Manufacturing Transfers for Medtech OEMs

Part 1: *Quality Management Considerations When Selecting a Medtech Contract Manufacturing Organization*

For medical device manufacturers, the prospect of transferring any part of their company's operations to an outside vendor is among the most complex and difficult processes they will ever undertake. Whether the transfer involves reliance on an outside product design and development firm, the complete replication of manufacturing and assembly lines at a vendor's location, or simply hiring a specialized packaging and distribution firm to take on order fulfillment, the manufacturer's entire business is always at stake. Contract manufacturing organizations (CMOs) that cannot meet the quality requirements of their OEM customers can do permanent harm to the manufacturer's reputation, regulatory status, and customer contracts—not to mention the potential for increasing risks to patient safety.

To make sure that they do not misstep when taking on the process of selecting outside vendors, manufacturers should pay particular attention to the quality management capabilities of the firms they are considering. To find out what this process looks like in detail, we spoke with Jonathan Wacks, principal of Jonathan Wacks Consulting (Chicago) and formerly vice president for quality at Flexan LLC (Lincolnshire, IL), a CMO specializing in product development and cleanroom manufacturing of silicone and thermoplastic components for medical technologies.

Jonathan Wacks, principal, Jonathan Wacks Consulting (Chicago).

Starting Points

Quality management is a mission-critical function of all medtech manufacturers. By design, quality management permeates every aspect of a company's business, and should exert a decisive influence over the company's policies, procedures, and day-to-day operations.

In the modern medtech supply chain, quality management requirements are put in force through frequent FDA and third-party inspections and manufacturer audits.

"Depending upon where a company is in the supply chain, it may be subject to any number of national or international regulatory schemes," says Wacks. "For example, a CMO that is a supplier to a company that's selling in Japan may receive all kinds of questions from the Japanese Ministry of Health, Labor, and Welfare about the products or components that it's supplying. If the CMO is deemed a 'critical supplier' under the EU Medical Device Regulation (MDR), it may be subject to unannounced quality inspections by the customer's notified body."[1]

Quality management is a mission-critical function of all medtech manufacturers. Attention to quality issues when selecting vendors and partners can help manufacturers prevent downstream issues. Image by Ievgeniia Ocheretna courtesy Dreamstime (ID 115711521).

To meet FDA requirements, a company first needs to determine whether the products it makes are finished medical devices, device accessories, or device components. Manufacturers of finished medical devices must register with FDA, and are subject to direct regulation by the agency. Manufacturers of components are not directly regulated by FDA, but are subject to audits and quality management systems controls imposed by their customers, who are, in turn, ultimately responsible for meeting FDA requirements.

Attention to quality issues when selecting vendors and partners can help manufacturers prevent downstream issues. Since quality management requirements also extend to all of a medtech manufacturer's vendors, the best way to begin the assessment of a contract manufacturing organization is to review the company's quality management system.

Manufacturers are obligated to manage their suppliers under FDA's purchasing control regulations (21 CFR 820.50), which are a part of the agency's Quality System Regulation.[2] "In general, manufacturers must demonstrate to FDA that they have done an appropriate risk assessment for every item they purchase," says Wacks. "Further, based on that risk assessment, manufacturers must develop a strategy on how to identify qualified sources, establish contract specifications, and perform all the other operations associated with purchasing a component or service."

Performing a risk assessment for every aspect of a supply chain requires a significant effort by manufacturers but will vary according to the component being supplied. "The risks

associated with purchasing a commodity carton made out of 200 lb. test corrugated paper, for instance, will be very different from the risks associated with an implantable-grade component that is expected to stay in the body and perform without fail for the next 20 years," says Wacks.

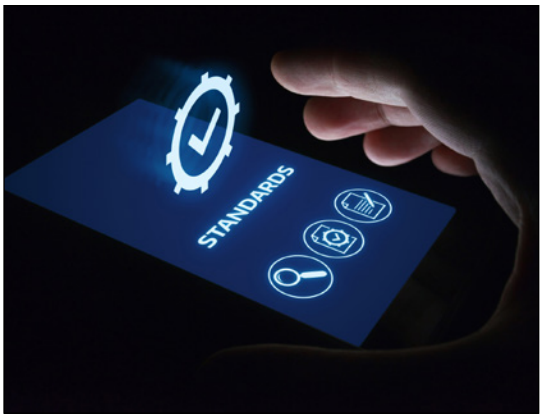
As part of its purchasing strategy, it is the manufacturer's responsibility to demonstrate to FDA that it has performed the appropriate risk assessment and has implemented the proper risk mitigation.

Credentials

When a medtech manufacturer is searching for an accomplished CMO with a wide range of capabilities, qualifications like being an FDA-registered manufacturer, or having ISO 13485 certification are just the starting point.

"Qualifications such as those are now just the table stakes needed to get into the device business," says Wacks.

The vast majority of medical device manufacturers require that their vendors be certified to either ISO 9001 (the original quality systems standard) or ISO 13485 (the medtech-specific version), depending on what kinds of components are being purchased.[34] A device manufacturer seeking to source a high-volume transistor, for instance, will probably be dealing with suppliers that are certified only to ISO 9001 because they have no specialized interest in the medical device market. Contract manufacturers and other medical device component suppliers typically apply for and secure pertinent ISO certifications—including ISO 9001 and ISO 13485—even though they are not technically manufacturers of finished products.



Today's medical device manufacturers typically require that their vendors be certified to appropriate standards, beginning with either ISO 9001 (the original quality systems standard) or ISO 13485 (the medtech-specific version), depending on what kinds of components are being purchased. Image by Alexandersikov courtesy Dreamstime (ID 117538884).

"The bottom line is that most medical device manufacturers expect that their vendors will have some kind of pertinent registration or certification, or will have passed some form of formal audit," says Wacks.

FDA registration is now generally available only to companies that have filed a premarket submission—a 510(k) or PMA, for example—and are therefore legitimate manufacturers in their own right. So, for the most part, suppliers and CMOs that serve other medtech manufacturers don't have their own FDA registration.

The European Union's scheme is a bit different. The latest requirements for the European market have been expanded over what they used to be, now also including requirements about purchasing practices and training.

"The new EU Medical Device Regulation defines a new designation of 'critical supplier' that imposes a higher level of quality systems compliance than for other suppliers," says Wacks. Medical device subcontractors that make components considered critical must adopt a quality management system that is commensurate with the requirements of medical device manufacturing, and typically they must also accept the contractual obligation of permitting unannounced audits by their customer's notified body at any time.

"The EU MDR has now made these unavoidable conditions for all medical device manufacturers that wish to sell in the European market," says Wacks.

Apart from the need to meet regulatory requirements, the reality is that the quality of a device manufacturer's products is only as good as the quality of the components, subassemblies, or services that they ask their vendors to supply. There have been enormous changes in how the top transnational medical device companies source, buy, assess, and audit components, products, and services.

"In effect, these device companies are making the same transformation that the automobile industry did in the 1970s: consolidating their supply chain to reduce the number of vendors; working closely with vendors to get the broadest horizontal offering; and spending an enormous amount of time auditing, inspecting, and invariably cooperating with that supply chain," says Wacks.

Quality Management Structure

An important way to gauge the quality management capabilities of a contract manufacturing organization is to look at how the company's quality systems are integrated within its overall structure and business culture.

Many CMOs start as capable job-shops with expertise in a specialized area, and then find that their services are in demand among medtech customers. Companies of this type often seek to expand their medtech business, but usually without adding very much depth of expertise to their offerings.

Alternatively, some CMOs have a management team with deep expertise in medical device development and manufacturing, and a detailed understanding of what medtech OEMs are trying to achieve. Those companies have a leg up when they are working with OEMs, because they understand that their clients are usually looking to streamline their supply chain by working with suppliers that can take responsibility for multiple aspects of a product's journey toward commercialization.

"Today's CMOs have to know the medtech market well enough to supply customers with multiple commodities and allied products, enabling customers to narrow their supply chain," says Wacks. "Customers that are doing their own manufacturing may be searching for CMOs that can perform specialized operations such as biocompatibility studies, sterile packaging, terminal sterilization, or final product release. They may even need help with regulatory issues such as remediating a technical file or submitting a premarket notification (510(k)) to FDA.

"Companies that are not situated to provide those services are no longer competitive, and will likely find themselves losing business to companies that have those capabilities," says Wacks.

Seeking Capabilities

The shape of a CMO's quality management structure—its management team and quality systems protocols—can tell prospective customers a great deal about the capabilities and expertise of the company. But getting at further detail about a candidate CMO can be tricky.

"Right from the start, it's important to note that medtech CMOs are very often bound by confidentiality agreements that make it impossible for them to reveal or discuss what they are doing, how they are doing it, or for whom," says Wacks. "As such, assessing or auditing a CMO first-hand and seeing their actual operations is the first step in understanding their capabilities and expertise."

One way to approach this question is to look beyond the equipment a CMO has, or the certifications it lists, and to focus instead on what additional services the company is able to perform. A CMO that can demonstrate its capability to execute an end-to-end solution—including assistance with product and process design, regulatory support, test method development, and other ancillary services—should be considered a strong contender.

When a medical device manufacturer is selecting a supplier, the track record of that supplier is critical. Manufacturers should ask about the CMO's internal audits for compliance with FDA regulations as well as with the ISO 13485 quality systems standard for medical devices. Image by Alexandersikov courtesy Dreamstime (ID 121903568).

Candidate CMOs should be asked to demonstrate that they have the requisite knowledge and expertise to handle all of the functions they are offering. If the company offers to perform logistical support, for instance, will it set up a kanban to manage the inventory workflow? Will the company build products and act as stock warehouse and inventory distributor? How will the company guarantee that the customer gets best pricing, or that the customer isn't harmed by long lead times?

If any of the CMO's responses raise concerns, now is the time to explore alternatives and weigh the differences in experience and capabilities for each company. Often it may be very difficult to glean everything that should be known about a company. A company's case studies and white papers can be indicative of the breadth of the company's services. Some publications may be revealing about a company's experience in meeting regulatory requirements, maintaining a design control system, supporting regulatory filings, or other pertinent issues.

CMOs that can take on tasks in more than a single field of expertise certainly have an advantage in this marketplace. When an OEM is looking for a packaging and sterilization subcontractor for a product, an existing CMO that can develop the sterilization process, arrange for packaging, and arrange for terminal sterilization and product release will have an advantage over its competitors—even if none of those operations is actually carried out within its own walls.

"Medtech manufacturers are doing business in a really busy global environment," says Wacks. "CMOs that can give them solutions, as opposed to just components, will have a sustainable competitive advantage—even if those added capabilities aren't all in-house."

If products are being manufactured for markets outside the United States, manufacturers should also ask about the CMO's international experience. Not every CMO has experience working with Japanese or Chinese regulators, or with authorities in countries that don't formally recognize ISO 13485 as the accepted standard for quality management in medical device manufacturing. Asking about a CMO's international experience is also a good way to get a sense of the company's breadth of knowledge and expertise.

Audits and Outcomes

When a medical device manufacturer is selecting a supplier, the track record of that supplier is critical. The most important thing to know is how critical that supplier is about its own operations. How robust is the supplier's internal auditing system? Has that system identified any major or minor nonconformities? Has it generated continuous improvement observations? Knowing that a supplier is prepared to ask hard questions on its internal audits provides a good yardstick for assessing how critical the supplier can be about its own operations.

If the CMO is an FDA-registered company, it may be possible to piece together problems in the company's track record through FDA notices of inspectional observations (Form 483s), warning letters, consent decrees, close-out reports, or other agency communications that can be obtained from the FDA website or via a Freedom of Information Act request. The manufacturer should try to discover what problems the supplier had, how they were resolved, and whether FDA returned to perform a follow-up audit. Also, it is useful to know when was supplier was last audited—because being audited 10 years ago is not the same as being audited today.

The same types of questions should be asked about the CMO's audits for compliance with the ISO 13485 quality systems standard for medical devices. Did those audits reveal any major or minor nonconformances, and did any of those observations recur in later audits?

"A CMO that has had a checkered history needs to be looked at very closely," says Wacks. "Even when a supplier's previous difficulties have been resolved, they may still raise a red flag. On the other hand, there could be legitimate reasons why a supplier encountered problems, and then a new management team came in and cleaned it up."

Any combination of a lax or check-the-box internal audit, a checkered history with FDA, or ongoing problems revealed in

notified body audits should be considered warning signs that the manufacturer should not just walk away, but should run away.

"When the smoke is that dense," says Wacks, "there's almost certainly a big fire somewhere."

When FDA issues a Form 483 or warning letter, it may identify and name only a few items of nonconformance. But it would be wrong for the manufacturer to conclude that fixing just those items will be sufficient to satisfy FDA.

"The agency's correspondence always ends with the caution that the named violations are not intended to be an all-inclusive list, and that it is the manufacturer's responsibility to investigate and correct all violations in order to bring the company's products and processes into compliance," notes Wacks. "Just turning on the fan to get rid of the smoke doesn't put out the fire."

To comply with current requirements for quality management systems—both in the United States and internationally—manufacturers must also integrate risk management into everything they do. Every time a company moves a piece of equipment, proceeds through a phase of development, or buys or develops a new manufacturing technology, some level of risk is always present. Companies must be able to demonstrate that for everything they do, they have considered, understood, and mitigated all of these associated risks.

To comply with current requirements for quality management systems—both in the United States and internationally—manufacturers must also integrate risk management into everything they do. Image by Egor Kotenko courtesy Dreamstime (ID 110563901).

"For a variety of reasons, most companies don't do a very good job of fulfilling these obligations," says Wacks. "Many companies believe that if they have performed a design failure mode and effects analysis (DFMEA) or a process failure mode and effects analysis (PFMEA), they have done enough to manage their risks. But these strategies are not at all sufficient for managing risk, because they don't address the need to integrate risk management across all of a company's functions."

For companies that are in the business of making life-supporting or life-sustaining medical devices, meeting functional requirements is only 50% of the companies' operations. The other 50% is dealing with what can go wrong or, in other words, meeting the requirements of a risk management program. Companies that can't demonstrate they have integrated risk management into all of their processes are probably going to get bitten—and bitten hard.

Reviewers expect that a company will be able to demonstrate that it has a risk management program, that it actually follows the procedures defined by that program, and that it has more than just a PFMEA in its design history file (for FDA) or technical file (for international entities).

"Companies that embrace and apply risk management strategies effectively will inevitably perform better than their competitors," says Wacks. "To my mind, having a strong risk management profile is one of the most important factors that distinguish world-class medtech companies—and the suppliers to those world-class companies—from less-capable vendors."

Jonathan Wacks is principal of Jonathan Wacks Consulting (Chicago). He was previously vice president for quality at Flexan LLC (Lincolnshire, IL), a contract manufacturing organization specializing in product development and cleanroom manufacturing of silicone and thermoplastic components for medical technologies. Wacks can be reached via jlwacksconsulting@gmail.com.

References

[1] European Union Medical Device Regulation (EU MDR) (Regulation (EU) 2017/745). [Consolidated text: Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) no. 178/2002 and Regulation (EC) no. 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.] Available at: **https://eur-lex.europa.eu/eli/reg/2017/745/2017-05-05**.

[2] Quality System Regulation Medical Devices; Current Good Manufacturing Practice (CGMP) Final Rule; Quality System Regulation (21 CFR parts 808, 812, and 820). *Federal Register*. 1996;61(195):52601–52662. Available at: **www.fda.gov/medical-devices/quality-system-qs-regulationmedical-device-good-manufacturing-practices/medical-devices-current-good-manufacturing-practice-cgmp-final-rule-quality-system-regulation**.

[3] *Quality Management Systems; Requirements* (ISO 9001:2015). Geneva: International Organization for Standardization, 2015: Available at: **www.iso.org/standard/62085.html**.

[4] *Medical Devices: Quality Management Systems; Requirements for Regulatory Purposes* (ISO 13485:2016). Geneva: International Organization for Standardization, 2016. Available at: **www.iso.org/standard/59752.html**.

Next Up

Part 2 of this series will look at how medtech manufacturers and contract manufacturing organizations can align their goals and processes when creating plans for a manufacturing transfer. Stay tuned!