# FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE, HFD-003

## PRODUCT AND PROCESS DEVELOPMENT WORKING GROUP MEETING OF THE PROCESS ANALYTICAL TECHNOLOGIES (PAT) SUBCOMMITTEE

Meetings held in Gaithersburg, Maryland
June 12, 2002, 3:00 pm to 5:00 pm
June 13, 2002, 8:30 am to 12:00 noon

**Working Group Discussants**

Judy P. Boehlert, Ph.D., Chair, and Member, Advisory Committee for Pharmaceutical Science
Ronald Miller, Ph.D., Bristol-Myers, Squibb
David R. Rudd, Ph.D., GlaxoSmithKline
John G. Shabushnig, Ph.D., Pharmacia Corporation
Gopi Vudathala, Ph.D., Sanofi-Synthelabo
Walter Dziki, Ph.D., Abbott Laboratories
R. Thomas Cambron, Ph.D., P&G Pharmaceuticals
Brian Curtiss, Analytical Spectral Devices
Anserd Fraser, AAI International
Colin Walters, Schering-Plough
Efraim Shek, Ph.D., Abbott Laboratories
Yuan-yuan Chiu, Ph.D., CDER, FDA
Frank Holcombe, Jr., Ph.D., CDER, FDA
Thomas Layloff, Ph.D., Center for Pharmaceutical Management

Notes were recorded by: Rajendra Uppoor, Ph.D., CDER, FDA.

Limited ad-hoc participation by members of the public who were in attendance at the meeting was also permitted intermittently by Dr. Judy P. Boehlert, on both days, June 12 and 13, 2002.

## NOTES OF PUBLIC MEETING "AS-IT-WAS-RECORDED" DURING THE MEETING

Note: These notes constitute written "transcript" of recordings, which was displayed in public to all attendees who were present as the meetings.

- Spectroscopic and acoustic methods for granulation.

- Desired signal signature/pattern and unsatisfactory signal for undesired end point.
- Correlated with particle size of granules.
- For new products.
- For existing product.

- Equivalence to a standard method for replacement.

- Suitability of method for all.

- Replacement test correlated with something else.

- Correlate process end point/signal to at test?
- Acoustics signal: Size, shape, hardness.
- Feature detection of signal.
- Mathematics can be added.
- Defined point on a trace (a cartoon was drawn, and it is not shown here).

- New specification based on a new method?

- Sensor suitability.
- Remain suitable?

- NIST workshop September/October 2002.

- Process Control End-points. Signal to a threshold.

- End point models are easy to implement?

- Physical domain, chemical domain: Univariate correlation?

- Scale up differences have to be determined.

- Distance of sensor/probe.
- Interface change.

- Demonstrate basic scientific principles

- Suitability of parameter, equipment, equipment design, vendors (outside of scope?)
- Sensors: Where? How many? Effective sample size, consider these ..
- R&D and Operations differences.
- Differences in signal.

- Guidance in writing, with specifics, "What to do when there is a sensor failure".

- PATs more sensitive to mishaps. Hence guidance in case of sensor failures.

- Normal signals, maintenance signals, error signals, out of trend signals.

- Process to a desired signal, than to a fixed time, through a signal route, time.

- Add a discrimination power?

- Remain sensitive to manufacturer (component) change?

- Understand/investigate change(s) noted.

- 483: "Mix until dissolved".

- Raw material differences; "signature" for defining end point.

- Q # 3: Built-in redundancy

- Calibrations are on-going, continue to maintain calibrations.
- Equal to, or better method.

- List in-process measurements predictive/replacement/reflective/correlative of product characteristics.

- "Decision is equivalent" - measurement/test may not be. Batch quality decision has to be established.

- Technique-End points" have to be validated.

- Parking lot items: Key glossary items, signature, fingerprint, in-line, on-line, at-line, off-line.

- Multiple tests to measure same attributes.

- PAT breaks? Then what?
- Go to chemical/wet chemistry?
- E.g., Acoustic signal and particle size: Write a SOP that way.
- Several tests together to get same information.
- Alternate tests/methods to measure an end-point.

- Refinement of definition (PAT)

- Safe harbor.
- In guidance.
- Public domain.
- Impact to other regulatory agencies: TGA, MCA, EMEA.
- Get to ICH stage.

- End point is harmonized - How to get there is not.

- Concept of selective rejection. Broken tablets in blisters removed.

- Identify critical parameters: Addition rate, mixing rate.

- Create a profile "you want".
- "Process measurement" versus "process control".

- Process deviation "catching" ability.

- Guarantee "performance" in drug products.

- "OOS" issue using PATs.

- How long "time" for development?
- Parallel testing with approved methods, until satisfactory information using PATs.
- Voluntary - until ready for regulatory use by the developer.
- Different/related acceptance criteria with PAT testing.
- Re-evaluated/renegotiated acceptance criteria for PATs.
- Correlation based/reliable test. Lower/higher linked to PAT observations, in a range (A cartoon was drawn with PAT acceptance criteria range on the Y-axis correlated to the approved chemical test acceptance criteria range on the X-axis).

- Reject bad tablets on-line? Cost?

- SOPs to reject "bad" based on PATs and process capability.
- Use PAT to get "partial release" of batch.
- Characterize process, out of trend analysis.

- Can not correlate current method to PAT data?

- "Trend analysis" and new requirements using PATs.

- Test and limits should be linked. Different test, then different limits.

- Increased data density, then new limits?
- What is quality? ± what? For intended use, re-establish PAT criteria.

- Goal is probably not to "improve" quality - current quality is good.

- Shift population model, then shift acceptance criteria.

- Evaluate many factors and arrive at new criteria.
- Could cost "twice" if PAT gets used to "improve" quality.

- PAT applications with well behaved products - should not become "gold standard".

- Slide # 11 (of Ajaz's presentation on June 12, 2002)

- Identify process parameters.
- Experimental design to look at what are important variables.
- "Good predictor" for final product quality; by current testing, then with PAT testing?

- No "sample" with PATs. Use PATs for different reasons, and in different ways. Not direct interpretability on end product quality.

- Identify critical variables. Develop robust product, based on data captured. PATs provide more information than "now".

- Appropriate PAT to measure or control desired variable.

- Quality is decided by "current end product specifications". Not as effectively met by current methods.
- PATs facilitate/enable "discovering" critical process parameters which have direct influence on end product quality, performance, process control, other..
- Blending speed, addition rate, time, case by case ..

- Make a change and see the effect in instrument/equipment, that may/will affect quality. Now it is not visible until end product testing.

- Operating window can be defined. "Specification is not changed".
- Ability to meet current standards with PATs.

- Incentive? For R&D?

- Decreased rejection in manufacturing.
- Increased speed.
- Increased profits.
- Better process transfer.
- Capital cost is small. Development/discovery cost is high.
- R&D leads the process.
- Compounds are becoming potent, with side effects.
- Tools to control quality.

- R&D should become comfortable in using PATs.

- R&D, regulatory, quality to be trained by industry also.

- Process signature

| PAT Measurement | End product attribute |
|---|---|
| … | Dissolution |
| … | Hardness |
| … | Content Uniformity |
| … | … |
| Perform multivariate analysis. | |

- May get signal, but not understand its implication such as stability.

- Signature

- Description of acceptable variability in population. E.g. Spectrum converges to a defined variance "window".
- Link between parameter and product characteristic.
- Surrogates/scientific basis.
- Hardness, potency, particle size are part of signature. Put it all together, you have a signature.
- In-process signature is important. End process signature could be late.
- Move measurement to process parameters, to meet process specification.

- Signature utility

- Multidimensional measurements in signature.
- Granularity, hardness, flowability, particle size.

- What data to keep?

- File is large?
- Too much data could lose significance?
- In R&D, keep everything.
- Manufacturing asks R&D, and they want what is important.

- Issue guidance, Workshop, Training, Communication back and forth with Industry; Case studies from Industry.

- Team review-inspection will help.

Note: Portions of the above notes were used in preparing the "Summary of Discussions" of Product and Process Development Working Group deliberations. Dr. Judy P. Boehlert presented the "Summary of Discussions" to the PAT Subcommittee, in the afternoon session of the meeting, on June 13, 2002. That document can be found on FDA's website, http://www.fda.gov/ohrms/dockets/ac/acmenu.htm.