

Keynote Presentation:

“Pharmaceutical Quality in the 21st Century:
Personal Reflections ”



Ajaz Hussain, Philip Morris International

Pharmaceutical Quality in the 21st Century: Personal Reflections

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27 September 2011, Boulder, Colorado

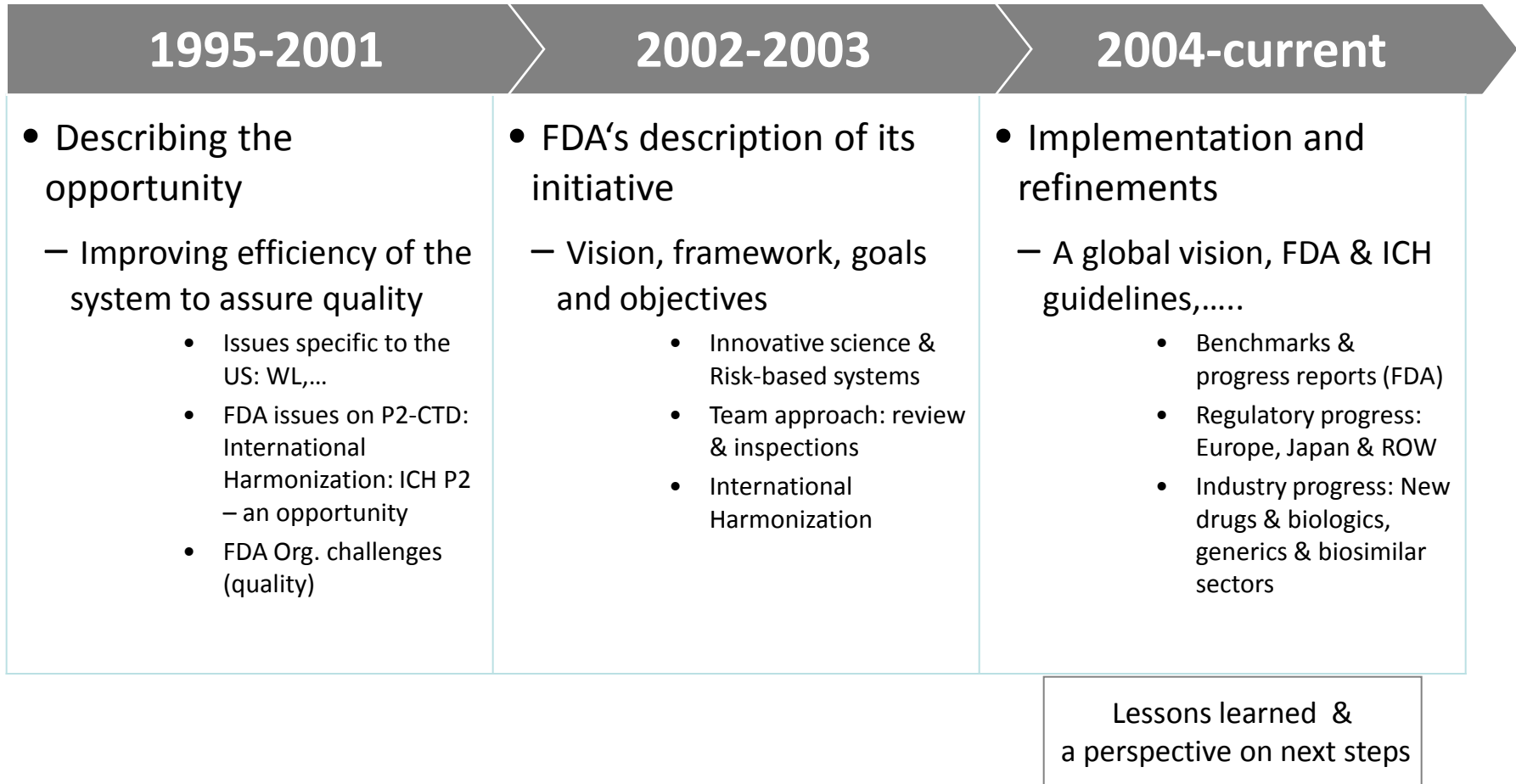
Outline

- Background (prior to 2002)
 - The FDA Initiative on Pharmaceutical Quality for the 21st Century was launched in 2002: Why and How?

Audience participation: Q&A

- Progress (2004- current)
 - An analysis of progress reports - an industry perspectives
- Challenges yet to be addressed
 - Reflections (lessons learned)

Presentation Overview



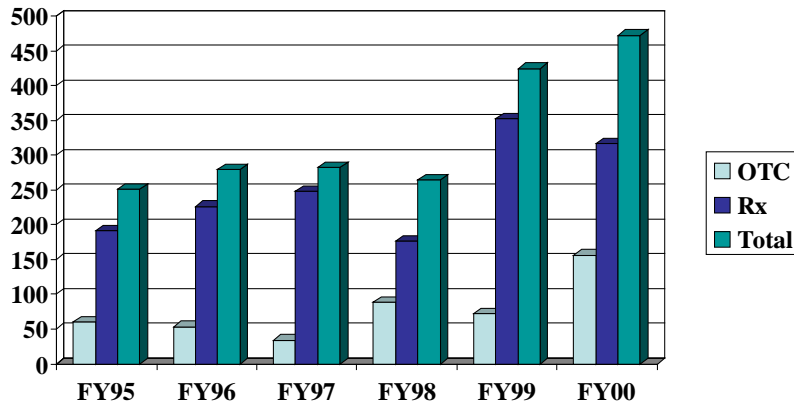
Reference: For more detailed information please review the FDA Final Report (2004) Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach and the White Paper entitled [Innovation and Continuous Improvement in Pharmaceutical Manufacturing](#) (The PAT Team and Manufacturing Science Working Group Report: A Summary of Learning, Contributions and Proposed Next Steps for Moving towards the "Desired State" of Pharmaceutical Manufacturing in the 21st Century

The FDA Initiative on Pharmaceutical Quality for the 21st Century was launched in 2002: Why and How?

Describing the opportunity

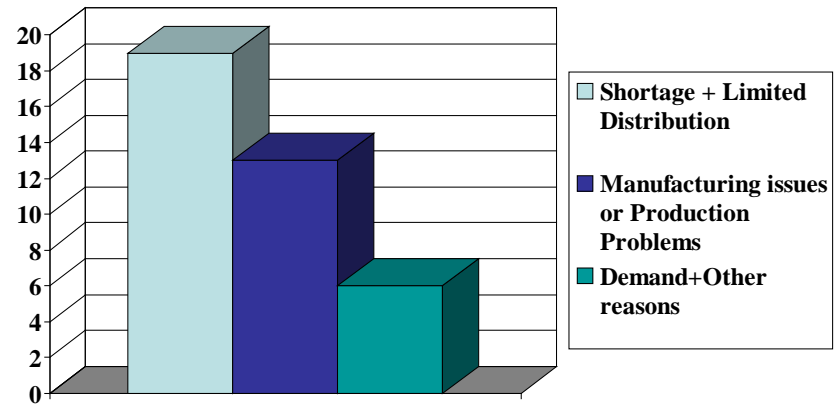
Quality Issues: Product Recalls, Shortages, and Detection

Recalls

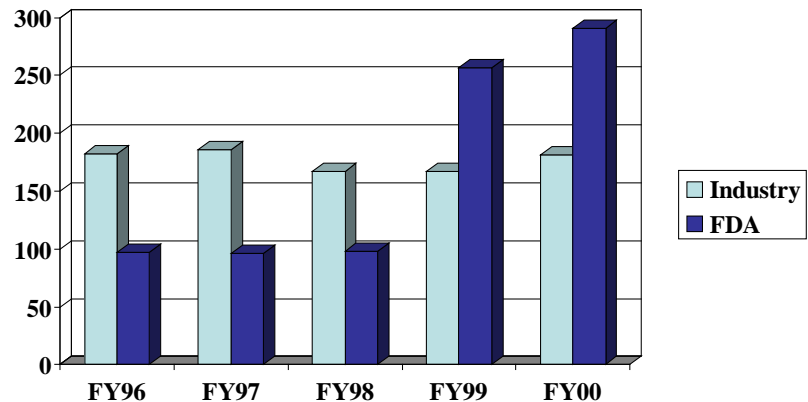


FDA data (2000), Mike Verdi. DMPQ/OC/CDER

Shortages



3/8/02, <http://www.fda.gov/cder/drug/shortages/#Current>



Defect Discovery: Who?

Debates within FDA

- “Will this \$ X00 million “consent decree” improve quality of the real product?”
- How effective is “process validation”? Is it not just a “well rehearsed demonstration.... 3 times”?
- Is our system truly a “modern quality system”?
- Are our “specifications” based on sound science and risk principles?
- How is “c” in cGMP established?
- Do current regulations support “continuous improvement”?
- How efficient is pharmaceutical manufacturing?

Arduous Negotiations on ICH CTD Section P2: Pharmaceutical Development

Washington 2/98	Tokyo 9/98	Brussels 3/99	Washington 8/99	Tokyo 3/2000
<ul style="list-style-type: none"> • Development Pharmaceuticals No agreement • Expert Report and <i>GAIYO</i> listed as regional requirements and not in scope of CTD 	<ul style="list-style-type: none"> • Proposal from E.U. to include Development Pharmaceuticals in CTD • PhRMA agreement to consider • FDA and MHLW neutral to proposal 	<ul style="list-style-type: none"> • Discussed industry concerns of including 'development data' in the CTD • U.S. industry generally against • Evening meeting at Restaurant Vincent (FDA, E.U., PhRMA) 	<ul style="list-style-type: none"> • Agenda for EU seminar • How reviewed in the E.U. • Role of Development Pharmaceuticals in E.U. review process • Role of Expert Report in the E.U. review process 	<ul style="list-style-type: none"> • Consensus on including Pharmaceutical Development in CTD (EU-PhRMA) • 'Development data' generally limited to studies on commercial formulation (not a comprehensive development history)
<p>Different approaches to regulatory science: Utility of pharmaceutical development information in CMC review and cGMP inspections.</p>				

Adapted from the presentation by Robert G. Baum, Ph.D., Pfizer Global R&D, at the 2004 PDA SciTech Summit (March 10, 2004)

Pharmaceutical Development: Confronting Inter-disciplinary Tensions

- Inter-disciplinary tensions
 - Familiar from academic days, needed a direct confrontation
- Art vs. Science Debates
 - FDA's CMC review staff did not see much utility of 'trial-n-error' data, and in some instances penalized those reviewer who reviewed P2 section, for informing regulatory decisions (e.g., setting product specifications)
- Higher acceptance in EU (and Japan)
 - A higher proportion of Industrial Pharmacy and Pharmaceutical Engineering disciplines in EU (and Japan)

Table I: Profile of the typical pharmaceutical industry employee working in the United States and in Europe.

	United States	Europe
Gender	Male	Male
Age	42	42
Highest level of education	Bachelor's	Masters
Field of study	Analytical chemistry	Pharmaceutics/pharmacy
Years of professional work experience	16	18
Type of employer	Private industry	Private industry
Job function	QA/QC	QA/QC
Years at current employer	6.8	10.6
Hours worked per week	46	45
Vacation days taken per year	12	23
Mean base annual salary	\$84,477	\$70,131

Pharmaceutical technology 2003

*A question for the audience:
Process **Control** vs. Process **Validation**;
What is the difference?*

Requirements for Change Control & Validation of New Methods in EU

- Although regulators in EU were utilizing Development Pharmaceuticals information
 - Their approach to change control and validation of new analytical methods also did not adequately support innovation in the manufacturing sector
- Need for supporting innovation and improvement was clear based on available data on manufacturing inefficiencies
- In the UK the ongoing efforts of the New Technologies Forum (RPS) provided a significant impetus to move forward in the US on PAT

Table 1: Benchmark data from Benson & McCabe

Measure	Pharmaceutical industry	A winning pharmaceutical factory	A world-class factory
Stock turn	3-5	14	50
On time in full delivery	60-80%	97.4%	99.6%
Right first time	85-95%	96.0%	99.4%
Process capability CpK	1 to 2	3.5	3.2
Overall equipment effectiveness	30.0%	74.0%	92.0%
Cycle time (hours)	720	48	8
Safety/100,000 hours	0.100	0.050	0.001

Benson, R. S. and D. J. MacCabe. "From Good Manufacturing Practice to Good Manufacturing Performance." Pharmaceutical Engineering. July/August 2004. vol. 24, no. 4: 26-34

Describing the Opportunity

Awareness of the 'Challenging Opportunity'

THE WALL STREET JOURNAL

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WEDNESDAY, SEPTEMBER 4, 2002 - VOL. CXXIII NO. 43 - WWW.B100

Factory Shift

New Prescription For Drug Makers: Update the Plants

After Years of Neglect, Industry
Focuses on Manufacturing;
FDA Acts as a Catalyst

The Three-Story Blender

By LEILA ABOUD
And SCOTT HENSLEY

Main points from this:

- High tech in R & D
- Relatively low tech in Manufacturing
- It matters
 - Big Pharma manufacturing costs are \$ 90 Bn
 - Significantly more than R&D

*Quality by Design: A Challenge to the
Pharma Industry*

(CAMP, R. Scherzer, FDA Sci. Board, 4/9/02)

CAPA is not Continual Improvement

EVOP

Proposed in 1957 by **G. E. P. Box**

(Evolutionary operation: A method for increasing industrial productivity. Applied Statistics. 6: 81-101 (1957))

KAIZEN
(Ky' zen)

A Japanese word introduced in the West (~late 70's)

and translated as "Continuous Improvement"
- slow, incremental but constant.

QS-9000

"For those product characteristics and process parameters that can be evaluated using variable data, continuous improvement means optimizing the characteristics and parameter at a target value and reducing variation around the value.."

Quality System Requirement QS-9000, 3rd edition, element 4.2.5 – Continuous Improvement (1998)

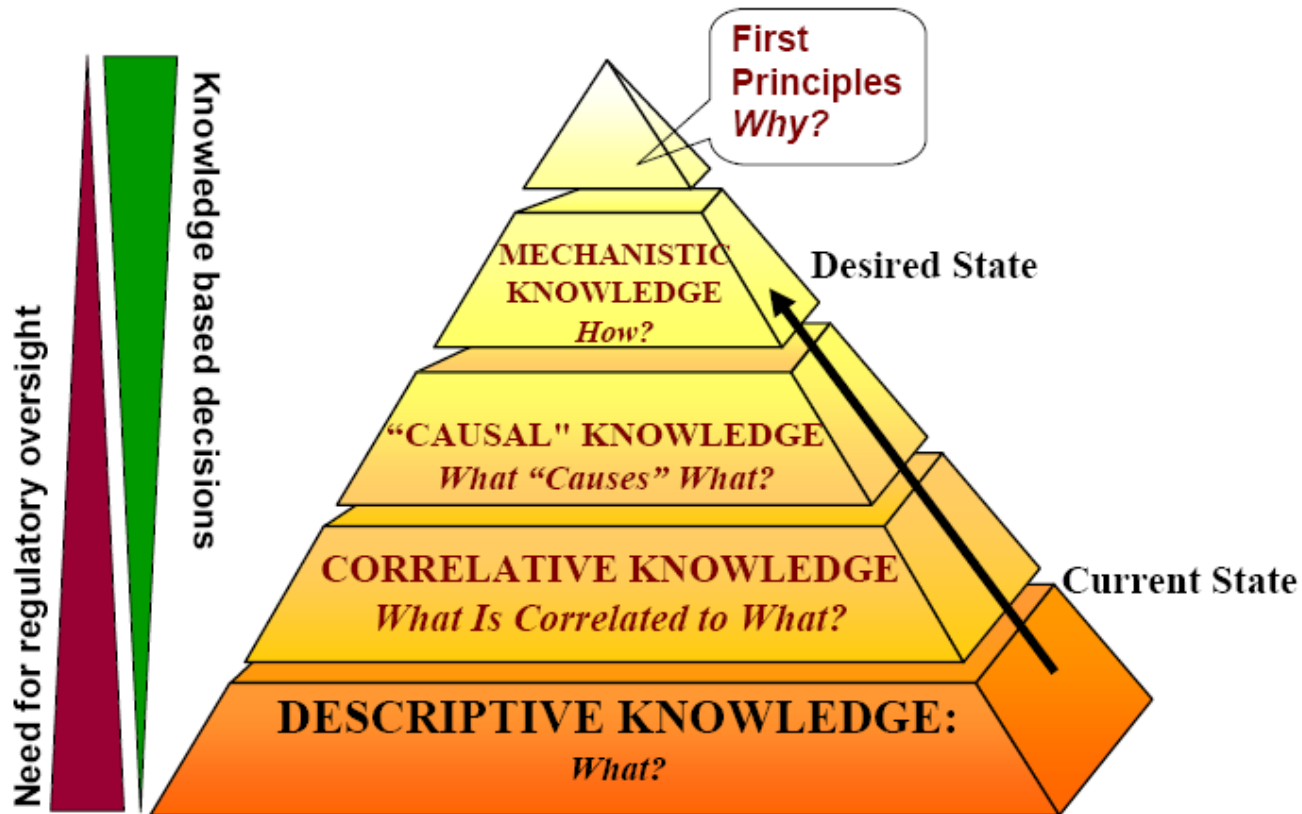
MB Award,..
Six-Sigma.....

- **Structured development then EVOP** -approach based on statistical DOE's –EVOP protocol
- **Empowerment through training**
- **Specifications** - attribute data - continuous improvement is not possible until characteristics are conforming.
- **CAPA Vs Continuous Improvement Vs. Innovation**
- If attribute data results do not equal zero defects, it is by definition a nonconforming product. Improvements made in these situations are by definition corrective actions, not continuous improvement.

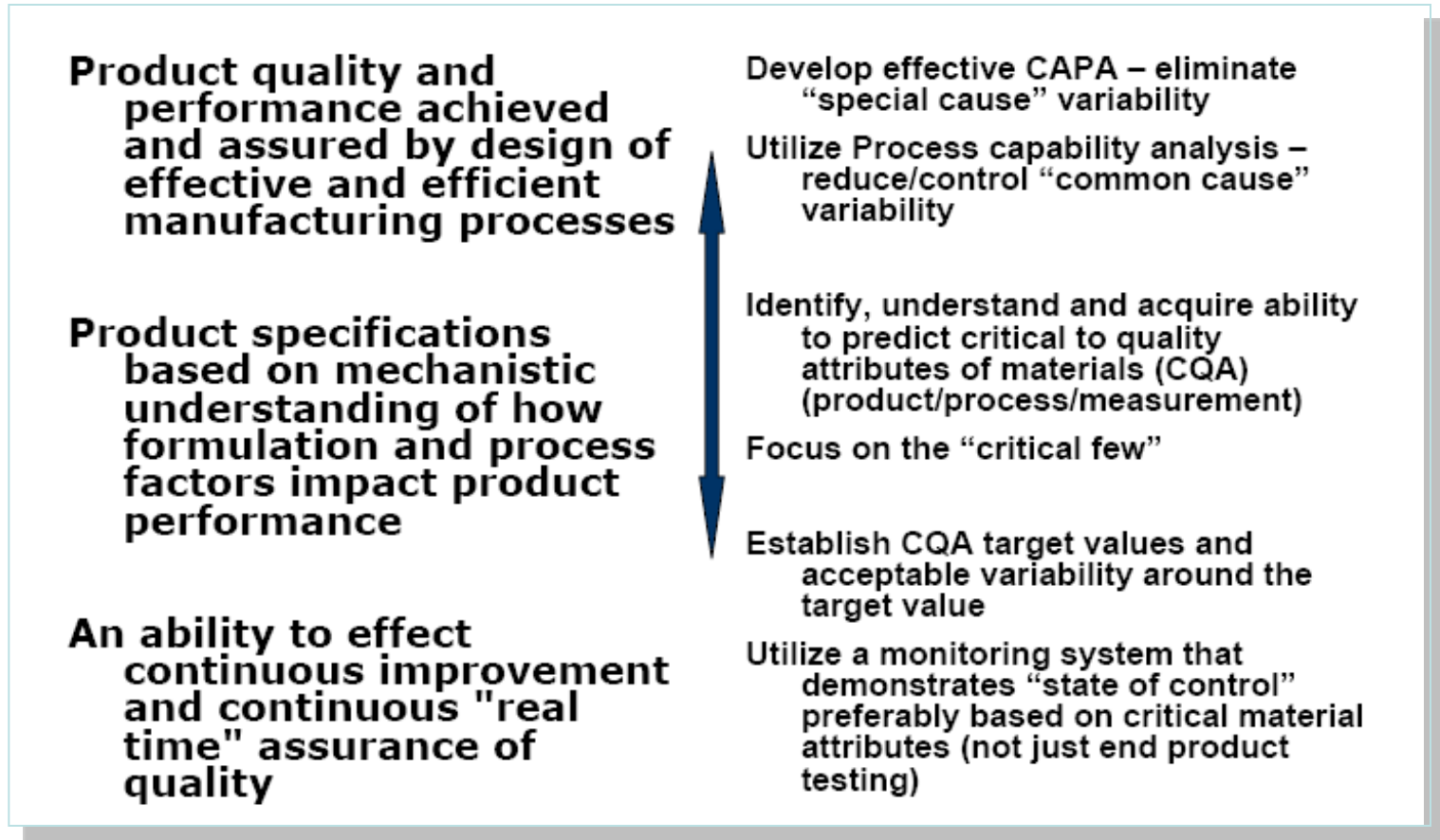
No lurching from "fad to fad"- focus on solid foundation!

Science and Risk-Based Regulatory Decisions

Regulatory oversight can be tailored to reflect scientific rigor demonstrated in an application when it is realized through company's robust quality system



The Desired State



Tradespace & Design-space

Case Application: Satellite Radar

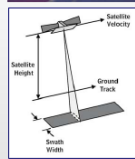
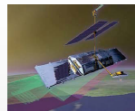
- Critical issue in national security space
- Unique all-weather surveillance capability
 - Opportunity for impact given ongoing studies
 - Rich multi-dimensional tradespace

Unit-of-analysis: SR architecture

- Radar payload
- Constellation of satellites
- Communications network

Availability of data

- Systems Engineering Advancement Research Initiative (SEARi)



(CBO 2007)

Case Application Goal

To assess potential satellite radar architectures for providing the United States Military a global, all-weather, on-demand capability to track moving ground targets; supporting tactical military operations; maximizing cost-effectiveness; and surviving disturbances in the natural space environment.

MIT Engineering Systems Division

Phase 2: Generate Concepts

Design Value Mapping Matrix establishes traceability between value-space and design-space

		ATTRIBUTES													Total Impact								
		Mission						Programmatics															
		Tracking			Imaging			Cost		Schedule													
DESIGN VARIABLES	Variable Name	Definition	Range	Minimum	Target	RCS	Min. Detectable Velocity	Number of Target Boxes	Target Acquisition Time	Target Track Life	Tracking Latency	Resolution (Proxy)	Targets per Pass	Field of Regard	Revisit Frequency	Imaging Latency	Baseline Cost	Actual Costs (Era)	Baseline Schedule	Actual Schedule (Era)			
		Peak Transmit Power	1.5 10 20 [kW]	9	9	9	3	1	1	9	9	9	0	1	9	9	9	9	9	9	9	9	96
		Radar Bandwidth	.5 1 2 [GHz]	9	9	3	3	1	1	9	9	9	0	1	3	3	3	3	3	3	3	3	66
		Radar Frequency	X UHF	9	9	3	3	1	1	9	9	9	0	1	3	3	3	3	3	3	3	3	66
		Physical Antenna Area	10 40 100 200 [m^2]	9	9	9	3	1	1	9	9	9	1	1	9	9	9	9	9	9	9	9	97
		Receiver Sats per Tx Sat	0 1 2 3 4 5	9	9	3	3	1	1	9	3	3	1	1	9	9	9	9	9	9	9	9	79
		Antenna Type	Mechanical vs. AESA	9	9	9	3	3	1	9	9	9	1	1	9	9	9	9	9	9	9	9	99
		Satellite Altitude	800 1200 1500 [km]	9	9	3	9	9	3	9	9	9	9	3	1	1	1	1	1	1	1	1	85
		Constellation Type	8 Walker IDs	0	0	1	9	9	3	0	0	3	9	3	9	9	9	9	9	9	9	9	73
		Comm. Downlink	Relay vs. Downlink	0	0	0	0	0	9	0	0	0	0	0	9	9	9	9	3	9	9	9	48
		Tactical Downlink	Yes vs. No	0	0	0	0	3	9	0	0	0	0	0	9	9	9	9	3	9	9	9	51
		Processing	Space vs. Ground	0	0	0	1	0	3	1	0	0	0	3	9	9	9	9	9	9	9	9	44
		Maneuver Package	1x, 2x, 4x	1	1	1	1	1	0	1	1	1	1	0	9	3	3	3	3	3	3	3	27
	Tugable	Yes vs. No	1	1	1	1	1	0	1	1	1	0	9	9	9	9	9	9	9	9	9	45	
	Constellation Option	none, long-lead, spare	0	0	0	0	0	0	0	0	0	0	0	9	9	9	9	9	9	9	9	36	
	Total		65	64	42	39	30	33	66	58	62	23	33	106	100	88	100						

An Approach to Overcome Inter-disciplinary debates and Inter-organizational issues

- “Turf” battles >> Team Approach
- Vocabulary: Negative >> Collaborative (“process validation >> process understanding”)
- “Process control”: “Static” >> “Dynamic” concept (part of “design space”)
- “Pharmaceutical Development” information kept at site >> shared with CMC reviewers (Quality by Design -ICHQ8)
- Risk-based decisions (ICH Q9)
- Minimize *Prior-Approval Supplements* >> Change Control within company Quality System (“ICH Q10”)
- Reduce regulatory fear to promote continues learning
- CAPA >> Continues Improvement

The CMC – cGMP Divide at FDA



PAT Team & Guidance: The “Pull”

The PAT Framework: Based on well established principles (Fisher + Shewart + Deming”)

Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)
Pharmaceutical CGMPs
September 2004

Regulatory strategy accommodating “process understanding” based regulatory flexibility for innovation and continuous improvement



The diverse and determined PAT team has good reason to smile.

Pharmaceutical Manufacturing • www.pharmamanufacturing.com



Summary: Why Pharmaceutical Quality for the 21st Century?

Challenges (FDA)	Questions (FDA)	Answers (FDA)
<ul style="list-style-type: none"> • Manufacturing issues <ul style="list-style-type: none"> – Warning letters, Consent decrees, .. (Drug shortages) • FDA Org. key challenge: <ul style="list-style-type: none"> – CMC Review vs. cGMP Inspections (Specifications vs. Process Validation) • FDA ICH key challenge <ul style="list-style-type: none"> – Lack of consensus (industry and regulators in US, EU, Japan) on the content of the section 3.2.P2 (Pharmaceutical Development Report) of the Common Technical Document (CTD) 	<ul style="list-style-type: none"> • How effective is the current approach for ensuring confidence and availability of quality drug products? • In-part related to above: How to improve and align CMC review & cGMP inspections?* • Can CTD-P2 be a means to address these questions (above)? • (And, can these effort, in part, help to align drugs & biologics; therapeutic proteins with drugs and the advent of biosimilar products?) 	<ul style="list-style-type: none"> • Not as effective as it can and should be (transparent discussion, FDA Sci Board) • Need better information to make science and risk-based decisions • The ICH P2-CTD can be an opportunity – need appropriate information • Start with Process Analytical Technology (PAT) Guidance and team approach to CMC Review and cGMP inspections for PAT applications

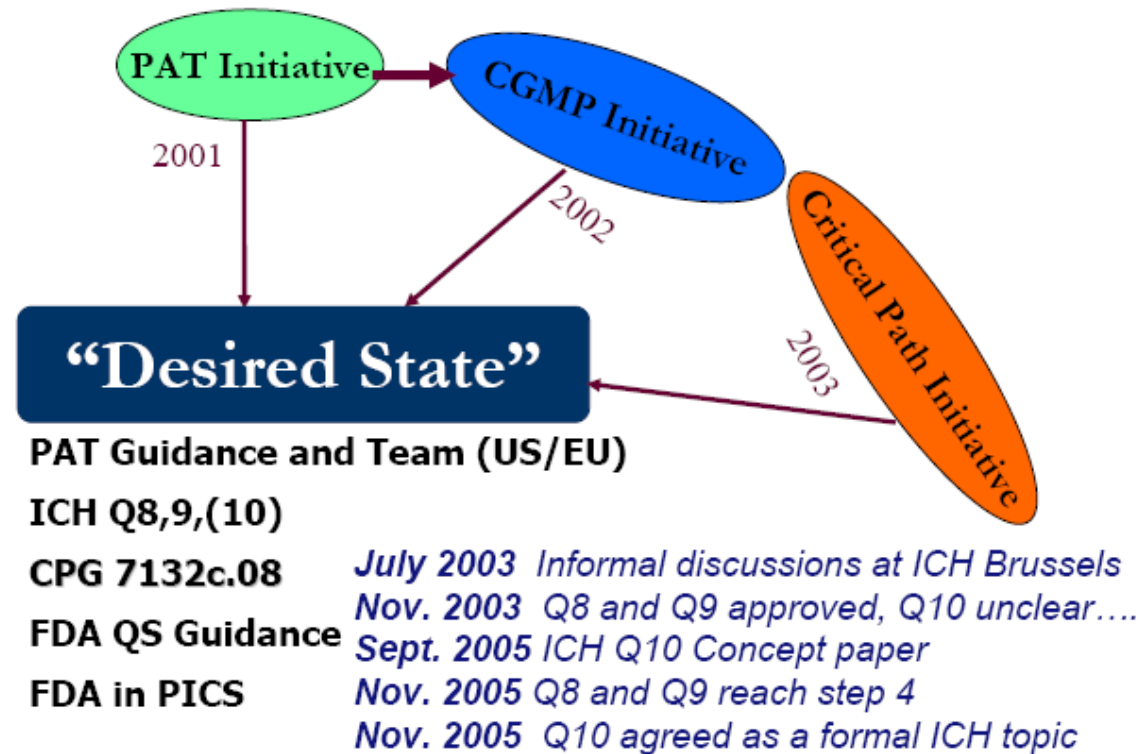
* To achieve this without compromising current level of confidence in the quality of marketed products

An Analysis of Progress – Perspectives

Audience discussion: Q&A

PAT: Opening the Door

PAT: Opened the door for ICH Q8, Q9, Q10, FDA/OGD's Question based Review, etc.



Stepping Aside in 2005

Acknowledgements



Design Space

Procrustean

Epistemological

ICH Negotiations 2004, Kyoto, Japan (Courtesy: John Berridge)

The new paradigm: - What's in it for Industry?

Consistency	Standardisation and globalisation
Regulatory Submissions	Align CTDs Move to comprehensive QOS leading to faster review Regulatory Contract: << post-approval supplements/variations
Validation	Continuous verification, no 'redos' - faster launches, supplies reliability
Process Efficiency	Less waste, fewer 'redos' We know what we are doing and why 'Real-time release'
Continuous Improvement	Improved compliance, CAPA facilitated (emphasis on P) Innovation and change encouraged

This is more than a new paradigm – a potential revolution?

Since the Launch of this Initiative

- Significant progress in the development of ICH and other regulatory guidelines
 - and numerous conferences and workshops
- PAT Team dissolved at FDA, guidance not utilized.
 - EMA PAT Team and QbD efforts still appear to be inspired by the PAT Guidance
- EMA Biosimilar pathway and approvals
 - US FDA still struggling, progress suggested in the very near future
- Recent industry comments suggest an ongoing struggle
 - For example, “QbD is in its infancy” or “not focused on QbD”
- July 27, 2011 Meeting of FDA Advisory Committee for Pharmaceutical Science
 - State of QbD Implementation: Adoption, Success and Challenges (McKinsey Report)

Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach (September 2004)

- Encourage the early adoption of new technological advances by the pharmaceutical industry
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance
- Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas
- Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
- Enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by further integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities

Problem to solve?

Progress?

Challenges?

Points of View on the FDA's Initiative on Pharmaceutical Quality for the 21st Century?

- Problem to solve?
 - Improving reliability and productivity of pharmaceutical manufacturing through science and risk-based regulatory decisions and creating opportunity and flexibility for innovation and continuous improvement
- Measuring Progress?
 - Over the past decade (2000-2011) to what extent have the *pharmaceutical science, technology, and regulatory science* increased their problem solving ability and have created regulatory flexibility for innovation and continuous improvement
- Challenges?
 - Has the initiative maintained its focus on the problem to be solved and not inadvertently introduced new problems that may be preventing further progress?

Challenges yet to be addressed

Concluding remarks

Reflections (Lessons Learned)

- Scale-Up & Post Approval Changes
- In Vitro to In Vivo Correlations
- Biopharmaceutics Classification System
- Process Analytical Technology & Process understanding
- Quality by Design & Design Space
- Biosimilar development and approvals in EU, ROW, in US
- Plant-based vaccines
- Tobacco harm-reduction

- Public Health
- Regulatory science

- Science-based & Risk-based decisions
- Trans-disciplinary

**Separation of
uncertainty & variability**

Quantitative risk assessment models

Risk-perception

Human behavior