Pharmaceutical manufacturing

– working towards a cure for automation headaches

Introducing bespoke automation means a commitment to a high capital value investment and facing up to some degree of technical risk. Fortunately, techniques borrowed from medical device and pharmaceutical product validation can help ensure the outcome is positive for all concerned.

FEW would argue that automation offers compelling benefits in productivity, consistency, and cost effectiveness. That being said, engineering a new process or automating a previously manual operation requires both careful management and an understanding of the potential pitfalls in converting a user's aspiration into a piece of machinery.

Automated assembly and on-line test machines are often designed for purpose, and specific to a product or process. As a result, each system is unique and invariably complex, carrying with it a degree of technical risk. In the extreme, the project runs the risk of escalating alarmingly in budget; indeed, we are all too familiar with the headlines when this happens to large public sector IT projects. Even when successfully implemented – and the automated process equipment installed and operating – the operator may still be required to undergo lengthy training so as not to press the wrong button at the wrong time. Similarly,

systems can work effectively when nursed by their supplier, only to suffer recurring problems as soon as the maintenance engineer has relinquished control of the machine.

Such problems are sadly all too familiar, despite tools being available to identify and control technical risk. Indeed, the engineering industry is well acquainted with the process of a Failure Mode Effects Analysis (FMEA) to ensure product quality. One such example is the SAE J1739 standard used in automotive manufacture, which specifies a Machine FMEA in tandem with a separate process FMEA. At GB Innomech, we favour the use of Failure Modes Effects and Criticality Analysis (FMECA), which encompasses all aspects of the system.

However, the benefits such methodologies can bring about depend greatly on how they are implemented. To quantify, the nature of these analyses can encourage a very narrow focus on the detail of the machine's operation, which can, in turn, divert attention from opportunities to improve processes and identify further critical factors. What is needed, undeniably, is a wider remit to identify and control all risk factors, and we shall argue for such in this article.

Pharmaceutical product development and manufacturing is an industry where risk management remains essential, with patient safety concerns driving product quality, and coupled with a rigorous documentation trail. In this arena, there are well-established methodologies and validation approaches, such as ASTM 2500 and GAMP 5, specifically applying to automated systems, and these can serve as a model for use more widely. Such processes provide a framework for system validation that encourages examination of fitness for purpose and assessment of risk at every stage in the design, implementation, and supply of equipment. Nonetheless, the principles inherent in such methodologies can equally be applied to a wide range of projects, and not simply those in the pharmaceutical sector.

Looking for trouble

The number of potential failure modes in a complex new system can be considerable, particularly when integrating new materials, technologies, and functions, and coupled with striving to meet demanding user expectations of performance. Consequently, every custom machine should be subject to an acceptance test that demonstrates its correct operation, a reality that, in the pharmaceutical sector, can be unduly onerous.

Indeed, it is not untypical to find much of the test and compliance efforts being addressed worryingly late in the project, with FMEA only applied to a finalised design. In such cases, the aim is to confirm that any potential dangers to the quality of the delivered product have been identified, and, should the need arise, dealt with.

Whilst on the one hand, this approach allows the system specification to be met, any retrospective analysis is liable to overlook the intended purpose of minimising risk through design, given that even if valuable improvements are identified, it may be too late to incorporate them into what is delivered. Worse yet, in narrowly focusing on the confirmation of tight statements of functionality, the risk analysis and testing strategy does not encourage a consideration of how a system might fail in practice, an oversight which may well have usefully informed the original design process.

For example, one function of an automated test platform for a medical device is to ensure that two similar mechanical components in the appliance have not been erroneously exchanged during the assembly process. If this had indeed occurred, the device would appear normal but, crucially, fail to operate effectively. Whilst the test was feasible, and the testing machine worked reliably, a more efficient solution – if recognised earlier through a comprehensive examination of risk – would have identified a design modification to one of the components, thus making it impossible for them to be confused during assembly.

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Scope for uncertainty can similarly be found in the assembly of optical tiles for large area video display panels, whereby a vast image is produced by tiling together numerous individual display units. Here, the quality of the displayed image relies on the precise registration of thousands of individual lightguide elements to the pixels of luminescent display units within each shoebox-sized tile, a process complicated by the fact that each line of lightguides in the tile is a different shape to the ones either side of it. Consequently, the assembly machine must thermoform individually shaped lines from stock mouldings and assemble them into a truncated pyramid to form the tile through the use of a specially developed adhesive. As is to be expected, registration accuracy can be unduly affected by both the thickness of glue dispensed and the precision of thermoforming process, together with the repeatability of placement of the parts relative to each other.

It was not difficult to identify that, for example, a vision system would be required to guide and verify positioning. However, only in a more detailed analysis of possible exceptions did it become evident that the part handling mechanics would need to be repeatable to a few microns in order to ensure the necessary consistency of registration in the assembled product. Understandably, this required exceptional design effort, but by accommodating this challenging requirement in the engineering specification from the process' outset, the end result was an automated platform capable of routine production of units of superb quality.

Conversely, if this analysis had been overlooked, the vision guidance would have proven to be inadequate and the quality of the resulting product vastly inferior, arguably to the point where a substantial redesign exercise would have been required in a machine that was already designed and constructed. By this stage in a project, there is a huge inertia to be overcome in updating design documents, revisiting testing specifications, and deciding what retrospective retesting might be involved after implementing the change, together with the cost of writing-off the wasted implementation. At best, the change adds cost and potential delay to the supply of the assembly system. At worst, however, the supplier loses money and the launch of the end user's display product will be severely delayed.

Keep on looking

As projects develop, the aim must be to highlight and seek to resolve known risk factors. It is nonetheless recognised that focussing only on factors already identified runs the risk of degenerating into a reductive exercise, whereby items are simply ticked off one-by-one. It is therefore important to accept that in the lifetime of a project, new risk factors may well emerge at any time, and similarly, the nature of previously identified risks will change. Taken as a whole, this means the risk analysis is ultimately an ongoing process through the life cycle of a project.

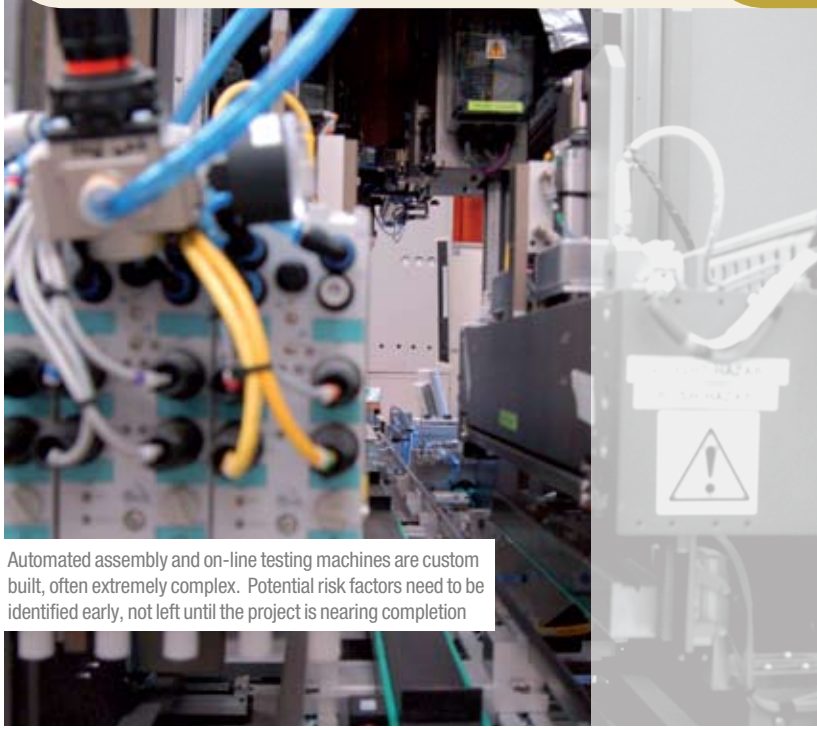
We firmly believe that manufacturers will find their product cycle becoming exponentially more effective if this way of working can be shared between automation provider and the automation user. In many cases, whereas the automation engineers may be fully able to identify failure modes, the user may be better placed to determine the impact, and by working together, it is often possible to work out a mitigation that is simpler and more cost effective than either side would have developed working autonomously. Whilst this is easier said than done, the techniques and accumulated experience within an automation consultancy or by in-house specialists should provide a toolkit for addressing these issues.

Such an enlightened approach to risk management will lead to automated production systems that not only function to specification in producing output of the optimal quality, but equally, are robust in use and not solely dependant on having the right operator working the controls. Lastly, projects are much more likely to be delivered on time and to budget, further increasing the incentive to implement such processes, if indeed any were needed. End

About Peter Woods

Dr Peter Woods is an acknowledged expert in the development of advanced automation systems who has spent the bulk of his career in the pharmaceutical sector. In 2008 his team was one of four finalists for The MacRobert Award, from The Royal Academy of Engineering, for pioneering work on the Polar system for UK Biobank.

Peter has a PhD from University of Manchester; a first degree in physics from University of Bristol and started his industrial career developing image analysis systems for automotive production lines in Germany.



Automated assembly and on-line testing machines are custom built, often extremely complex. Potential risk factors need to be identified early, not left until the project is nearing completion

References

ASTM 2500: ASTM Standard E 2500 – 07 is the Standard guide for Specification, Design and Verification of Pharmaceutical and BioPharmaceutical Manufacturing Systems and Equipment, published by ASTM International.

GAMP5: Originating in the UK, GAMP© stands for Good Automated Manufacturing Practice. The 5th version of the GAMP guidelines were published by the International Society for Pharmaceutical Engineering (ISPE) in January 2008.