WHITEPAPER

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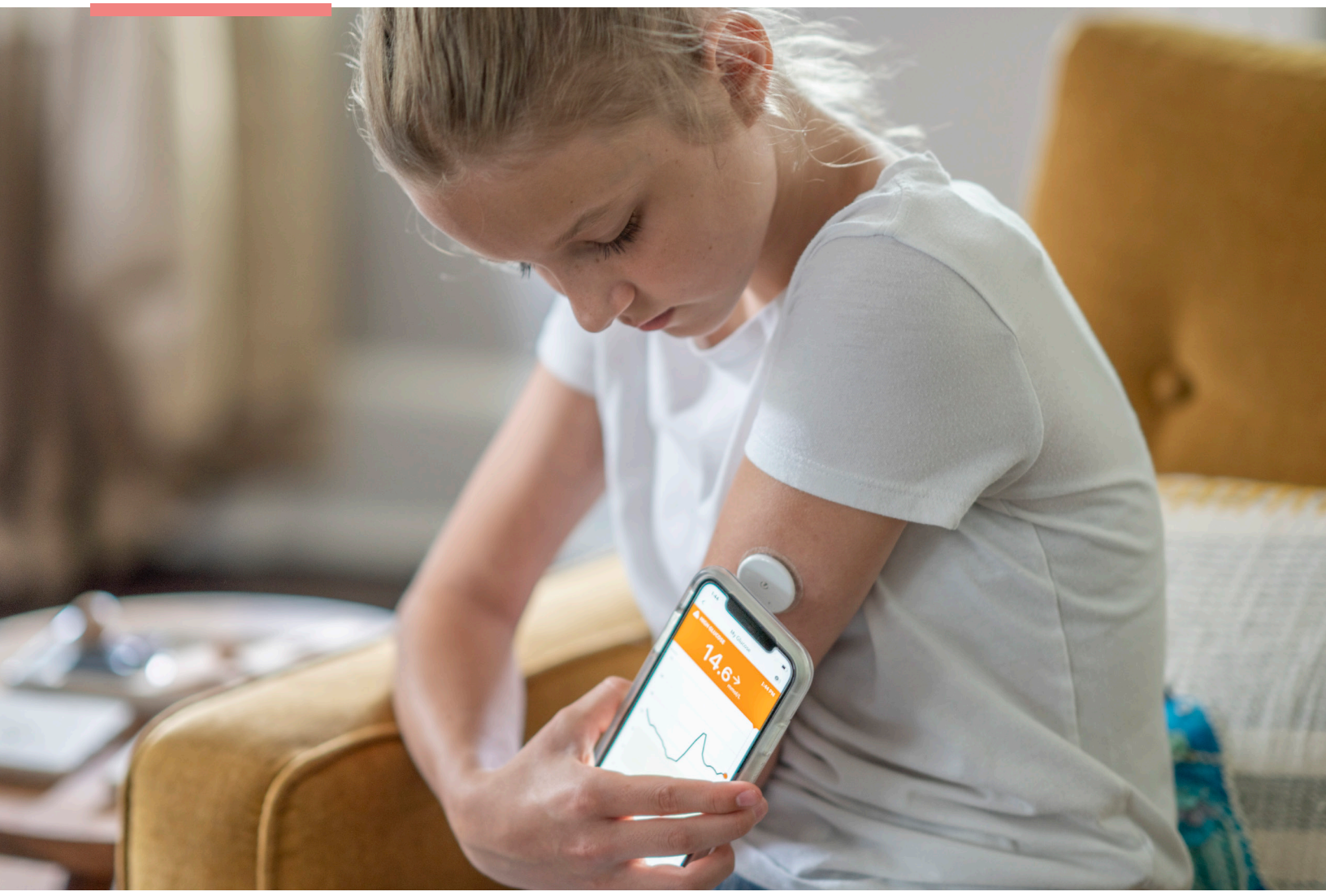
Drug Delivery Devices and Combination Products:
Making Informed Choices for Agile, Efficient Development



Introduction

Designing, producing and delivering a new commercially available market offering can be a long and arduous process. These existing challenges become even more demanding when the goal involves creating a drug delivery device or combining a drug with that device. While most pharmaceutical and biotech companies don't have the in-house expertise necessary for agile device development—largely because it doesn't represent their core business—a high-quality means of patient-administered delivery can greatly enhance a given drug's success in today's competitive industry landscape. That's why companies developing new drug delivery devices or combination products should consider the benefits of enlisting external collaborators such as contract development and manufacturing organizations (CDMOs), design/innovation consultants or a blend of both.

This whitepaper outlines several challenges inherent in today's drug delivery device and combination product development process, addressing the ways different types of outside collaborators can lend skilled support. The stakes are extremely high with so many key factors to consider, so an external firm with end-to-end production expertise can often contribute substantial insights and efficiencies. No matter which type of organization is chosen, however, close collaboration and clear communication among all stakeholders is the only real path to success.

CDMOs and Design/Innovation Consultants: Defining the Difference

First and foremost, when selecting *any* outside development contractor, it's important to clearly understand that firm's fundamental capabilities. CDMOs and design/innovation consultants embody different core competencies, so each one brings different skills and strengths to the table. Generally speaking:

CDMOs are typically characterized by an all-in-one structure that houses several specialized disciplines within the same organizational framework. As such, they provide comprehensive services that range from initial design through product development and manufacturing at scale. CDMOs differ from traditional contract manufacturing organizations (CMOs) in that they offer enhanced pre-production and development proficiencies—hence the "D" in the acronym. These augmented capabilities can enable more comprehensive customer support in the fast-evolving drug delivery device space.

Design/innovation consultants can often provide a broad spectrum of specialized technology and product development services. Their capabilities may include gathering and analyzing market data and user insights, creating and evaluating initial product concepts, testing, prototyping and—in some cases—guiding engineering development as well. As their name implies, however, design/innovation consultants are not equipped to actually *manufacture* the final drug delivery device or combination product.

While design/innovation consultants don't typically offer on-staff manufacturing expertise, many do have established relationships with trusted external manufacturing resources. CDMOs, conversely, have the in-house ability to provide knowledgeable manufacturing insights and recommendations from the earliest stages of product design. This distinction is crucial in today's multifaceted product development landscape for four fundamental reasons:

1. Drug Delivery Devices Are Increasingly Complex

A drug-specific combination product is essentially a drug delivery device that transfers a specified therapeutic agent or biologic onto or into a patient's body. The ongoing introduction of new pharmaceuticals, along with corresponding advances in delivery technology and design, are collectively spurring rapidly increasing complexities in this space—complexities that directly impact product development, quality assurance and regulatory compliance. There's a current trend toward devices that can deliver a larger payload, for example, thereby reducing the frequency of patient dosing. This leads to higher drug concentrations and increased viscosity, with larger volumes necessary to avoid molecular damage and ensure patient comfort. (On a related note, this shift may also set the stage for increased use of larger-volume drug delivery devices like on-body injectors or OBIs[1]).

Taking key considerations like this into account requires a comprehensive evaluation of functionality, safety, potential interactions and overall performance throughout the product development lifecycle. Engaging a development partner with extensive technology insights helps ensure that mechanical systems—and advanced electronics, where applicable—are well-understood from a design standpoint. Finding a firm with robust supply chain connections is equally essential to deftly navigating the ever-present development tradeoffs between device usability and cost of goods. CDMOs, especially those offering platform solutions that may help reduce risk and time to market, can provide one-stop access to all these critical capabilities.

2. Brands Are Seeking New Ways to Stand Out

With the pharmaceutical sector becoming increasingly competitive[2], it's worth noting that 107 drug patents are set to expire between 2023-2025[3] — with 51 existing patents expiring in 2023 alone[4]. This large and ongoing wave of expirations has been termed the "patent cliff," and it paves the way for other pharmaceutical firms to develop, package and market lower-priced generics. Given the range of industry mergers and acquisitions projected to take place[5], certain brands could potentially explore drug delivery packaging as a way to differentiate themselves. While generics don't traditionally employ delivery devices in this manner and many drugs coming off-patent—tablets, powders, etc.—would involve alternate means of dosing, the inherent cost and usability tradeoffs[6] previously noted remain significant drivers to market success. This may inspire some novel competitive strategies going forward.

3. Advanced Delivery Devices Are Becoming More Common

The number of combination product submissions to the U.S. Food and Drug Administration (FDA) increased roughly 10% year over year from 2014 to 2019[7]—while the global market value of combination products is projected to reach $139 billion by 2025.[8] The drug delivery system market itself, meanwhile, is projected to grow to more than $70 billion by 2029.[9]

Several converging factors are likely contributing to this growth. For example, the recent push toward value-based care[10] and connected health[11] acknowledges that chronic disease monitoring and some level of ongoing home-based intervention can play a key role in well-being, convenience and quality of life. For overburdened providers and health systems themselves, the need for more flexible, convenient delivery options has never been greater. The overarching takeaway is that competition in the drug delivery device and combination product space appears set to ramp up substantially. This means that commercial success may largely hinge on product differentiation using more patient-centric drug delivery technology, combined with more efficient time to market.

4. Quality and Regulatory Concerns Are Gaining Visibility

Increasing access to real-world data is prompting a growing awareness of product experience and risk. The FDA's Adverse Event Reporting System (AERS) database[12], for example, compiles detailed listings of adverse events in an accessible dashboard format. Open-source data analysis platforms[13] are further boosting public access to global health authority databases—and perhaps even more importantly, public sharing on social networking and media sites is now commonplace. All this is contributing to a perpetually escalating mindfulness surrounding quality issues, errors and adverse events related to a wide range of pharmaceuticals and associated delivery products. At the same time, the growing complexity of drug delivery systems is also amplifying regulatory ambiguity.

The primary regulatory designation of a given combination product, for instance, impacts its risk classification[14] and the quality strategy steering its development. Ensuring safe, consistent performance across that product's entire lifecycle means incorporating rigorous and risk-informed quality checks[15] throughout production. That, in turn, requires careful compliance with appropriate regulatory guidelines from initial design through full-scale manufacturing.

Beginning With the End in Mind

For all of these interrelated reasons, clear communication and stakeholder awareness are absolutely crucial at every stage of combination product and drug delivery device production. Certainly, contractors with tightly collaborative external relationships—a design/innovation consultant with an established outside manufacturing resource, for example—may be quite capable of providing this. However, integrating a wide range of collaborative specialists under one roof helps an organization begin with the end in mind, keeping every stakeholder clearly informed throughout product development. This is known as design for manufacturability (DfM), and it's especially important given a modern supply chain that has evolved into a complex network of organizations operating from multiple locations. Design engineers specifying key components need to be fully aware of potential sourcing hurdles early on.

They also need hands-on plant floor experience to avoid making recommendations that could hinder manufacturing down the line.

CDMOs, as their name suggests, are specifically structured to offer manufacturability insights even during the earliest product development stages. Their all-in-one capabilities can therefore foster synchronized thinking, DfM awareness, process ownership and stakeholder buy-in. This, in turn, may help a drug delivery device or combination product move more seamlessly from initial design through full-scale production and ultimately, successful market introduction. CDMOs can also accept full ownership for both design *and* manufacturability when engaged to verify particular aspects of a product offering, such as usability or market fit.

A select number of CDMOs, moreover, own existing drug delivery platforms that have already been fully designed, quality-checked and safety tested for manufacturing at scale. An industry organization contracting with such a firm can custom-tailor this established technology to help facilitate flexibility and control costs. Platforms may introduce some short-term complexity to ensure a design is capable of supporting multiple drugs—but when a development contractor offers strong analytical engineering skills plus all-in-one developmental expertise, overall production efficiencies tend to readily offset this. Risk is likewise reduced because CDMOs take overall responsibility for the platforms they develop, and can also offer supplemental services such as drug handling or specialized market support.

There are, of course, specific cases where a heightened emphasis on design is not only appropriate but absolutely essential. It may be necessary, for example, to ensure straightforward and user-friendly device functionality for a particularly inexperienced, young or capability-constrained patient group. In such instances, a skilled design/innovation consultant may be better positioned to gather early market insights that help inform initial concept creation—later overseeing key phases to make sure these market insights are fully addressed as development and full-scale manufacturing are transitioned over to a CDMO. Increasingly, however, such design-related undertakings are also offered by CDMOs, with some larger pharmaceutical firms simply electing to perform them in-house.

Regardless of which outside contractor assumes the lead, there's no dodging the fact that design and manufacturing are inherently interconnected processes. It's often been postulated that product design determines a large percentage of overall production costs, so decisions made during the design phase of product development can have irrevocable impacts on manufacturing and ultimate market success. Similarly, however, key design insights need to remain top-of-mind throughout production to avoid cost-prohibitive judgment calls. Nowhere are these dual dynamics more imperative than with highly regulated offerings like drug delivery devices and combination products, where poorly informed adjustments can have vastly unwanted effects on time, expense, component sourcing and/or regulatory compliance.

All this serves to illustrate another compelling point: Before enlisting *any* type of outside contractor, make sure there's a way to ensure internal operational awareness and ownership of that strategic relationship. Any organization considering the development of a highly regulated product—one that will likely take many months or years to finalize—needs to possess the internal bandwidth and dedicated fortitude to see that multi-disciplinary initiative through to completion. This is where a skilled internal product manager can furnish critical oversight. While a qualified external contractor will do everything possible to provide knowledgeable assistance along the way, a dedicated internal product manager can monitor progress and course-correct as needed. This important topic will be addressed in a future article.

"Pharmaceutical and biotech companies, large and small, benefit from using a CDMO where demonstrated design capabilities are integrated into the CDMO. These CDMOs have fewer interfaces for the drug company to deal with—less risk—and typically allow for a speedier and higher quality technology transfer, from design and development to industrialization. The end result is a better product ready for market faster."

Paul Jansen
Drug device development consultant; retired Head of Devices at Sanofi; board member for Subcuject; advisory board member for Evoleen, Windgap Medical and Kymanox

Constructive Collaborations: Making an Informed Choice

All the interrelated dynamics previously noted create an exceedingly complex product development environment that demands specialized expertise in several areas. Choosing a CDMO or design innovation consultant—or selecting a combination of the two—is driven by a different set of factors for every business. When considering the services of a specialized development contractor, however, there are several key areas to evaluate during the decision-making process:

1. Manufacturing Insight
Verify an established relationship with design engineers who have actual hands-on manufacturing insight that involves physically walking the plant floor, viewing machinery in action and seeing the production process up-close. There's no substitute for firsthand manufacturing knowledge that can help identify issues *before* they lead to expensive setbacks impacting efficient manufacturability. Any organization relying on external manufacturing expertise needs an extremely clear, synergistic communication strategy at each stage of production. Given today's complex regulatory considerations and global supply chain constraints, every new external relay introduces added risks that can impact communication, budget, process synchronization and the finished deliverable's marketability.

Actionable Tip:
Generate a detailed statement of work (SOW) or request for proposal (RFP), asking potential contractors pointed questions about integrated capabilities and applied, hands-on manufacturing expertise. This type of document can help highlight areas of proven proficiency, minimizing the chance of an unproductive mismatch. Even if end-goals aren't entirely mapped out, the SOW/RFP process can help illuminate essential needs by outlining areas of uncertainty. It also provides a prime opportunity to request specific elements up-front—including team biographies and relevant portfolio examples.

2. Synchronized Support
When design and manufacturing teams are closely aligned, they help key deliverables stay on time and within budget at every stage of production. An integrated, open-door environment allows experts across multiple disciplines to collaborate in real time. Teams immediately begin building a design that keeps manufacturing, component sourcing, regulatory concerns and scalability top-of-mind. This, in turn, often makes important production and deliverability insights easier for customers to obtain at every juncture. It also means that one organization can take clearer ownership of design and manufacturing, which may help avoid costly misunderstandings and/or finger-pointing later on.

Actionable Tip:
Ask questions focused on structure and process synchronization during the selection phase. Which disciplines are represented under one roof or within the parent company? Are collaborative team members connected in-house, or outside providers? How are customer concerns and inquiries addressed—and specifically, what kind of support is offered at each stage of the product development process? Look for organizations that have evolved and expanded organically. Prioritize engineering proficiency, an established quality assurance protocol, a customer-first culture and a proven track record of satisfaction. Pay close attention to how quickly prospective contractors respond to an initial inquiry, too. The way each organization replies early on can tellingly reveal its attention to detail, general customer focus and internal team coordination.

3. Industry Experience
Some contractors only specialize in one or a few industries—and certainly, what's most important is ensuring that product development needs precisely align. Remember, however, that more expansive industry experience may often facilitate out-of-the-box approaches that can help control costs, incorporate innovative capabilities and/or streamline time to market. Also keep in mind that broader, more integrated in-house teams often have a wider network of industry connections. This can make a profound difference if, for example, supply chain issues arise and alternate providers need to step in. When entering a new or especially crowded market, selecting a provider with limited experience or connections can escalate risk considerably.

Actionable Tip:
Look for a provider that not only offers drug delivery device expertise, but also a broad industry network and specialized awareness of supply chain dynamics in highly regulated sectors. This often helps facilitate flexibility and innovation if unexpected issues arise, such as a global health emergency or political unrest.

4. Diversified Presence
Although manufacturing doesn't necessarily need to take place in the country of sale, an experienced contractor can apply localized knowledge during the development stages to help the process proceed more smoothly. Such knowledge may derive, for example, from a greater understanding of end-user needs and nuances informed by prior experience—or, to a lesser extent, from closer familiarity with the requirements of regional regulatory bodies.

Once it's time for mass production, established processes can then often be replicated, fine-tuned and expanded. Fully validated production lines can usually be moved almost anywhere the customer desires—so a development contractor with global presence and a broad network of industry connections can help ease the market transition to another geographic region.

Actionable Tip:
During the selection process, ask which geographical areas an organization has served in the past. Keep in mind that Europe, North America and Asia are typically considered best-in-class regions. Prospective contractors with a truly broad presence should carefully review customer goals, then proactively suggest a phased manufacturing approach that aligns accordingly—a smaller localized initial run, for example, followed by wider expansion to global production at scale should that apply.

Other Key Considerations

Several other key capabilities speak to an outside contractor's customer focus, adaptability, established industry network and general approach. Consider these additional factors to help identify the appropriate development contractor relationship and narrow the field of candidates:

- **Target Costing**
Product pricing is a significant decision for any company releasing a new drug delivery device or combination product. Target costing is a focused strategy that helps organizations ensure the targeted prices for their new products *prior* to manufacturing. It's particularly beneficial when a minimum profit margin would be required to make a product offering feasible. If it's determined early on that a given product just isn't workable, the product plan can be amended or abandoned entirely. Development contractors with demonstrated proficiency in this proactive costing method can help introduce considerable process efficiencies, so it's worth asking about prior experience.

- **Design for Excellence (DfX)**
This may sound like something of a buzzword, but it's actually a programmatic toolbox for proactively evaluating end-user experience during the product development phase. Development contractors adept at implementing this specialized set of technical guidelines closely examine opportunities to save money at each new developmental stage. Because this involves actively applying a DfM mindset that begins with the end in mind—which means consulting with the right experts at optimal times—CDMOs are generally better-positioned to offer this approach given their integrated, all-in-one organizational framework.

- **Risk Analysis and Mitigation**
Product risks that manifest during commercial use often have upstream origins in either the design or manufacturing phase.[16] For this reason, risk management needs to be an ongoing process that occurs throughout the product lifecycle. Development contractors should proactively create a detailed risk analysis and mitigation approach that evaluates potential

hazards—then continually review its effectiveness and amend as necessary. This often involves accessing a customer's design history file (DHF) and design verification testing (DVT) records to generate detailed documentation that can eliminate production pitfalls and speed regulatory approval. The integrated risk management process for drug device combination products typically requires organizations to abide by established guidelines, such as Quality Risk Management (ICH Q9) and Medical Device Risk Management (ISO 14971). Ask about a prospective contractor's familiarity with these key capabilities—and request examples.

- **Technology/Capability Portfolio**

Specifically look for extensive expertise bringing highly regulated products and drug delivery devices to market—yet also consider industry experience with other technology products, which fosters innovative thinking. Also examine whether a given contractor has the backing of a dedicated parent company. This can provide ready access to augmented capabilities should the need arise.

- **Project Management Approach**

Always ask if a prospective contractor employs a stage-gate project management process—sometimes also called a waterfall or phase-gate approach. Optimized for development projects that involve numerous steps, diverse teams and/or multiple key stakeholders, this risk-management methodology subdivides initiatives into a series of stages with decision points or "gates" between them. At each of these junctures, work is strategically reviewed to determine whether the project can efficiently move to its next phase while addressing all stakeholder needs. This approach requires close cross-functional team collaboration and clear stakeholder communication—so its use indicates strong cooperation, adaptability and a customer-focused mindset. Given the integrated organizational structure of a CDMO, these types of firms are usually much more proficient at stage-gate project management that fully considers a broad set of stakeholder requirements: manufacturing, quality, supply chain, regulatory and of course, the customer and patient.

The market for combination products and drug delivery devices is growing significantly given the confluence of new technological advances, emerging healthcare and costing models, and a growing awareness of health equity and patient/provider experience. At the same time, there's increased cognizance regarding product quality and adverse events—making insightful production and risk mitigation practices more crucial than ever.

Outside contractors offering a proven track record in highly regulated industries, a collaborative project management blueprint, diverse provider networks and well-integrated team dynamics can often substantially enhance product development agility and efficiency. Given their all-in-one organizational structure, CDMOs can frequently provide these critical capabilities along with enhanced communication, adaptability, customer responsiveness and lower management overhead. Thinking a CDMO could offer more comprehensive, cost-effective support for an upcoming drug delivery offering? Continue reading for additional insights.

Additional Questions?

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