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Issue 6 2011

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PAT
SUPPLEMENT

IMPLEMENTATION OF MODELLING APPROACHES IN THE QbD FRAMEWORK: EXAMPLES FROM THE NOVARTIS EXPERIENCE

Dr. Marianna Machin, Dr. Lorenz Liesum and Dr. Antonio Peinado
Novartis Pharma AG

The fundamental concepts behind the FDA PAT initiative are driving the pharmaceutical industry to put greater emphasis on the scientific understanding of their manufacturing processes, thus focusing its efforts both on ensuring product quality compliance through end product testing, and on understanding the impact of the manufacturing conditions and process variability on the quality attributes. In this respect, multivariate data analysis (MVDA), used for statistical process control, can be very useful and effective to ensure that a process is under control and, consequently, that it meets the quality specifications. At the same time, MVDA is a valid tool to improve the understanding of the process, to increase its efficiency e.g. in terms of yield and throughput time and consequently, leads to reduce costs. As the setting for this paper, the MVDA principles and tools, benefits and challenges are discussed prior to the review of two examples of application of MVDA at Novartis. Specifically, pharmaceutical and biopharmaceutical processes are discussed.

The use of Multivariate Data Analysis (MVDA) in the framework of Quality by Design and Operational Excellence initiatives to gain increased process understanding and, ultimately, process control is an area of growing interest and under great expansion in the pharma industry.

With the implementation of Process Analytical Technology (PAT) and modern automation infrastructures, numerous process variables are on-line available describing physical and chemical properties of the process, the raw / intermediate materials and the final products. These vast amounts of data are registered with various sensors, either PAT (NIR, Raman and UV-VIS) or classical probes (pH, T). To extract relevant information out of the primary data retrieved, multivariate statistical process control (MSPC) is used for efficient process control, data trending and early fault detection taking the dynamic and multidimensional nature of these processes into account. Furthermore, MVDA is gaining importance, supporting and enabling real time release by an efficient control of the variability of the process using qualitative MSPC or even applying predictive models for certain critical quality attributes.

The main benefits expected to result from the application of MVDA can be categorised in the areas of process understanding and process control. During process development, MVDA contributes significantly in a structured way to evaluating and visualising data stemming from lab and pilot scale and therefore supports a better understanding and interpretation of the process data. In particular, the main benefits where MVDA can add value to process development are:

- identification of influential and critical process parameters
- identification of correlation pattern among the process parameters
- generation of process signatures
- relationship between process parameters and quality attributes by multivariate regression analysis

After the successful transfer of a product from pilot plant to commercial scale, the available and achieved process understanding needs to be embedded and translated into an appropriate process control strategy. The benefits of using MVDA in this context are:

- efficient on-line tool for multivariate statistical control (MSPC)
- analysis of process variability
- enabling on-line early fault detection
- enabler for time resolved design space verification (real time quality assurance) – Real Time Release (RTR)
- predicting quality attributes based on process data
- excellent tool for root cause, trending analysis and visualisation

This paper will give two examples from pharmaceutical and biopharmaceutical processes.

Case Study I: MVDA used for multivariate statistical process control (MSPC) in pharmaceutical unit operation content

In the first example from pharmaceutical production, MVDA is used for an on-line assessment of the process parameters in order to detect any tendency of deviating from the normal operating ranges. In **Figure 1a**, an MVDA model of a granulation, comprising the different phases of drying, water addition, granulation and kneading is displayed. The control limits marked in red are set as three times the standard deviation from the average, which is shown as a pale green curve in **Figure 1b**. In such a model, many process parameters, for instance temperatures, agitation speeds, torque and power consumption, are included in the model as shown in **Figure 1a**. These univariate process variables are condensed into latent variables by means of linear combination, whereas the linear coefficient reflects the impact of the specific univariate variable on the impact on the process variability.

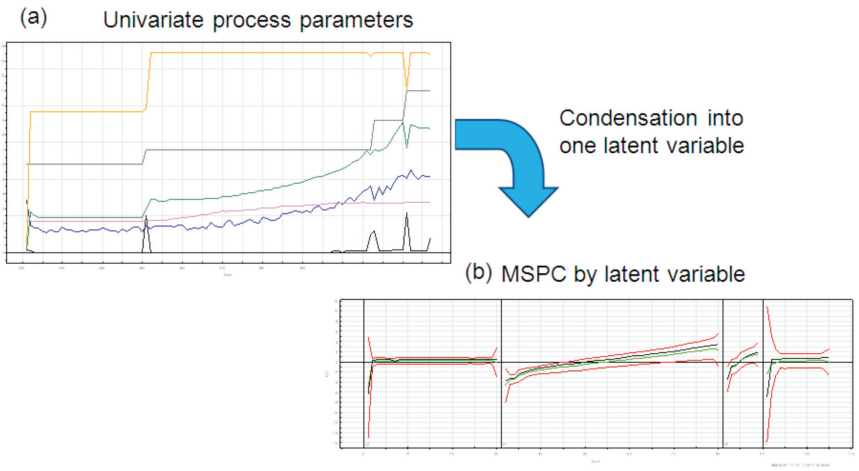

FIGURE 1 MSPC model for a granulation process including drying, water addition, and granulation and kneading

These models reflect the inherent variability of process and are based on empirical production data. New batches can be assessed by these models in order to evaluate whether they fall within the expected ranges and therefore yield the desired quality.

These models can be used for information only in order to enhance process understanding or for providing release relevant information. For the latter application, the methods have to be embedded into the quality system of the firm. This entails a complete qualification of the used automation and IT infrastructure as well as the validation of the methodology itself. Special effort has to be taken on defining the procedures to handle deviations and the involved function from production, engineering to quality control and assurance.

Furthermore, the maintenance plan of the MVDA monitoring system has to be defined. As an example, batches of a review period of one year are shown in **Figure 2**, proving that the model still covers the normal variability of the process.

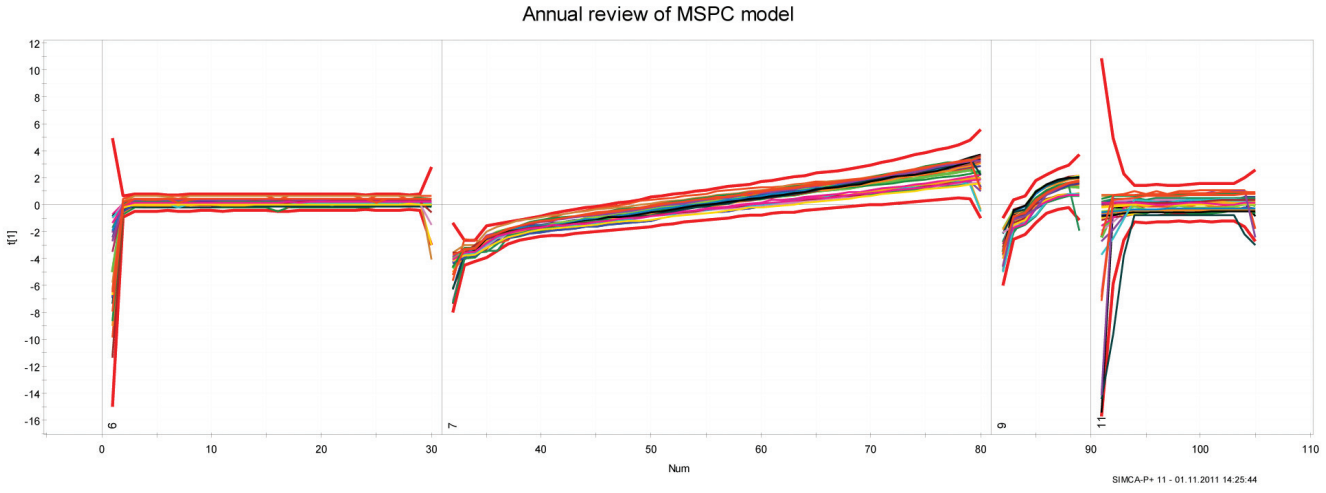

FIGURE 2 Assessment of recently produce batched by the model

Case Study II: Review of the historical in-process control data from a cell cultivation process using multivariate data analysis

The scope of this work is to improve the understanding and the reduction of the batch to batch variability in terms of antibody yield for a cell cultivation process. Specifically, the upstream manufacturing process (seed and main bioreactor) is discussed herein.

All the batches in scope of the MVDA model provided drug substance batches of the same quality. Nevertheless, some variability in the antibody yield at the end of the harvesting phase was observed. MVDA has then been used to better understand the differences in yield at the end of the harvesting phase. Furthermore, it has been used to investigate whether there is any correlation between the upstream behaviour of the cell culture and the quality attributes of the molecule produced.

The modelling approach used to develop the MVDA models includes time-dependant variables as described by S. Wold *et al*[1]. Particularly, MSPC and batch-level multivariate statistical process control were used here. The process variables, typically recorded during the different phases of the upstream manufacturing process, were included in the MVDA model. The batches that produced the highest amount of antibody at the end of the harvesting phase were

> **“ During process development, MVDA contributes significantly in a structured way to evaluating and visualising data stemming from lab and pilot scale ”**

defined as reference (golden). All other operations in scope of the present study have been assessed by comparing them against the MVDA model, based on reference batches. As an outcome of this work, reference trajectories based on the golden batches were established for the most important process variables, namely viable cell density, medium feeding rate and cell aeration rate. Drug substance release attributes have also been modelled to establish whether there is any correlation between the behaviour of the cell culture and the quality attributes of the molecule produced.

Figure 3 (page 42) is a MSPC chart generated from the cultivation data for the so-called golden batches (golden MSPC model). Cross-validation identified two principal components scores (i.e. t1 and t2) for this phase. The first principal component, which captures most of the variability within the dataset, is shown in **Figure 3** on page 42. The explained variability is about 90 per cent. The green line is the average or expected process signature for the golden batches. The red curves (±3 standard deviations from the golden average) represent the variability of the golden batches and therefore lines correspond to the statistical process limits.

The golden batches were used to define reference trajectories for the different cultivation variables. All the non-golden batches were assessed by comparing them against the golden MSPC model to better understand why these batches showed lower productivity. In summary, the most influential variables appeared to be viable cell density, medium feeding rate and aeration rate through the sparger.

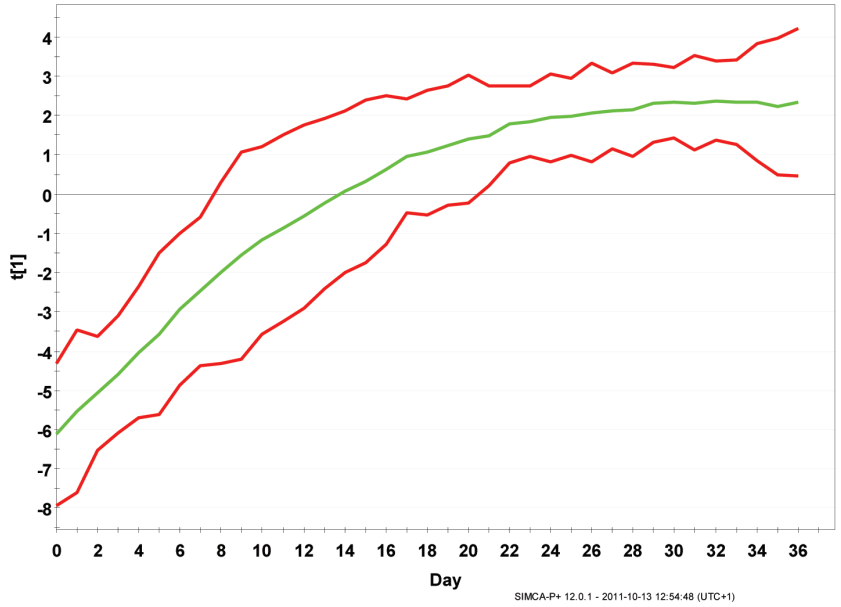

FIGURE 3 Golden MSPC model for the main bioreactor. The average or desired process signature is also shown (pale green trace). The red traces are indicative of the variability between reference batches (±3 standard deviations from the average)

In addition, the inoculation density of cells to the main bioreactor appears to be important and the medium feeding rate should be a function of the actual viable cell density in the main bioreactor phase. Generally, it appears important to maintain the aeration rate at a lower level at the beginning of the culture.

All the batches have then been summarised by combining all the process data (both seed and main bioreactor) over time and the DS quality attributes at the batch level (i.e. using a Batch-level Statistical Process Control modelling) in **Figure 4**. Two are the principal component scores (i.e. t1 and t2), as per cross-validation, explaining about 60 per cent of the variability. Each batch is now represented by one single data point of coordinates (t1, t2).

> "MVDA is a valid tool to improve the understanding of the process"

As can be seen in **Figure 4**, all the manufacturing operations fall within the 95 per cent confidence ellipsoid, no matter if golden or not. This indicates an overall similarity of behaviour across all the operations in scope of the MVDA. We could therefore conclude that the behaviour during the upstream process does not appear to have an impact on the final DS characteristics.

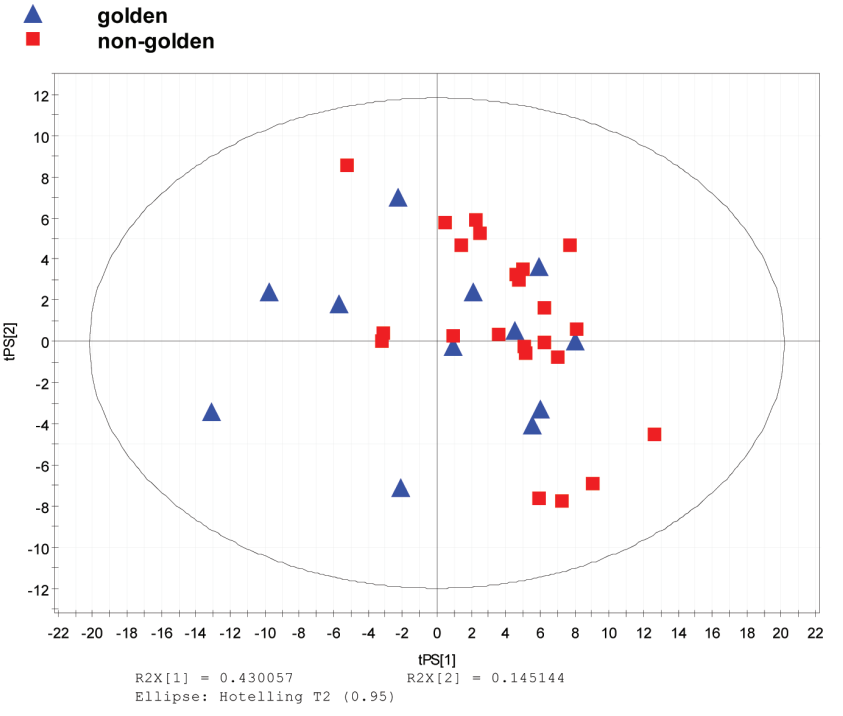

FIGURE 4 Batch-level principal component analysis score scatter plot obtained by Batch-level Statistical Process Control (BSPC) modelling which summarises the cultivation data for each operation into a single data point. Golden batches are represented by blue triangles and non-golden batches by red squares. All the batches lie within a 95 per cent confidence interval

REFERENCE

1. S. Wold et al. Multi- and Megavariate Data Analysis Part 1, 2nd edition – chapters 12 and 13

BIOGRAPHY

Dr. Marianna Machin is currently Senior Process Analytical Technology Expert at Novartis. She is responsible for MultiVariate Data Analysis and Process Analytical Technology within Global Technical Operations. Prior to taking her current position, Dr. Machin worked at GlaxoSmithKline as Quality by Design Champion in the Pharmaceutical Development department and also worked on analysis, interpretation and representation of PharmacoKinetics data in the Clinical Pharmacokinetic Modelling and Simulation group. Marianna is a chemical engineer by background and holds a PhD in bioengineering from Padua University in Italy in collaboration with The Scripps Research Institute (La Jolla, California).

BIOGRAPHY

Antonio Peinado Amores is currently a senior PAT expert in Global Pharmaceutical Engineering at Novartis. His current position involves implementing NIR and Raman solutions for monitoring pharmaceutical processes and using Multivariate Data Analysis for Process Understanding and Troubleshooting. Previously, Antonio worked for five years in Pharmaceutical Development at GlaxoSmithKline. Antonio obtained his PhD at the University Autonomas of Barcelona in 2004. He completed a post-doc in chemometrics sponsored by Total-Fina-Elf at CNRS-Lille.

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Lorenz Liesum is currently a senior PAT expert in Global Pharmaceutical Engineering at Novartis and is leading PAT projects within the manufacturing department. Previously he worked in chemical and pharmaceutical development for Roche and Novartis as an analytical scientist. Lorenz is a chemist by training and obtained his PhD at the ETH Zurich in the field of magnetic resonance spectroscopy.