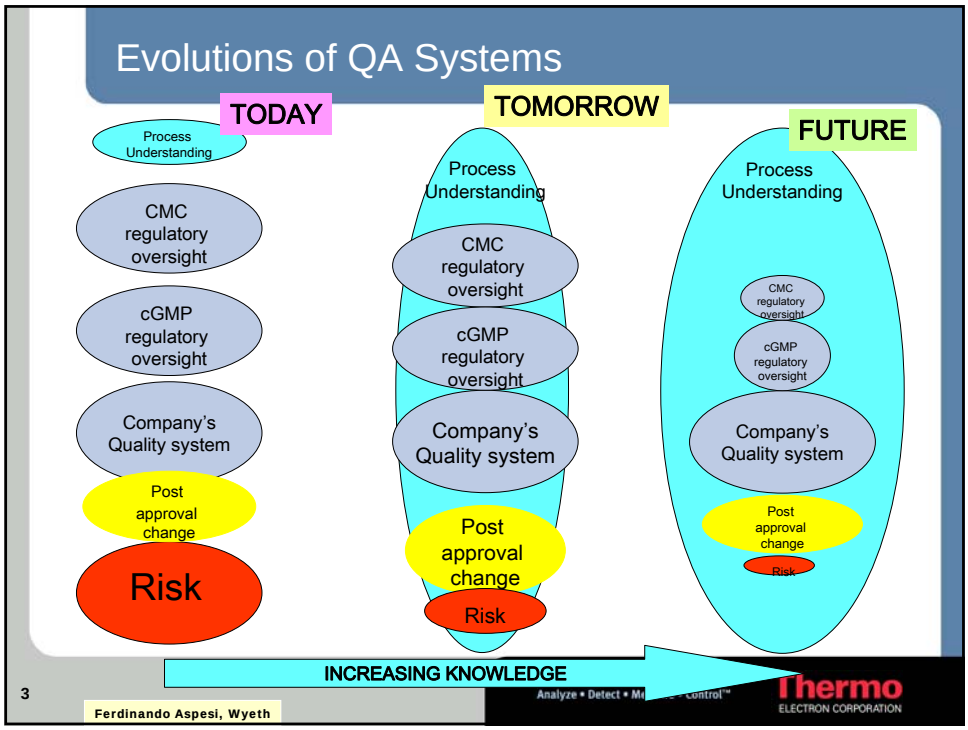
Beyond Process Analysis – Lessons Learned from a Holistic Approach to PAT

Heidelberg PAT Conference 2006

David Radspinner, Ph.D.
PAT Business Development Director
Thermo Electron

Acknowledgements

- Content
  - *Dr. Gawayne Mahboubian-Jones, Optimal*
  - *Dr. Ferdinando Aspesi, Wyeth*
  - *Matt Richards, VP Finance, Thermo*
  - *Gary Larson*
- Inspiration
  - *FDA PATRIOT*
  - *Aventis PAT Team*


Evolutions of QA Systems
TODAY
TOMORROW
FUTURE
Process Understanding
CMC regulatory oversight
cGMP regulatory oversight
Company's Quality system
Post approval change
Risk
Process Understanding
CMC regulatory oversight
cGMP regulatory oversight
Company's Quality system
Post approval change
Risk
Process Understanding
CMC regulatory oversight
cGMP regulatory oversight
Company's Quality system
Post approval change
Risk
INCREASING KNOWLEDGE
3
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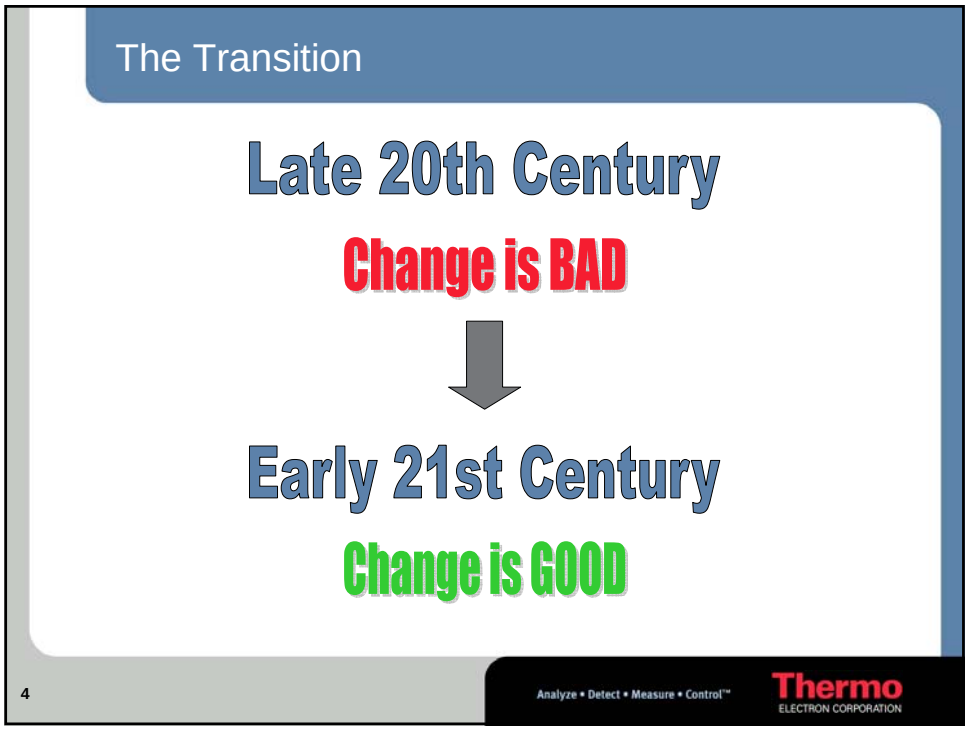
The Transition
Late 20th Century
Change is BAD
Early 21st Century
Change is GOOD
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A definition of PAT

- *PAT* is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality

A definition of PAT - WHAT

- *PAT* is a **system** for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality

PAT is Not Just Process Analytics

A definition of PAT - WHAT

- *PAT* is a system for **designing**, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality

Design for … (Quality, Reliability, Efficiency)…

A definition of PAT - WHAT

- *PAT* is a system for designing, **analyzing**, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality

… with insight on the Material …

A definition of PAT - WHAT

- *PAT* is a system for designing, analyzing, and **controlling** manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality

… so that an action can be taken…

A definition of PAT - WHY

- *PAT* is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of **ensuring final product quality**

… to ensure quality.

A definition of PAT - HOW

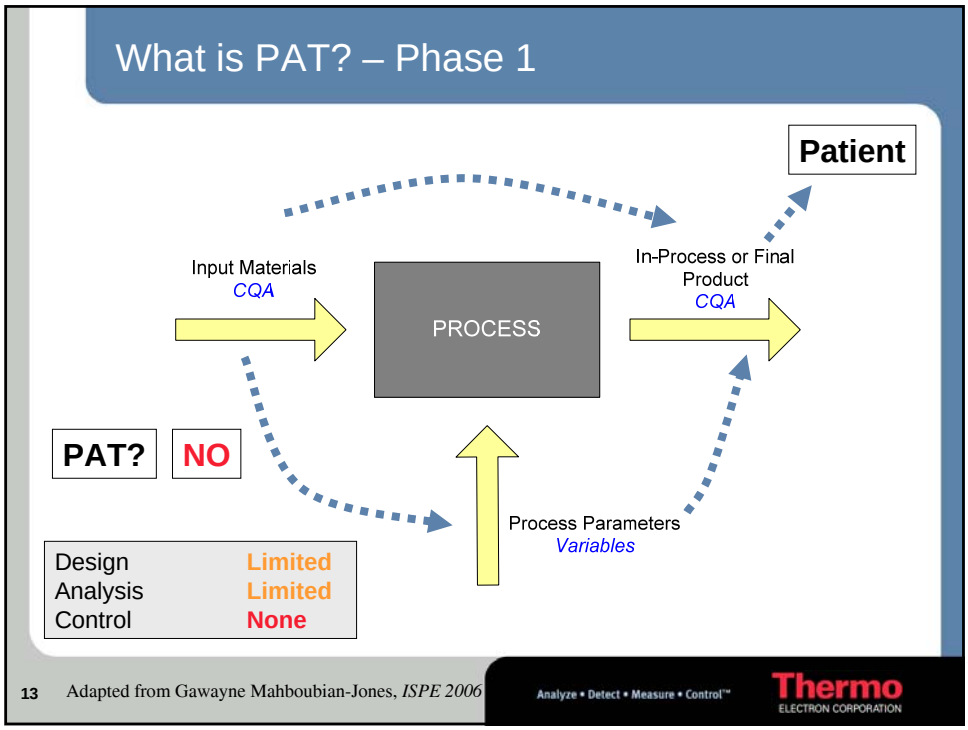
- *PAT* is a system for designing, analyzing, and controlling manufacturing through **timely measurements** (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality

By looking at the Attributes of the Materials

A definition of PAT - WHAT

- *PAT* is a system for **designing**, **analyzing**, and **controlling** manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality

For PAT, we must do all three


What is PAT? – Phase 1
Patient
Input Materials
CQA
PROCESS
In-Process or Final
Product
CQA
PAT?
NO
Process Parameters
Variables
Design
Analysis
Control
Limited
Limited
None
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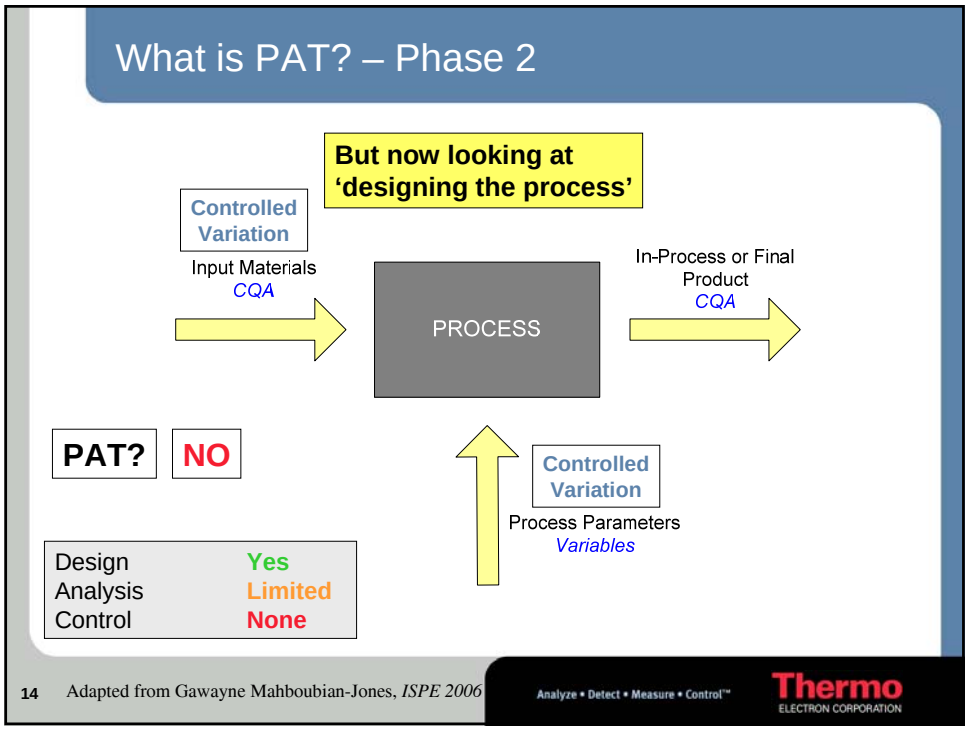
What is PAT? – Phase 2
But now looking at
'designing the process'
Controlled
Variation
Input Materials
CQA
PROCESS
In-Process or Final
Product
CQA
PAT?
NO
Controlled
Variation
Process Parameters
Variables
Design
Analysis
Control
Yes
Limited
None
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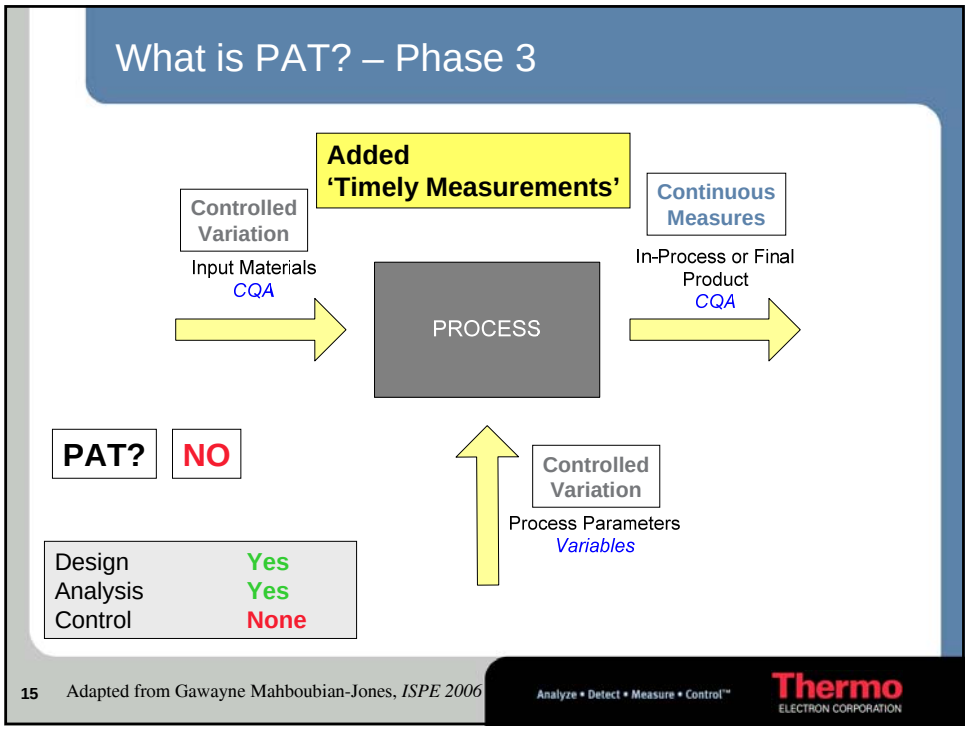
What is PAT? – Phase 3
Added
'Timely Measurements'
Controlled Variation
Input Materials
CQA
PROCESS
Continuous Measures
In-Process or Final Product
CQA
PAT?
NO
Controlled Variation
Process Parameters
Variables
Design Yes
Analysis Yes
Control None
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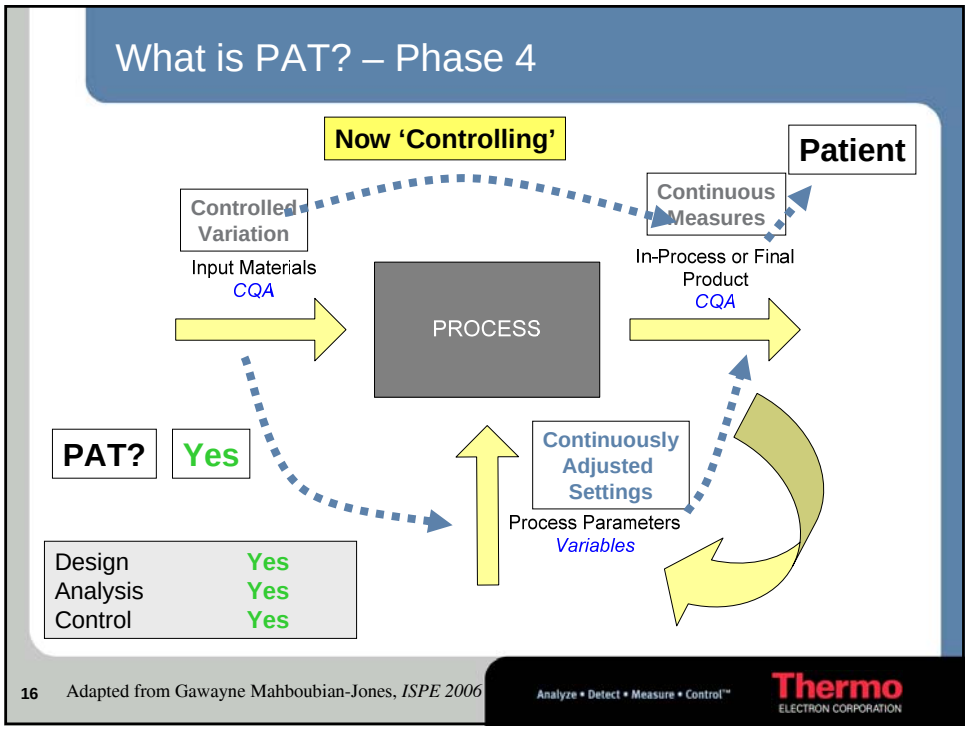
What is PAT? – Phase 4
Now 'Controlling'
Patient
Controlled Variation
Input Materials
CQA
PROCESS
Continuous Measures
In-Process or Final Product
CQA
PAT?
Yes
Continuously Adjusted Settings
Process Parameters
Variables
Design Yes
Analysis Yes
Control Yes
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Parametric vs. Functional Process Description

- Processes can be described parametrically or functionally
  - *Parametric – a description of process parameters (physical constraints and settings) and ranges that are maintained to achieve a target unit quality*
    - E.g. dryer design and volume, air flow, temperature, humidity, etc.
  - *Functional – a description of the attributes and ranges of the material under processing that when generated through process control will ensure the target quality is met with the least risk*
    - E.g. dry to achieve moisture, polymorph, particle size, purity, etc.

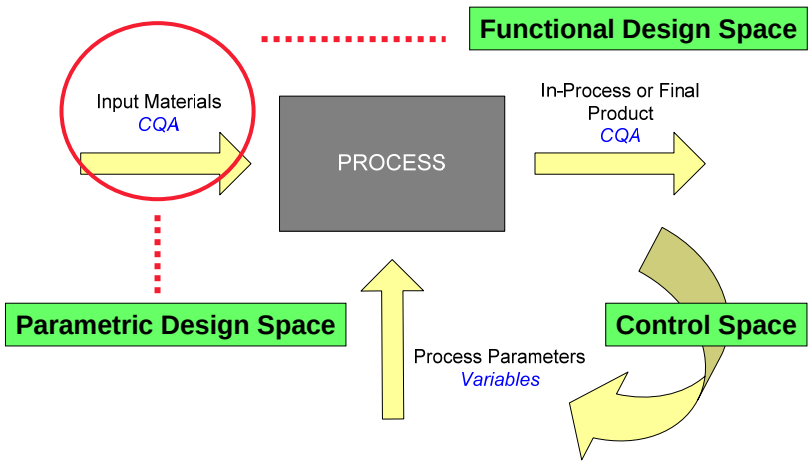
Parametric Description

- Advantages
  - *Easy to describe*
  - *Easy to audit*
  - *Matches control space*
- Disadvantages
  - *Scale limitations*
  - *Differences in environments and equipment*
  - *Is it any different from what we've done?*

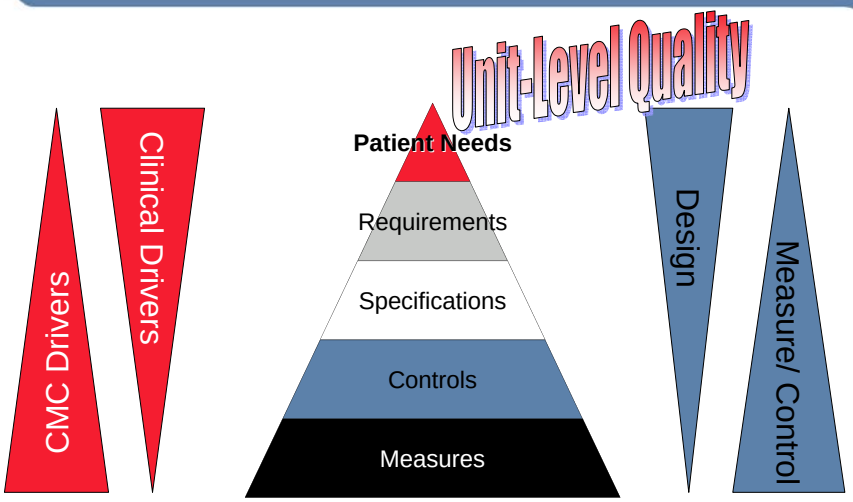
Functional Description

- Advantages
  - *Description tightly linked to patient performance*
  - *Scalable*
  - *Transferable*
  - *Allows parametric flexibility*
- Disadvantages
  - *More difficult to describe*
  - *Technology limitations*
  - *It's different!*

Design Space – Parametric vs. Functional



Quality by Design – From Process to Patient



Practical Impact of Effective Risk Evaluation

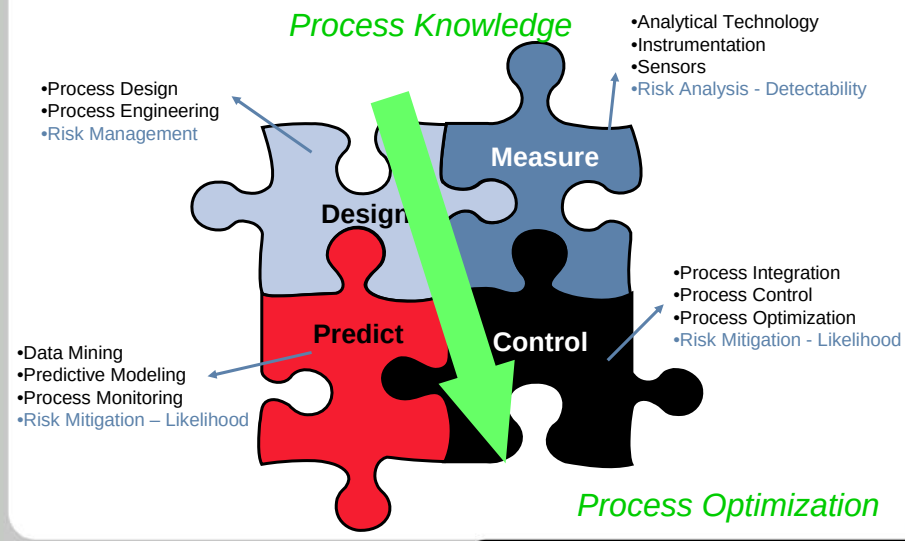
- This phase compares the identified and analyzed risk against given risk criteria.
- Criteria for evaluation are normally set by the organization but guidance exist.

  ASTM E55 – "Risks which are identified during an analysis should receive a proportionate response.

  Q9 – "The evaluation of a risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient

  Q9 – "The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk

PAT – The Framework and Tools



A Typical PAT Solution Consists of…

- Multivariate Tools for Design, Data Acquisition and Analysis
  - *DOE, Chemometrics, etc.*
- Process Analyzers
  - *Chemical, physical, biological, etc.*
- Process Control Tools
  - *MVA, SPC, mSPC, Control electronics, etc.*
- Continuous Improvement and Knowledge Management Tools
  - *MVA, self-learning algorithms, organizational management, training, education, etc.*

PAT is Not Just Process Instrumentation

Customer Drivers

- Quality – Safety, purity, efficacy, performance
- Cost
  - *Cost of Goods*
  - *Yield*
  - *Working Capital*
  - *Productivity*

- Speed of Change
- End User / Consumer Expectations

Does Quality Matter?

- Meeting Specifications vs. Quality
  - *Is meeting specification enough? NO*
  - *Most specifications today have limited relationship to patient functionality – this may change*
  - *Reducing variation allows your business to…*
    - Operate closer to ideal conditions
    - Manage inventory and WIP closer to demand
    - Improve cash flow
- Process Understanding leads to Predictive Controls
  - *Measure*
  - *Evaluate*
  - *Understand*
  - *Predict*
  - *Control*

Anticipate and Act

Drivers on Return on Investment

Supports ROI

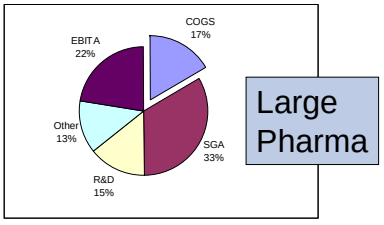
- Speed of implementation
- Reusability of applications
- Knowledge management skills
- Streamlined regulatory communication
- Long product life cycle

Detracts from ROI

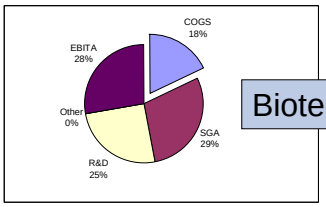
- Regulatory delays
- One-off solutions
- Poor resource utilization
- Short patent life on product
- Internalization of effort

Strategic approach - Focused execution - Prioritization

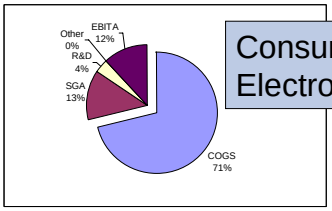
Cost of Goods as a Percent of Revenue



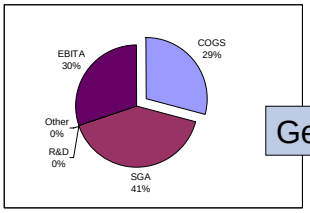
Large Pharma



Biotech



Consumer Electronics



Generics

COGS dominates as price drops and market changes

The ROIC Framework

Value is Created When…

$$ROIC = \frac{\uparrow REVENUES - COSTS \downarrow}{INVESTED\ CAPITAL \downarrow} > \textit{Weighted Average Cost of Capital (WACC)}$$

Cash
Inventories
Receivables
PP&E
Less: Current Liabilities

The ROIC Framework

Understand your Economic Trade-offs

Does your decision…

- *Reduce Costs?*
- *Improve Asset Utilization?*

Attractive Positioning — Attractive Markets

Price x Volume

GOOD

BAD

Shareholder Value:

ROIC > WACC

$$ROIC = \frac{REVENUES - COSTS}{INVESTED\ CAPITAL}$$

Working Capital: Ca$h, A/R, Inventory (F.G, W.I.P., Mats.)

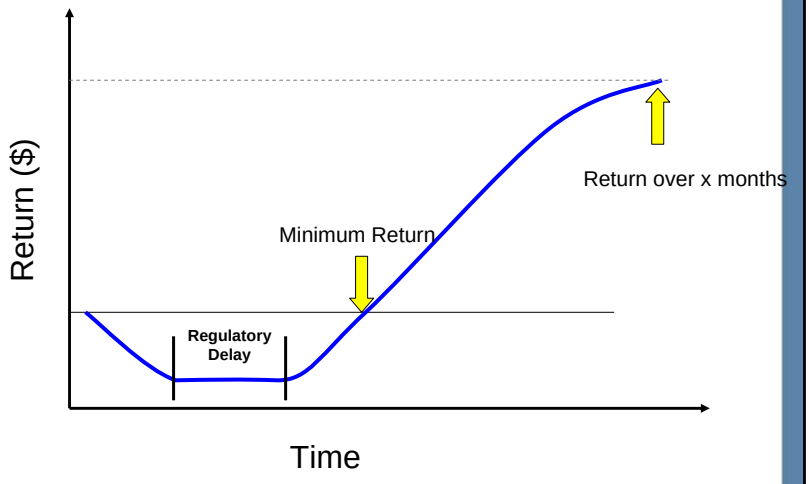
Current Liabilities

P,P & E

Cash is King!

Assets are not free!

Investment Life Cycle



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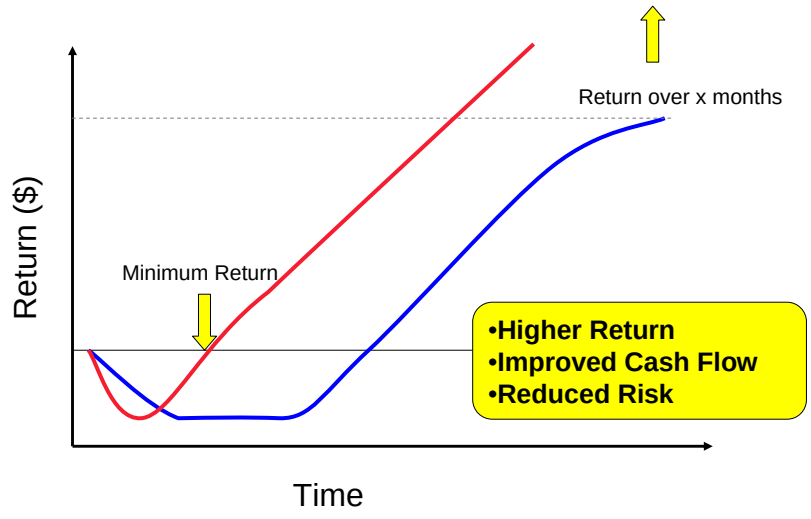
Investment Life Cycle



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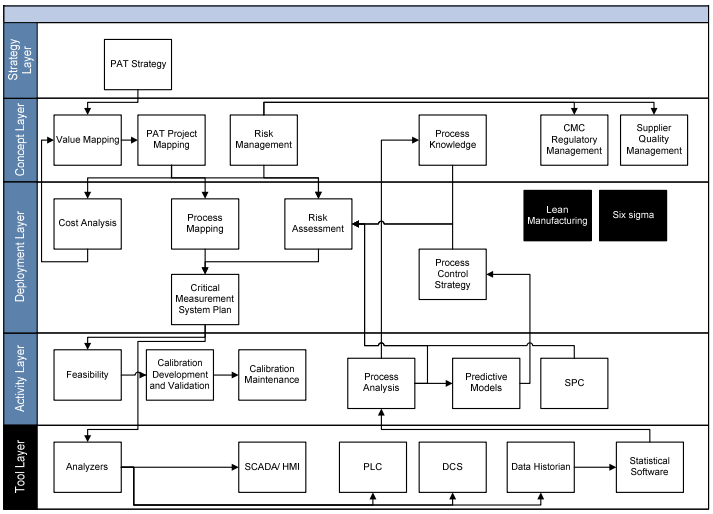
Implementation

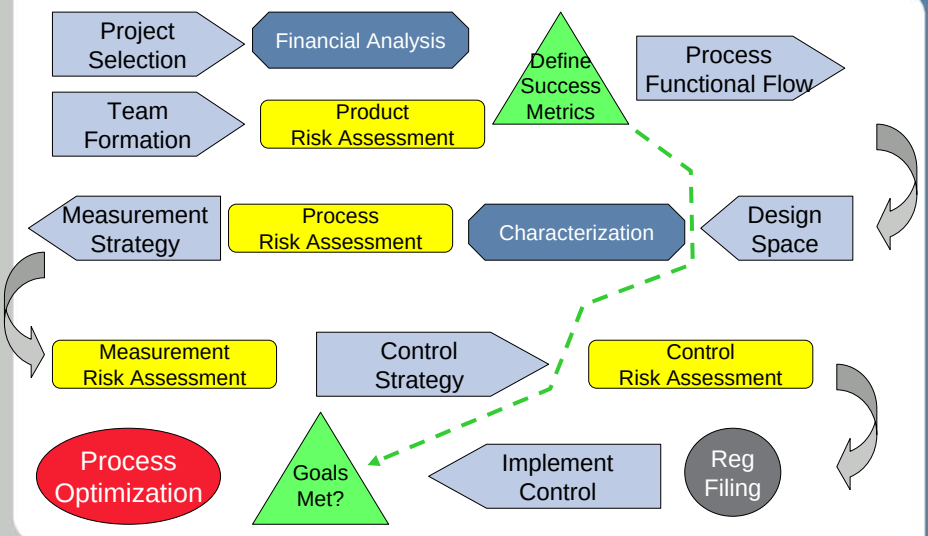
Many Strategies for PAT Implementation

- Pharma firms are developing different approaches to exploit PAT.
- These range from using the initiative in a tactical manner to 'fix' poorly performing processes and move to a 'right-first-time' manufacturing regime through to those with a developed business strategy for PAT that will imbed it into their business process.
- This deep PAT strategy requires the integration of:
  - *measurement technologies*
  - *application development*
  - *process interfacing*
  - *to measure the process and the use of informatics tools to gain process knowledge and ultimately control the process through feed forward or feed back protocols.*
- Measurement technologies are required to be robust and designed for operating in the process environment in what could be a 24/7/365 mission critical application.

Components of a Successful PAT Program



Modern Process Optimization



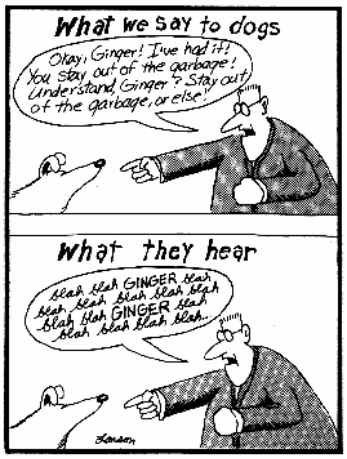
Identify and engage key stakeholders

- Senior Management
  - *Identify a 'Champion'*
- Quality
- Manufacturing
- Finance
- Internal Regulatory Group
- External Regulators
  - *Local agency*
  - *International agencies*
- Establish their Needs, Wants and Expectations early

Speaking the Right Language

Stakeholders

PAT Leader



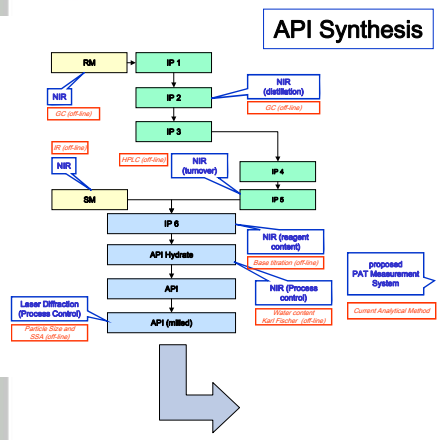
- Cost
- Time
- Risk
- Resources
- Material

- Improved Quality
- Knowledge
- Understanding
- Efficiency
- Rough ROI

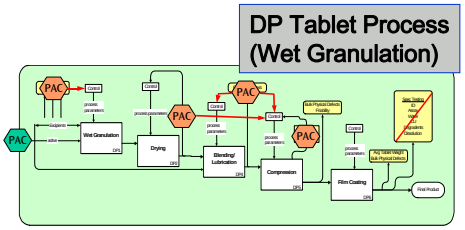
Identify and obtain key capabilities needed for a successful project

- Strategy Setting
- Project Management
- Financial
- Quality Management
- Regulatory
- Technical
- Scientific
- Engineering
- Integration
- Validation
- Support

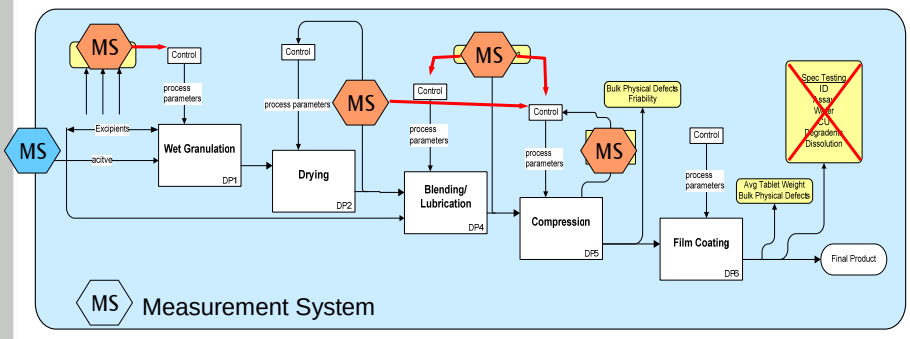
Scope – API Production to Tablet Manufacturing



- More than 15 Measurement systems
- Multiple models
- etc.

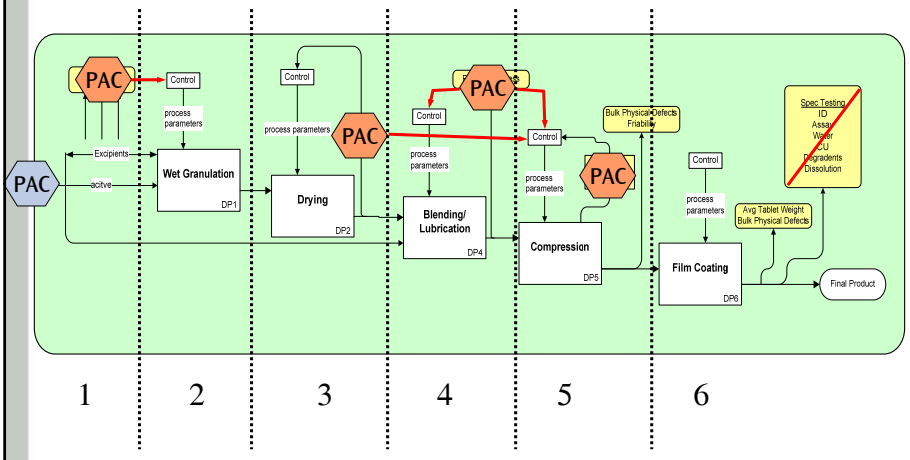


An Example of Tablet Manufacturing – Through PAT



- With real-time analysis, prediction and control based upon process understanding
  - *Rapid optimization and control*
  - *Reduced risk*
  - *Potential to reduce working capital (goods in, work in progress, finished goods)*
  - *Reduce cost of conformance*
  - *Accelerate change cycle*

Elements of Model Building – Holistic View



Control vs. Measure

- You can't **improve** or **control** what you can't **measure**

Corollary

- Just because you can **measure** it doesn't mean you can **control** it
- Just because you **can** measure it doesn't mean you **should** control it

Control Philosophy

- What are you controlling?
  - *List is simple, high-level terms*
  - *Link to product performance and quality*
    - *Tightening drying end-point moisture control*
- Why are you controlling it?
  - *Is it critical to quality, safety or processability?*
  - *Is it linked to your risk management?*
    - *Variation in moisture leads to variation is blend compressability, flow and tablet active content. Processability and dissolution are positively impacted by additional control of moisture.*
- How is it being controlled?
  - *High level, simple, concise*
  - *Diagrams and process flow charts work best*
    - *On-line real-time determination with Near Infrared (NIR) spectroscopy*
    - ***NOT** – determination with a Vendor X, Model Y, NIR spectrophotometer with optical probe (vendor #, model #) installed 3.6m below coupling flange x (see figure x). NIR spectra preprocessed with SNV, then quantified with a PLS model in the following wavelength regions (….) etc.*

Critical Content of a PAT Filing

- Process and Product Knowledge
  - *Design Space*
  - *History*
  - *Relationships (correlations and causations)*
- Risk Management
  - *Pareto Principle*
  - *"80% of the variation is most likely caused by 20% of the parameters"*
- Control Philosophy
  - *What, why, where, how, how often*
- Continuous Improvement
  - *How, so what?*

Impact on Qualification and Validation

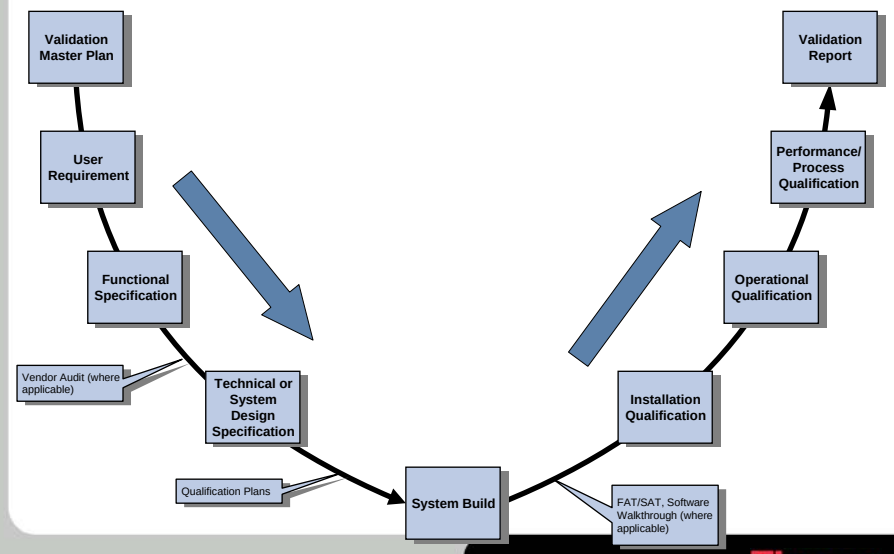
Considerations to Accelerate and Reduce the Complexity of Implementation

- Can you apply today's quality procedures to my PAT project?
  - *You can try, but I suggest you will struggle*
    - Same concept of quality systems,
    - But risk based to focus on critical items
  - *Focus on quality concepts (spirit remains the same) not on procedural steps*
- What has to change?
  - *Risk based approach*
  - *Iterative, continuous improvement approach to learning*
  - *Rethink of how we use the term "validation"*
- Example
  - *Iterative, risk based approach to system qualification/ validation*

Implementing Modern Practices within Today's Systems

	Old Paradigm	New Paradigm
Validation	Generality; protocol-centric; 3 batches with extra testing; event-driven	Risk-based; effort proportional to risk; continuous quality verification (CQV)
Qualification	Protocol-centric; complex multi-layered;	Risk-based; effort proportional to risk; continuous assessment of capability
Change Control	All changes important; document centric; objective is regulator	Risk-based; centered on risk assessment and mitigation; quality-centric
Material Management	Universal specifications; pharmacopeia acceptance; laboratory controls	Performance-based; rapid assessment at receipt and use; limited inventory
Product Release	Meet Spec; keep sample size small; end-product testing; significant testing lag with high levels of WIP	Real-time assessment/ prediction; process monitoring; rapid release; reduced WIP

Validation V-Model (Example of Current State)



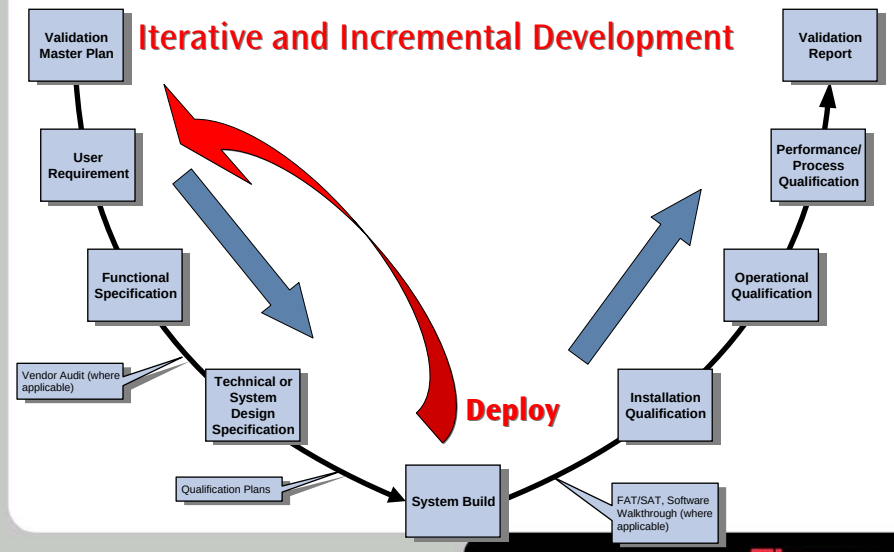
The Issue: Current Qualification Approach

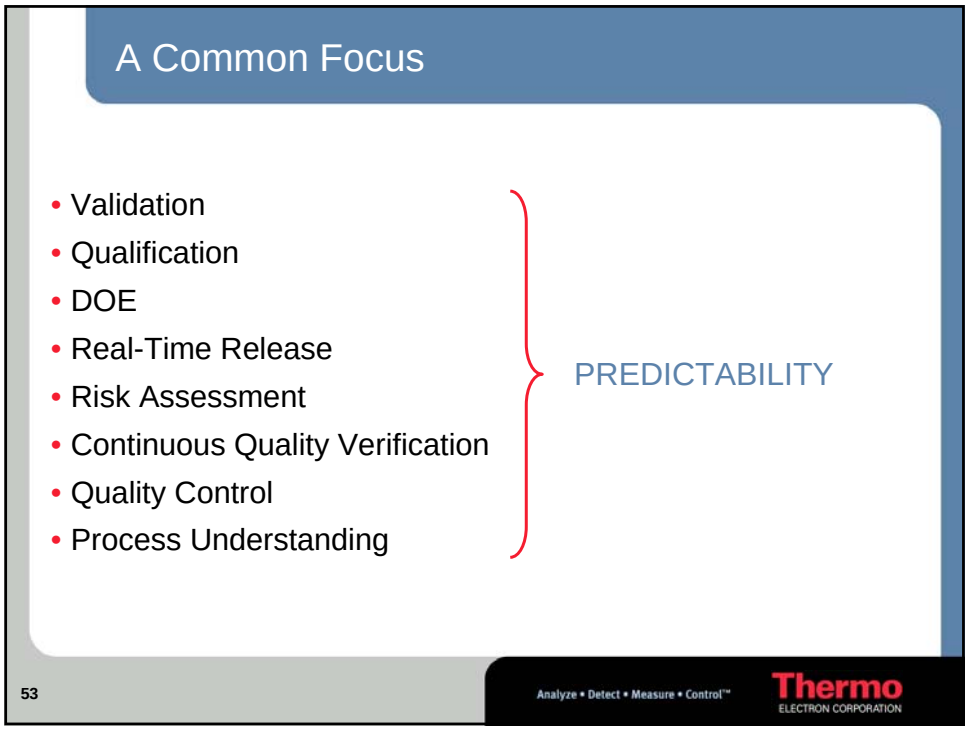
- Single path (predetermined, non-iterative) based upon user requirements
- Assumes: Users know exactly what they want and can communicate this …
  but
  - *… no details will be discovered once well into implementation;*
  - *… the complexity of multi-component system is well understood by all parties;*
  - *… no external force will lead to a change in requirements.*

The Issue:
Current Qualification Approach (cont')

- All requirements (and systems in some cases) are of equal criticality
- Success is determined by completion of documentation not reliability of the system
- Approach to risk assessment is very limited
- Not reflecting actual process requirements

Validation V-Model




A Common Focus
• Validation
• Qualification
• DOE
• Real-Time Release
• Risk Assessment
• Continuous Quality Verification
• Quality Control
• Process Understanding
PREDICTABILITY
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