The many mergers and acquisitions of the last 5 years often involved moving legacy products from sites where they were manufactured for decades. Perhaps they were even developed there. Here are some tips on making it a smooth transition.

t’s always a little heart-breaking to learn that a manufacturing facility will shut down because the people running it couldn’t achieve compliance or because a Big Pharma company is “rationalizing” its manufacturing network. In many such cases, the products must be transferred to a new site, and the destination could be another plant the company owns, a different company’s manufacturing site, or a plant run by a contract manufacturing organization.
I've helped transfer multiple products from mature facilities, and in this article I share some of what I've learned. The focus is on how to collect the information you need to gain enough process and product understanding to facilitate a successful site change without disrupting supply. The article doesn't discuss how to handle shutdowns of new facilities when volume falls short of expectations or corporate strategy changes.

Old facilities

One cause of obsolete production environments is a management decision to save money by not investing in new equipment, even though it would increase efficiency and improve operator safety. Of course, that decision only hardens once managers learn that a divestiture is looming, and instead of being upgraded, such facilities may become donor sites.

These facilities—working time capsules many of them—often use manufacturing processes that were adapted to suit the site's physical limitations. At some facilities, for example, the clearance between the ports of the V-type blenders and the ceiling is so tight that they must be loaded by an operator with acrobatic skill. In other cases, workers must scoop the compression blends into the tablet press hopper because it's impossible to discharge them from a lifted container or from an upper floor. I've seen a few cases where workers were allowed to charge the V-type blenders indiscriminately via the two ports. In short, there are almost as many different setups as there are companies when it comes to loading mixers and blenders, holding or storing powders, and feeding tablet presses and capsule fillers.

Today, companies transfer products into manufacturing environments that have a smaller process footprint and require fewer workers. And the high ceilings popular in facilities built after World War II, which allowed powder blends to free-fall into the press hopper, are disappearing because process engineers recognize that long chutes can cause powders to segregate. Bin blenders are the modern approach.

How and where to recover information

The black notebook. FDA-approved processes must be run by the book, but if you want to know how things really work at legacy sites, ask long-term employees about their "black notebook." It's usually concealed in their back pocket or locker. While the practices it describes may not meet GMP, the notebook is a valuable source of information because it reveals key process parameters and/or specific product handling methods that are sometimes decisive in whether a legacy product passes or fails. I remember asking one senior operator whether he had kept notes or drawings from the time when the product ran well. He had indeed, and that information helped me set up a roller compactor properly. I also recall a notebook that reported that the operators intentionally left compressed cores to "relax" for a few minutes before they were measured for hardness. Good to know!

Operators. Even if it's not recorded, the information that long-term employees can provide is nearly unlimited and is crucial for understanding how legacy products are made. These people could be the only ones who remember how things were done before the facility was extended or reorganized. Some might even recall the initial product and process transfer from R&D.

Sugar coating is a good example. It was once prevalent, and required operators to master the art of a confectionery process instead of how to click through drop-down menus on a human-machine interface of a film coater as they do today. In North America, sugar coating has all but disappeared, but in Europe it and other old techniques are still used. They're difficult to validate but these practices continue nonetheless thanks to the expertise of the operators. Ask them how they make these processes successful.

The tooling room is one of my favorite places to explore, and if you're involved in technology transfer, take the time to speak to the employee in charge of the punches, dies, and other change parts. This person can inform you how frequently tooling is ordered and tell you about the specific features of the tooling design, including the addition of special treatments, such as a chrome coating. Whoever is in charge of the tooling room will also know about the tablet presses and the change parts they use, including the force feeders and turret, and how to set up the press. Ask how the staff conducted troubleshooting of the tablet presses and capsule fillers. What worked? What didn't?
Beware of recycling old equipment

It’s an understatement to say that the pharmaceutical industry is conservative: Some facilities still use equipment and processes from the 1970s and 1980s. In fact, it’s not unusual. The industry abounds with painted-frame tablet presses that require operators to turn hand wheels to adjust performance. At some facilities, nothing has changed since the process was conceived and the equipment installed.

Perhaps that’s OK if the process works, but when new equipment eventually replaces the old, beware of repurposing the old machines in-house. I’ve seen equipment that should have been sold or scrapped but was instead transferred to the product development section. That seems like an economical and sound decision, but it often isn’t. After all, your colleagues would inherit a machine that has no equivalent elsewhere and/or uses a different principle of operation than the modern production equipment. Examples include planetary mixers and old tablet presses with worn turrets. I understand it may be difficult for the R&D people to refuse no-cost equipment, but that’s what they should do in most cases. In fact, it’s counterproductive to accept the outdated equipment because its performance will never be representative of the process at a larger scale. In addition, because of wear and tear, old machines will likely generate unreliable data.

Installing donated equipment at another production facility isn’t usually a good idea either. It can take a long time to fit the outdated equipment in with more recent equipment and connect it to process controls.

Consider Manesty’s DryCota tablet press, which was used to develop many tablet-in-tablet products during the 1970s, 80s, and 90s (photo). Those products were eventually transferred to a facility equipped with 21st-century tablet presses like IMA’s S-250 and Kikusui’s Libra 2 DC. The switch to modern machinery, though challenging, enables operators to confirm online that the cores are present, which the original equipment didn’t.

I can’t stress enough the importance of making time to monitor—in depth—the donor sites to understand how the equipment there is installed, how it operates, and how it fits in the process. Ideally, come with an experienced operator from the receiving site and take photos or videos. Survey different operators to find out how they have tried to change the process, how different setups/adjustments affect results, and what they have observed behaving differently under certain circumstances. These could include seasonal changes, changes in flow behavior, and day versus night shift. Operator seniority could also have an impact because sometimes only senior operators know how to run hard-to-handle products, an ability they mastered from years of experience. The most interesting observations are those not documented in the batch record. Be sure to include them in your unofficial product history.

Case study: Hicups after upgrade

Years ago, I was asked to help transfer an old product that had run on the press for 15 years. The product was running well at an output of 1,300 to 1,500 tablets per minute (tpm), and there were no problems with flow or content uniformity during the initial process validation. The product was then moved to a new facility where the press typically produced in the range of 3,500 tpm. During the trial batches at the receiving site, the product wouldn’t flow at all. A long investigation and root-cause analysis revealed that at the previous site, the old, mobile press had been brought to the production area at the start of each campaign. It was also standard practice not to level the press, which caused it to vibrate. That helped the powder to flow. Of course, operating the press at a lower speed also helped with weight uniformity, but the vibrations were the main reason because the blend at both sites had the same particle size distribution. With no slower press available at the receiving site, the solution was to reformulate the blend to improve its flowability and content uniformity so it would run on the high-speed press.

Validation and process understanding

In some cases, the processes used to make legacy products were never validated or validated retrospectively based on the history of the process and product. That works well if it’s done properly using, for example, statistical tools such as control cards or a process-capability index—often denoted Cpk—on relevant process parameters and/or controls. If no validation was done, your company’s specialist in technology transfer or a consultant will have to pull executed batch records from a representative number of lots and analyze the data. That will give you an unbiased picture of process behavior at the donor site. It will also help you design the technology-transfer plan and help you draft a comparability protocol.

Other important documents

Data from the site to be closed usually includes master batch records and product and raw materials specifications. Within the master batch records, there is typically a section that lists the history of changes and the corresponding change-control numbers. With that information you can find reports and/or justification of the changes in the process, materials, and equipment.

Several other documents can provide more details that will help you continue manufacturing within-spec legacy products. They include:

• A certificate of analysis (CoA) for each active ingredient, excipient, and primary packaging component. The CoA will list a specific grade of material and the manufacturer’s code for it, enabling you to order the exact same material.
• Use the most recent CoA to procure the material. One caveat: The specifications of some lots of excipients...
within the same technical grade could fall in a narrower range when tested a certain way, but that information is unlikely to appear anywhere.

Additionally, the last three CoAs will indicate whether the lots were trending in terms of some physical characteristic, such as particle size distribution, density, or specific surface area. If you change any of your sources, compare the new supplier’s data to those of the previous supplier and be sure you can demonstrate that the new material meets the critical material attributes.

• Executed batch records. These contain data for actual process parameters and in-process results. For legacy products, the actual operating values tend to be close to the upper or lower limits of the in-process specification. Sometimes, that’s the only way the product can be manufactured and still meet other parameters. A classic example is setting a broad tablet hardness specification and then keeping hardness in a narrow upper range so that the tablets withstand subsequent handling and coating.

• Annual product report. This key document lists the number of rejected batches and, more rarely, the number of reworked batches, if any. It will also cite any major deviations. From this information, you’ll know fairly quickly whether you need to dig into the archives to find out what could go wrong with the product and process when you transfer them to a new site.

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