PAT and beyond
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CHAPTER 4: A THEORETICAL FRAMEWORK FOR REAL TIME RELEASE OF PHARMACEUTICAL PRODUCTS.

The introduction of the FDA's Process Analytical Technology (PAT) Initiative [http://www.fda.gov/cder/OPS/PAT.htm] has shed new light on Real Time Release (RTR) or the Parametric Release concept [Box 1]. In this paper we use Parametric Release and Real Time Release interchangeable. In 2001 Parametric Release was presented by the European Medicine Evaluation Agency (EMEA) as a method for ensuring product sterility without performing the actual microbial analysis. The guidance document also stated that the concept was applicable to any manufacturing process considered. This was a dramatic suggestion considering the extensive end-of-line quality testing performed today in pharmaceutical manufacturing.

**Box 1. Definition of Parametric Release**

"Parametric release is a system of release that gives assurance that the product is of the intended quality based on the information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric release."

General questions to be addressed.

An RTR system is a system that ensures that when the last manufacturing step is passed all the final release criteria are met. Three basic questions have to be addressed for such a system:

1. Do we have a (preferably early) warning system if something is going wrong during manufacturing? – monitoring capability
2. Do we have an idea how to adjust the process, and whether it is possible? – control capability
3. If we monitor and control our processes, will the final product meet its quality criteria? - RTR capability
The overall purpose of this discussion is to provide a theoretical framework for RTR. This is done first by discussing two types of monitoring, their distinctions and potential associated process control (Box 2). Suggestions for how the monitoring and control tools can be applied to the manufacturing process are presented.

For reasons of simplicity this discussion concerns only batch processes with the natural characteristics of these. Typically in batch process manufacturing a product undergoes a series of individual process steps or unit operations. Each unit operation is normally operated by a recipe with fixed process variables e.g. defined processing time. During processing or after finalization of a unit operation step, measurements can be applied e.g. temperature, humidity, flow and spectroscopy. The measured variables are named quality variables while fixed and controlled settings are named controlled variables.

**Box 2. Definition of Process Control.**

Process Control is the active changing of the process based on the results of process monitoring. Two types of intervention (process control) are possible. The first is based on engineering judgment while the other is automated.

Once the process monitoring tools have detected an out-of-control situation, the person responsible for the process makes a change to bring the process back into control. *Out-of-control Action Plans* (OCAPS) detail the action to be taken once an out-of-control situation is detected. A specific flowchart, that leads the process engineer through the corrective procedure, may be provided for each unique process.
Advanced Process Control Loops are automated changes to the process that are programmed to correct for the size of the out-of-control measurement. A classical example of automated process control is the control of base addition in a fermentation process based upon the response from a pH electrode submerged in the fermentation tank; this is an example of feed backward control.

Monitoring and control.

We present two classes of monitoring: statistical monitoring (A) and monitoring based on regression models (B). The two classes are listed in Table 4. The regression models are divided into three models depending whether the intermediate or final quality parameters are predicted and depending on how much of the entire manufacturing process has been completed when prediction is performed. For convenience each class is provided with a symbol which will be used in the text.

Table 4. Model classes.

<table>
<thead>
<tr>
<th>Class</th>
<th>Model symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>A. Statistical model</td>
<td>A</td>
<td>Statistical model comparing current process observations with historical process observations e.g. multivariate statistical process control (MSPC) models.</td>
</tr>
<tr>
<td>B. Regression models</td>
<td>B.1</td>
<td>Intermediate quality predictions. A regression model between predictors and intermediate quality parameters. For example, used for feedback control.</td>
</tr>
<tr>
<td></td>
<td>B.2</td>
<td>Final quality predictions. A regression model between predictors and final quality parameters at a point where the entire manufacturing process has not been completed. For example, used for feed forward control.</td>
</tr>
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</table>
Final quality predictions. A regression model between predictors and final quality parameters when the entire manufacturing process has been completed. Used for RTR.

Figure 13 illustrates how the various model types can be applied and how process control can be associated with the models in a manufacturing process constructed of individual unit processes (P1, P2 and P3). Each process step can be evaluated based on measurements during and after finalization of the process step called intermediate quality characteristics (e.g. Q2). The entire manufacturing process is evaluated on the final quality characteristics (Qfinal).

Figure 13. Graphic presentation of the models, applications and control over the entire manufacturing process. P_{\text{index}} symbolize different unit operations. The X_{\text{index}} symbolize measurements from a unit operation. Q_{\text{index}} symbolize quality characteristics. One sided arrow (→) symbolize a regression model and double sided arrow (↔) a statistical model.
**Statistical monitoring.**

The purpose of the statistical monitoring is to provide the operator with a monitoring tool to observe the "state of the process". There is no direct link between the observations and the final product quality. There is only a link between the observations and the historical observations which are selected by evidence of providing an acceptable summary of intermediate and final product quality characteristics.

Based on a historical dataset, statistical control limits can be derived for each of the individual unit operations using quality variables from that particular step. Using the statistical monitoring strategy it can be verified up to the point of monitoring whether the process is within the normal operating conditions (NOC) or whether it is out of control. In case of an out-of-control situation the operator inspects a contribution chart. The contribution chart shows what variable or variables that causes the out-of-control situation and the operator can react and try to get the process back to NOC state.

The methodology does not provide the operator with a forward predicting capability of final product quality parameters. It allows the operator to compare the process at a given point in time with a historical dataset. In case of an out-of-control situation the operator can identify the process variables causing the upset by exploring contribution plots\(^7\). Using that information in combination with mechanistic process knowledge obtained from designed experiments during the process development phase the operator can choose a strategy to force the batch back into an NOC state i.e. a process control tool.

A classical method which can be used for the statistical monitoring strategy is multivariate statistical process control based on developing a Principal Component Analysis (PCA) model\(^7\) on NOC batches and two control charts for the operator based on \(D\) and \(SPE\) statistics. In case that an observation is
exceeding the limits in the control charts the operator can switch to the contribution plot and identify what caused the process disturbance.

**Monitoring using regression models.**

There is a two-fold purpose when using regression models. The first is to predict the outcome of the process (stage) i.e. intermediate or final quality characteristics. The second is to provide a tool for process control.

Using multivariate regression models it is possible to predict intermediate and final product quality characteristics. A calibration stage is needed for developing regression models between data blocks (predictors) and quality parameters. It is possible to use controlled variables, quality variables and combinations thereof as predictors. In Table 4 the difference between the three types of regression models was presented. An example of intermediate quality prediction (B.1) is to monitor the evolution of a quality parameter during processing and use the prediction to control the duration of the process this is called end-point monitoring e.g. water content during drying. When a regression model is used for prediction of final quality two different approaches can be viewed. In the first approach final product quality characteristics are predicted at a given point during the process chain with the measured data available up to that time point as predictors (B.2). With this approach the final quality is estimated prior to process finalization giving the answer to the question - *are we on the right track?* This approach was already demonstrated by Nomikos and MacGregor\(^7\)\(^8\).

The last approach (B.3) is an extreme of class (B.2). When the last process step is finalized all data blocks can be used for prediction of the product quality characteristics (B.3) i.e. substitution of time consuming end product quality control (QC) tests. If the product meets release specifications it can be shipped immediately without storage during time consuming QC tests.
In case predictions indicate that final product quality will not be of an intended quality intervention with the process should be initiated i.e. process control. The process control could be performed by the operator according to an Out-of-control Action Plans (OCAPS) or an automated control.

The control could be feed back\textsuperscript{79} or feed forward. Most typically the feed back control includes adjustments of process variables in real-time based on in-line measurements or end-point control. An example of feed forward control could be that based on the measurements of the raw materials or intermediate quality different selections of process settings can be chosen for the process steps ahead. This type of process control has not been investigated in depth by the chemometric society but recent examples are Jørgensen and Næs\textsuperscript{80} and Gustafsson et al.\textsuperscript{81}. In both examples infrared spectroscopic assessment of raw materials were used as predictors. Westerhuis et al.\textsuperscript{82} demonstrated how in-process measurements during tablet manufacturing could be used to predict settings of the final tableting step in order to achieve a certain quality characteristic of the tablet. What type of process control strategy to apply is case dependent and no general recommendations are hard to give. But what can be said is that forward control is desirable because usually more opportunities exists for changing quality characteristics of the product while feed backward control often is more strict in the sense that the product has gone through some processing before the feedback control is initiated and less opportunities for changing quality characteristics exists. The drawback of feed forward control is that designed experiments are needed and more batches compared to a simpler feed back control.

Multivariate regression methods e.g. PLS\textsuperscript{83}, multi-block PLS\textsuperscript{84}, N-way PLS\textsuperscript{85} and other regression techniques can be used to develop models for predicting intermediate and final product quality parameters.

The pros and cons for both components are summarized in Table 5.
### Table 5. Summary of statistical monitoring and monitoring based on regression models.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>Statistical monitoring</td>
<td>Algorithms are known. Statistics are well understood. Diagnostics are easy. Out-of-control situations can be early detected and actions can be initiated based on the diagnostics of the contribution plot i.e. <em>Out-of-control Action Plans (OCAPS)</em>.</td>
<td>Not possible to predict final product quality characteristics. Requires numerous NOC batches with known and acceptable quality profile. Also batches that have quality defects needs to be used in order to validate an out-of-normal batch are identified.</td>
</tr>
<tr>
<td>Monitoring with regression models</td>
<td>A direct link between the process and the product is established.</td>
<td>Requires a calibration step and designed experiments. This might be very time and resource consuming if all process variables have to be spanned independently. To develop feed forward control strategies detailed knowledge is required about the process equipment capability.</td>
</tr>
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</table>

No general rule is derived for a RTR system. Such a system is product and process specific. Generically viewed, an RTR system begins with risk assessment and designed experiments for each unit operations individually and/or several unit operations in conjunction, and an assessment of how they contribute to the final quality characteristics.
By identification, monitoring and control of the variation in the process stream, consistent quality is achieved and the need for final quality tests removed i.e. a complete RTR system is implemented.