Risk Assessment in Supporting the Implementation of a PAT Technology and some thoughts about QbD

-Issues for Consideration-

Kevin O’Donnell, PhD

Mobile Course on QbD & PAT, University of Eastern Finland, Kuopio, Finland
February 3rd & 4th, 2015
Topics for today…

• How QRM fits in with PAT – and why is it important
  – Some thoughts for consideration

• Where is the Industry right now in its use of QRM for PAT applications?

• What Competencies in QRM are needed to get the most out of risk-based PAT work?

• Case Study - Review of a PAT Risk Assessment involving a Focussed Beam Reflectance Measurement (FBRM) analyser

• Some thoughts about QbD from a QRM perspective

• Looking towards the future…
How QRM fits in with PAT

• From a regulatory view, PAT had its very grounding in Quality Risk Management work

For example, the term ‘analytical’ in PAT was viewed by FDA to include chemical, physical, microbiological, mathematical, and *risk analysis* conducted in an integrated manner.

• At a higher level, FDA’s early work on PAT was embedded in quality risk management generally

  – It formed part of its “Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach” initiative.

  – *Manufacturers were ‘encouraged to use the latest scientific advances in pharmaceutical manufacturing and technology’*
How QRM fits in with PAT

QRM work is important in PAT because it facilitates process understanding and the control of variation:

• Understanding the sources of variation is important

• Understanding the impact of variation on the process and ultimately on the product allows one to control the variation ….

    …. in a manner that is commensurate with the risk it represents to the process and product
How QRM fits in with PAT

QRM work is important in PAT because it facilitates process understanding and the control of variation:

- Understanding the sources of variation is important

- Understanding the impact of variation on the process and ultimately on the product allows one to control the variation ….

  …. in a manner that is commensurate with the risk it represents to the process and product

QRM, if done correctly and scientifically, can help one understand and manage such risks.
Where are we right now....

- The regulatory environment we now work within seems to have all the elements in place to facilitate the use of risk-based PAT applications
  - To drive innovation and efficiency
  - To better understand processes
  - To use more effective control strategies
  - And to produce safer medicines

- Regulators have worked to change the GMPs and the regulatory environment generally to facilitate PAT applications
- The industry has developed PAT tools and applications
- Applications of PAT are making their way into the Pharmacopoeias
- Detailed guidance is in place which supports PAT applications
  - ICH Q8R2, ICH Q9, Various PAT Guidances, ICH Q10
Where are we right now….

But why are PAT applications still relatively few?

• Why is this area under-developed relative to other areas?

• While some companies make a large use of PAT, as Inspectors, we don’t see very many PAT applications generally, and when we do, they are often not registered in MAs

• However, PAT is being used to monitor processes in a manner that *supplements* official controls
  
  — e.g. In a crystallisation process, while the IPC sample may still be taken, a PAT application may be in place to monitor the batch, to determine when the IPC sample should be taken.
Reasons ???

There are probably many contributing factors

- Technology costs
- Perceived or real regulatory hurdles
- The need for external expertise in areas that may be lacking in some companies
  - e.g. statistics-based approaches to process control strategies
  - e.g. materials science
  - e.g. the challenges of determining relevant multi-factorial relationships among material, manufacturing process, environmental variables, and their effects on quality (i.e. process understanding).
Other Reasons???

- Another contributing factor may be the lack of scientific risk assessment and QRM approaches in the GMP environment generally
  - Current approaches to Risk Assessment and QRM often suffer from a lack of good science and rigour
  - They do not lend themselves to achieving good process understanding, let alone risk-based validation and control strategies
  - There has not been the same investment in getting the QRM aspects of PAT right compared to the development of PAT tools and applications
  - Competencies in QRM have probably not developed in the GMP environment as they should have done
The industry has probably not invested in researching and developing its own risk-assessment and QRM tools and approaches, that are tailored for GMP applications.

- e.g. QRM tools that assist with the identification of risk-based CQAs and CPPs and which translate those into risk-based validation and control strategies.

- Many companies are still using the same old FMEA approaches to everything.

  - Standard FMEAs are not very good at supporting the development of risk-based control strategies and validation protocols.

  - Various reasons for this (another day’s talk)
Competencies in QRM (2)

- The industry has not yet developed competencies in tackling the problems of **Subjectivity & Uncertainty** that affect so many Risk Assessments

  - What does the GMP environment know about the potential problems presented by human heuristics and risk perception during brainstorming sessions?

  - How much does the GMP environment know about how best to elicit opinion from experts
    - especially when probability ratings are being estimated?

  - **Note: these areas are probably equally challenging for Regulators!**
• The industry has not developed sufficient competencies in QRM generally to ensure that its application of risk assessment and QRM is based on *good science*

  – *e.g.* current QRM approaches provide few if any effective ways of **measuring how much risk reduction** is being achieved via the QRM work that is done

  – *Note: this area is probably equally challenging for Regulators!*
Overall...

Problems in QRM are important during discussions about PAT

• Because one of the key **pre-requisites** in achieving effective PAT-based control strategies is the ability to perform **effective risk assessment** and QRM work
Problems in QRM are important during discussions about PAT

• Because one of the key pre-requisites in achieving effective PAT-based control strategies is the ability to perform effective risk assessment and QRM work

More work in these areas would probably be beneficial!
Various kinds of QRM work can support PAT Applications
The different types of QRM work that can support PAT Applications

Risk Assessment & QRM work supporting PAT applications can take many forms

1. **Risk Assessments** can be done to identify the Quality Attributes and the Process Parameters in a product and process that are important in managing variation

   - If done well, these can facilitate:
     
     • Better process understanding
     • The development of more effective control strategies
     • The development of risk-based validation approaches, etc.
The different types of QRM work that can support PAT Applications

2. **Risk Reviews** can be done to assess the *earlier* implementation of PAT tools and applications into a process

   - They can help identify whether the PAT application *added* risk into the process that was not initially understood or managed
   - They can also lead to additional process understanding
The different types of QRM work that can support PAT Applications

3. Risk Communication work that assists with the development of regulatory submissions

- To describe the basis for the PAT application
- And why it leads to enhanced process understanding and control

- Such communications can address the risk-basis for that part of the control strategy that relates to the PAT application

  • e.g. why the registered IPC or an off-line finished product test should be dropped in favour of the in-line PAT measurement
4. **Risk Assessments** that assess the potential risks to product quality presented by the PAT application itself

- This area is probably somewhat under-developed at this time
- If a poor job is done on such risk assessments, an Inspector’s confidence in the PAT application is undermined

    ….. **regardless** of how good the PAT application may have appeared to be earlier!

- This can create substantial difficulties for companies
The different types of QRM work that can support PAT Applications

4. **Risk Assessments** that assess the potential risks to product quality presented by the PAT application itself

- This area is probably somewhat under-developed at this time
- If a poor job is done on such risk assessments, an Inspector’s confidence in the PAT application is undermined

…… **regardless** of how good the PAT application may have appeared to be earlier!

- This can create substantial difficulties for companies.

The next part of my talk presents a Case Study in this regard
PAT Risk Assessment Case Study – FBRM

Dynamic monitoring of the chord length distribution using focused beam reflectance measurement

In situ concentration monitoring using ATR-UV/Vis spectroscopy coupled with chemometrics
Case Study

FMEA Exercise to support the introduction of a PAT Particle Size Analyser at an API site

- After recrystallisation, the API is in slurry form

- Currently, an off-line in-process particle size test determines if the crystallisation process is complete and if the particle size of the slurry is within-spec
  - This test takes 4 hours
  - The test result is used to decide whether to isolate (filter) the batch and then dry it, or, to repeat the crystallisation step
Case Study

Proposed Change:

– Install a Particle Size instrument to monitor the physical characteristics of the slurry in real-time, in-line

  • A Focussed Beam Reflectance Measurement (FBRM) instrument

– If successful, this will eliminate the in-process off-line test (as well as a later in-process bulk density test)

– No need then for any in-process slurry sample to be taken

– Potential time and cost savings

– A reduction in operator exposure to the hazardous material via reduced sampling and testing
A Risk Assessment was performed to assess the risks presented by the proposed introduction of the PAT analyser

- A customised FMEA tool was used
- This contains:
  - A Severity Scale (1-10)
  - A Probability Scale (1-7)
  - A Detectability Scale (1-5)
- An RPN of >180 was taken to indicate a Major Risk
  - RPNs of 180 and lower were regarded as lesser concerns
- The tool provided a list of items to be checked for their potential to have failure modes relating to them
  - e.g. Cross Contamination
  - e.g. Data Loss and Back-up
Let’s review the various aspects of this Risk Assessment exercise
The S, P & D Scales – Comment 1

Are there any issues with the kind of Severity, Probability, or Detectability scales used in this exercise?

– Are they suitable for this kind of risk assessment exercise – relating to a proposal to introduce PAT into process?

The Severity Scale:

– Good that it reflects the impact on patient health and on GMP Compliance
– But does it reflect the consequences of failure modes relating to the introduction of a PAT analyser into an API process?

The Probability Scale:

– Are the definitions for Frequent,. Moderate, etc., useful?
– Do they in any way reflect the likely usage rates of the PAT analyser in the API process???
What is the basis for the RPN cut-off figure of 180?

- Is this useful?
- Are there dangers with such an approach?
- How else might one view and prioritise the RPNs generated in the exercise?
Looking at the list of items to be checked for their potential to have failure modes relating to them….

- Are these useful in a PAT risk assessment exercise?

- There are several positive features to the list:
  - It requires us to consider failure modes relating to cross-contamination as a result of piping and seal problems
  - It requires us to consider failure modes relating to GMP alarms
  - But are they all relevant to the PAT proposal under consideration?

- Are there things missing that might be important??
  - Does it reflect potential failure modes that may result in invalid test results (e.g. chord length distributions) being generated?
  - Does the list adequately address potential software-related issues?
The Risk Question – Comment 4

In the FMEA table – is the Risk Question appropriate for this PAT Risk Assessment exercise?

“What could impact quality and patient safety of the product along its life cycle?”

– Does it adequately reflect what is being risk-assessed here?
– Is there a better question that might be asked?
– How about:

  • “What could impact the generation of accurate particle size or chord length distribution results by the PAT analyser?”

– Was this question ever asked during the FMEA exercise? Let’s see!
In several cases, the causes documented in the FMEA exercise were essentially the same as the associated failure modes

- e.g. Risk No. 1
  - Potential Failure Mode = Instrument Breaks
  - Potential Cause = Instrument Breaks

- e.g. Risk No. 8
  - Potential Failure Mode = Fouling of Instrument
  - Potential Cause = Build up of product on glass probe

- e.g. Risk No. 10
  - Potential Failure Mode = Iron ingress
  - Potential Cause = Iron contamination

- This results in meaningful root causes not being identified
- And in risks not being properly managed!
Current vs. New Controls
– Comment 6

In several cases, the action items identified to reduce risks were documented as *currently in place* controls, yet those controls were not actually in place

– e.g. Risk No. 6

  • *Potential Failure Mode* = Cleaning for calibration
  • *Potential Effects* = Foreign matter ingress
  • *Potential Cause* = Taken out to calibrate
  • *Current Controls* = Work order, permit to work & team leader check  
    *(SOP to be developed)*

– Poor approaches like this can result in overlooking important risk mitigating actions
Several very low detection ratings were not supported by any meaningful detection controls

- **e.g. Risk No. 9**
  - **Potential Failure Mode** = Compatibility of seal with solvent
  - **Potential Effects** = Seal fails
  - **Potential Cause** = Incompatibility of use
  - **Current Controls** = Must be compatible
  - **Detection Rating Assigned** = 2 (Regularly Detected)
    - **RPN** = 60

- Approaches like this can lead to a false sense of security that problems will be detected when they wont be!
Severity Ratings – Comment 8

Several very low severity ratings were not formally justified, but they had a big effect on the risk assessment outcomes

– e.g. Risk No. 11

- Potential Failure Mode = Confusion as to which reactor is being read by the instrument
- Potential Effects = Incorrect Results
- Current Controls = Programme tested
- Severity Rating Assigned = 1 (Effects do not cause a risk to health and don’t affect the quality or regulatory compliance of the product)
- RPN = 1

In this case, no meaningful controls supported the Severity Rating of 1 for a failure mode with such serious effects (incorrect results)
What are the consequences for companies of generating Risk Assessments like this??
Several Negative Consequences...

- Regulators will be less willing to accept the PAT proposal when they see a risk assessment that is so flawed
  - This is regardless of how good the PAT proposal may have appeared initially
  - A poor risk assessment exercise will likely cast doubt in the Regulator’s mind that the proposal is safe to approve

- More work will be needed by the company to persuade the Regulator that the proposal is scientifically sound
  - Additional Cost, Implementation Delays, etc.

- Such risk assessments can raise serious Quality Management concerns in an Inspector’s mind
  - Increased scrutiny is then applied to other risk assessments
Key Learnings from this
Risk Assessment
Case Study
Key Learning 1

• Ensure that your risk assessment approach is customised for the PAT application being risk-assessed

  – Choose Severity, Probability and Detectability scales that are relevant for the PAT application
    • e.g. Think about what might constitute severe consequences if the PAT application fails or is flawed
      …… and design your Severity scale accordingly!

  – Define probability scales that reflect the likely usage of the PAT instrument
    • If it is used every day, does the scale reflect that?
Key Learning 2

- Ensure that the failure mode identification process is robust and suited to a PAT-related risk assessment
  - One size does not fit all – what works for one kind of risk assessment may not work for a risk assessment on a PAT proposal
  - Spend time understanding how the PAT instrument is designed and how it works, and identify potential failure modes from that.
    - In a *Focussed Beam Reflectance Measurement* instrument, there may be a rotating crystal in the laser unit, rotating at a certain speed (e.g. 2m/s)
    - There may be an air source
    - There may be a required speed of the fluid passing over the instrument, etc.
  - Examine how the instrument is to be used, and identify potential failure modes from that, etc.
Key Learning 3

• Ensure that the *Risk Question* underpinning the Risk Assessment exercise is directly relevant to the PAT application

  – Many risk questions can be too high level and are not useful for the exercise at hand
  
  – Many PAT applications will measure some attribute(s)
    
    • So tailoring the risk question to *measurement problems* can be useful

    • *e.g. “What may lead to the instrument generating invalid results or contaminating the batch?”*
Key Learning 4

- Ensure that **Good Science** is built into the Risk Assessment exercise so that problems of subjectivity and uncertainty can be minimised

  - *This is especially important when assigning ratings for P, S & D*

- e.g. In this exercise, an Iron test during the OQ was referred to in Risk 10, resulting in a Detection rating of 1 (*Failure Immediately Identified*)

  - *Was this rating justified? Where did it come from?*
  - *How effective is this OQ test as a risk mitigating control?*
  - *What are the LOQ & LOD of the test method for Iron?*
  - *At what level will the Iron cause a problem if ingress occurs?*

- **Where is the science here??**
Final thoughts...
What makes it a true PAT Application???

*If a measurement is made at-line, in-line or on-line, does this make it a PAT application?*

- Not necessarily!
- It is useful to ask:
  - Does use of the ‘PAT’ tool result in more process knowledge?
  - Does it enhance understanding and control of the manufacturing process?
  - Does it facilitate innovation and continuous improvement, and the development of science-based risk-mitigation strategies?
  - Can it be used with mathematical models and statistical tools
    - e.g. to provide a mechanistic explanation of causal links among the process, material measurements, and target quality specifications?
What makes it a true PAT Application???

If a measurement is made at-line, in-line or on-line, does this make it a PAT application?

- Not necessarily!
- It is useful to ask:
  - Does use of the ‘PAT’ tool result in more process knowledge?
  - Does it enhance understanding and control of the manufacturing process?
  - Does it facilitate innovation and continuous improvement, and the development of science-based risk mitigation strategies?
  - Can it be used with mathematical models and statistical tools, e.g. to provide a mechanistic explanation of causal links among the process, material measurements, and target quality specifications?
Thoughts about QbD

6 key elements in a QbD Approach as per ICH Q8R2

- Defining the Quality Target Product Profile
- Identifying the CQAs of the DP, DS and Excipients
- Developing the formulation to ensure a DP of the right quality can be delivered
- Selecting an appropriate manufacturing process
6 key elements in a QbD Approach as per ICH Q8R2

• Defining the Quality Target Product Profile
• Identifying the CQAs of the DP, DS and Excipients
• Developing the formulation to ensure a DP of the right quality can be delivered
• Selecting an appropriate manufacturing process
• Systematically evaluating, understanding and refining the formulation and the manufacturing process
  – Identify the material attributes and process parameters that can have an effect on the products CQAs, via prior knowledge, experiments, risk assessment
  – Determine the functional relationship that link material attributes and process parameters to product CQAs
• Establish an appropriate control strategy using enhanced product and process understanding, and QRM
Thoughts about QbD

6 key elements in a QbD Approach as per ICH Q8R2

- Defining the Quality Target Product Profile
- Identifying the CQAs of the DP, DS and Excipients
- Developing the formulation to ensure a DP of the right quality can be delivered
- Selecting an appropriate manufacturing process
- Systematically evaluating, understanding and refining the formulation and the manufacturing process:
  - Identify the material attributes and process parameters that can have an effect on the products CQAs, via prior knowledge, experiments, risk assessment
  - Determine the functional relationship that link material attributes and process parameters to product CQAs
- Establish an appropriate control strategy using enhanced product and process understanding, and QRM

From a risk assessment viewpoint, where are the challenges here?
Many challenges!!!

- e.g. when doing risk assessments to link process parameters with CQAs
  - It is important to understand how much risk reduction or risk control a process parameter provides towards meeting a CQA
  - But how is this degree of risk reduction or risk control measured?
  - The industry is currently very weak in this aspect of QRM
Thoughts about QbD

Many challenges!!!

• e.g. when doing risk assessments to link process parameters with CQAs
  – It is important to understand how much risk reduction or risk control a process parameter provides towards meeting a CQA
  – But how is this degree of risk reduction or risk control measured?
  – The industry is currently very weak in this aspect of QRM

• e.g. what elements of QRM are needed to facilitate enhanced product and process understanding???
  – What should risk review activities look like here? Currently under-developed
  – How is ongoing process data (deviations, rejects, change control outcomes, OOSs, complaints, CpK data, etc.) translated into real process understanding via risk assessment?
Looking towards the future…

- **The evolution of QRM in the GMP Environment for PAT and QbD applications will take additional work!**

  - ICH Q9 is now 9 years old
  - Other industries such as Nuclear Power and Aeronautics are much more advanced in their use of Risk Management
    - but they took 40 years to get there!!
    - and they still have not always gotten it right!
Looking towards the future…

The evolution of QRM in the GMP Environment for PAT and QbD applications will take additional work!

- ICH Q9 is now 9 years old
- Other industries such as Nuclear Power and Aeronautics are much more advanced in their use of Risk Management
  - but they took 40 years to get there!!
  - and they still have not always gotten it right!

While the GMP environment is on the right road, there is still a lot to do!
Questions & Discussion....