Implementing PAT – Industry Example

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Summary

- Why did Aventis pursue PAT?
- How does Aventis see PAT?
- What is our PAT Pilot?
- How did we handle the communication with the FDA?
- What are the opportunities in PAT?
- Personal Learnings

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Background – The PAT Journey at Aventis

2000 – Integration of HMR and RPR.

2001 – Fixing broken processes.

- Trying to fix manufacturing processes without knowing the science behind it.

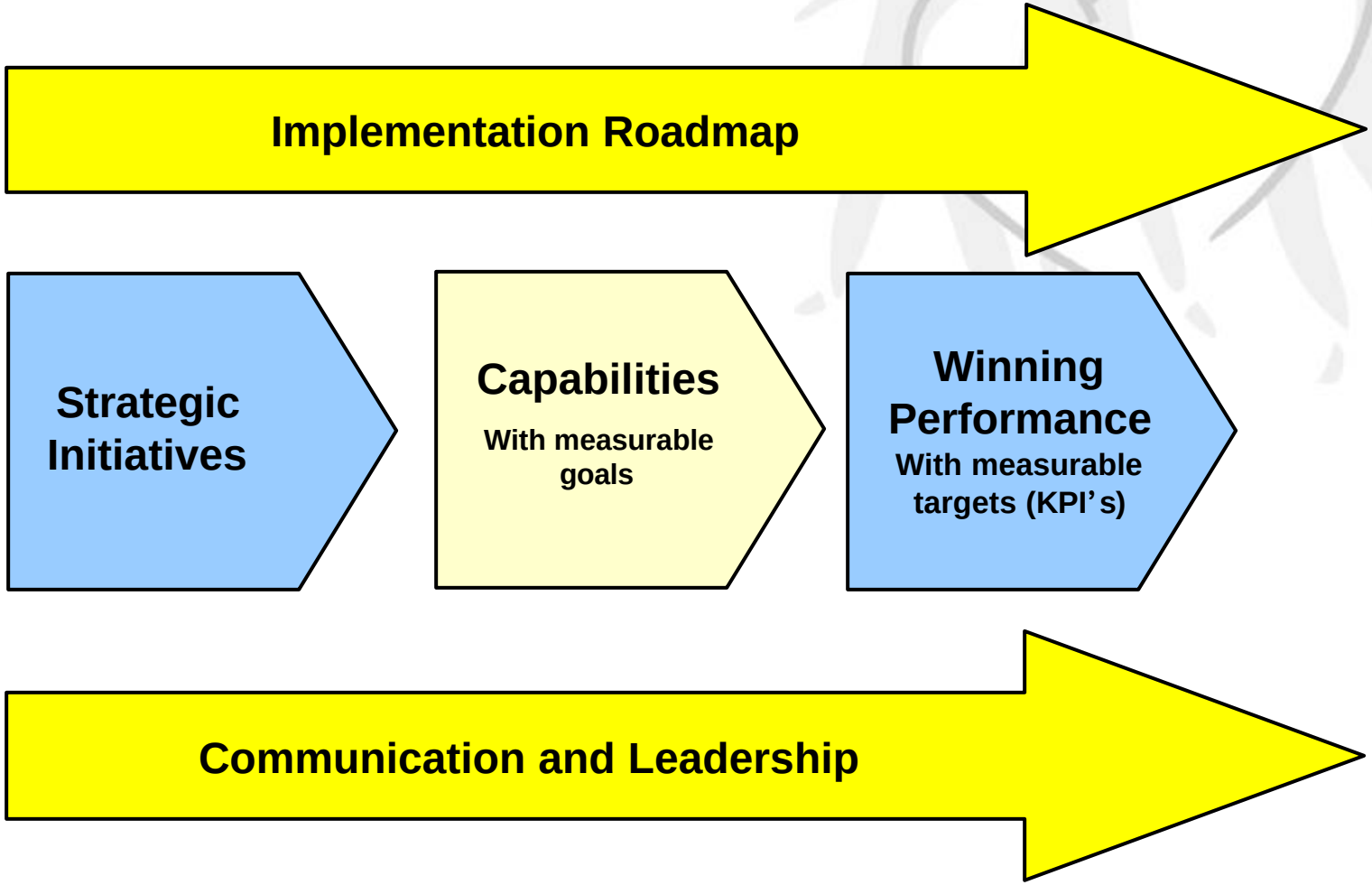
2001 – Industrial Operations strategy identified and agreed

- Need an opportunity to improve manufacturing processes.
- Industrial Excellence roadmap identified.
- Process robustness and statistical evaluation of finished product quality attributes.

2002 – PAT not well defined.

- October 2002: decision to proceed as Strategic Initiative and to engage with FDA.
- Create environment conducive to mentality change.

Strategic Initiatives Create Winning Performances



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PAT Environment

- **Strategic motivation – achieve measurable business results**
  - **Integral to Manufacturing Excellence**
  - **Priority – supported by top Industrial Operations Management**
- **Six Sigma mentality – Process Robustness**
- **History of new product transfers through multifunctional Tech Transfer Teams**
- **External partnerships – CAMP**

Pilot Objectives

- Demonstrate ability and establish capabilities - industrial scale
- Understand what it takes
  - competencies needed
  - connect multiple functions
  - learning - what needs to be addressed
- Pilot regulatory strategies

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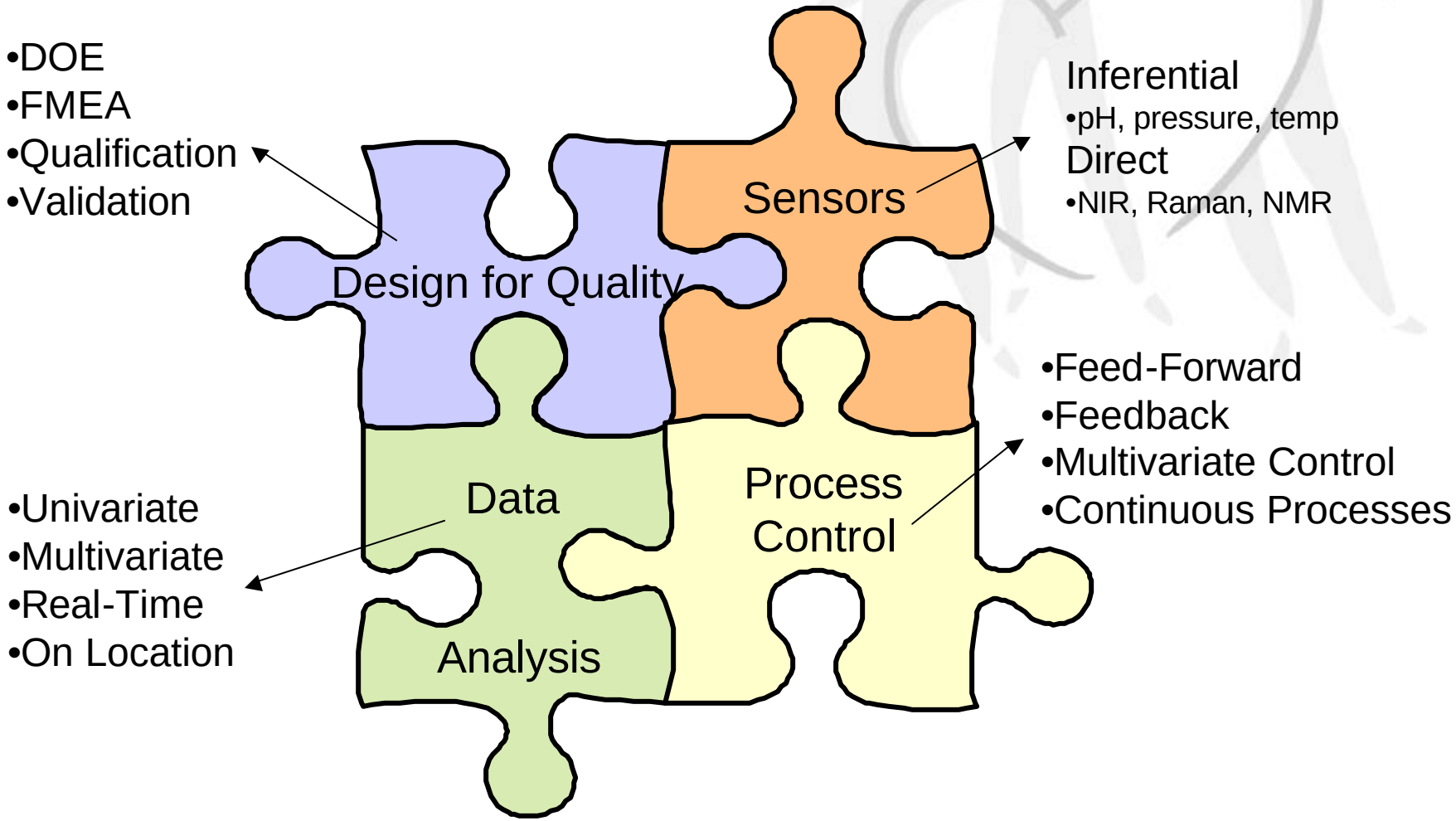
What is PAT? – Aventis View



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Pilot Approach

Go for high impact and high probability of success

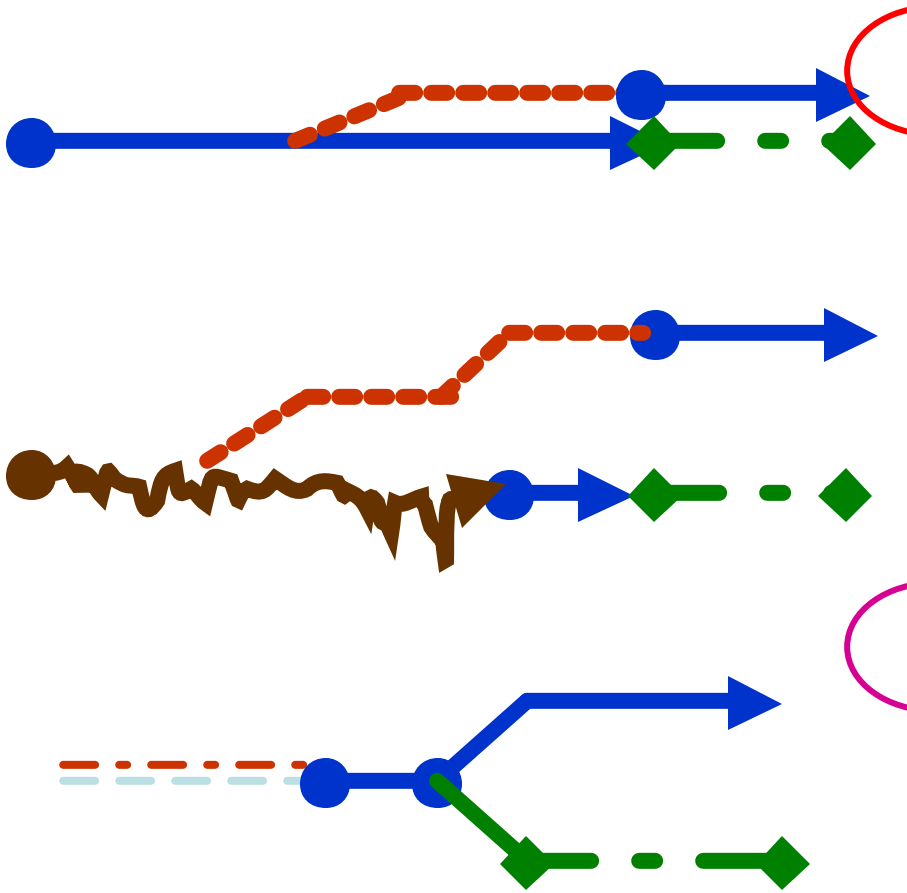
- Select a 'safe and robust pilot process'
- High volume, large number of batches

Focus on whole process

- Integration of API and DP as a seamless process

Allow time

Options for Introducing PAT



A. Currently marketed "robust" products. PAT to improve efficiency (minimal improvement in quality assurance)*

IO Pilot

B. Currently marketed products that need improvement. Step-wise PAT approach - First improve quality and then improve efficiency

R & D

C. New products. PAT utilized throughout development and scale-up. Lab based tests to ensure shelf-life and/or for establishing "public standards".

* Note that a step-by-step approach, one unit operation at a time similar to option B, is also an option.

Organization and Structure

Driven by top-management

- **Head of Quality is the sponsor**
- **Industrial Operations in leading role**
- **R&D involvement with longer time window**
- **Dedicated PAT Strategic Initiative leader**
  - "Make it happen" - multifunctional approach, focus existing approaches, work with site organization, etc.

Work with the Manufacturing Sites

Team building

- Key expertises – chemometry, computer systems, control systems, process etc.

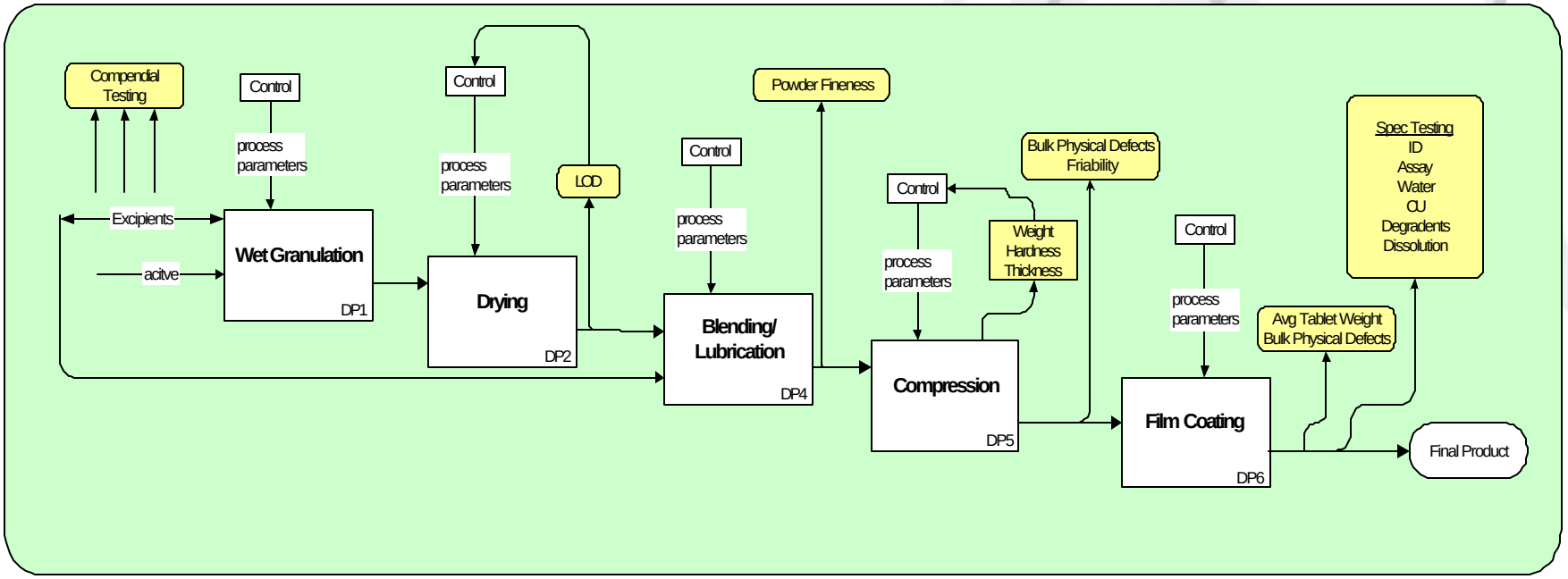
Establish infrastructure

- Scale-down lab (API) ~ transfer scenario
- Lab /DP (scale-down possibilities) ~ work directly integrated in manufacturing

Global co-ordination – consistent approaches, define rules

Site functions support

An Example of Tablet Manufacturing – Current State



- Fixed process conditions
- Limited confirmation of quality during processing
- Limited sample sizes

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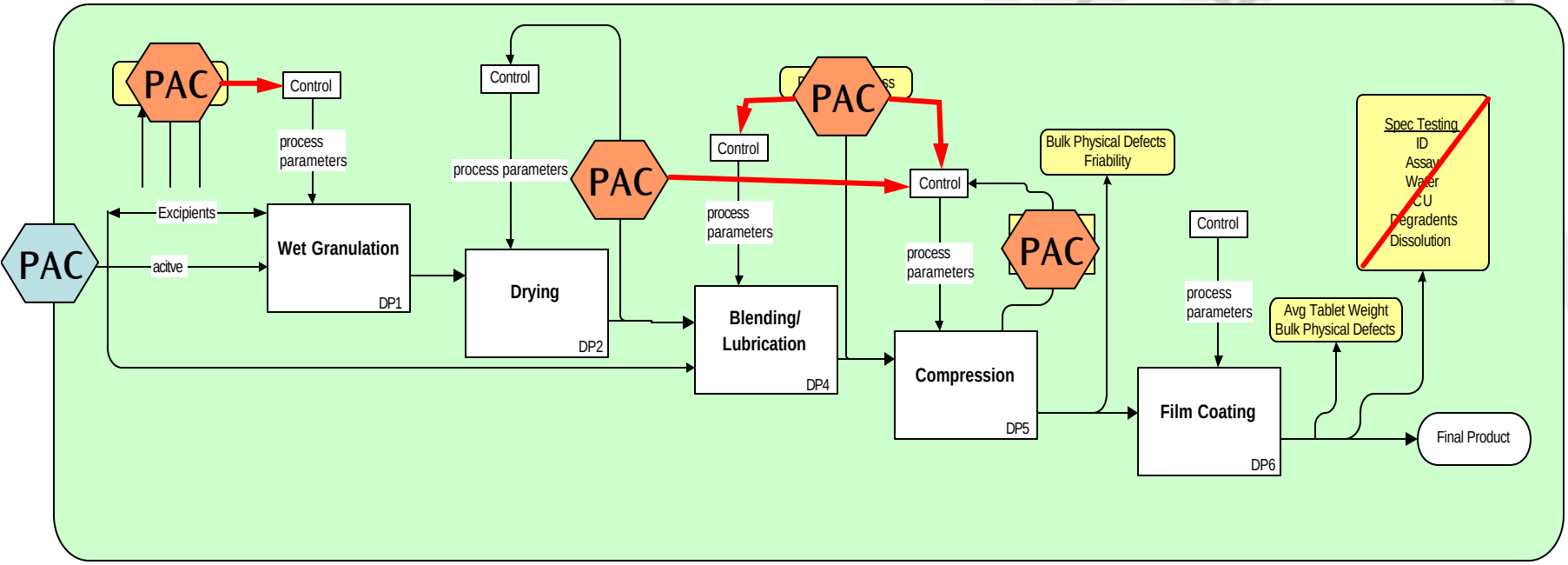
An Example of Tablet Manufacturing – Through PAT



With real-time analysis

- Rapid information
- Useful for process control
- Potential to adjust the process to achieve target quality and reduce variation
- Replace costly, time consuming off-line, laboratory based testing

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Links between API and DP

Focus on physical properties is a core element of PAT

- Look on API physical quality attributes
  - What was the reason to set specs as they are ?
- Look on drug product performance specifications
  - Processability
  - Operator's observations
- Design measurements capable of taking up relevant parameters
  - Learn from data → correlation & evaluation
  - Built understanding how parameters are interrelated

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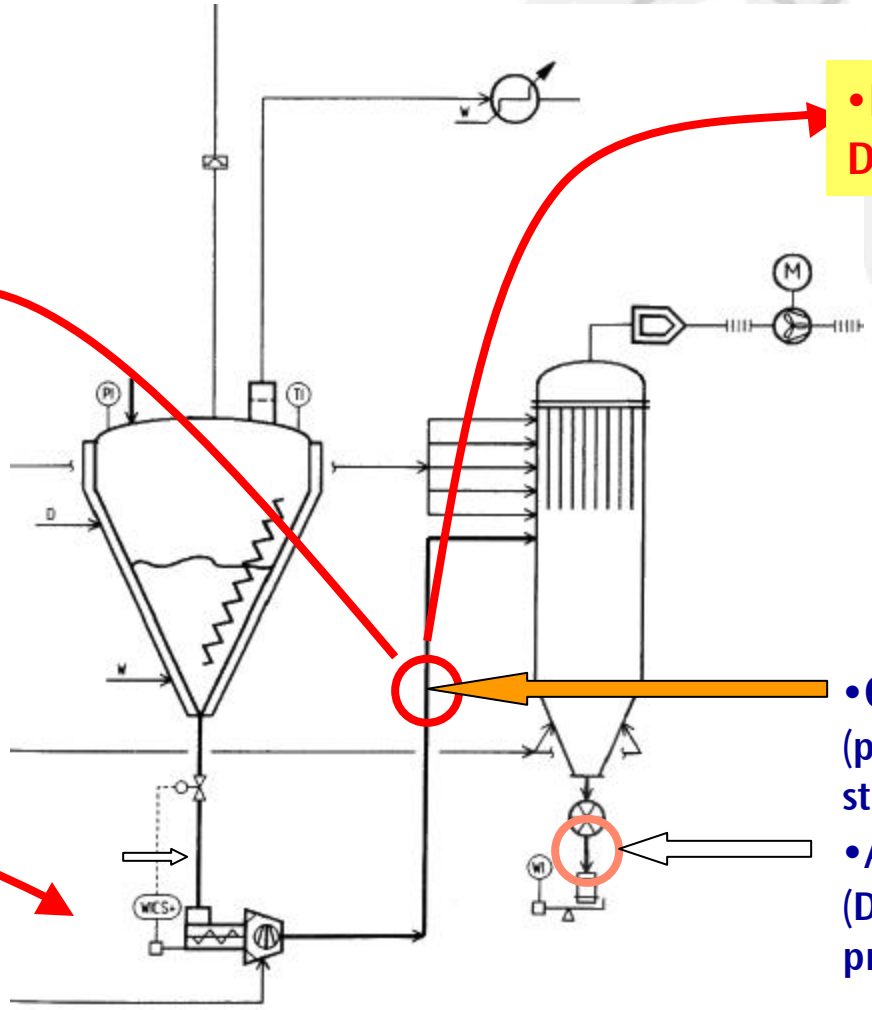
API On-line PSD

•FEED-BACK to milling step



•FEED-FORWARD to Drug Product…

•On-line PSD (powder transport stream)

•At-line SSA (DSC during milling process)

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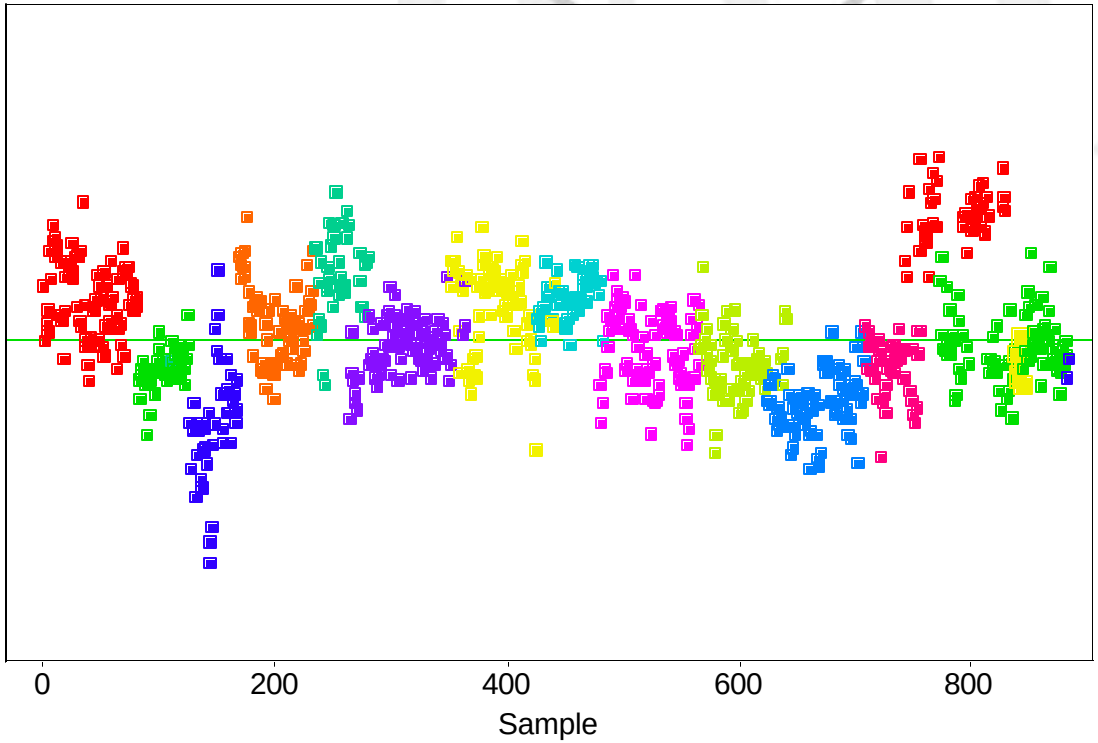
At-line Raw Materials Evaluation at Dispensing



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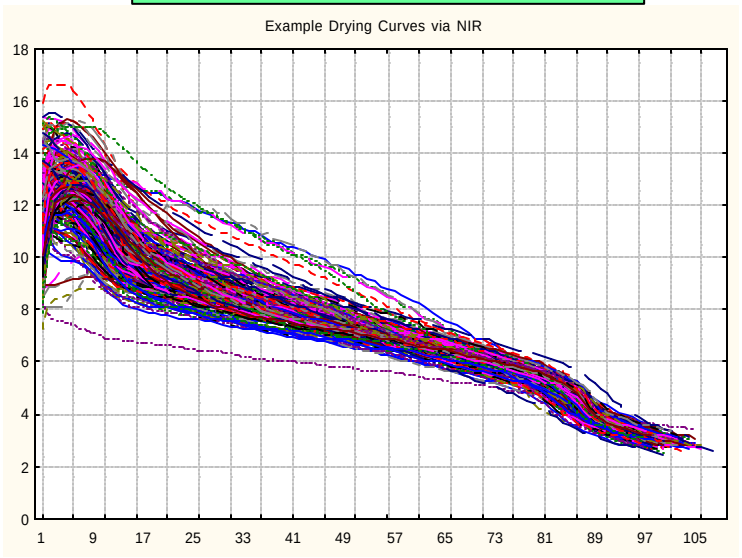
On-line Moisture Monitoring – Drying



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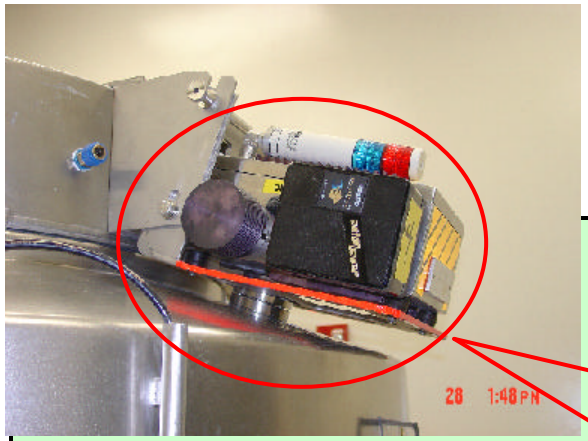
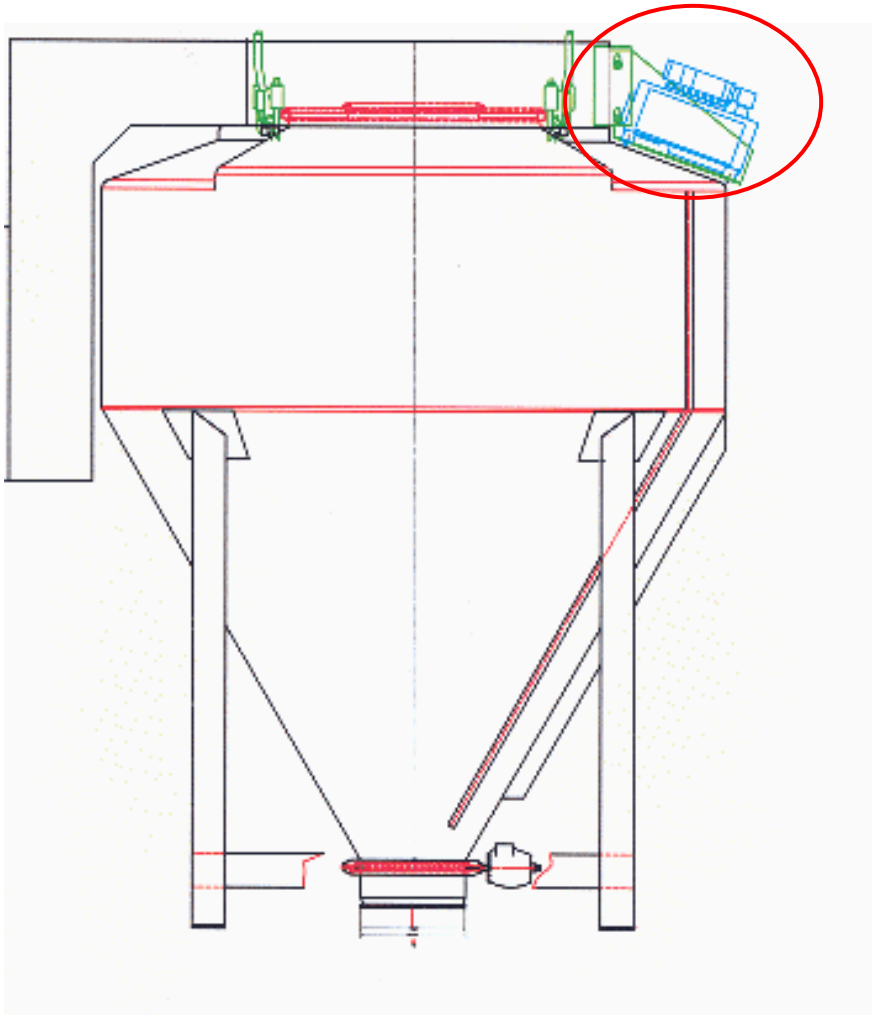
On-line Blending and Lubrication Monitoring and Control



Wireless NIR Blend Monitor



- AOTF NIR
- Battery Operated
- Wireless
- Real-time transfer of spectra to host PC
- Mounted off-axis in conservative location
- NIR beam focused through sapphire viewport

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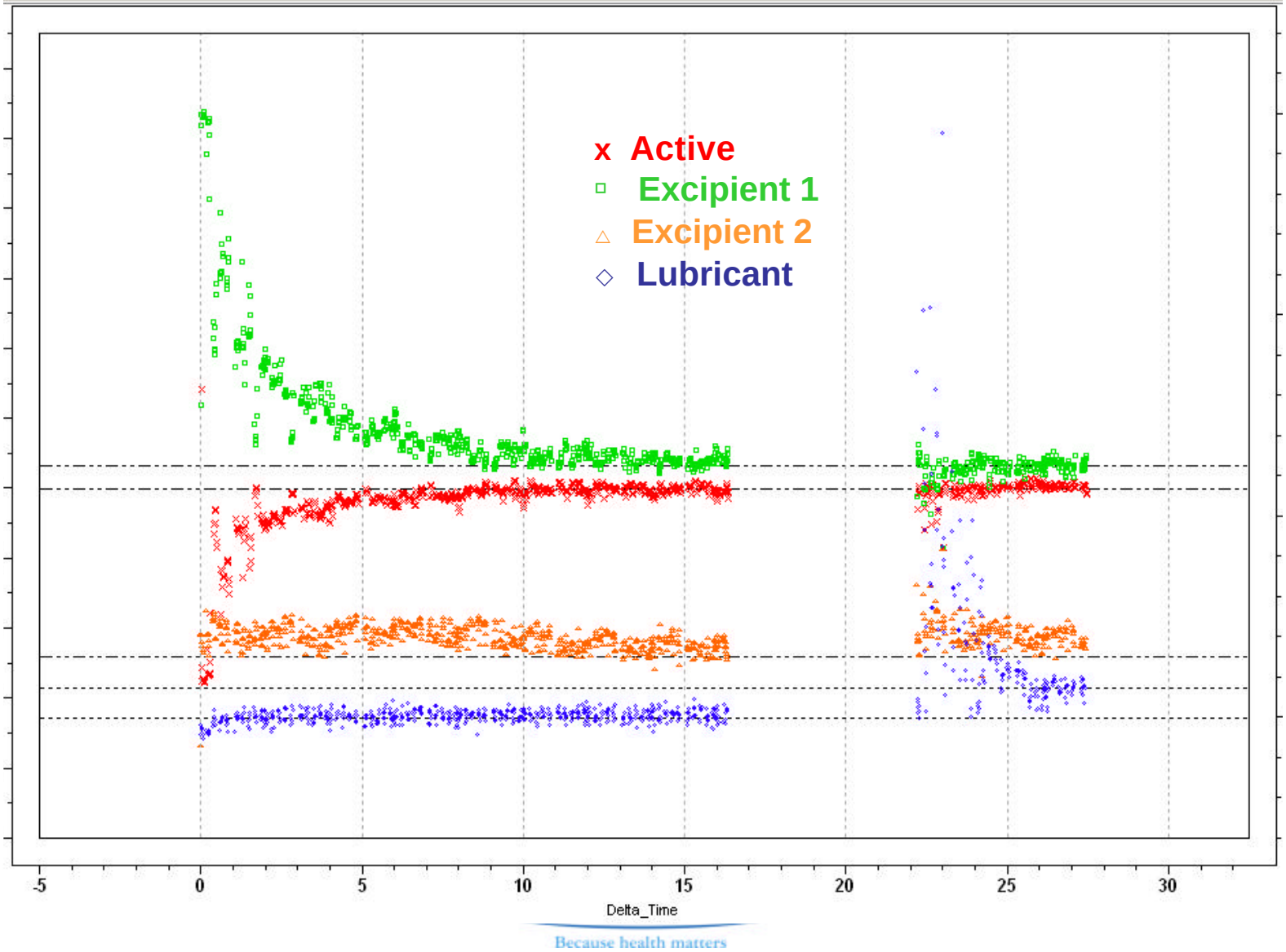
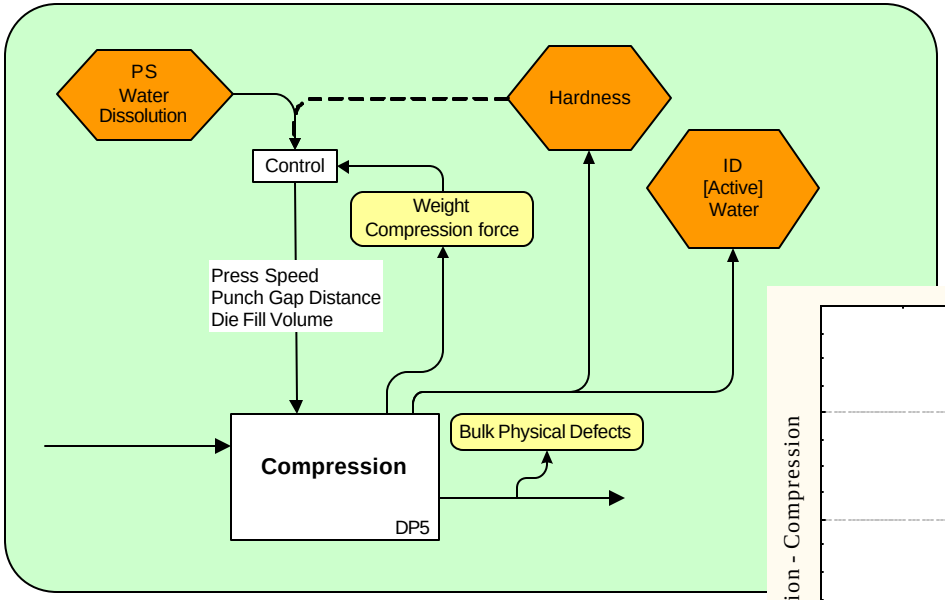
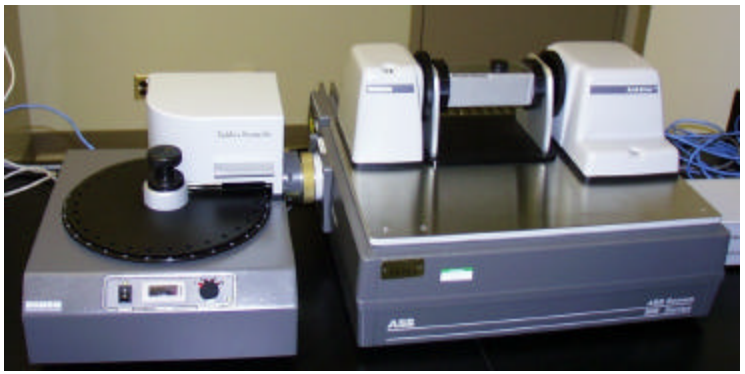
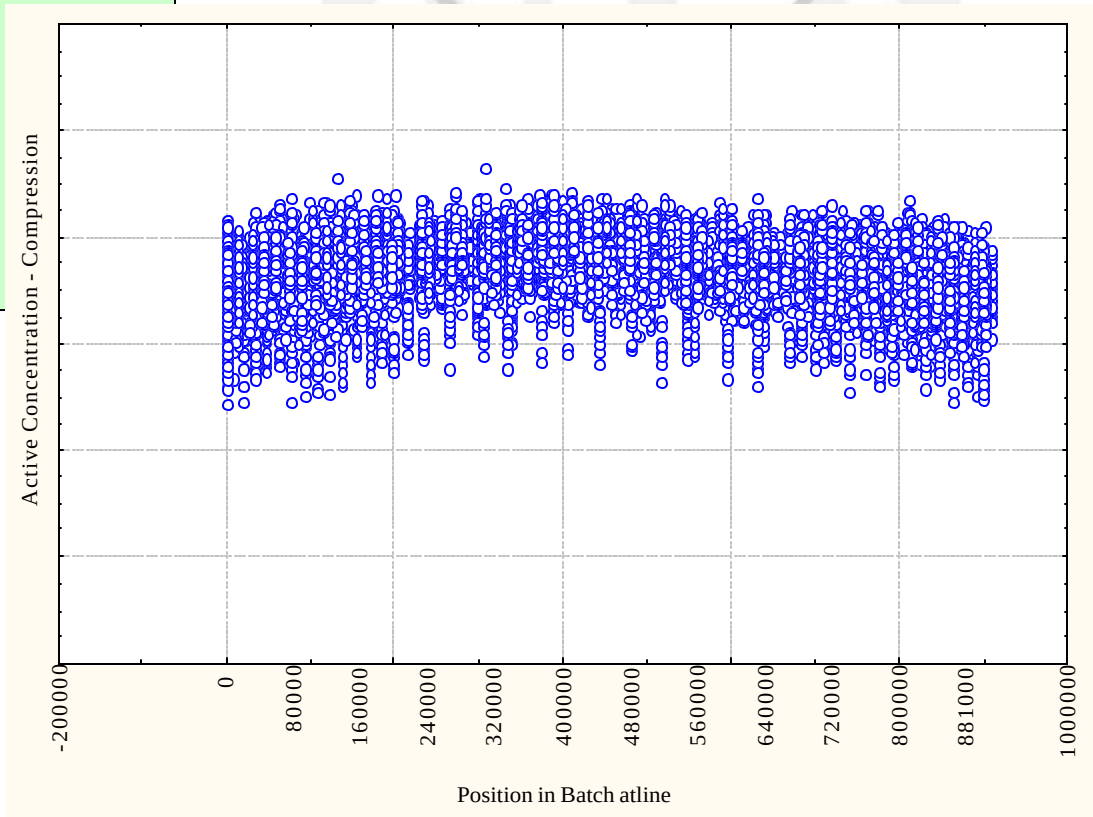
Blend Monitoring – Full Scale Batch Example



At-Line Tablet Analysis - Compression







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Working with FDA

- Shared vision - 'partnership' for common good
- Building trust and mutual understanding
- Communication non-inspectional but science and technology based
- Communication to assure consistent views
  - relentlessly open
  - had to be learned – regulatory, science
  - concerns … legal ...

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FDA Dialogue Chronology

Q3/Q4 2002 - PAT laboratories organization defined and pilot projects selected

January 2003 – Project kick-off meeting

May 2003

- **Full project presentation to FDA (Rockville, MD)**
- **PATRIOT member visits API PAT laboratory**

July 2003

- **PAT team staffing completed**
- **Investment capital approved**

August 2003 – Follow-up with PATRIOT

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FDA Dialogue Chronology (cont')

- September 2003 – FDA PAT Guidance draft
- Q4 2003 to Q1 2004 – Ongoing review and adjustment of project detail plans based on early learnings and shifts in FDA guidance
- November 2003 to July 2004 – Aventis shares several draft CP versions with PATRIOT
- August 2004 – FDA pre-operational site visits
- October – PAT CP submission

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FDA Pre-Operational Visit (POV)

Tablet manufacturing and API production

FDA visit team

- **Rebecca Rodriguez,**
  Office of Regulatory Affairs/SJN-DO (Inspector)
- **Albinus D'Sa,**
  CDER (Compliance Officer)
- **Vibhakar Shah,**
  CDER (Reviewer)
- **KC District Representative (DP Only)**

FDA POV - Aventis Objectives

- Building confidence on PAT implementation approach.
- Confirm a consistent understanding (science, technology, regulatory).
- Understand submission and approval process.
- Discuss future quality system adaptations.
- Establish communication mechanism.

FDA POV - Scope

Science and technology.

- Measurement systems, models for data assessment, etc.

Implementation / industrialization aspects.

- Data architecture and software, vendor issues, etc.

Thought processes, rationales.

- Process Understanding, risk evaluation, etc.

Approaches.

- Measurement system performance verification, etc.

FDA POV - Approach

Approach, focus, and style → 'new way'

- **Process Understanding → learnings, rationales, approaches, and processes.**
- **Not inspectional - science & technology , and rationales that support quality decisions**
- **Comparability Protocol details, filing mechanism**

Building trust / reciprocal - mutual understanding of needs

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Comparability Protocol

How to convey Process Understanding ?

When to submit ?

- Draft documents during all project stages
- Final CP reflects deployment stage (systems operable on industrial scale)

Content

- Project status and rationales
- Plan for remaining steps up to complete implementation
- A scientific document - not a 'normal CP'

'Comparability' – Scope and Focus

- Measurement and sampling systems,
- Models and data systems to evaluate, store, and retrieve data,
- Enhanced understanding of processes
  - variabilities and their impact on processability and critical quality attributes,
  - correlation and causation with processability and critical quality attributes between drug product and API quality parameters
- Process monitoring and control strategies.

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Conclusion

Positive work with FDA

- Dialogue focussed on science and technology – not inspectional.

Need to rethink approaches

- Quality systems, e.g. validation
- QA/QC tasks and deployment

Learnings

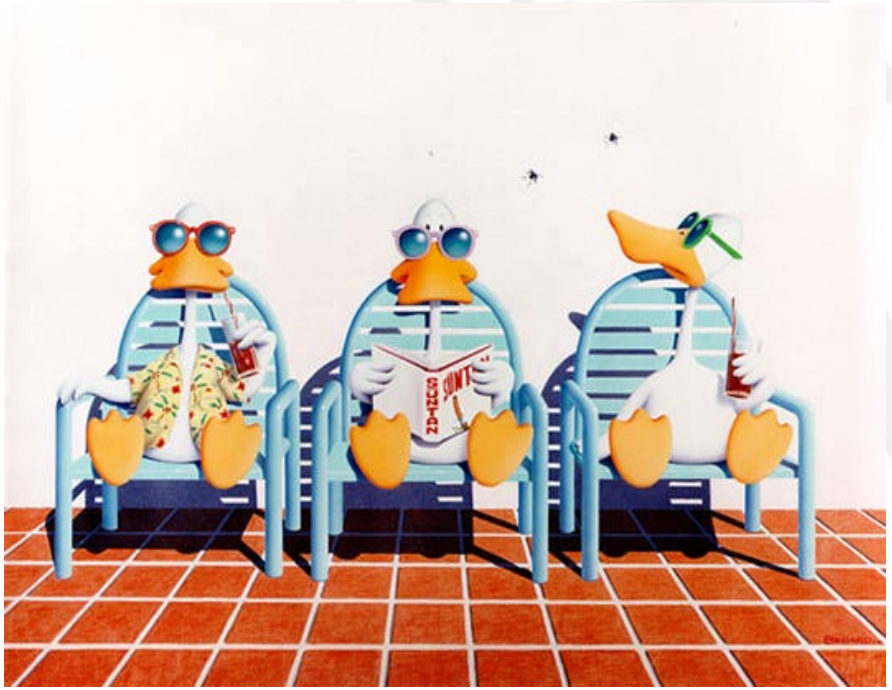
Things I would do the same again…

- Think outside the box
- Drive from factory floor
- Don’t go in with any assumptions
- Be relentless

Things I would do differently…

- Deploy more rapidly
- Evaluate historical data in greater depth prior to initiating project
- Push more activities to vendors (custom code)

Acknowledgements



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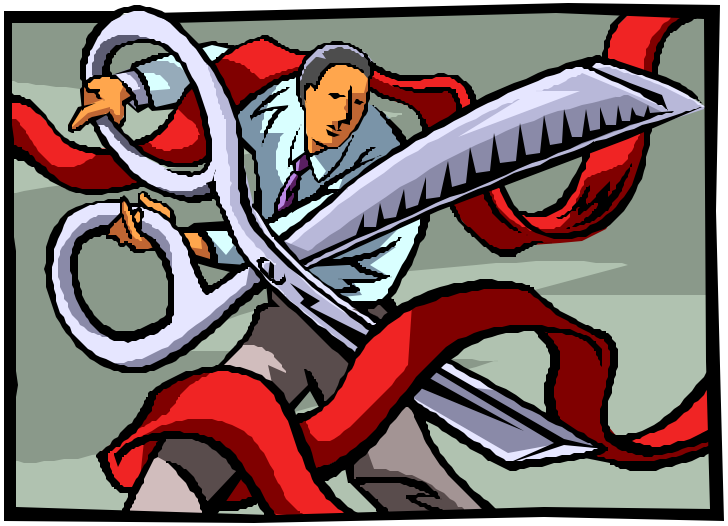
“The reasonable man adapts himself to the world; the unreasonable one persists in trying to adapt the world to himself. Therefore, all progress depends on the unreasonable man.”

George Bernard Shaw

Irish dramatist & socialist (1856 - 1950)



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