

Continuous Improvement in Validated Process

IVAX (part of the Teva Pharmaceutical Industries Ltd), is a global pharmaceutical company specialising in the development, production and marketing of generic and proprietary branded pharmaceuticals and active pharmaceutical ingredients. The production unit of its Inhalations Division at Waterford, Ireland, selected Wonderware products for its validated process lines. They have fully utilised Continuous Improvement features to provide major benefits in throughput, downtime avoidance and repeatable quality in the system delivered by ONG Automation of Cork.

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IVAX markets a variety of asthma drugs in aerosol formulation. They also market Steri-Neb® formulations of ipratropium bromide and salbutamol for use in nebulizers to treat asthma and chronic obstructive pulmonary disease. The production process at Waterford is bulk batch formulation in a mixing vessel which is then supplied to a complex multi-head filling line, the quality checked canisters then being fed to a separate packaging line for assembly, labelling, further quality checks and

Board requirements.

Continuous Improvement...

Production is in high volumes from several recipes, the key issue being repeatability with consistently 100% quality. All the systems in use within the facility use real-time data that produces information that is displayed on large format screens around the plant. What is immediately observable is that machine availability and performance are their key variables within O.E.E. (Overall Equipment Effectiveness), the Quality component being 100%.

IVAX has found that the key to continuous improvement is to ensure that assets are used optimally. This has to be approached with due acknowledgement to the validation of the process and the resulting costly revalidation if the process is changed.

In the bulk end of production large mixer tanks are used to produce the active components of the inhalation. These batches are actively supervised by Wonderware's InBatch software and visualisation of the process is provided by Wonderware's InTouch HMI, the integrated system has in built capability to ease FDA validation and to comply with FDA21CFRPart11. This is done by InBatch software's S88 structured approach that divides batch preparation into phases, each phase being validated in its own right, thus greatly facilitating process commissioning and tuning. This benefit can be seen when any plant changes are made such as increased batch volume in that only the changed phases incur revalidation cost.



IVAX automated nebulizer filling line

trade packaging. Additionally some products are further checked for environmental performance especially where high ambient temperatures are experienced. The whole process is validated to FDA and Irish Medical



IVAX Batch process

Batch Management...

When a batch is to be started InBatch software completely sets all machine and plant controllers to undertake that batch. InBatch software completely controls the bulk batching of the solution that is to be produced and with the integrated HMI visualisation operators can see the progress and status of each Batch. The inhalations market is huge and batch sizes reflect this, with key management attention being placed upon plant performance whilst maintaining quality.

Quality...

The prepared solution is then delivered to the filling line to be inserted into canisters that are then pressurised with propellant. Inhalers are calibrated to deliver a fix dose to the user (usually “two puffs of n micrograms”); this is achieved by a calibrated valve in the canister’s throat that is critically crimped into position in manufacturing. The weight of the filled canister ensures that the guaranteed number of doses (or “puffs”) is delivered. These are key quality measurements, with crimp position and geometry as well as filled weight being recorded by Wonderware’s QI Analyst software from electronic gauges and check weighers. QI Analyst software is then use to generate a quality report and normal distribution graphs on the batch and alarms when trends indicate that without intervention the filling process will become unacceptable. The machinery is 100% automated and is highly complex with multi-head assembly units to deliver the required throughput.

The filled and quality assured canisters are then routed for assembly, labelling and trade pack packaging. Where required some batches are fed through a further quality stage that exposes each canister to high ambient temperature to test for temperature induced leakage, this is typically specified when customers are in hotter

parts of the world.

All data is archived for analysis and regulatory compliance in a data historian server that includes Wonderware Historian that allows high data volumes to be handled in real-time and also provides fast information retrieval.

Root cause fault analysis...

The key to the core IVAX success at Waterford is dealing with the complex production facility, in obtaining real-time insight to the process and producing an environment that is efficient in what it sets out to achieve. In many ways this has been catalysed by the use of a further integrated Wonderware product, DT Analyst software. DT (Down Time) Analyst software handles fault and stoppage information in real-time so that any operator, supervisor or manager can readily see what is going on immediately over the IVAX intranet using any web browser. ONG Automation has made a full exploitation of this product for IVAX.

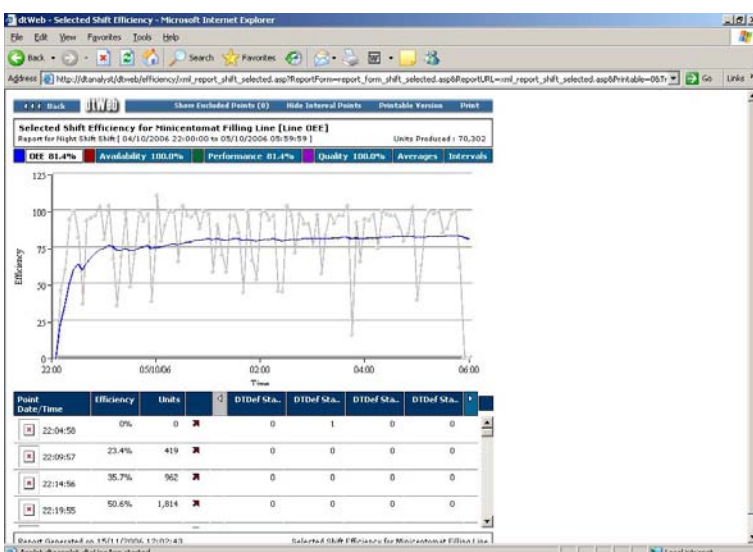
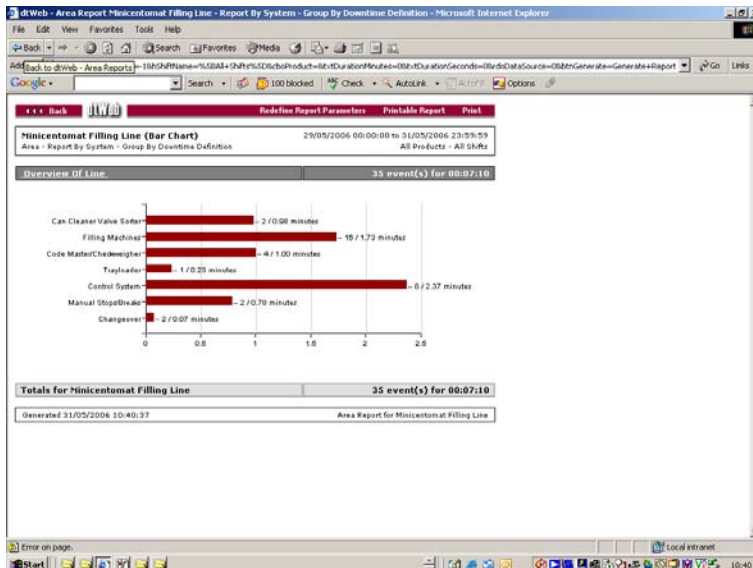
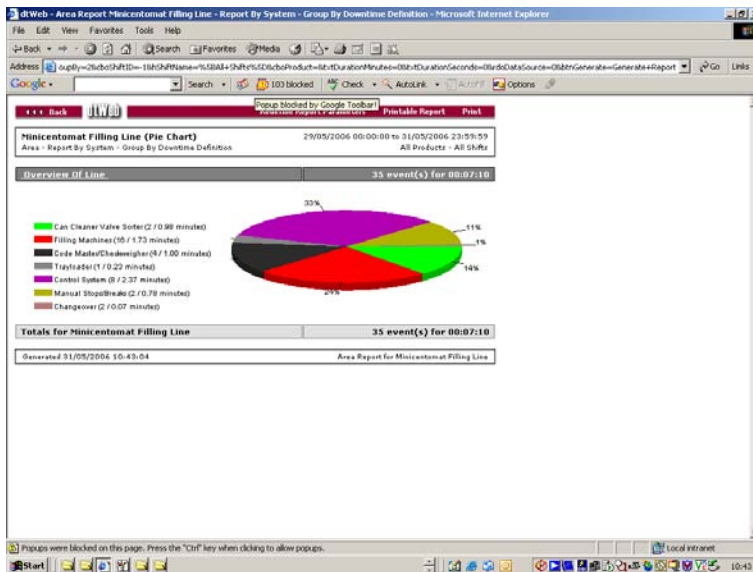
On initial inspection the opportunities to provide an ethos of Continuous Improvement in a validated process appear limited, without incurring continual revalidation costs that would most likely negate any improvement. However, insight into real canister filling operation functionality has been made possible through DT Analyst software; allowing very fast and accurate problem root cause analysis for continuous improvement.

DT Analyst software takes data from the automation controllers and other sensors within the machinery. It uses this to provide down time information and to produce O.E.E. calculations. It is frequently found that the exact condition cannot be directly sensed and that a combination of conditions is required to indicate a particular root cause. DT Analyst software can do this in a non-invasive way that is external of the validated system, its communication being validated. The internal DT Analyst software logic engine allows the combination of sensor and other data to be made to produce accurate downtime information, without making such changes to the validated controller code. This unique technology is especially applicable to validated processes in pharmaceutical industries. This also allows ongoing continuous improvement to take place by adding and recombining data to produce further insight as the control engineer progresses with such improvements.

The uptake of the use of such information from Wonderware at IVAX is exemplary. DT Analyst software is now being further deployed in final assembly, labelling and packaging of the inhalers, where machine vision systems are also used to check correct label, label positioning and legibility. To further effectively utilise DT Analyst software technology all new machines

“It encourages a ‘let’s do it’ culture and has become the heartbeat of the business”

**Mr Paul Power,
Plant Manager**



OEE Pie & Bar Charts and OEE trends

bought by IVAX have to have additional sensor and data flags available within their controllers, the specification of which was obtained from insight obtained from DT Analyst software information.

Real time Management...

Mr Paul Power, Plant Manager Inhalations Waterford, said, "This (DT Analyst software) has delivered huge potential for 'management in real-time', with one set of numbers and a total overcoming of the effects of insufficient agreed data", further he added, "It encourages a 'let's do it' culture and has become the heartbeat of the business". The team effort between IVAX Controls and Engineering people and ONG Automation with its professional understanding of the capabilities of integrated Wonderware products has paid high dividends to all involved at the IVAX inhalation production unit at Waterford.

Wonderware Ireland wishes to thank the following companies for their valued contribution to this success story...

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