced by Trelleborg Healthcare & Medical. (Credit: Trelleborg Sealing Solutions)



The combination of drugs with medical devices has the potential to take patient care in an entirely new direction. The power of these products is that they can deliver a precise amount of a drug to a precise location at a precise time — ensuring better patient compliance and potentially helping other therapies to be more effective.

This market is poised for tremendous growth. Allied Market Research published a report in September 2018 predicting that the global drug-device combination products market, which generated \$81.3 billion in 2017, will reach \$139.2 billion by 2025. From delivering drugs via bio-absorbable ophthalmic wafers to adding anti-inflammatory and antimicrobial agents to implants, the opportunities to develop successful new products are virtually endless.

This article discusses several combination products being developed in three areas — along with critical considerations for designing and specifying combination products. These three areas are precision drug delivery, drug additives, and innovative drug delivery.

Precision Drug Delivery

One reason for the rapid growth in this market is that combination products enable the release of a drug over a long period, typically 18–60 months, to a precise location.

For example, one area of drug-delivery innovation is aimed at patients suffering from retinal disease or macular degeneration. For years, treatment was dependent on, and compromised by, patients forgetting eye-drop doses. Current combination drug-device treat-



3 Areas of Innovation

ments are still limited, but having the ability to dispense a precise dosage via a bio-absorbable combination device could significantly advance treatment.

Ophthalmic projects in development include bioresorbable wafers administered on the sclera and micro-pellets injected into the posterior eye chamber. Getting the proper dosage into the eye is so critical that treatment can be compromised by dilution from tears; bio-absorbables eliminate this issue by precisely delivering extremely small doses of medication per day directly into the eye.

Contraceptive implants are another prime example of precision drug delivery, this time eliminating the need to take a tablet each day in an effort to reduce issues associated with missed doses. And there is continued innovation in this space; for example, vaginal rings containing multiple drugs have great promise. Because the drugs are held in separate areas of the device, there is no chance they'll combine and interfere with each other's efficacy. They are simply being delivered by the same mechanism, allowing a single ring to deliver both a contraceptive and (for example) an anti-retroviral drug for STD prevention, even if those drugs need to be delivered at different dosage rates.

Drug Additives

For years, drug additives have been applied to implanted devices to prevent inflammation, reduce the risk of infection, promote local healing, and reduce pain.

For example, steroids have been added to pacemaker leads to reduce post-surgical inflammation. Similarly, antimicrobial agents can be added to an artificial knee or hip replacement prior to implantation to reduce infection risk, and antibiotics can be added to the silicone used in advanced wound dressings.

Advances continue to occur in this space. As the demand to monitor glucose levels and increase insulin rises with the rapid increase in diabetes around the world, there is new focus on implantable devices that reduce the issue of patient compliance. For example, a new continuous glucose monitoring product recently approved for three-month implantation in the United States uses a sensor about $\frac{3}{4}$ in. in diameter that is implanted in the

underside of the arm, allowing diabetics to monitor blood glucose levels without a finger prick. This product has a steroid applied to help reduce swelling and ensure that the body doesn't reject the implanted device.

Innovative Drug Delivery

There are a wide variety of external drug-delivery devices in development, with more on the drawing board. As noted earlier, there is significant innovation occurring in the diabetes and ophthalmic spaces. Pain management is another area being carefully explored — external pumps make it possible for patients to receive a precise amount of a narcotic at exact intervals with no risk of accidental overdose.

Chemotherapy drugs are also prime candidates for both external micro-pumps and implanted pumps that deliver complex doses of potent drugs with no patient action required. Nonconventional energy sources have the potential to be used to distribute implanted drugs internally, such as a small inflated bladder used to apply pressure to a small drug reservoir that dispenses the drug through a valve, eliminating the need for battery, motor, and syringe.

One of the most exciting drug-delivery advances on the horizon is personalized product formulation, in which an exact dosage is calculated based on data about how an individual's cells react to a certain drug. An implantable or bio-absorbable device could then be custom formulated for that individual.

Design and Manufacturing Considerations

It goes without saying that designers of combination products must work with a manufacturer capable of producing the small-to-microscopic parts involved with items such as micro-pumps, implantable devices, and bio-absorbable devices. Specifically, seek out vendors with expertise in manufacturing a wide variety of items such as microtubing, molded O-rings, molded elastomer components, and

drug reservoirs. Ideally, a contract manufacturer will be able to provide assembly services in addition to individual components.

Consider that production of combination products involves a series of basic manufacturing capabilities for cleanroom, storage, quality management, and disposal. A cleanroom should be designed for medical device manufacturing, such that drug particles from the manufacturing process cannot flow into other areas of the facility. As far as drug storage, it's imperative that they are stored during the manufacturing process securely and at the temperature needed to prevent degradation. Medical device makers should utilize a specially designed quality system that meets all federal and state regulations, including accurate record keeping that can withstand scrutiny from regulatory bodies. Lastly, look for the ability to safely dispose of scrap material, some of which may be considered hazardous waste.

Combination medical device manufacture requires an additional level of expertise in a few areas. First, partners should be aware of the temperature parameters beyond which the specific drug being combined with the silicone or polymer will degrade.



In addition, there are limits imposed on molding or extrusion by the drug being added and that should be closely adhered to. Be aware of the effect that the drug being added will have on how much shear load can be applied to the material containing it. Lastly, know how to create the desired release rate for a specific drug contained in a specific material.

Conclusion

The potential to provide effective treatment for patients through combination medical products is inspiring significant innovation and growth in the space. Currently, there are three main areas of focus in the world of combination products in this industry segment: drug-delivery products, drug additives to existing medical devices, and new types of external drug-delivery devices.

Regardless of the type of device being developed, it is critical to work with a supplier that understands the intricacies of how the base material of the device interacts with the drug being used and that can support the strict regulations manufacturers must comply with while providing innovative solutions. Look for those with extensive experience in the testing and manufacture of these devices for successful outcomes going forward.

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A robust process for micro-assembly is a critical process step to product performance and reliability.
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