

Perspectives on Combination Products, Part 2

The marriage of a medical device with a drug or biologic has been increasing significantly within healthcare. The combinations have resulted in numerous benefits that could not have been realized with just one of the elements being indicated on its own. For this month's Perspectives, we asked what the future holds for these types of devices and what technologies would provide aid in their success.

What types of devices will see the marriage of drug/biologic and device in the future that aren't currently commonplace in medicine and what technologies will aid in the success of these devices?



Thad Wroblewski

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As medical devices become more complex, new considerations in sterilization technologies and processes arise. Today, the same issues remain with radiation processing, such as materials compatibility and lower doses driven by lower bioburden. Colder temperature processing, such as with dry ice, along with highly defined dosimetry associated with product configuration during processing, are utilized to better control dose ranges. With ethylene oxide, different specialized cycles are considered for those products that may have reactive chemistries. Cycles with lower temperature and humidity levels aid with the processing of such devices.

The evolution of combination devices will drive changes to sterilization and equipment and processes. The sterilization industry is already working towards developing new methods for determining sterility assurance level (SAL) standards. Lowering the current standard of 10^{-6} to 10^{-3} will potentially allow the sterilization of

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a range of radiation-sensitive devices and products that are currently processed aseptically. Ethylene oxide processing systems will also evolve along with devices. Specialized systems, such as those combining all-in-one processing in high performance vessels with packaging, perhaps with inert atmosphere packaging capabilities, could occur at the contract sterilizer or the end of the production line.



Jan-Willem Boode

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Cardiovascular diseases are the leading cause of death today, accounting for approximately 30% of deaths worldwide. And they are likely to remain so for a while due to aging populations and an explosion worldwide in chronic diseases. Given the need, it's not surprising that many clinical researchers and product developers are working on next-generation combination devices that will increase effectiveness, patient comfort, and safety of cardiovascular interventions.

While much of the first wave of convergent technologies was similarly focused (for example, drug-eluting stents married pharmaceuticals to medical devices), we see that recent advancements in drug-delivery technology, enabled by polymeric materials, have laid the foundation for a new generation of combination devices with the potential to truly transform medicine.

Developers, like DSM Biomedical, are utilizing these advancements and working on transforming medical solutions based on biostable polymer coatings into biodegradable solutions that release their therapeutic payload and then disappear, which helps the body maintain long-term biologic integrity. This trend is already visible in the current generation of drug eluting stents.

Another emerging combination product in the cardiovascular field is the drug-eluting balloon catheter, designed to open up clogged blood vessels (balloon

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angioplasty) and locally deliver an anti-restenotic drug, while reducing the need to implant permanent devices. Such an improved balloon catheter platform is expected to open up multiple cardiovascular indications that are currently inaccessible to traditional stenting.

Polymer innovations also fuel advancements in orthopedics and pain management that have the potential to address one of the most pervasive medical conditions: lower back pain. DSM Biomedical is focused on utilizing resorbable polymer technology in delivering drugs or biologics directly to the problem site, which has the potential to greatly relieve post-operative pain and even support healing.

The technologies that will aid in the success of these devices include material and drug-delivery technologies but they alone won't turn promise into reality. Achieving these and other advancements requires the medical community, academia, and industry (pharma/biotech, device, biomaterial, and others) to work together and in a multidisciplinary matter. Large companies with broad materials and life sciences portfolios like DSM are well-positioned to achieve this, but they can't do it alone. Collaboration, partnership and a shared commitment to improve the quality of life must be the common goal of all who can play a role in delivering the transformative technologies to address our most pronounced medical needs.



Dr. Paul A. Magill

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Microscopic thermoelectric devices can be used to generate electricity, to cool and heat objects, or even to measure the heat flow into or out of the body. The factors that now allow us to integrate this type of thermal management into the human body are two-fold: the miniaturization of these devices so that they are not disruptive when embedded, and the ability to more rapidly and precisely control the temperature over a small region. Thin-film thermoelectric devices are quite small, and a single element may be as small as 100 microns in diameter and no more than

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60 microns in height, which would enable novel applications for drug delivery systems and for treatments of a variety of maladies. Following are two examples for these types of applications.

One type of drug delivery system incorporates a semi-permeable membrane whose permeability is a function of temperature. As the temperature changes, the membrane could allow certain molecules to pass through from one side to the other. Embedding a thermoelectric device with temperature control circuitry within a drug delivery system could control the rate at which a medication is delivered.

Another example of the integration of thermoelectric devices into biomedical devices can be seen at Cerene Biomedics. Cerene is developing an implantable medical device using thermoelectrics to help control epileptic seizures by cooling a local surface area of the brain. Brain cooling has been shown to be a safe and effective means to control seizures when applied locally to the seizure focus.



Jean Colombel

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Combination products can range from preloaded syringes to an implantable insulin pump, but these combined products create new challenges from a regulatory perspective. There is a mixture of requirements and regulatory constraints coming from the engineering world of the medical device domain and the molecule world of the pharmaceutical industry. Therefore, an innovative approach is needed to achieve FDA compliance. Having an advanced product lifecycle management (PLM) technology that enables cross-functional product development and supports various regulatory requirements allows manufacturers to create a major competitive advantage and deliver combination products.

For example, Dassault Systèmes' solutions around Corrective and Preventive Action (CAPA) propose to address 21 CFR 820.100 (for medical devices) CAPA obligations,

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as well as those described in 21 CFR 211.192 (for pharmaceutical industry). This will allow engineers to manage both medical device and pharma data from concept, design, and regulatory filing to labeling and package management. The convergence of this data on a single technology can expedite and simplify the creation process and increase time-to-market.

The CAPA solution, as part of the ENOVIA Life Sciences Accelerator for Quality Issues, provides capabilities to ensure complete resolution of systemic quality issues when developing a combination product. The solution provides a request phase, where the CAPA site leader can determine if the CAPA request is, in fact, a CAPA or should be handled by a different process such as a non-conformance (NCR) or an engineering change order (ECO). Once a CAPA is instantiated, an investigation is conducted, which considers various risk factors and root cause analyses. Depending on the results, workflow events may be automatically initiated or setup manually by the investigator. The action plan is then reviewed and approved by appropriate personnel across the various divisions. Once the CAPA is approved it is executed, which may result in the execution of other processes such as a project or ECO. When the action plan is completed, the CAPA is moved into the effectivity stage where its status is tracked at the enterprise level.

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