

Product & Process Working Group

February 26, 2002

Questions to the Working Group

- What considerations, during product development, are needed to ensure optimal application of PATs to realize "quality by design" through better understanding of processes and determination of performance-based process controls/end points?
- Benefits of PAT are under realized
- Companies have not always seen the benefits they expected

Question 1 continued

- Still some selling that needs to be done
- 6 sigma is too high, 3-4 sigma may be more realistic

Questions to the Working Group

- What areas, from raw material identification/characterization to finished product manufacturing, are amenable to monitoring and control using process analytical technologies?
- Applicable to most areas of the manufacturing process. Different levels of maturity.
- Applicable to most areas of the manufacturing process, but different levels of maturity.
- Nature of the ingredient is a factor. May not work in all cases.

Question 2 continued

- PAT Technology allows the incorporation of feed back controls such that a whole batch need not be lost
- Goal during development is to understand and develop robust processes
- During development look at a lot of parameters to identify what will be important monitor in actual practice.
- Evaluation of other technologies from other industries may be helpful

Question 2 continued

- Unit operations (where we have the history) and possible technologies that may be used, should not exclude other promising technologies, we don't want to limit alternative approaches

Questions to the Working Group

- How do you anticipate PAT application will change the process for identifying critical process variables, their control, and establishment of product specifications?
- Development function. Structured approach. Getting into the process early. Process of optimization allows you to identify critical parameters and develop metrics. How you control it is up to you.
- Online sensors give you additional information to identify your critical endpoints.

Question 3 continued

- Multivariate approach/strategy
- Identifying new variables that may be more pertinent to the process
- Correlate PAT and specifications where relevant
- Look at raw material, quality is a key factor

Questions to the Working Group

- What are some of the issues that arise during the scale up of pharmaceutical manufacturing, using PATs?
- Do PATs help in the scale-up situations? **Yes.**
- What is the endpoint that you're working towards? Need to know what the process looks like when it's working well.
- Insight when the process is working well and when it's not. Getting an endpoint to work towards.
- You'll know where problems may exist and what to monitor.
- You can often calibrate PAT to scale up and develop scale up coefficients

Question 4 continued

- Do they cause problems? **Yes.**
- Limitations in existing “gold standard” method
- Engineering issue - Ruggedness of engineering. Critical implementation issue. Applying design to equipment
- Business issue: Addition of PAT must be value added
- For new products sensor applications for up-front equipment are easier to put in place and employ
- PAT measurement may not match your submission parameters but your finished product is still good. The mechanism in which these changes are submitted needs to be clear.

Question 4 continued

- Moving from a parameter control to an endpoint control. Have to set boundaries (upper limits, work within this window)
- Low dose drugs, low potency, may be many more exceptions
- Do they make scale-up transitions easier, and if so, why?
- Yes. Better understanding of your process always helps

Questions to the Working Group

- In some situations, PATs may be used only for certain specific unit operations within the overall scheme of a dosage form manufacturing. What are some of the advantages and disadvantages for doing so?
- No technical downside. It's a business decision. Has to be "value added"
- Accurately reflecting what's going on, it can't be a disadvantage.
- Overall weakness, e.g. blend homogeneity does not mean you will not have other problems down stream

Question 5 continued

- “Go for new technologies, you pay for new technologies”
Business decision, development time lines. Speed to market, Cost in time. Allocation of resources (human)
- Advantage – single implementation, supports doing it incrementally for other similar processes, e.g. dryer

Questions to the Working Group

- How can PATs be used to minimize, or prevent “out of specification” incidents?
- If you’re are allowed to go to an endpoint, it will help decrease OOS incidents
- It will decrease incidents proactively because the developed process is more rugged.
- Can drive more scientific investigation of problems. Gives you more data to trouble shoot problems.

Questions to the Working Group

- How can PAT tools be used for predicting the performance of a drug product (e.g. dissolution) based on causal links and data based correlation?
- Certainly possible. Need to develop correlation's
- Exercise in benefit/risk assessment
- More work needs to be done, e.g. use of acoustic data. There are measurement technologies that could be used, but they are not yet mature.

Question 7 continued

- Case by case basis.

Questions to the Working Group

- Can PAT tools be used for predicting the stability of a drug product? If yes, what are the factors that should be considered prior to using them?
- No. Can't replace stability study.
- PAT may be used as a predictor.
- Yes for physical instabilities.
- Can be possible, but in the general sense it's pretty limited
- May reduce risk, but you'll still need to test.
- May be able to predict, but will still need data to confirm stability

Question 8 continued

- One benefit, batch release will be higher quality, product failing during shelf life will be less likely
- More consistent product

Questions to the Working Group

- What factors should the Industry and the Agency consider while implementing the use of new PATs for already approved drug products?
- Benefits – product capability. Building the quality in. You can't do that retrospectively.
- Continuous monitoring of an on-going process may yield higher quality product
- Considerably more prospects with new products

Question 9 continued

- View from industry “If it’s not broken, don’t fix it”
- **When vendor changes, it’s an opportunity to use PAT. Honeymoon period to collect parallel data**
- Team inspections are being planned – review chemist and inspector will work together. Decisions based on sound science.
- Manufacturers may look at implementing PAT when other changes are made, e.g. site change

Draft Guidance

Table of Contents comments

- combine III & VI
- V. What types of data do we need?
- IV. Facilitation of PATs. Agency is open to parallel testing. Should be expanded.
- Add reason for doing this in I.Introduction
- Use of PATs in product development
- Enabling technology (including chemometrics)
- Relationship to finished product specification
- Worked examples for different product types, e.g. three different dosage forms

Draft Guidance

Table of Contents comments

- Section VII change to review of PAT information in an application
- Guidance should address roles and responsibilities of different groups, e.g. quality unit, engineering, process technology as well as the scale mixes