

Pharmaceutical Companies: Outsourcing Combination Product Manufacturing



Phillips-Medisize Corporation
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Expertise of device companies also helps you poise your combination product project for success.

“The future is combining devices and drugs.”

– Ralph Larson
Chairman and CEO of
Johnson & Johnson

Combination Products, Defined

Combination products are therapeutics that combine two or more products (drug/device, biologics/device, biologics/drugs, or drug/device/biologics), regulated and sold as a single unit. Examples of combination products include drug-coated implantable devices, drugs packaged with delivery devices in medical kits, and drugs and devices packaged separately but intended to be used together.

The Rise of Combination Products

Combination products have been proving to be more effective drug-delivery approaches for pharmaceutical and device companies alike. In fact, both healthcare sectors have found that, in many cases, a single combination product containing both drug and device components can be more effective than either one of the components acting alone².

Given the success and potential of combination products, it's no surprise that the market size of all combination products in 2004 was around \$6 billion³, and is expected to cross the \$20 billion mark by the end of 2012⁴. Furthermore, the next decade will witness the introduction of numerous additional combination product solutions that converge biologics, medical devices and drug-delivery systems, as well as electronics and nanotechnology.

The Power of Drug-Device Company Collaboration

Combination products currently in the marketplace have already proven to be profitable⁵. However, guiding a new combination product, particularly combination drug-device products, from initial design through commercialization can be compared to navigating a maze.

Both drug and device companies encounter obstacles in complying with both the FDA drug and medical device regulations during the development phases as well as other global regulations that determine which current good manufacturing processes (GMPs) and quality system regulations apply for product manufacturing. Add to these challenges the need to manage complicated supply chain logistics, from design, testing and development through low volume clinical trial manufacturing and scale up into higher-volume production for commercialization.

The most minor detail can derail a successful product development effort, resulting in time and resources lost and crucial deadlines missed – potentially causing the product development or regulatory submission to stall before it ever reaches the market.

¹ Frontline Strategic Consulting. Combination Products: An Impact Analysis on the Convergence of Medical Devices and Therapeutics. Navigant Consulting/Front Line Strategic Market Reports, San Mateo, CA, 2003.

² Bafan, M. Combination Products – Union of Pharmaceutical and Medical Device Industries Brings Opportunities, Ezine article, 2007.

³ Soloninka, J. Convergent Medical Technologies Local Impacts, Global Opportunities. YORKBiotech Inaugural Meeting, Ontario, Canada, November 2-3, 2005.

⁴ GlobalData. Combination Products – Evolution of the Medical Equipment Industry, December 2008.

⁵ Bafan, M. Combination Products – Union of Pharmaceutical and Medical Device Industries Brings Opportunities, Ezine article, 2007.



Avoiding delays can make the difference between a winning combination product and one that stalls in clinical trials.

When combination product launch success depends upon speed-to-market, drug and device companies benefit by joining forces. Such partnerships can free you to focus on your core competencies, while leveraging your supplier's existing, proven, regulatory-compliant manufacturing processes and infrastructure. Tapping into the expertise of device companies also helps you poise your combination product project for success. Early collaboration, from initial design concept phase, allows your device company partner to help you anticipate potentially problematic areas that can occur during pilot production, clinical trials, and eventual high-volume manufacturing.

By anticipating potentially problematic areas in your projects in partnership with a device company, you can significantly increase the odds of generating new combination products that are developed and launched according to plan. As a result, you help ensure the product achieves speed-to-market, thereby becoming competitive and profitable in the marketplace.

Combined efforts between you and your supplier can also help differentiate your combination product from competing solutions in the same therapeutic category. With help from an experienced contract manufacturer, you can more readily incorporate leading-edge technology and design into your drug-delivery devices. This allows you to further optimize your combination product for patient convenience, comfort and/or efficacy of administration.

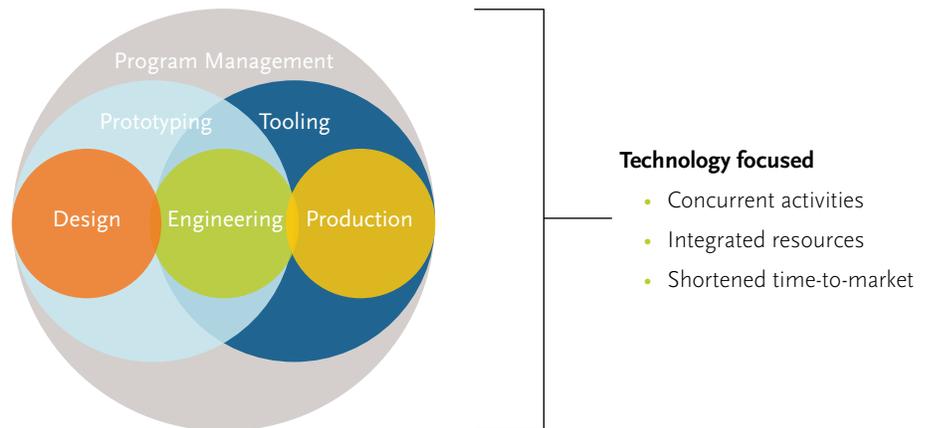
Critical Factors to Consider in Building Your Supply Chain

Your project success, and your ability to control the many variables in combination product development, depends upon your ability to select the right device manufacturing partner, with the right mix of development support and commercial manufacturing service offerings, to help guide your project.

Oftentimes, project complications and delays can arise as a result of collaboration among disparate organizations. For example, a design firm might not understand, first hand, all that can be achieved in injection molding processes. Further, designs may not be optimized for manufacturing or assembly. Or critical tolerances may not be fully understood. When your design partner is also your manufacturer, or when you engage your manufacturer early on in the development process, you eliminate the need to perform knowledge and technology transfer. Exchange of information and data becomes seamless, and you enhance your ability to meet key delivery and launch dates.

Platform Medical Manufacturing

Pharmaceutical companies save money and time partnering with a medical device manufacturer that provides full, one-stop service from concept through commercialization. The following timeline represents how integrated resources are able to reduce a product's timeline.



The Vital Importance of Quality Systems Management

The right partner for your combination product development efforts will have – in addition to the other necessary capabilities – comprehensive experience in quality systems management.

This experience is vital because there is considerable overlap in the drug and device regulations. For the most part the overlap is apparent. For example, both establish requirements for management, organization, and personnel; both require documentation and record keeping. The U.S. Food and Drug Administration (FDA) considers both regulations to be similar, and meant to achieve the same goals. However, each set of regulations is somewhat different because each is tailored to the characteristics of the types of products for which they were designed.

The combination product manufacturer you choose will need to assess how best to comply with both sets of regulations, during and after joining the constituent parts together, by carefully considering the requirements of the current Good Manufacturing Processes (cGMPs) and Quality Systems (QS) regulations in relation to the constituent parts, and the combination product(s) they manufacture.

Partnerships for Success

Partnerships between drug and device companies can streamline efficiencies, enhance financial gains, and bring innovative combination product solutions to patients. The key to bringing a successful and profitable new combination product into the market is to keep the development process as seamless as possible, from concept through commercialization.

This target is best met by working with a single supplier able to handle and package drugs,

demonstrate complete knowledge of the complexities of medical product development, and offer a full range of engineering and product development services.

By applying adequate due diligence in choosing your partner, you can improve the odds of launching a successful new combination product into the marketplace – on time, and on budget.

Questions to Ask Prospective Contract Manufacturers

- Do you have first-hand knowledge of cross-industry best practices and technological developments to potentially apply to our program?
- Do you employ experienced engineers of varying disciplines, as well as additional professionals able to support our new development opportunities?
- Do you demonstrate a true commitment to understanding not only our needs, but also the needs of the patient or end user of our combination product?
- Are you committed to improving the patient's quality-of-life?
- Do you have a high level of commitment to confidentiality and protecting our intellectual property?
- Are you backed by financial strength and stability required to be with us for the long term?

Examine all of the previously-listed aspects carefully when planning your combination product development efforts. Failing to address these issues in the beginning can create expensive delays in putting your product into the marketplace. Historically, avoiding such delays can make the difference between a winning combination product that sells millions of units and one that dies in clinical trials.

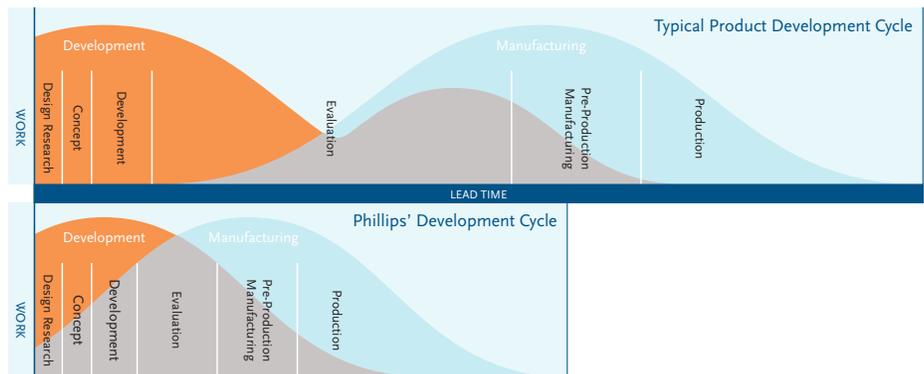


Figure 1

Initial Design Through Commercialization

Bringing a new combination product design to market encompasses more steps than might seem necessary in the early stages of the project. Insufficient attention to detail at any point, can require a return to earlier stages. For a breakdown of these steps and how the design and pilot phase overlay the process, see Figure 1 above.



ISO 13485 with design control allows your manufacturer to work on your device, from design through commercialization with the confidence their procedures are as stringent as your own.

Concept Phase: Idea Creation and Concept Development

- Develop design inputs and product concepts as well as assess risk management and preliminary product specifications
- Establish full preliminary understanding of end-user interactions
- Create a workable preliminary project plan that encompasses timing, budgeting, marketing forecasts, and resource planning

Phase I: Feasibility

- Evaluate preliminary end-user needs
- Make a full examination of all regulatory requirements
- Gain a full understanding of the performance characteristics of the design; perform risk assessments

Phase II: Design Output and Development

- Perform failure mode and effects analyses (FMEAs) and develop testing methodologies
- Create a complete set of drawings and specifications, and conceive preliminary specifications for packaging and labeling the finished product
- Develop working product prototypes and begin preclinical testing of the prototypes; define current Good Manufacturing Practice (cGMP) for final manufacturing; initiate preliminary designs for manufacturing (DFM) and designs for automation (DFA)

Phase III: Design Verification/Pilot Phase

- Creating pilot units for market entry and testing pilot units against design specifications; performing final risk analyses
- Final development of production specifications, test methods, and control plans; also development of protocols for verification and validation
- Conceiving support processes for marketing, packaging, and distribution, then entering clinical trials and evaluations

Phase IV: Market Launch and Design Transfer

- Produce final specifications for design, product, and processes; perform process validation
- Develop final device manufacturing requirements (DMR)
- Submit the product for marketing and enter full-scale production

Figure 2

Research and Development

Design Research
Exploration
Refinement

Engineering

Mechanical Design
Electronics Integration
Design Analysis
Prototyping
Design Verification

Pre-production Builds

User Studies
Engineering
Validation Protocol Development and Execution
Clinical Study Builds
Design Validation

Design Transfer

Process Validation
Supply Chain Management
Distribution

Design

Product Conceptual and Industrial Design
Mold Flow Analysis
Diligent Tolerance Analysis (CETOL)
Design for Manufacturing (DFM)

Development

Prototypes
Prototype Tooling
Rapid Prototyping
Stereolithography (SLA)
Fused-deposition Modeling (FDM)
Clinical Builds

Testing

Product Testing Laboratories
Feasibility
Design Verification
Pilot Verification
Validation and Metrology Services
Finite Element Analysis (FEA)
Ability to Perform:
Vision Inspection, Automated Testing, Flow and Leak Rate Testing, Force – Torque Analysis, Seal Strength, Cleanliness Testing, Bioburden Testing, Inline Vision Measurement and Sort, Strain and Compression, Vacuum and Pressure Decay, and Displacement and Cavity Pressured Testing

Manufacturing Methods

Automation Design
Inset, Multi-shot, and Overmolding
Injection Molding
Lean Manufacturing
Capabilities to Mold Plastics, Metals, Magnesium and Ceramic
Tooling

Decorating and Secondary Operations

Sonic Welding
Pad Printing
Corona Treatment
Annealing
Laser Decorating and Engraving
Screen Printing

Assembly

Semi-automatic and Automatic Assembly
High-speed Packaging
Clean Room
Robotic Assembly
Heat Staking
Gluing
UV Curing
Swaging

Packaging and Sterilization

Automated Parts Handling and Packaging
Drug Packaging
Sterilization
Device Assembly
Tyvek Sealing

Commercialization

Manufacturing Scale-up
Market Launch
Drug Packaging, Sterilization and Assembly Services

World-class Facilities

State-of-the-Art Equipment
Dedicated Team of Engineers
Clean Room Space Engineered for Particulate and Bioburden Management
Automated Building Management Systems
Scalable Space Available to Support On-site Collaboration and Pilot Manufacturing
Class 7 and Class 8 Clean Rooms
Around-the-clock Operations
Established Offshore Partnerships and Global Capabilities

Supply Chain Management

Design through Distribution
Supplier Quality Engineers
Offsite Inventory Near Customer Locations
Experience Managing Numerous Suppliers for Various Processes
Supplier Approval Process with Part Qualification

Global Approval Experience

European Medicines and Healthcare products Regulatory Agency (MHRA)
Japan Ministry of Health, Labor and Welfare (MHLW)
U.S. Food and Drug Administration

Drug-delivery Program Expertise

Long Track Record of Drug-delivery Product Development
Drug Handling and Drug Packaging Capabilities
Full Understanding of Drug Product Liabilities
Controlled Substance Regulation Understanding
Product Labeling Requirement Knowledge

Quality Certifications and Compliance

Prior Successful Implementation and Maintenance of applicable Food and Drug Administration (FDA) current Good Manufacturing Practices (cGMPs), for 21 CFR Parts 210/211 Drug Packaging Requirements and FDA 21 CFR Part 820 Quality System Regulations
ISO 9001, 14001, and 13485
Ability to Provide a Full Range of Phase I through Phase IV Product Development Capabilities, Including Design Verification and Clinical Builds



Partnerships Built on Innovation

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