



Manufacturing and Quality Problems in Pharmaceutical Manufacturing

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Many pharmaceutical and biotech companies put their trust in contract manufacturers when they outsource their GMP production. Even though there are many controls as part of Good Manufacturing Procedures, there are often problems that surface. One of the best ways to overcome problems is to first understand what they are. To this end we collected background information for an article comparing traditional paper-based pharmaceutical manufacturing with electronic manufacturing using an internet survey. We used this survey to ask “what were your most serious manufacturing and quality problems you have seen. The survey was sent to experts in manufacturing and quality assurance. This article summarizes their answers about the most serious production problems they faced and how quality could be improved when an electronic manufacturing execution system is used.

Improving quality and manufacturing of pharmaceuticals

Improvement in any area requires an evolution in processes and thinking. While the rate at which most technology is evolving is akin to a fish going to sleep at night and waking up with two opposable thumbs, pharmaceutical manufacturing is more like a sea sponge that rooted a few millennia ago and still hasn't woken up, it is still a sea sponge and not the hamburger-flipping cartoon variety. For us, the cutting of trees to allow manufacture of pharmaceutical products has long seemed archaic, and we have invested a large chunk of time and money into generating a system that uses recyclable silicon instead. In trying to convince the Pharma world that it really is time to move on, we wanted to obtain as unbiased a view as possible of the advantages and disadvantages of sticking to paper. With all our decades of frustrations, we know why we hate paper batch records, but we wanted to see what factors led others to the greatest despair, so we asked 185 expert users in the pharmaceutical industry to complete a five question survey. One of our questions was “What have been the most serious production problems you have experienced in paper-based pharmaceutical manufacturing?”

A big problem with paper-based manufacturing is paper

It surprised us little that most of the problems cited by our respondents were related directly to the fact that batch records are on paper. One key complaint was the frustrating slowness of paper. Review and approval of changes to either a master document or an executed copy are slug-like, as the single copy must travel from one desk to the next, often finding itself lost in a stack of other papers like a Kleenex inadvertently left in a library book. Just about all of us who have ever manufactured a First-in-Man batch know what it is like to wait around in our best fashion Tyvek because the last reviewer found a typo on page 57 and now someone needs do an intra-building decathlon, sprinting from



computer to printer to Manufacturing to QC to QA to Documentation before the blessed papers can enter Class 10,000 space and the real work can begin.

A surprising issue brought up by some respondents was safety. It was noted that paper batch records carry a risk to reviewers beyond paper cuts if the batch record has been used to manufacture a highly potent or cytotoxic product. Extraordinary measures are in place to protect personnel during such manufacturing, but batch records are typically exposed to whatever falls on them and cannot be readily decontaminated.

Those of us who came of age in the era of typewriters and fountain pens can attribute a percentage of our grey or absent hairs to some of the other frustrations that were cited by our survey respondents. For example, records can be irretrievably damaged, such as when an operator experimentally determines that 70% ethanol is a very good solvent for the ink he was using or a reviewer gets startled while precariously holding his fifth cup of Starbucks. And we all know that people who fill out batch records are masters of fitting lots of handwriting into tiny spaces but few are very good at making it legible. Documentation of errors, deviations, and abnormalities can quickly become a nightmare jungle of arrows and asterisks and dated initials suitable for transfer to the head of a pin. Additionally cited were the normal issues surrounding printing, accumulation of paper, missing paper attachments, illegible photocopies and scans, etc.

Unclear communication is a fundamental problem

While none of our respondents professed a love of paper, most attributed the majority of manufacturing and quality problems to human error and poor communication. Many problems occur because instructions, verbal or written, are unclear or misunderstood. Simple things like typographical errors can change the meaning of instructions, and what is crystal clear to one person may be river mud to another. Many batch records are simply not written well and, in part because change is so difficult, problems are ignored until a quality issue rears its ugly head.

Another related issue is poor communication between sales and production. Often a discrepancy between actual or current capacity and assumed capacity can cause commitments to be missed. When manufacturing schedules live on a whiteboard, paper calendar, or even an Excel spreadsheet your chance of finding up-to-date availability is sometimes iffy at best. An electronic system that keeps a single, real-time schedule with alerts and notices for errors in human scheduling greatly reduce the risk of running out of resources or capacity.

Key improvements can be made within the paper-based systems

Poor communication and poor training can happen whether documented by pigment particles adhered to cellulose fibers or by atomic-level changes in silicon. Addressing pharmaceutical manufacturing problems can start at the source – with the manufacturing personnel. Recruiting, training and supporting good, competent and qualified people is



the starting point. Next is improving lines of communication between all levels and all disciplines in the facility and providing visibility to key information and decisions. Needless to say, much of this is exactly what we have been talking about for years and would have implemented years ago if reality didn't keep getting in the way.

How silicon can help

An electronic batch record cannot make operators more careful or production managers better writers, but it does address many of the faults of the paper system. For example, because failsafe controls and the ability to make rapid changes can be integrated into the system, the propensity for errors and miscommunications can be significantly reduced. Since the batch record can be viewed simultaneously by numerous on-site and off-site personnel, deviations can be addressed in real time, and review can occur concurrently rather than sequentially. Many types of errors, such as using incorrect lots of materials or ignoring out-of-spec in-process results can be controlled, since raw material inventory and electronic data are incorporated into the system. If a step requires QA approval or an in-spec test result, an operator can be blocked from proceeding until the necessary measures are taken. Most importantly, entries are kept legible, and you just can't spill coffee or solvent on an electronic record.

We greatly appreciate the time taken and the thoughts provided by those of you who responded to our survey. We hope to work with many of you in bringing the manufacture of drugs into the current century.

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