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"Paper on Glass" User Centric Batch Operations – A Productivity Game Changer for Paper Driven Pharmaceutical Production

by Robert Harrison

This article presents how technology has advanced electronic batch record into solutions which compete one-to-one with paper flexibility, opening the door to game changing production efficiencies in pharmaceutical production.

People deal with complexity and abnormality very well. The flexibility an operator gives to the nature of production in the lifescience industries is an extremely valuable resource. However, production complexities and quality demands continue to increase, using paper to drive the operator and record events may have outlived its welcome. We all feel comfortable with paper; it is something we can touch, see, and feel progress as it grows during the batch. Because you can touch it, it makes you feel like you have full visibility on the process and people's activities, paper's history in pharmaceutical production is a little like religion and its scriptures, they are deemed paramount and carry with them emotion which is never questioned.

Challenges of Managing Paper Based Production Operations

Paper and its long term storage has a large effect on pharmaceutical production cost. Pharmaceutical production requires that significant post batch analysis and reporting must be carried out. Manually extracting and analysing paper production data is an intense and demanding activity which involves highly educated and experienced people. The major cause of rejects and reworks in paper-based batches are the result of 1. missing entries and 2. errors in paper documentation. The batch ran physically perfect, only the recording of this perfect execution failed, and proving its innocence costs serious revenue. Each batch can involve about 1000 manual entries with a human failure rate of 1×10^{-2} (i.e., one in on hundred)[1] – the probability of significant failure is too high. Each of these manual paper records require Standard Operating Procedures (SOPs) from each process, which amounts to a long paper audit trail and needs to be stored in a secure location. The risks to keeping such an inefficient system are great, the cost of quality is high, which is reflected in the cost of production.

We can identify many areas where human error can enter into the system: a person generates and issues the paper documentation, the operator reads the SOP, then reads the equipment, and writes the result on the batch record. The records are then read by another person and inputted into a computer for analysis and reporting as seen in Figure 1. With each human activity, the risk of failure is increased.

When investigations are carried out, the whole paper documentation needs to be obtained and analysed once again. What happens with missing entries? What happens with entries entered incorrectly? What happens with lost paper or paper delivered to the wrong person, or the wrong SOP is issued for a particular batch?

"Benchmarks for Pharma vs. Other Industries,"[2] the

1.	The operator: • Read the SOP → Execute the command(s) on the equipment • Requested to read process values → Read the equipment process values • Record the information in the correct location on the batch record sheet • Sign the record A potential violation is noticed → the violation is flagged, the operator contacts the quality responsible. ! Or the operator makes a judgement call that the violation is only minor → and continues.
2.	Post batch • All batch records are manually transferred to a computer system • Individual machine data is time-lined as a process • The process data is analysed • A batch report is generated
3.	The whole paper documentation, analysis, batch reports and supporting documents are secured in a large air conditioned and protected storage unit. The documentation remains in storage, in some cases for many years.

Figure 1. A basic workflow for a paper based execution of production.

"first pass yield – zero defects" indicates right first time with a value of 60%, this hints that pharmaceutical production has significant benefits to gain from the addition of technology. Right first time in paper driven production environments is far less estimated to be at 47% with the major causes of rejects or reworks being 1. errors in paper documentation 38% and 2. missing entries 29%.

Manual paper-based processes record and store production data in a disconnected and difficult to access medium. Decisions need to be made on these manual processes and with paper systems, there is a significant time delay to get the data into a usable format. This is an area where EBR aims to improve.

Current EBR limitations

Electronic Batch Record (EBR) systems are designed to gather accurate and complete information critical to compliance. With paper-driven processes, the operator and his or her memory is crucial to completing the batch information. EBR avoids mistakes common in manual transfer and integrates manual operations with automated processes.

The problem with EBR is the static workstation and its focus to the mechanical process. It relies on the operator to prove the flexible interface between what is required by quality and operations management; in some instances, this can be a large cognitive activity that the production operator needs to carry out. Paper on glass aims to be user centric and portable with the right tools available to understand how the person is linked to the process, and produce batches with little variation.

How EBR Evolves to Paper on Glass

Paper on glass is not a revolution in technology, rather a progression together of known technologies that easily interface in a high usability application to embrace the user centric environment it operates in. The key functionalities for paper on glass are:

- Mobile tablet usage is paramount for the application. Paper is portable and the application that replaces it also must be portable. With a client – server infrastructure to safeguard process information and keep a central control. The tablet can get lost or broken and the data remains secure.

Measure	Pharma	Automotive	Aerospace	Computer	Consumer Packaged Goods
Overall equipment effectiveness	10% to 60%	70% to 85%	50% to 70%	80% ti 90%	70% to 90%
Annual productivity improvement	1% to 3%	5% to 15%	5% to 10%	1% to 3%	5% to 15%
First-pass yield – zero defects	60%	90% to 99%	70% to 90%	90% to 99%	90% to 99%
Production lead times in days	120 to 180	1 to 7	7 to 120	5 to 10	3 to 7
Finished goods inventory in days	60 to 90	3 to 30	3 to 30	5 to 580	10 to 40
Labor value-add time	20%	60% to 70%	60% to 70%	60% to 70%	60% to 70%
Direct/indirect labor ratio	1:1	10:1	10:1	10:1	10:1
Pharma is decades away from achieving the performance, on key OpEx benchmarks, reached by other industries. But, experts say, pharma is still three to five times more profitable than they are. Chart source: McKinsey & Co., quoted in The Gold Sheet, December, 2009.					

Table A. Benchmarks for pharma vs. other industries.

- A batch control system which is compliant to the industry batch standard ISA 88, this gives flexibility to drive the process and usability to interact with the operator.
- Usability is of great importance as mobile tablets don't have large screens, and a batch system contains much information. Intuitive presentation of data is needed, multi-touch is an essential element linking the user to a known interface common to tablets and smart phones.
- Historian to archive batch operation data, weight dosing and media information, equipment usage, and operator events. The historian is central to batch compliance, automated archiving of recorded data provides data integrity.
- Complete batch documentation must be reported with automated analysis and clear information identifying weighing information, equipment usage, operator events, alarms, Critical Quality Attributes (CQAs) violation and electronic logbook.

To be able to stand on your own feet is a test of character, and the system outlined here supports this. However interaction with outside and connected systems is an equally important function. John Steinbeck, in his novel "East of Eden"[3] quotes *"Maybe a specialist is only a coward, afraid to look out of his cage. And think what any specialist misses—the whole world over his fence."* In pharmaceutical production, there are many sources of information that build up a batch record and additional information needs to be included. Standard industrial interfaces exist with for example SQL connectivity, MES and ERP have native mechanisms to embrace the whole supply and manufacture chain. This automates the batch record to accommodate specific batch needs.

Making the Move, What Are the Advantages and Challenges to "Paper On Glass?"

To replace paper with software requires an application with diverse behaviour. Mobile technology allows for intelligent and portable applications to be with the operator, high usability swaps their clipboard to a mobile workstation. EBR forces strict execution of the batch recipe, stage by stage requesting the operator to execute tasks and record information. The operator is not allowed to miss entries, each user input can be automatically verified to ensure correct entry of data, and violations are signalled in real-time through the correct channels. More importantly, potential violations can be alerted, key people then intervene to mitigate the situation. Batch analysis and reports need not be manual activities, these can be instant and automatic.

Any activity affecting how direct production is executed falls directly under quality management's scrutiny. The system proposed here makes no changes to the physical equipment and no changes to the current automation of the process. It does aim to replace the paper driven operator instructions, and replace the operator batch record, then digitally store the complete record. The process hasn't changed, only closer control of manual operations has been achieved with live verification of inputted information.

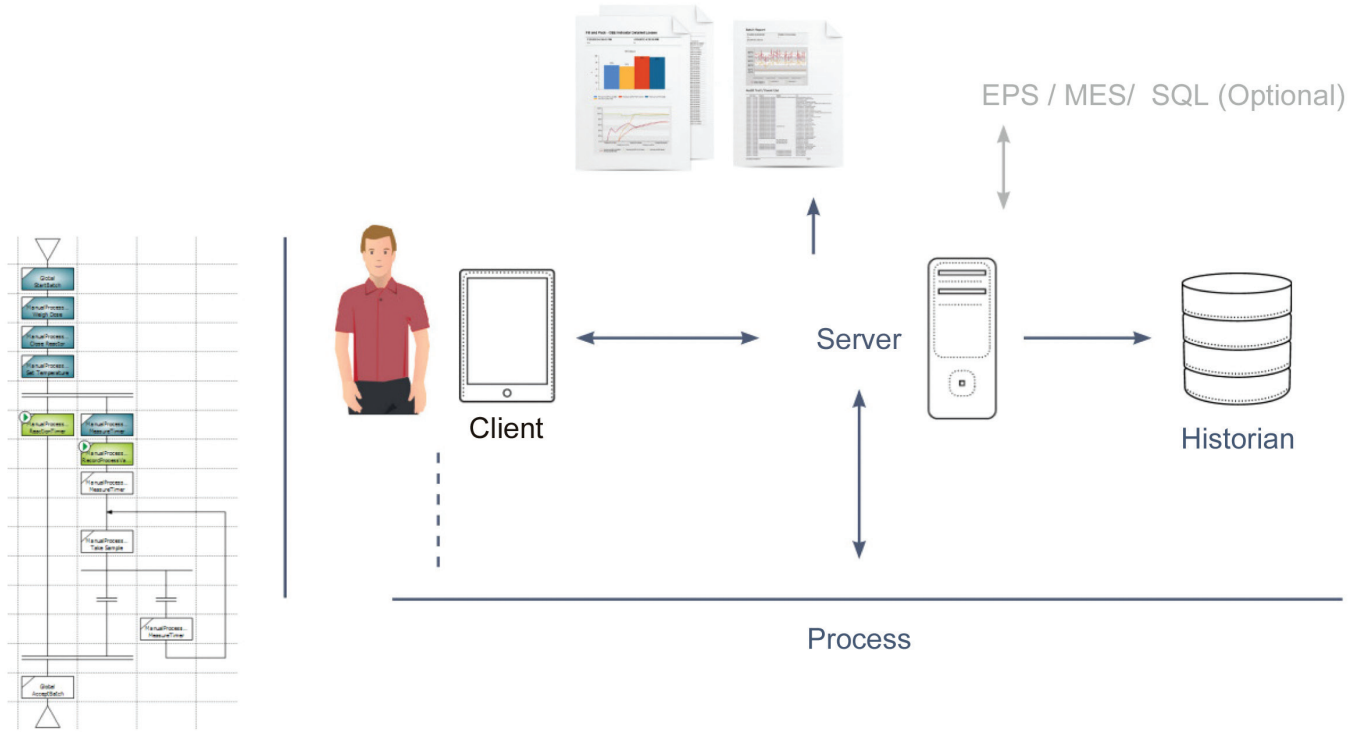

Figure 2. A simplified system overview demonstrates the linkage of the functionalities.

- Multiple batches operating concurrently
- Flexible visual recipe management
- Agile to different equipment, hardware and products
- Check, recheck, and query the operator
- Alert on violations and warnings, e.g. via SMS, email, or telephone
- Archive CQA's
- Automate analysis, Review By Exception (RBE), alarms
- Automated reporting
- Digital storage and retrieval

Figure 3. Paper on glass is more than EBR, it provides logic and intelligence to the operator.

As there are no changes to production processes, the current paper method can be executed concurrently with the digital "paper on glass" system; this would allow for several stages of production quality acceptance to be examined and tested without risk or stoppage to production.

Another challenge is that perhaps the current automation solutions in place today are not flexible enough to bring the required functions together in one portable system: Mobile tablet application, batch process understanding and operation, secure archiving of data, analysis, sophisticated reporting, real-time communication, FDA 21 CFR Part 11 compliance. Fortunately automation technology is an industry which never sleeps, these crucial individual mechanisms do exist in the market place, and can be configured to create an all-in-one mobile electronic batch record system.

Accuracy and Consistency

People are open to a wide array of influences: stress, lack of attention, attitude, sleep (the lack of it), or just having a bad day. Automated batch-driven processes repeat the same strict sequence each time and every time. Software can interrogate each user input within limits, determining at the point of entry if a human error has occurred, and with time-stamped accuracy. Electronic logbooks manage the abnormality with automated alerts and workflows enforcing the correct execution on violations.

Strict point-of-entry requirements and clarity of data is paramount to complete batch documentation and right first time. Missed entries and incorrect entries are minimized for consistent production and release.

Productivity

People and their motivation go a long way to achieve production success. Providing a familiar human interface with access to correct and complete information are the tools to work faster, smart companies create the perfect environment for increased productivity.

Production cycles can be reduced. Typical batch release cycle times of around 10 to 40 days can double in non-conformance situations. EBR forces consistent execution of the manufacturing sequence on a platform which provides accurate real-time view of process and deviation data. Time associated with detecting, tracing, and documenting deviations in the manufacturing process is much reduced. Analysis and reporting is automated, which accelerates batch release and reduces the head count of persons involved in this critical exercise.

Reduce Cost of Quality, Full Quality Compliance

Paper on glass ensures the batch documentation is correct and comprehensive. Compliance requires repeatability of batches, capturing information accurately, organizing and retaining the information, then efficiently analysing and presenting it. Do it right first time prevents errors through pro-active checks. Such mechanisms improve the demonstration of compliance to meet Good Manufacturing Practice (GMP) regulations.

Master recipe development and control recipe creation is on a graphical system with version control and recipe state control to managing GMP compliant processes. Automated batch reports easily separate production data, e.g., material weighing and dispensing data, equipment usage, CQAs and process values, user instructions and actions, electronic signatures, alarms and violations, audit trail and electronic logbook. Production is monitored as a process and not individual machines, allowing focused reports with specific analysis.

Critical Quality Attribute (CQA) deviations can be handled through automated workflows, and don't need to rely on the operator to flag violations. With automated alerts, the equipment can signal warnings via remote system such as SMS, email, or telephone. Post batch analysis can be made on non-conformities through Report by Exception (RBE) reports generated automatically from production data. Access to all information decreases the effort required to investigate product deviations.

Having data stored electronically has several advantages: information is readily available, it requires so little storage area in comparison to paper, digital data can be stored on redundant systems, and the information is widely available for example the progress status of each batch is visible across the company.

Cost Avoidance

Costs are mitigated on many fronts with 'paper on glass'. 1. Rejects and reworks are much reduced due to correct data entry and consistent production sequence. 2. Head count is reduced, as the batch information doesn't need to be re-entered into a computer system; therefore, data alignment of individual machines in to a process is automatic. 3. Paper doesn't need to be generated with automated master and control recipes. 4. Large volumes of paper don't need to be stored in a secure and controlled environment, the storage can be digital and redundant.

Improve Right First Time

Improvement in RFT comes from strict operator workflow and point of entry verification, which creates more consistent and repeatable batches with shorter release time. Paperless recipe systems reduce manufacturing errors, provide investigations with easy access to all required data, and instant batch analysis.

Conclusion

"Paper on glass" transforms a paper-based production system into something quite remarkable – without change to any production equipment or process. Automating the operator and production reporting means post batch analysis is reduced to an absolute minimum by removing the manual heavy element of batch analysis. Products are released to the market potentially faster than paper production methods. Quality is optimized and risk is mitigated as production flow is consistent between batches, execution is strict and no information is missing from the record. With errors in recording information as far as humanly possible eliminated, reworks and rejects are significantly reduced. The benefits of a complete batch control system, integrated on mobile tablets, avoids cost and is a game changer for pharmaceutical production efficiency. No paper needs to be generated with no mountains of paper to be stored in secure locations – instant batch analysis means instant revenue. Production activities are aligned in real-time to the gravity of business.

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