Tech Transfer for Oral Pharmaceutical Products

By Koshy George, Dylan Amig and Sundeep Sethia

If any of these scenarios apply to you, you likely need a tech transfer of your oral pharmaceutical:

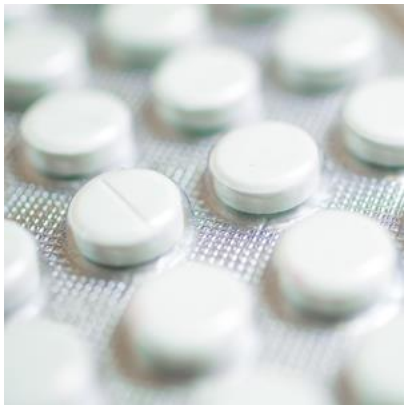
- You are in development and need spray drying technology that you are not experienced with or cannot access.
- You are ready to scale-up your soft gels process to commercial manufacturing but don't have the capacity.
- You have an old, discontinued tablet product that you want to repurpose and bring back to the market, but need to update its compliance with U.S. Food and Drug Administration (FDA) regulations.[1]

For these reasons and many more, tech transfer — the transition of the product/process/analytical method between development and/or manufacturing sites — to a contract development manufacturing organization (CDMO) is increasingly common.[2] CDMOs have proven they can significantly reduce costs and development time for pharmaceutical companies.[3]

This handover can be a daunting prospect for oral products with complex and highly sensitive formulations and manufacturing processes. But with the right CDMO, a proper tech transfer offers an opportunity to re-examine quality, process procedures, and supply chain issues, including provider partnerships.

This article will cover the high-level initial thinking that should launch building a tech transfer plan, what qualities to look for in a CDMO partner manufacturing oral pharmaceuticals, and the basic phases of a tech transfer.

Oral Drug Tech Transfer FAQ's



Two high-level questions that a CDMO needs to ask regarding a tech transfer are:

Why does the sponsor want a tech transfer?
It is important to clarify the purpose from the beginning. Knowing why a tech transfer is needed will quickly establish the drug sponsor's priorities and goals for the project. A tech transfer might be for a small- or medium-size company that wants to avoid the costs and time of hiring consultants, purchasing expensive equipment, and

tackling the FDA regulatory process alone. It could be a sponsor who wants to transfer the product's data to continue development elsewhere. Or an older product may need updated regulatory compliance. All of these reasons have very different demands and will result in very different types of tech transfers.

What are your business goals?
As part of a tech transfer, the CDMO must also understand your business success criteria. It could be that the current manufacturing site for a soft gel has failed inspections and a new CDMO needs to step in to save the product. Or perhaps your controlled-release capsule is ready to move to commercial manufacturing, but you don't have a large manufacturing capacity for its highly sensitive formulation. Your business goals will impact the tech transfer regarding timeline, costs, facilities, and resources needed for the manufacturing process.

What to Look for in CDMO for Oral Dose Tech Transfer

Experience in all Phases of Manufacturing
A CDMO with many years of experience at every stage of oral drug manufacturing—pre-IND, IND, NDA, ANDA, NADA, ANADA, Phase I, II, III, IV (CTM manufacturing), and commercialization — is invaluable. Each phase carries different regulatory considerations, different scales of manufacturing, and different financial priorities. A staff with experience in all phases will be better equipped to smooth over any hiccups during the transfer and beyond.

Mastery of Oral Drug Development Techniques
For successful oral drug tech transfer, a CDMO must understand and master all relevant techniques involved in most tech transfers. Examples for liquid-based systems include enhancement of solubility and bioavailability for poorly soluble compounds by solubilization with GRAS solvents for the desired drug load, lipid-based systems/self-microemulsifying drug delivery system (SMEDDS), nano-suspension, and inclusion complexes. Solid dosage forms include spray drying, roller compaction, tableting/encapsulation, etc.

Oral Drug Facilities
A CDMO for oral drugs should have cGMP and FDA-certified facilities, clean rooms, equipment to produce gelatin capsules, tablets, capsules, and non-sterile liquids/suspensions. Your CDMO will need containment facilities if you use highly potent compounds, cytotoxic materials, hormones, and DEA-controlled substances I-V. Bonus if your CDMO can source high quality raw materials and excipients at reasonable rates.

One-Stop-Shop
It is helpful if your CDMO is in one location and offers a gamut of services: project management, formulation and process development, supply chain management, technical services, validation, primary and secondary packaging, quality assurance and quality control, analytical and microbiological testing capabilities, and regulatory support. With one campus, it is easier to use the continuous manufacturing (CM) method to feed material through all the operations in a single equipment train. Being on the same

campus also allows for simpler logistics, less supply chain risk, better control for temperatures and humidity and one quality control and quality assurance system.

Cost Efficient
A CDMO should be able to deliver cost estimates and project timelines, all within a week of beginning the technical assessment. The CDMO must be aware of the budget at all times and have a record of saving sponsors money without losing product quality. Make sure your CDMO has a track record of delivering drugs to market quickly and efficiently, from preclinical to commercialization.

Expertise with Complex Products
While complex products are gaining popularity, and there are hundreds of advanced delivery platforms in development, only a handful of CDMOs can handle them. If your oral dose product is a complex formulation, a CDMO with experience in complex dosage forms, small and large molecule compounds, niche tech, NCEs, and NDAs is necessary for the tech transfer. Your prospective CDMO should also be able to handle complex processing challenges like milling/particle engineering, spray drying, extrusion, and particulate/bead coating.

Efficient Supply Chain
Due to the supply chain disruptions caused by COVID, it can take longer, often three to six months, to get materials from a manufacturer. But a CDMO with strong supplier relationships will not run out of supplies easily. For raw materials and packaging components, a CDMO must be in the practice of ordering as early, and as much, as possible to cover worst-case scenarios.

Once that contract is signed, orders should be made within a week because timeframes are currently extensive. Your CDMO should be clear and upfront about their process and progress. It should update you regularly about any supply chain issues until they are resolved.

Regulatory Support
Your CDMO must have regulatory experience to guide the tech transfer as per the current FDA regulations. Evaluation of the product specifications and analytical test methods against the current or new USP requirements needs to be done at the initiation of the transfer process.[4] Due diligence on regulatory aspects during tech transfer helps to get faster approval from the agency.

Awareness of International Standards and Requirements
Corporations are increasingly opting to send manufacturing overseas to cut costs. This has caused significant changes to how oral drugs are regulated. The requirements for APIs and excipients can vary from one country to another. More rigorous guidelines and inspections are being put into place to ensure compliance across borders.

Packaging preferences can also vary from country to country. For primary packaging, the US often favors bottles, where Europe prefers blister packaging. A CDMO must know these differences and make every effort to keep the product compliant in international markets.

How Tech Transfer Works

The tech transfer process involves the following two stages:

Developing the tech transfer framework

The tech transfer framework involves preparing a document that includes why the transfer is happening (cost savings, scaling up a product, additional manufacturing site, etc.), a communication strategy for the transfer between the entity that holds the product and the one receiving it, and a description of the teams and stakeholders and their roles in the transfer. It also includes a high-level list of anticipated changes such as sources of materials, equipment, and methods.

The framework will also include success and qualification criteria, the validation process, and deadlines. For oral dose, this will include documents about equipment qualification, raw materials, the API or multiple APIs, the history of the drug product's manufacturing process (batch records, any annual product reviews that spell out uniformity issues, breakage issues and customer complaints, product specifications, product development report, tooling drawings, validation reports, scale-up report, etc.), and the packaging process.

Developing the tech transfer plan

The tech transfer plan will include a gap analysis and risk assessment. There is risk in any manufacturing process and that is especially true in manufacturing oral dose forms where changes in the equipment and principle of equipment operation can result in product with different release rates and thereby bioavailability issues . Proper selection of tech and equipment is critical for a successful manufacturing process.

Because different products require different techniques and equipment, the assessment will include things like API, excipients, formulation, batch size, major equipment, test methods, packaging, and more. The assessment will describe the level of change, risk, and risk mitigation. A risk assessment and mitigation strategy improves the transfer process by bringing greater care to each step. Both the sending and receiving players must contribute to the assessment. These subject matter experts and technicians should meet before the handoff so the transfer is as smooth, expeditious, and safe as possible. The ISPE good practice guide describes the items that should be in this plan, for example, scope and objective, roles and responsibilities, equipment details, etc.[5]

A tech transfer includes validating the manufacturing and packaging processes. In general, even with a commercial tech transfer, the CDMO will still do engineering batches to confirm the transfer worked. If necessary, it will make adjustments and quickly begin successful scale-up manufacturing.

Tech Transfer at Pii

Pii's tech transfer planning process begins with a review of the dosage form's Critical Quality Attributes (CQAs), equipment train used, the excipient functionality, and process. Pii staff look at whether anything technically can be made better and will question the client's thoughts and intentions behind the process. Then they try to mold that process in the similar equipment train at Pii.

In one example, a drug sponsor contracted Pii for a tech transfer from a competing CDMO due to challenges at a competing CDMO. This was a first-to-market chewable tablet for veterinary use that comes in four strengths. These tablets have a unique shape and high tablet weight especially for the highest strength. In test production, it was discovered that the highest strength tablet would break and chip during the downstream processing. The high weight of the tablets resulted in plastic deformity and relaxation post compression, and the unique shape exacerbated the chipping issue.

In order to meet the sponsor's launch goals, Pii formulation and MSAT teams proposed a short- and long-term solution. In the short term, instead of one common blend for the four strengths, Pii modified the blend for the higher strength within the SUPAC guidance to reduce the tablet weight and minimize the

handling issues. For the long-term solution, Pii recommended round tablets to completely remove the chipping and breaking issues. The launch was on time and successful.

In another example, Pii handled the tech transfer of a liquid formulation, an Orphan New Drug Application (NDA). The liquid formulation drug was already developed at lab scale. After due diligence and creating a framework and tech transfer plan, commercial-scale production was set in motion with a specific equipment train.

During the engineering batch, particles were observed in the solution towards the later part of the filing process. The particles came from the gaskets of the displacement filling pump. The formulation developed was a simple solution of API in mostly water without any other excipients that can lower the friction between the gasket and the walls. This resulted in gasket wear out after a certain period of filling.

Options to change to different filling pumps were available, but involved more lead time and cost. Maintaining the launch time was critical for this product. The formulation and MSAT teams determined the exact failure point of the gasket and decided that the filling be validated with a specific number of bottles whereupon the gasket would be replaced to mitigate the issue. The sponsor was able to launch the product on time.

Key Takeaways

- A successful tech transfer works best when there is close communication and complete information sharing among the sponsor, sending manufacturer, and receiving manufacturer.
- The sponsor and CDMO should be clear on the sponsor's business goals and milestones.
- A CDMO with vast experience in every phase of oral drug manufacturing will smooth any hiccups that arise later when adept problem solving is required.
- Having the process, equipment, and facilities in one location makes continuous manufacturing feasible and eases logistics.

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Learn more about oral dose tech transfer at Pharmaceutics International, Inc.

ABOUT Pii

Pharmaceutics International, Inc. (Pii) is a US-based contract development and manufacturing organization (CDMO) located in Hunt Valley, Maryland. The experienced scientists, engineers, and staff at Pii pride themselves on adroitly employing a phase appropriate method of drug development for the prudent use of their client's resources as they solve challenging problems. In addition to offering end-to-end development services, Pii manufactures a variety of dosage forms to include complex parenteral

drugs and has a wealth of analytical testing capabilities. Its Hunt Valley campus has four aseptic suites with lyophilization capabilities. Our talented professionals stand ready to help!

ABOUT THE AUTHORS

Koshy George

Koshy George, Associate Director of the Manufacturing, Science and Technology at Pii, has more than 25 years of experience in Oral Dosage Formulation Development, Quality Compliance/Assurance, Manufacturing Science & Technology, Product Life Cycle Management, Process and cleaning validation, CSV, Calibrations, Tech Transfer, and Packaging with DSCSA emphasis. In addition to a Bachelor degree in Pharmacy, he earned a Master of Science in Pharmaceutical Sciences and a Master of Science in Biotechnology from the University of Maryland. He holds certifications from the National Institutes of Health (NIH) in Clinical Pharmacology and in Clinical Research and is affiliated with the International Society for Pharmaceutical Engineering and American Association of Pharmaceutical Scientists, through memberships and mentorship programs.

Dylan Amig

Dylan Amig is the Head of Manufacturing and Packaging for orals, solids, and non-sterile liquids. Dylan's

leadership has grown in increasing responsibility where he leads and supports strong Manufacturing Science & Technology (MS&T), Manufacturing, and Primary/Secondary Packaging teams. Dylan practically grew up at Pii, starting as a Manufacturing Technician for solid dose production in 1999 while still in high school. Mentored by Pii's founder and former CEO, Dr. Syed Abidi, Dylan went on to hold a variety of positions at Pii, including Production Supervisor; Senior Supervisor, Manufacturing; and Senior Manager, Manufacturing. Throughout those years, Dylan cemented himself as an integral part of Pii's growth, successfully working on programs from early stages of development and seeing them through to commercialization – having been an integral part of commercializing over 30 programs.

Sundeep Sethia

Dr. Sundeep Sethia, Senior Director of Research and Development at Pii, has over 18 years of experience in the pharmaceutical industry. His expertise is in drug development across a broad range of therapeutic areas and dosage forms. Dr. Sethia has a proven track record in drug development and approvals. He formerly served with Amneal Pharmaceuticals, Teva, and Barr Laboratories in R&D. Dr. Sethia earned his Ph.D. in Pharmaceutical Sciences from St. John's University, NY, and a Master and a Bachelor degree in Biotechnology and Pharmacy, respectively, from Jadavpur University in India. He has co-authored various peer-reviewed scientific publications and patents/patent applications.