The Why & How of PAT

The Process Analytical Technology (PAT) Initiative is the Food and Drug Administration's (FDA) preferred method of encouraging innovation in pharmaceutical manufacturing operations in an aim to build-in product quality in pharmaceutical processes worldwide. Compliance here has several benefits including reduced operating costs and reduced inventory of batches held awaiting test results. Reductions in the number of times, perhaps eventually to zero, the very time-consuming, and thus costly, procedures for investigating and correcting the causes of defective batches must also be invoked. These savings will, it is hoped, result in lower drug prices for the consumer.

Notice that we have not said safer drugs. Drugs today are safe because of testing and re-testing ***after*** every step of the manufacturing process. The penalty of this lays not so much in excessive testing, if there is any, but in ***not using the test results to correct the process while there is still time to do so*.**

The PAT Initiative desires to change the mindset of the pharmaceutical industry to replace "***test after*** each manufacturing step to find out what was made" to "***test and correct during*** each manufacturing step to ensure that what is made is only what is wanted". The drugs delivered to the consumer will be just as safe as they are today but with much less effort and cost for the manufacturer.

So to answer the question "why isn't this done already?" we divulge that it was not possible, simply because the solution to the technical problem at the root of it all didn't exist.

The root technical problem is that manufacturers need to be able to predict what the properties of the product at the end of the manufacturing step will be if they continue to operate in their present manner. They need to be able to perform these predictions from analysing the many other measurements that can be extracted during the manufacturing step and use their predicted values to alter some of the step variables so that ***the final result prediction can be corrected, if required, before an actual deviation occurs***. Think about this. Not only have they got to predict the consequences of how they are operating, which implies some kind of mathematical model, but they also have to do it before the thing they are predicting shows any change. This means an on-line analyser will not be much help. Following this they have to work out which of the many possible process variables to alter and by how much in order to correct the impending deviation.

What kind of mathematical model?

First-principles models which formulate and solve the basic equations of chemical kinetics, equations-of state, thermodynamics and mass balances are not generally available for the time-dependent complex chemistry of AI manufacture or the complex material re-arrangement processes that occur in a tablet press. Statistical and Chemo-metric models need considerable mathematical skills to create and maintain and do not reproduce the non-linear effects common in processes. Neural Net models when built with two hidden layers can reproduce non-linear effects but then become very difficult to train without over-training and so require constant expert support.

Geometric Process Control (GPC) technology based on multi-dimensional geometry offers a single solution to most of these difficulties and requires no mathematical knowledge to implement or maintain. Its models are the geometric envelopes of multi-dimensional operating points from past process history where the desired result was achieved. The process operating objective is converted to a geometric intention of being an interior point in the envelope. The usable space inside the envelope is easily found from the present operating points and shown to the process operator in an easily understandable visualisation in terms only of the existing process and predicted quality variables (see figure 1). Violations of the envelope are immediately apparent and Corrective Advice easily and automatically generated from geometry. The envelope model has a dual response to time-based events. This allows it to give very early indication with Avoidance Advice for potential deviations.

Several GPC systems are already operational in other parts of the process industries such as Chemicals, Food and Petrochemicals in both batch and continuous processes.

Curvaceous Software Ltd. from the UK developed the award winning Geometric Process Control technology. Widely reported in the media, Curvaceous has enquiries from potential customers from around the World. Licensees and trade partners are now sought from process control consultants in Ireland interested in learning these techniques.

Recently appointed Curvaceous Agents have been from North America and Australia – Curvaceous has selected these companies for their relevant experience and market knowledge, and provided training in the capabilities and use of the software.

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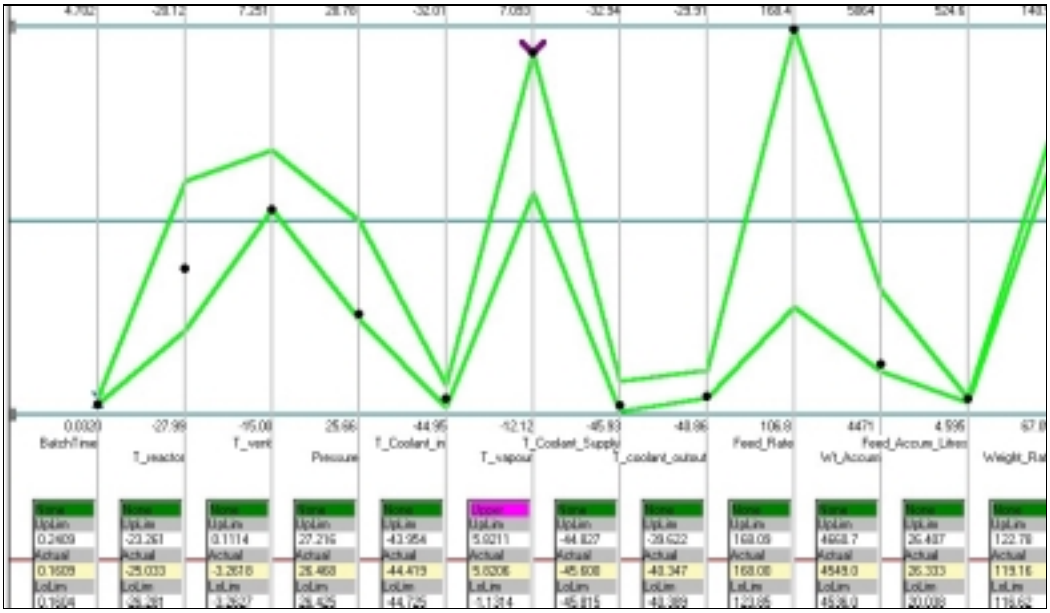

Figure 1 An example of a GPC Operators Display for a reaction in a Jacketed Batch Reactor