Pharmaceutical Quality by Design: Improving Emphasis on Manufacturing Science in the 21st Century

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August 5, 2004

Assigned Objectives

- Explain the concept of quality by design is a key component in modern, effective quality system
- Discuss manufacturing science and its ability to identify critical control points
- Discuss how the identification of critical control points through the application of manufacturing science is linked to risk management, and how it is linked to cGMPs
- Discuss how knowledge relating to critical control points allows an optimal focus on what is important in the manufacturing and documentation process

Dimensions of the FDA's Initiative on Pharmaceutical Quality for the 21st Century

FDA Unveils New Initiative To Enhance Pharmaceutical Good Manufacturing Practices
http://www.fda.gov/bbs/topics/NEWS/2002/NEW00829.html (August 21, 2002)

Outline

- Describe "Pharmaceutical Quality by Design" and "Manufacturing Science"
- Explain how a focus on manufacturing science leads to manufacturing ***process understanding*** and its ***control*** to ***mitigate risk*** of poor quality
- Discuss regulatory CMC and CGMP opportunities to improve our ability to maintain the gold standard of US pharmaceutical quality and facilitate innovation and excellence in US industry

"Pharmaceutical Quality by Design" and "Manufacturing Science"

- Our quality system, in principle, is based on the foundation that "quality can not be tested into products, it has to be built-in or has to be by design"
  - However, significant gaps exist in the application of manufacturing science principles that suggests that this principle may not be optimally realized
    - I.e., the quality system tends to lean towards "testing to document quality"
      - There are risks associated with this "inclination" that can be mitigated with an improved focus on manufacturing science to achieve quality by design

Product Quality
(Design, Specifications, ..)

An Approved & Validated Product

Your responses to FDA-483 points 6, 9, 11 (Warning Letter items 2b, c, d, respectively), FDA-483 points 7 and 8 (Warning Letter items 3 and 4, respectively) and FDA-483 point 3B do not adequately address the issue of partial releases. Released products are expected to conform to established specifications from the beginning to the end of production. Current regulations specify that drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed, provided certain criteria are met according to written procedures. The practice of partial releases, no matter how stringent the re-sampling, raises doubt as to the safety and efficacy of the product being released. It is not acceptable to substitute testing over adequate control of a process.

"Testing to Document Quality"
is unacceptable

Process Quality
(Design, Control,..)

Is this not a "design" issue?

Our investigation found the following deviations:

1) There is no assurance that the written production and process control procedures established for coating the [redacted] are sufficient to produce a product that has the quality it is purported or represented to possess. The duration of each coating cycle is determined by the pan operators and is based on a visual determination that the coating solutions are evenly distributed before proceeding to the next step. It was noted that 78 of [redacted] batches made in 1997, and 79 of [redacted] batches made in 1998 were rejected due to in-process dissolution failures.

What are the risk factors?
What are the critical control points?
How was this process "validated"?

Isn't the actual control of this process dependent on this guy?

"Spirit" of CGMP and Process Validation: A multi-factorial disconnect?

- Harwood and Molnar. Using DOE techniques to avoid process problems. Pharm. Dev. Tech. 1998.
  - "....well-rehearsed demonstration that manufacturing formula can work three successive times."
  - "It is authors' experience that ... validation exercise precedes a trouble-free time period in the manufacturing area only to be followed by many hours (possibly days or weeks) of troubleshooting and experimental work after a batch or two of product fails to meet specifications. This becomes a never-ending task."

Is this not a “design” issue?

The newly proposed the [redacted] in-process barrier coated tablets core dissolution specification for [redacted] is not acceptable. It should be significantly tightened, e.g.,

How reliable are these “in-process” tests?

How is this related to clinical performance?

"Testing to Document Quality"

- The phrase has many dimensions
  - In-process and end-product release and stability testing
  - Reliability of specifications (attribute, test method, and acceptance criteria)
  - Managing post approval changes/continuous improvement (e.g., reduce variability, improve efficiency,..)
  - Product and process knowledge acquisition and generalization

Pharmaceutical "Optimization", January 2004

In the Pharmaceutical environment, "Optimization" typically means:
Choose the best of three (or two, or four) and hope is good enough

- **Models are mostly heuristic – design is a highly empirical activity**
- **Systematic experimental design is rarely applied**
- **Statistics are widely used – but largely in a mechanical fashion**
- **Highly constrained process**
  - **Limited by a rigid regulatory corset**
  - **Fear of "bad results" limits amount of information usually gathered**
  - **Lack of fundamental understanding highly limits usefulness of information**
    Design is always restarted from ground zero, or close to it

"Process Control": another big difference in semantics

- "Pharmaceutical" process control is achieved when we can produce many sequential batches that readily meet specification. Established post-facto (open loop)

- "Engineering" process control is an automated system where an artificial intelligence, developed using a process model, continuously monitors and corrects the process to keep every variable as close to its set point as possible

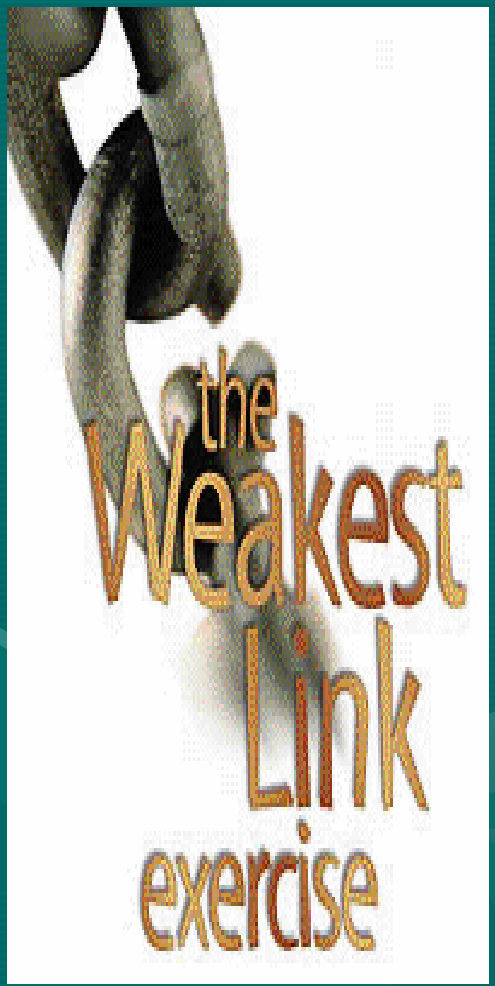
Testing to Document Quality: Requires Less Variable Test Methods

- The current USP 10-mg Prednisone Calibrator Tablets exhibit slower dissolution over time
- If the acceptable test equipment calibration limit is 28-54; what can we say about use of f2 criteria (~mean profile difference of 10%) as a way to document unchanged quality (e.g., SUPAC)?

Lot	Date	Mean (n=6)	SD (%)	USP Limit (%)
M	4/00	34.8	2.2	28-42
M	10/00	28.9	0.9	28-42
N	12/01	35.7	1.6	28-54
N	11/02	35.4	1.4	28-54
N	6/03	28.0	0.7	28-54

DPA/FDA Data using Apparatus 2; data from only one apparatus shown. Note the USP adjusts the limits of each new lot of calibration tablets to reflect the anticipated decrease in dissolution.

A Tale of two sample thieves



Chemical analysis involves three major operations--sampling, sample preparation, and measurement.

The quality of the data can be no better than the least precise operation in the method.

"The magnitudes of the variances indicate that the sampling is the weakest link."

Analytical Chemistry News & Features. August 1, 1999

Today Trial-Error is the Norm

Do SOP's reflect established Heuristic rules?

Segregation is not a serious problem if all the particles are smaller than 30 um or if they are slightly moist

Establish acceptance criteria for particle size distribution of excipients

Avoid bulk solids transfer where particles slide down a long, inclined chute

Segregation due to percolation is likely to be a concern if the particles of different density or size are poured into a heap or let slide on an inclined chute

The tendency of segregation of binary mixtures due to percolation decreases substantially if the ratio of particle diameters is lower than 1.3

Ensure mass flow in hoppers

Segregation during emptying of a storage unit is accentuated when funnel flow occurs

AIChE Journal 47: 107-125 (2001)

Risks when science-based validation is bypassed:

- Unexplained variation
- Unwarranted optimism
  - Artificial uniformity of validation runs
- Unknown representativeness
- Unknown interaction
- False causality
- Unobservable causality
- Incompletely specified control protocols
- Missing links with Critical Quality Attributes

Over the wall: Consequences

- Good biological properties
  - Potency, selectivity
- Little consideration of physical properties and their impact
  - Can slow down or even derail clinical development
  - Process and pharmaceutical development groups forced to “do their best” with what they get
- Final product may be less than optimal with consequences in terms of regulatory approval, manufacturing difficulties and market share

TRANSFORM pharmaceuticals

Collin Gardner, US Arden House 2004

What's wrong with the status quo?

- NDA focuses on future regulatory commitments
  - Sponsor generally doesn't describe how they designed their product
    - Creates a "check-list" submission and review paradigm
    - Current 'Development Report' aimed at successful PAI
- Regional disharmony
  - We have a P2 section in the CTD
    - Harmonised guidance on content would be helpful
  - Dev Pharmaceutics a 'cornerstone' of EU submissions

Limited (regulatory) incentive to truly understand our processes and products, and optimise them

THE WALL STREET JOURNAL.

WEDNESDAY, SEPTEMBER 3, 2003 - VOL. CCXLII NO. 45 - ★★★★ $1.00

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 Abboud
And Scott Hensley

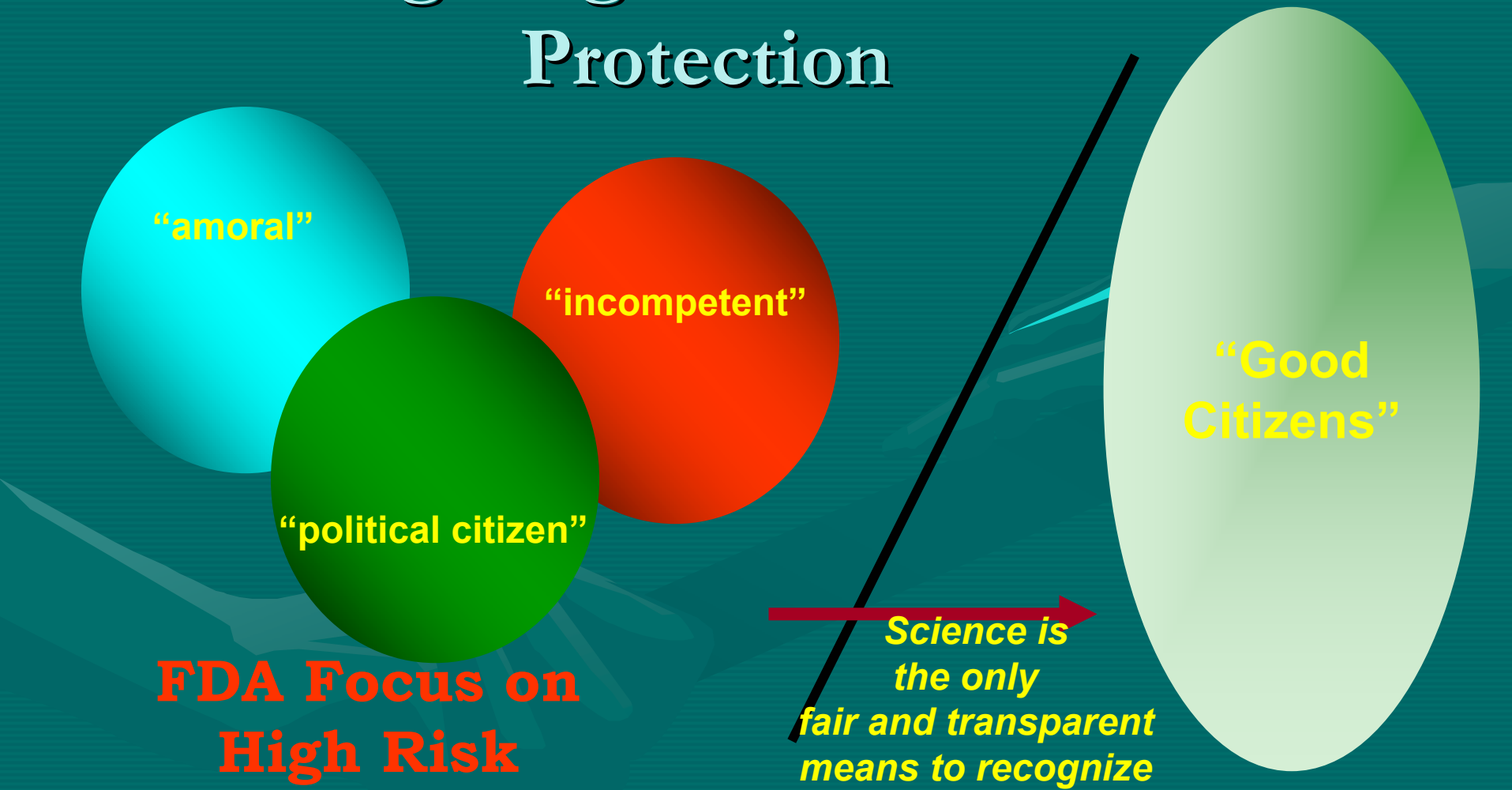
Main points from this:

- 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)

"I Can See Clearly Now": Targeting for Maximum Protection

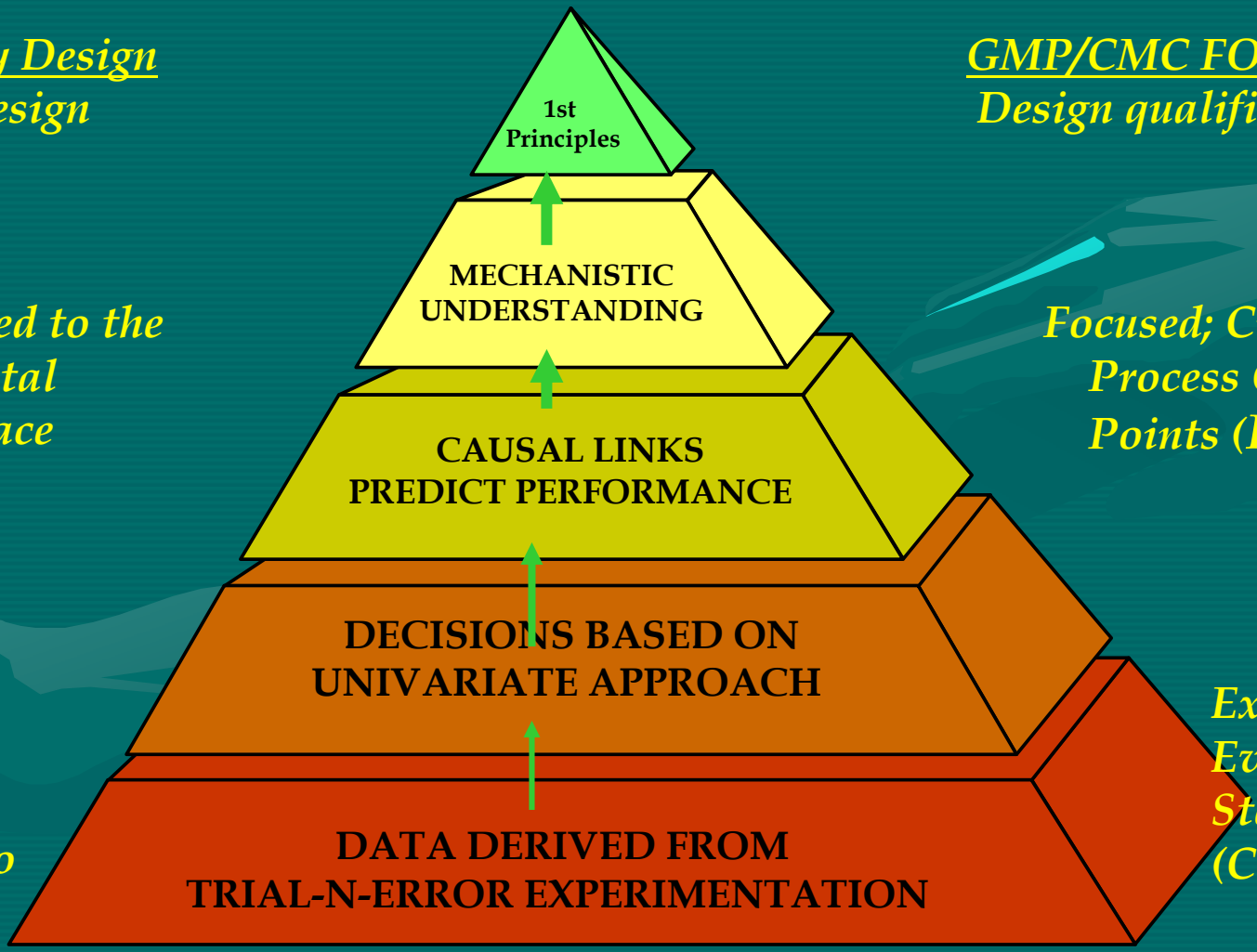


Kagan and Scholz. Perspectives on Regulation: Law, Discretion, and Bureaucratic behavior, May 1980.

Product and Process Quality Knowledge:
Science-Risk Based CMC & CGMP's

Quality by Design
Process Design

GMP/CMC FOCUS
Design qualification



Yes, Limited to the Experimental Design Space

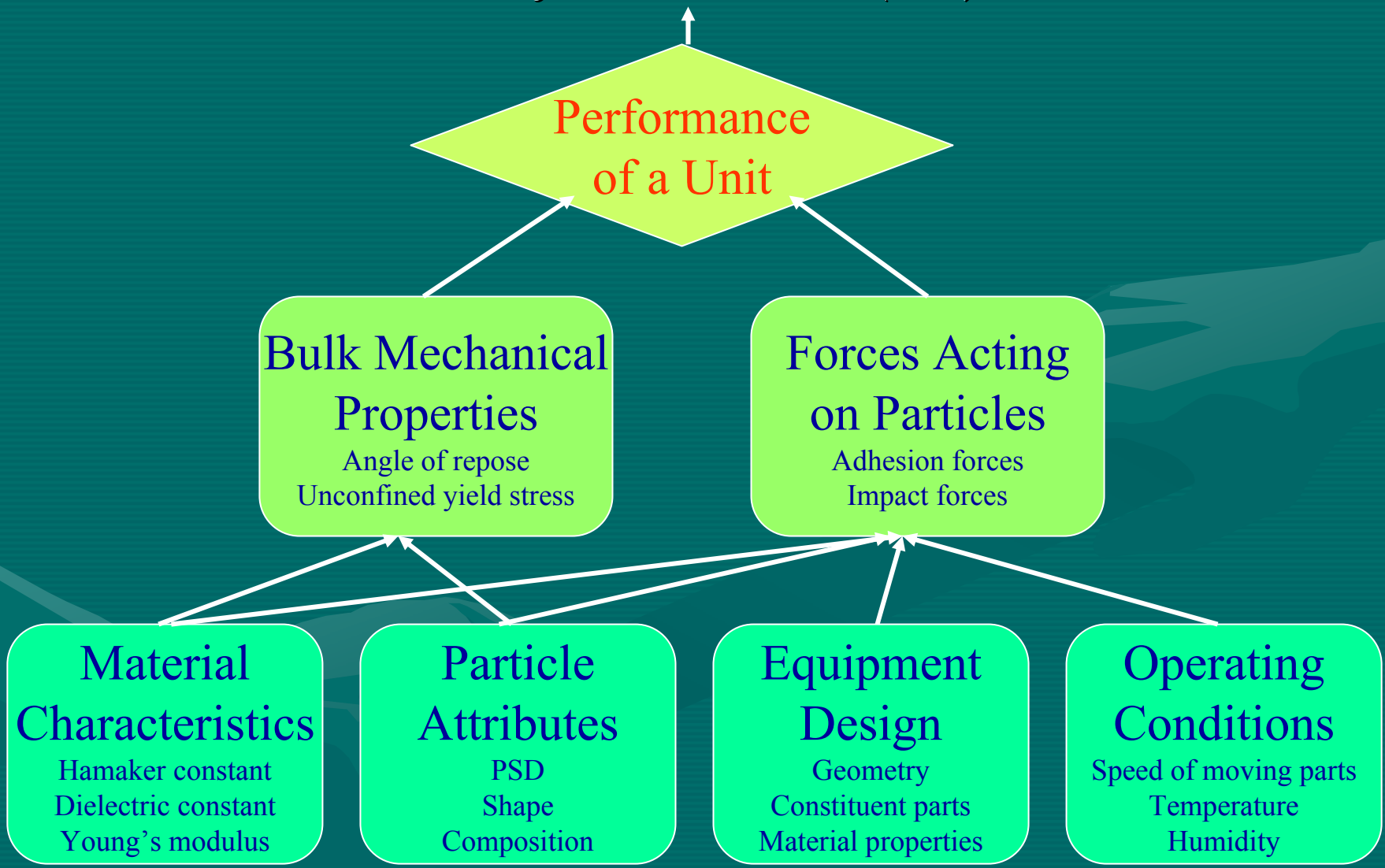
Focused; Critical Process Control Points (PAT)

Maybe, Difficult to Assess

Extensive; Every Step (CURRENT)

Performance of a Solids Processing Units

AIChE Journal 47: 107-125 (2001)



ELSEVIER

Journal of Controlled Release 59 (1999) 327–342

journal of controlled release

Identification of critical formulation and processing variables for metoprolol tartrate extended-release (ER) matrix tablets[1]

Gurvinder Singh Rekhi[b,*], Ranjani V. Nellore[c], Ajaz S. Hussain[d], Lloyd G. Tillman[e], Henry J. Malinowski[f], Larry L. Augsburger[a]

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[c]*Roche Bioscience, 3401 Hillview Avenue, Palo Alto, CA 94304-1397, USA*
[d]*Food and Drug Administration, Division of Product Quality Research, Rockville, MD 20857, USA*
[e]*Isis Pharmaceuticals Inc., Carlsbad, CA 92008, USA*
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Received 5 January 1998; accepted 3 December 1998

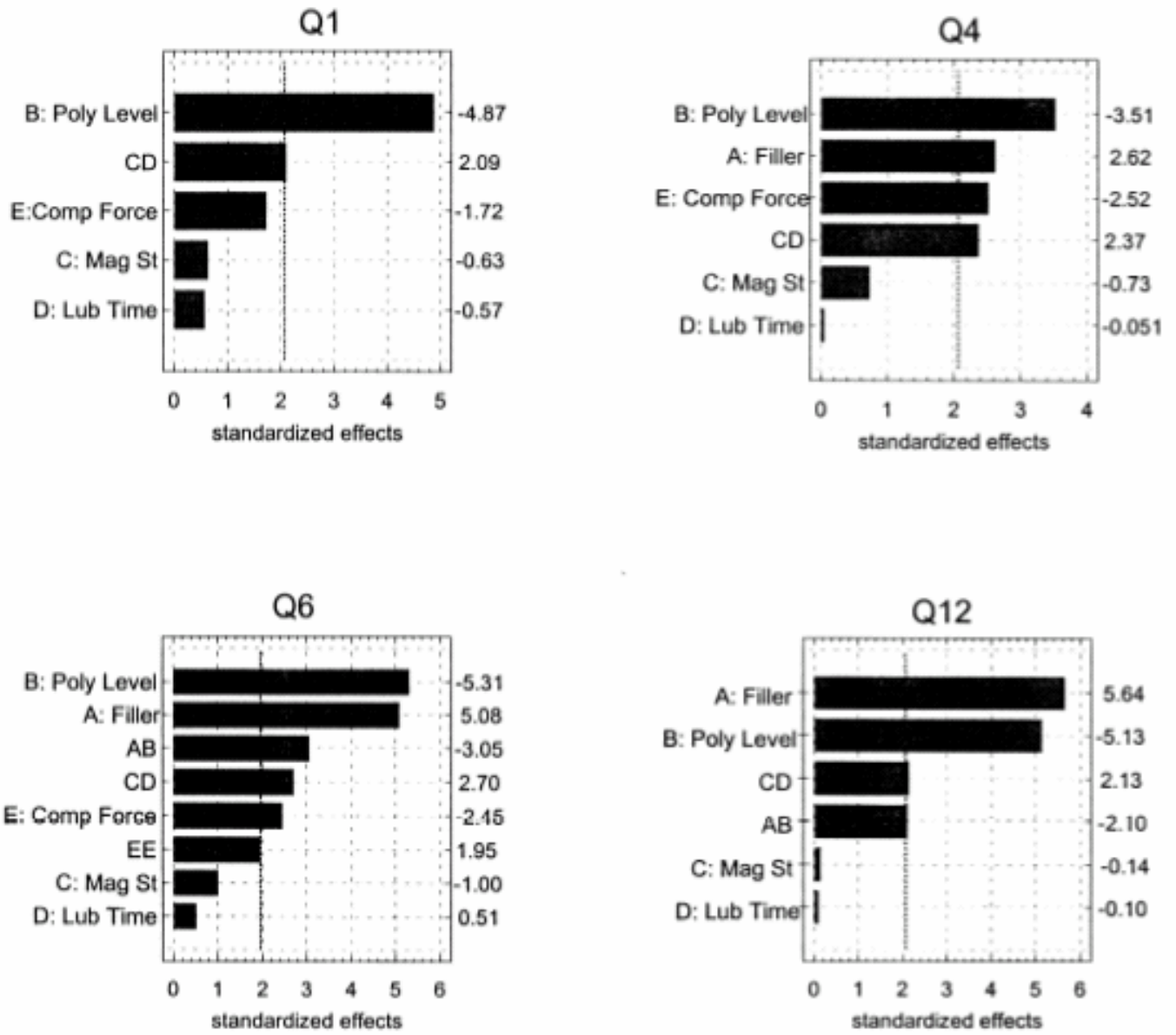

Fig. 3. Standardized Pareto charts for percent released (Q).

To determine the influence of formulation and process variables (Table 2) on drug dissolution, a face-centered central composite design (Table 3) was selected (29 runs, $2^{5-1}+10$ star points+3 center points). Of the five factors listed, the first three; filler, polymer and magnesium stearate level were considered to be 'critical' manufacturing variables as per the AAPS Workshop II recommendations [6]. This

Table 2
Formulation and process variables and ranges studied

Variables	Units	Low	Midpoint	High
(A) Filler (lactose: dicalcium phosphate)	%	0:100	50:50	100:0
(B) Polymer level (HPMC Methocel K100LV)	%	15	32.5	50
(C) Magnesium stearate level	%	1	1.5	2
(D) Lubricant blend time	min	2	6	10
(E) Compression force	kg	400	600	800

Process Characterization Studies

Pre-characterization Work

↓

Screening Experiments

↓

Interactions and Combinations of Key Parameters

↓

Process Redundancy / Robustness

AMGEN

James E. Seely, Ph. D., Amgen Colorado. US Arden House 2004

Pre-Characterization: Risk Analysis

- **Failure Modes and Effects Analysis (FMEA):** A Numerical rating system for determining the…
  - Severity of a process excursion
  - Occurrence of the excursion
  - Ability to detect the excursion
- Assigns relative risk (1-10, 1-5,..etc) for each category.
  - Risk priority number is a multiple of the relative risk score for each of these three variables
    - Severity X Occurrence X Detections
  - ***Do for each operating parameter of each process step.***

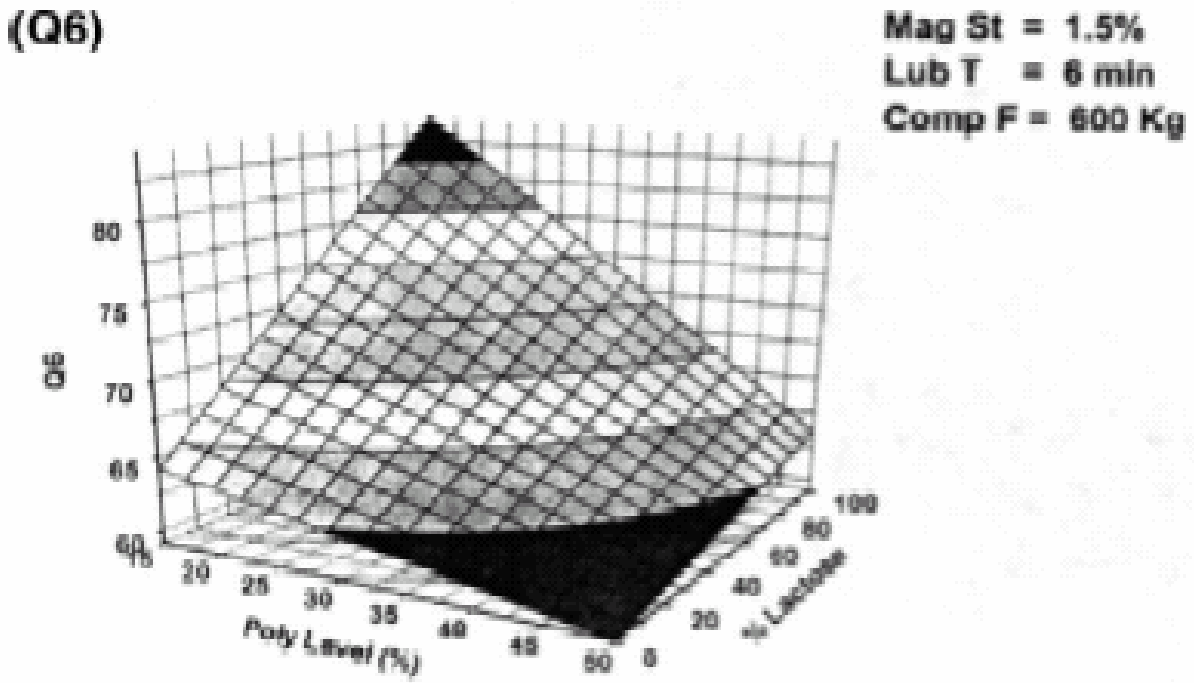
(Q6)
Mag St = 1.5%
Lub T = 6 min
Comp F = 600 Kg
Q6
80
75
70
65
60
15
20
25
30
35
40
45
50
Poly Level (%)
0
20
40
60
80
100
% Lactose

Table 8
Summary of actual versus predicted values for Q based on level 1 or 2 SUPAC changes

Run no.		Predicted	Actual	Predicted	Actual	Predicted	Actual	Predicted	Actual
15		25.3	23.4	55.8	52.7	67.7	64.9	89.7	87.2
3		30.1	30.1	62.3	67.4	75.0	96.3	89.8	99.7
8		21.0	20.7	49.5	46.8	58.9	57.9	86.2	80.1
Level 1 changes	%	Predicted values based on reg model				% Change from actual			
Run 15		Q_1	Q_4	Q_6	Q_{12}	Q_1	Q_4	Q_6	Q_{12}
Filler (±5%)	45	25.3	55.6	67.1	89.3	1.9	2.9	2.2	2.1
	55	25.3	56.1	68.3	90.1	1.9	3.4	3.4	2.9
Mag. stearate (±0.25%)	1.25	25.4	56.2	68.3	89.8	2.0	3.5	3.4	2.6
	1.75	25.1	55.5	67.1	89.7	1.7	2.8	2.2	2.5
Lub. time (min)									
Low	2	25.6	55.9	67.1	89.8	2.2	3.2	2.2	2.6
High	10	25.0	55.8	68.3	89.6	1.6	3.1	3.4	2.4
Comp. force (kg)									
Low	400	26.1	58.2	74.5	89.7	2.7	5.5	9.6	2.5
High	800	24.5	53.4	68.5	89.7	1.1	0.7	3.6	2.5
Polymer level (±2%)	30.5	25.5	56.2	68.5	90.2	2.1	3.5	3.6	3.0
	34.5	25.0	55.4	67.0	89.3	1.6	2.7	2.1	2.1
Level 2 changes									
Run 15		Q_1	Q_4	Q_6	Q_{12}	Q_1	Q_4	Q_6	Q_{12}
Filler (±10%)	40	25.3	55.3	66.5	89.0	1.9	2.6	1.6	1.8
	60	25.3	56.3	68.9	90.5	1.9	3.6	4.0	3.3
Mag. stearate (±0.5%)	1	25.6	56.5	68.9	89.8	2.2	3.8	4.0	2.6
	2	25.0	55.1	66.5	89.6	1.6	2.4	1.6	2.4
Polymer level (±5%)	27.5	26.0	56.8	69.6	90.8	2.6	4.1	4.7	3.6
	37.5	24.6	54.9	65.9	88.6	1.2	2.2	1.0	1.4

JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 92, NO. 3, MARCH 2003

Characteristics of Hydroxypropyl Methylcellulose Influencing Compactibility and Prediction of Particle and Tablet Properties by Infrared Spectroscopy

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ABSTRACT: Particle characteristics, chemical substitution, compaction behavior, and tablet properties of hydroxypropyl methylcellulose powders from two different suppliers were related using multivariate data analysis. By Principal Component Analysis it was shown that the the degree of substitution of the HPMC powders did not correlate to the particle and compaction properties as strongly as anticipated. Particle shape and powder surface area seem to be more important for the compaction behaviour of the powders than the degree of substitution. In addition, particle and tablet properties were predicted from infrared spectral data. Fourier transform infrared (FTIR) and near infrared (NIR) spectral data of the powders were combined with measured values of the particle characteristics, compaction behavior, and tablet properties using the multivariate data analysis program SIMCA 7.1. Properties like density, particle shape, tablet tensile strength, and drug release characteristics of the HPMC powders and corresponding tablets in this study could be predicted using Partial Least Squares models. In conclusion, the particle shape and powder surface area of HPMC powders seem to be important factors for the quality of tablet attained. Further, this study confirms that NIR and FTIR analysis used in combination with multivariate analysis are powerful tools for predicting the properties of materials and the quality of the end product. J Pharm Sci 92:460–470, 2003

Keywords: HPMC; tablet; particle shape; NIR; FTIR; MVDA; substitution degree

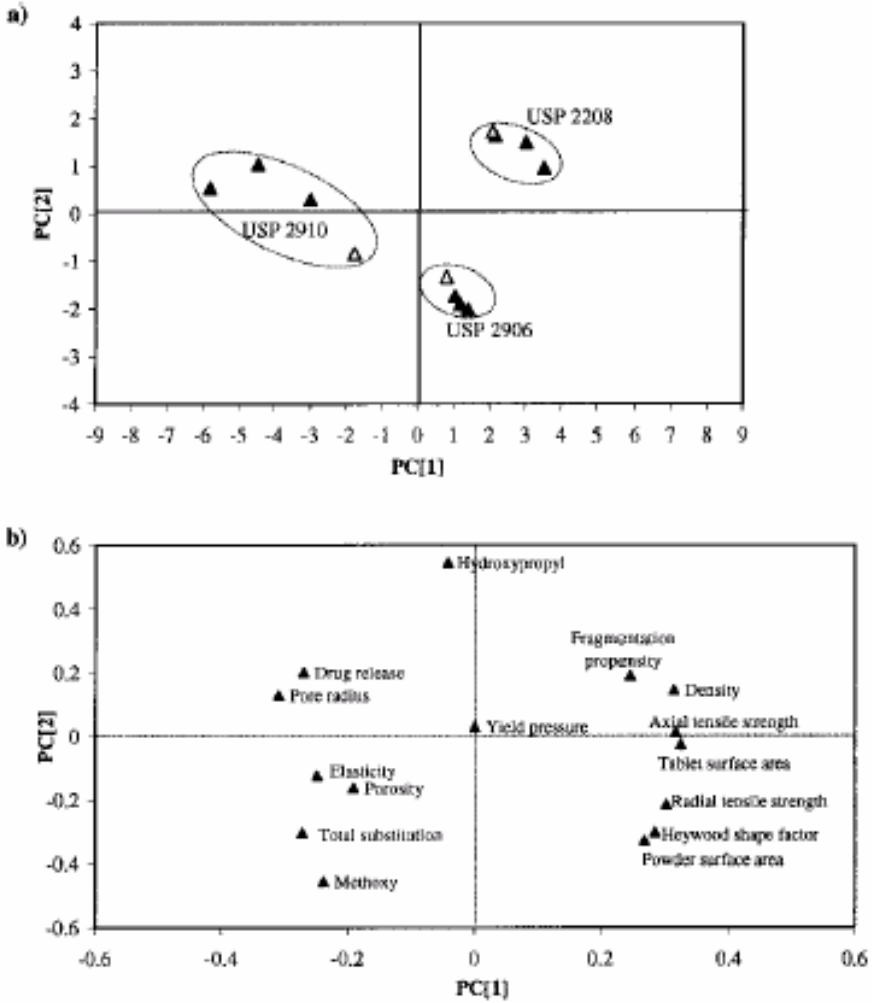

Figure 1. (a) PCA score plot of the materials, the filled symbols represent Methocel powders and the unfilled ones represent the corresponding Metolose powders. (b) loading plot of measured properties.

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Journal of Controlled Release 95 (2004) 209–216

journal of controlled release

www.elsevier.com/locate/jconrel

Prediction of drug release from HPMC matrices: effect of physicochemical properties of drug and polymer concentration

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Received 14 July 2003; accepted 20 November 2003

A working equation to predict drug release from hydroxypropyl methylcellulose (HPMC) matrices was derived using a training set of HPMC matrices having different HPMC concentration (w/w, 16.5–55%) and different drugs (solubilities of 1.126–125.5 g/100 ml in water and molecular volumes of 0.1569–0.4996 nm^3). The equation was $\log(M_t/M_\infty) = -0.6747 + 1.027 \log t - 0.1759 (\log C_s) \log t + 0.4027 (\log V) \log t - 1.041 C_H + 0.3213 (\log C_s) C_H - 0.4101 (\log V) C_H - 0.3521 (\log V) \log C_s$ ($n = 263$, $r = 0.9831$), where M_t is the amount of drug released at time t, M_∞ the amount of drug released over a very long time, which corresponds in principle to the initial loading, t the release time (h), C_s the drug solubility in water (g/100 ml), V the volume of drug molecule (nm^3), and C_H is HPMC concentration (w/w). The benefit of the novel model is to predict M_t/M_∞ values of a drug from formulation and its physicochemical properties, so applicable to the HPMC matrices of different polymer levels and different drugs including soluble drugs and slightly soluble drugs.

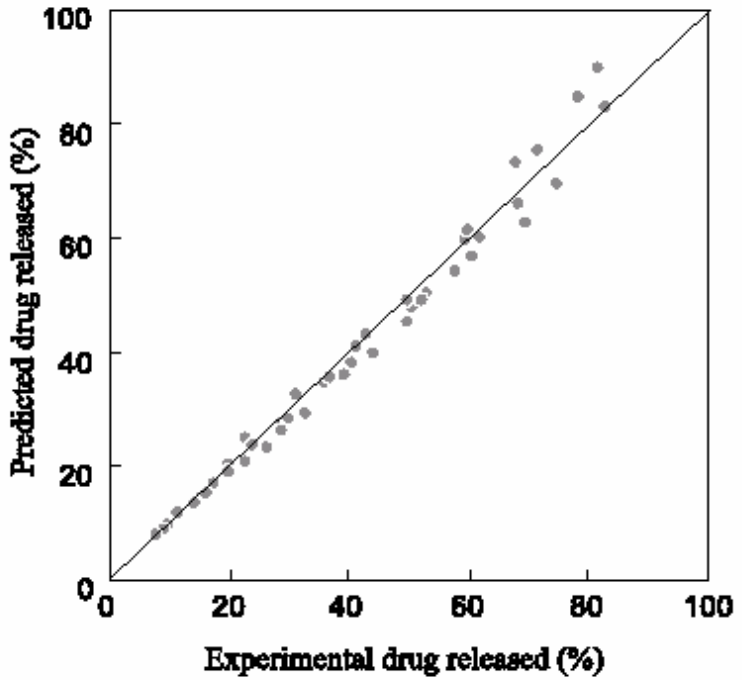
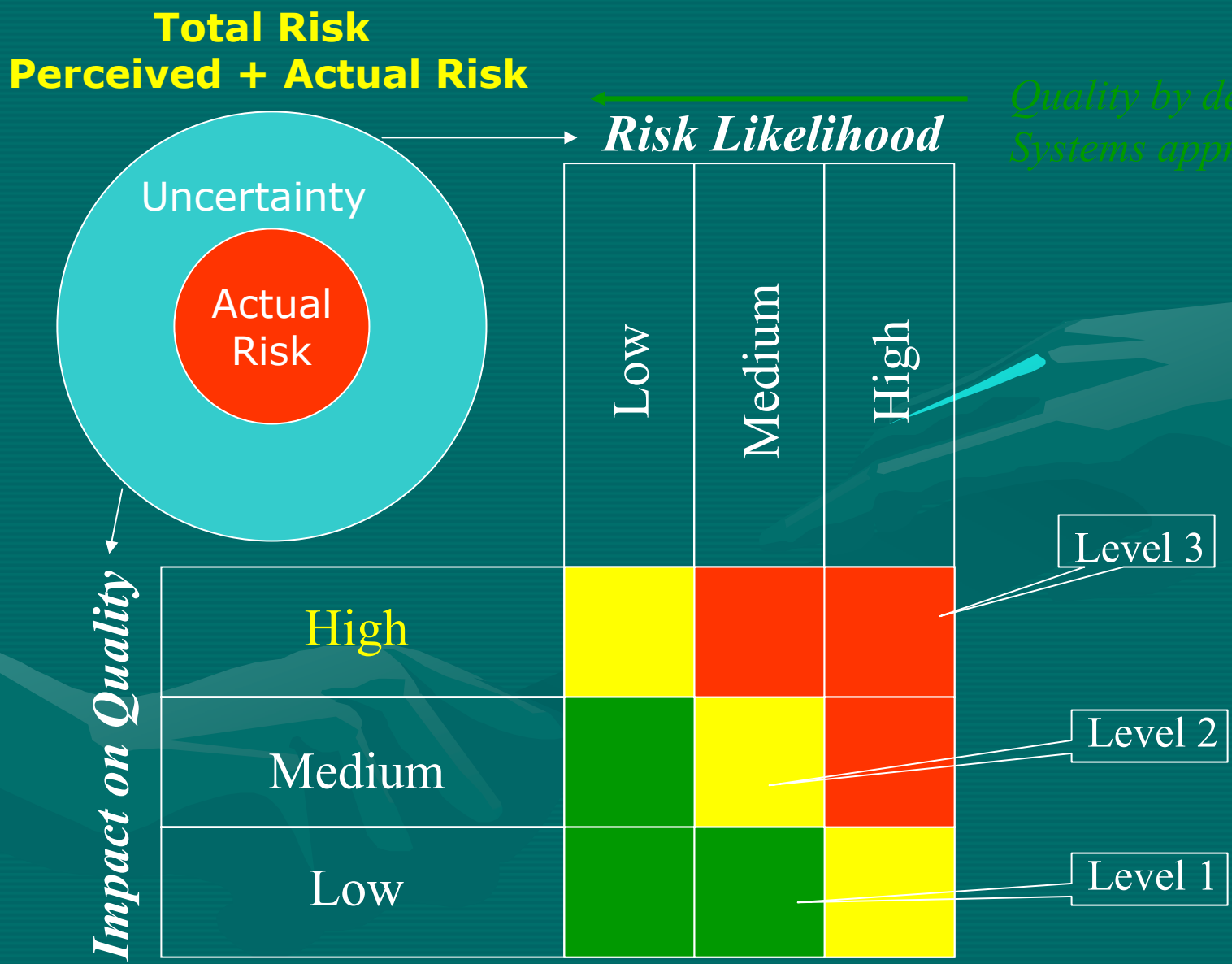


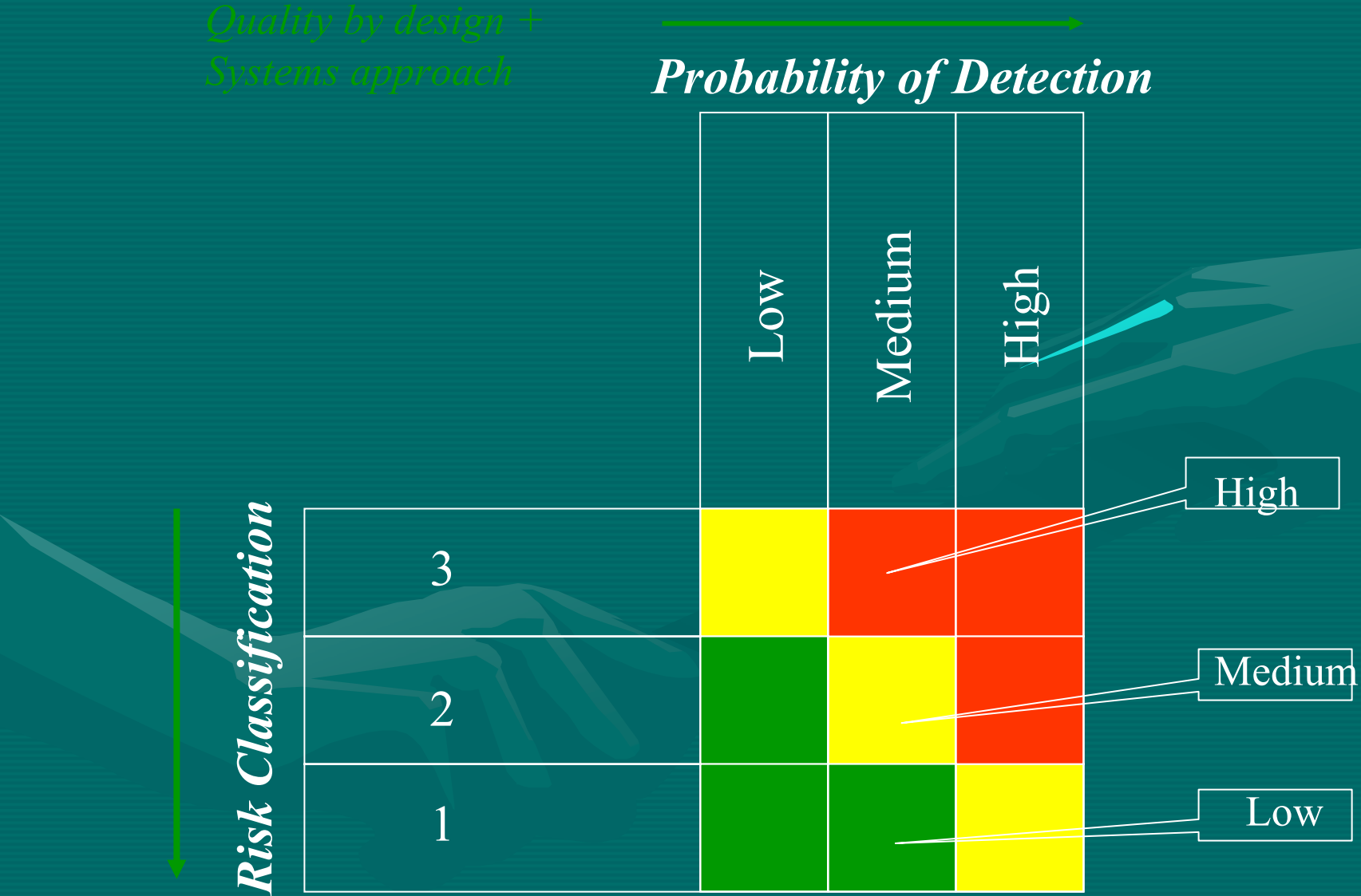
Fig. 2. Relationship between experimental and predicted M_t/M_∞ values of tinidazole.

Quality Risk Classification



Quality Risk Priority: Regulatory Oversight

Quality by design +
Systems approach



Unifying Principles and Vocabulary

Draft Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

Draft PAT Guidance: Vocabulary

PAT is a system for:

- designing, analyzing, and controlling manufacturing
- timely measurements (i.e., during processing)
- critical quality and performance attributes
- raw and in-process materials
- processes

"*Analytical*" includes:

- chemical, physical, microbiological, mathematical, and risk analysis
- conducted in an integrated manner

PAT = Process Understanding

- A process is well understood when:
  - all critical sources of variability are identified and explained
  - variability is managed by the process
  - product quality attributes can be accurately and reliably predicted
- Accurate and Reliable predictions reflect process understanding
- Process understanding inversely proportional to risk

Tools for Process Understanding and Control

- Multivariate data acquisition and analysis tools
- Modern process analyzers or process analytical chemistry tools
- Process and endpoint monitoring and control tools
- Continuous improvement and knowledge management tools

Process Understanding - Validation

- Can provide a high assurance of quality on every batch and provide alternative, effective mechanisms to achieve validation
  - process validation can be enhanced and possibly consist of continuous quality assurance where a process is continually monitored, evaluated, and adjusted using validated in-process measurements, tests, controls, and process endpoints
  - ***"A process is controlled using validated controls"***

Opportunity

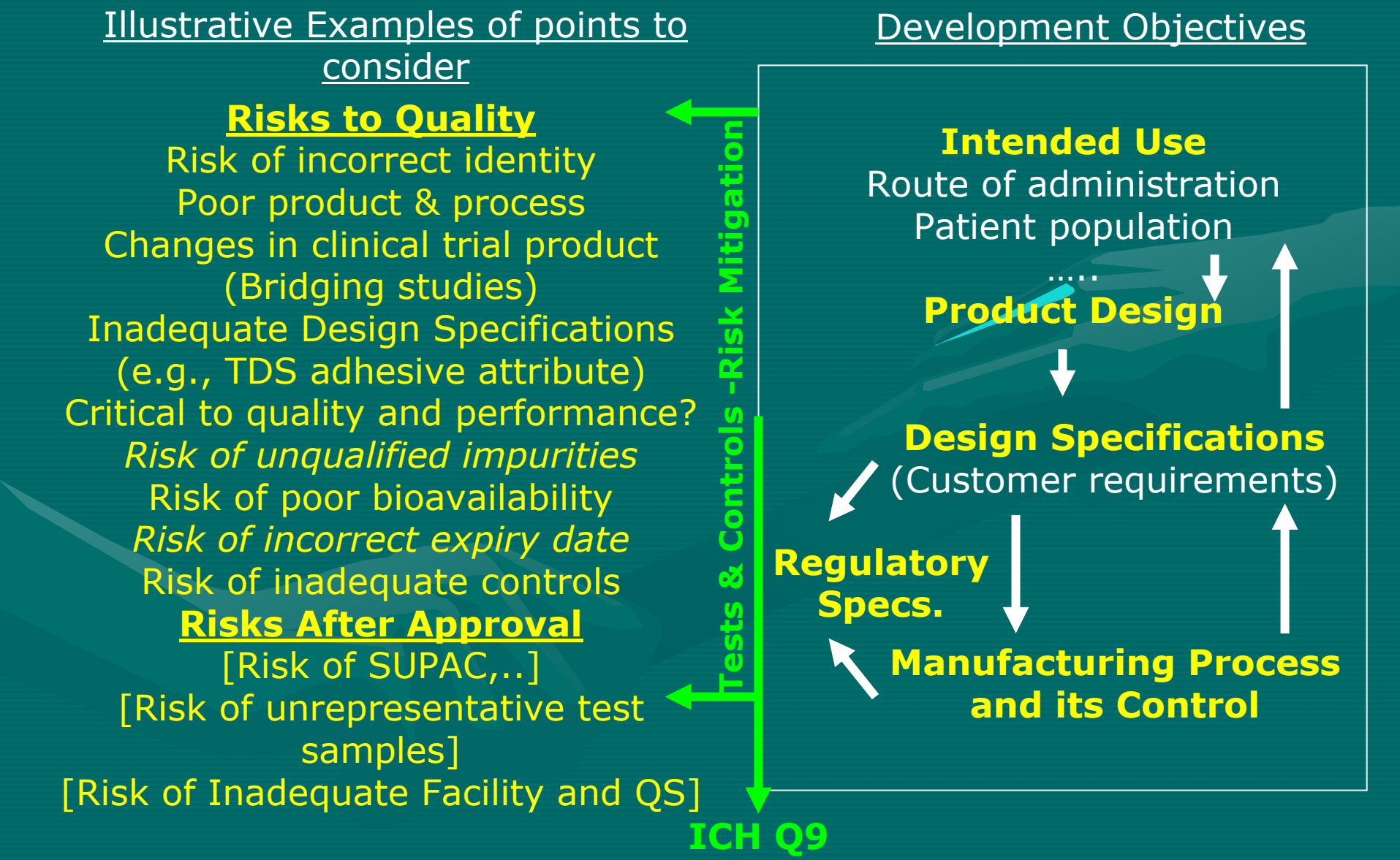
- For companies that acquire extensive understanding about their product and manufacturing process and share this with the regulators
  - Enhanced science and risk-based regulatory quality assessment will be possible
    - Setting specifications
    - Reduction in the volume of data to be submitted – replaced by more knowledge based submissions
    - Flexible post approval continuous improvement

Quality by Design

- Stipulate (postulate) key performance parameters early in development process
- Design product & process to be robust for these parameters

Janet Woodcock, M.D.
May 19, 2004

ICH Q8: Integrating QbD and Risk Mitigation Dimensions



Adoption of Q8 delivers a new state:
(as agreed by EWG)

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- An ability to effect Continuous Improvement and Continuous "real time" assurance of quality

John C Berridge, Q8 Rapporteur (EFPIA).
FDA Manufacturing Subcommittee, July 2004

Q8 & Regulatory Flexibility

IF

- Relevant (scientific) understanding (e.g., stability and bioavailability)
- Ability to predict quality/ performance
- Confidence that product and process critical variables are controlled
  - with an appropriate ability to detect and prevent deviations
- High confidence in the value of regulatory specifications and process validation

THEN

First cycle CMC review more likely

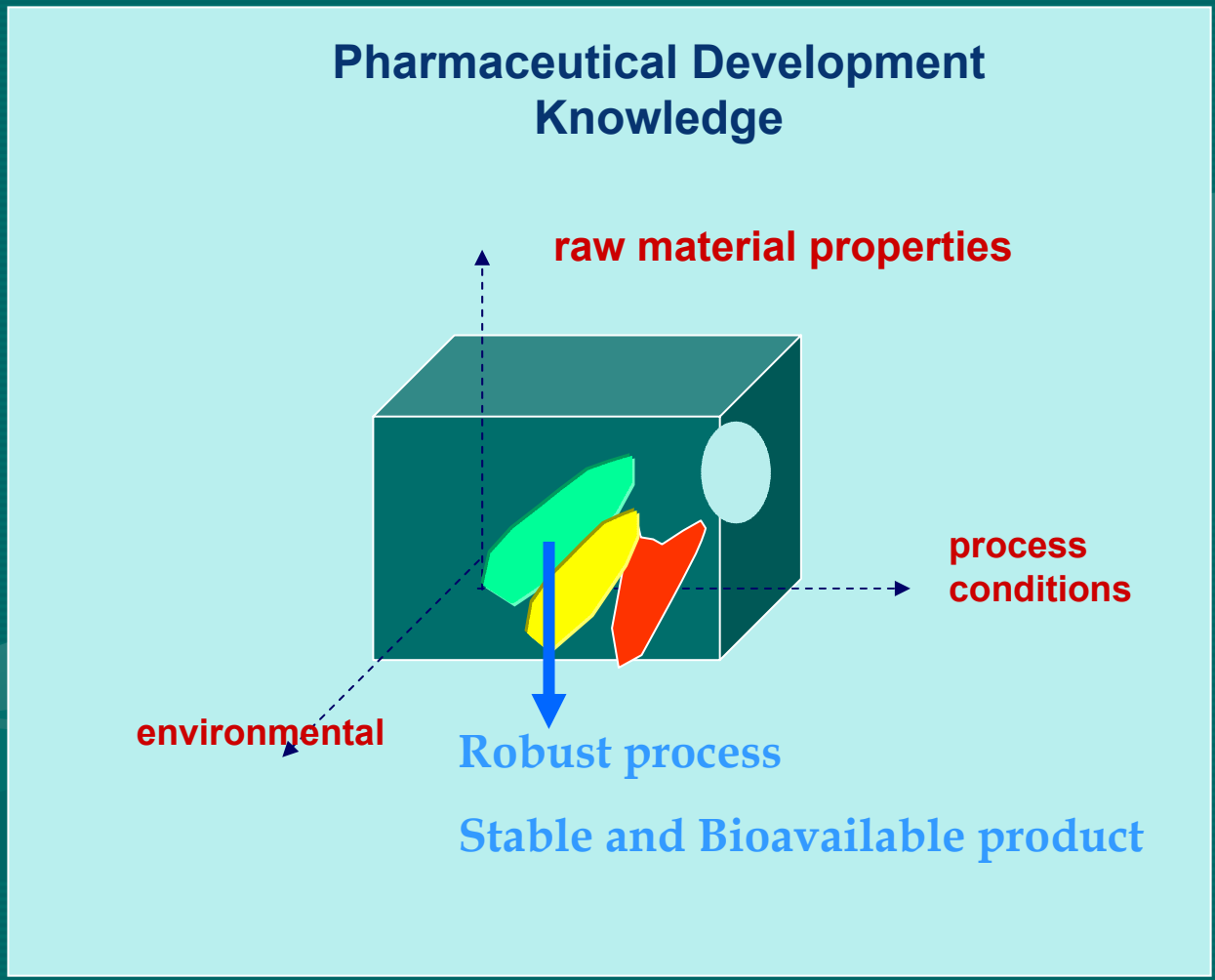
Process optimisation possible without prior approval

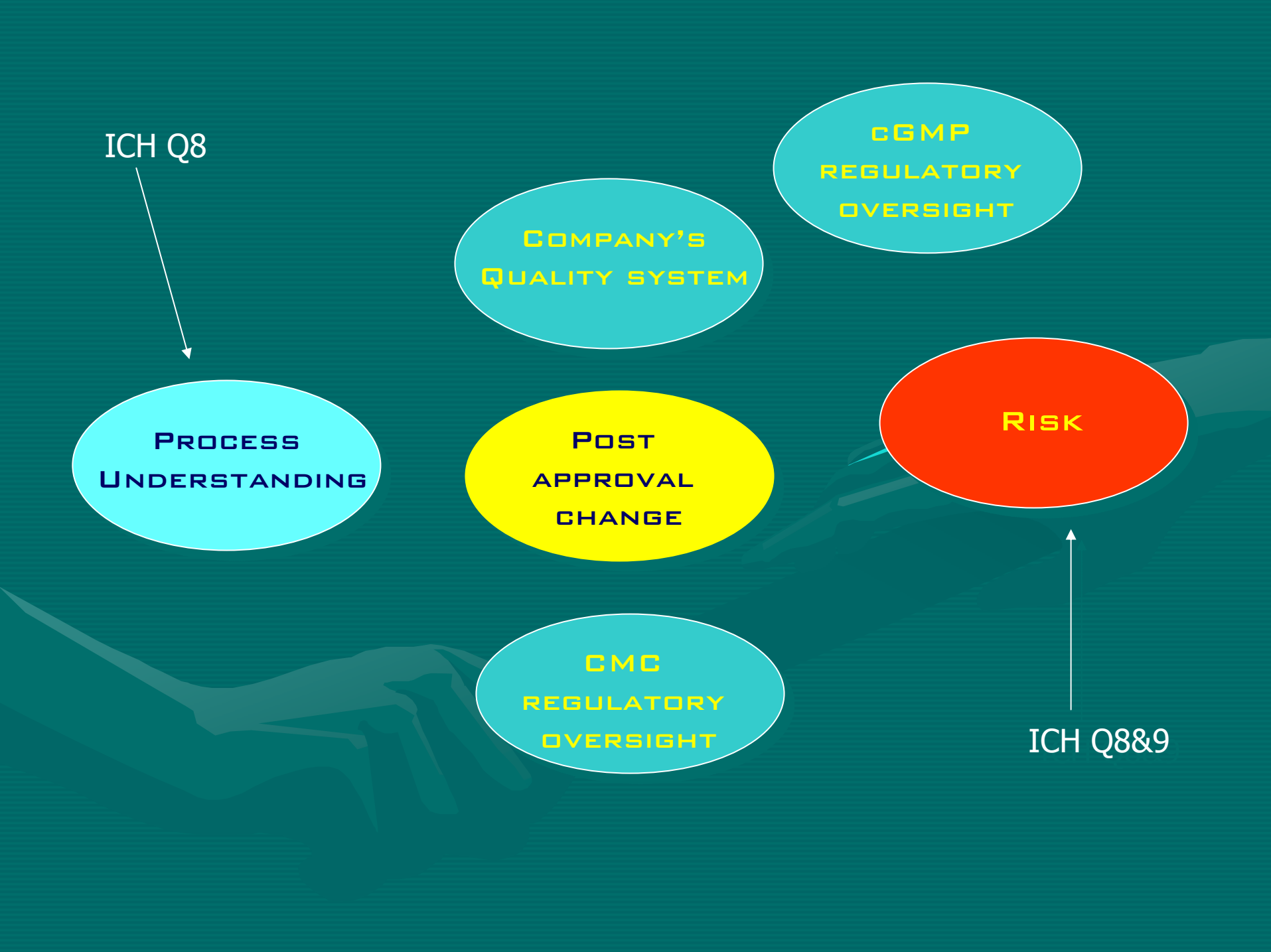
Risk-based Inspections feasible

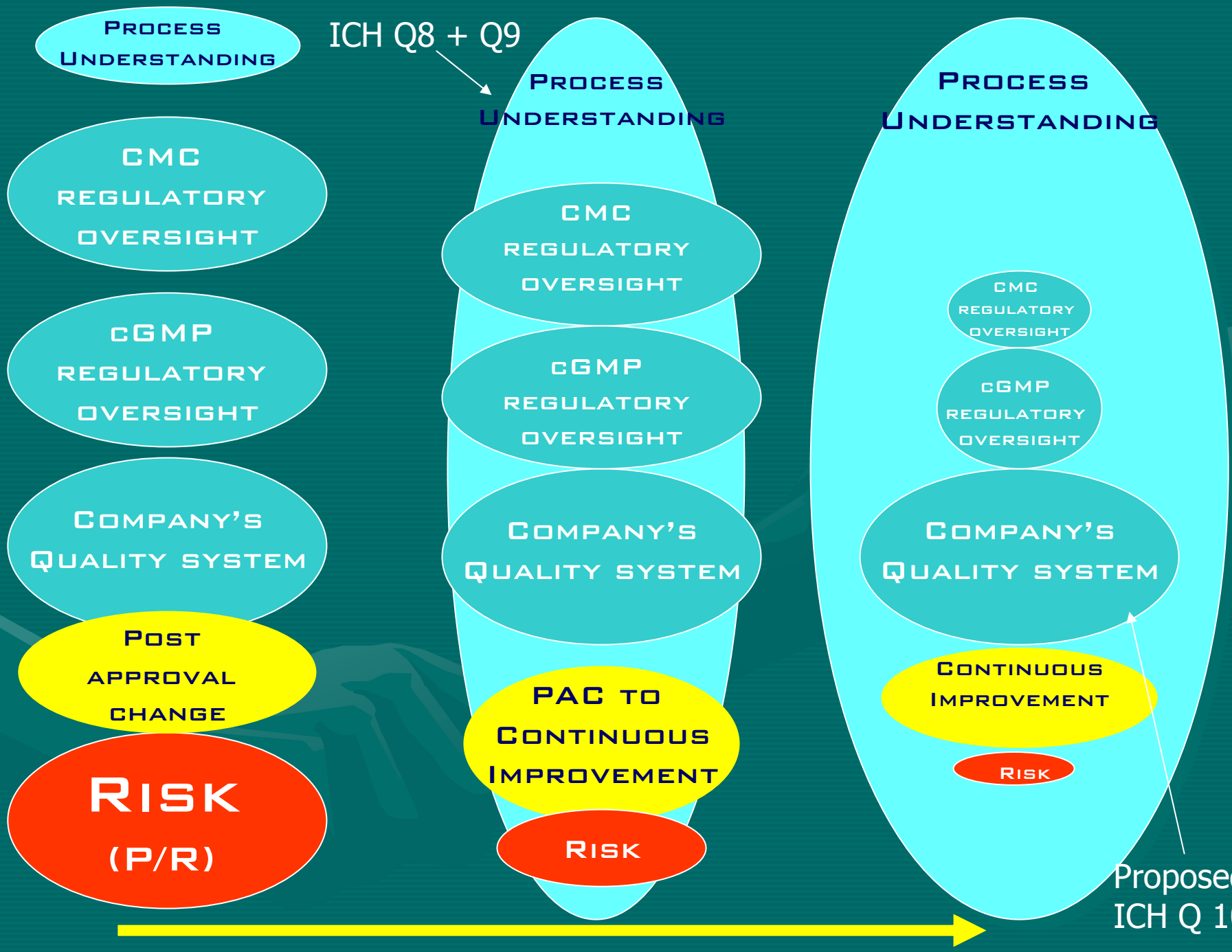
- Based on identification of critical product and process parameters

John C Berridge, Q8 Rapporteur (EFPIA).
FDA Manufacturing Subcommittee, July 2004

Knowledge based decisions: Improved Ability to Generalize




ICH Q8
cGMP regulatory oversight
Company's Quality system
Process Understanding
Post approval change
Risk
CMC regulatory oversight
ICH Q8&9


Process Understanding
ICH Q8 + Q9
CMC Regulatory Oversight
cGMP Regulatory Oversight
Company's Quality system
Post approval change
Risk (P/R)
Process Understanding
CMC Regulatory Oversight
cGMP Regulatory Oversight
Company's Quality system
PAC to Continuous Improvement
Risk
Process Understanding
CMC Regulatory Oversight
cGMP Regulatory Oversight
Company's Quality system
Continuous Improvement
Risk
Proposed ICH Q 10

The FDA PAT Team (ORA, CDER, CVM)

PAT Steering Committee

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Dennis Bensley, CVM/FDA
Patricia Leffler, ORA/FDA
Joe Famulare, CDER/FDA
Keith Webber, CDER/FDA
Frank Holcomb, CDER/FDA
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Ajaz Hussain, Chair, CDER/FDA

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PAT Training Coordinators

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Rosario D'Costa (CDER)
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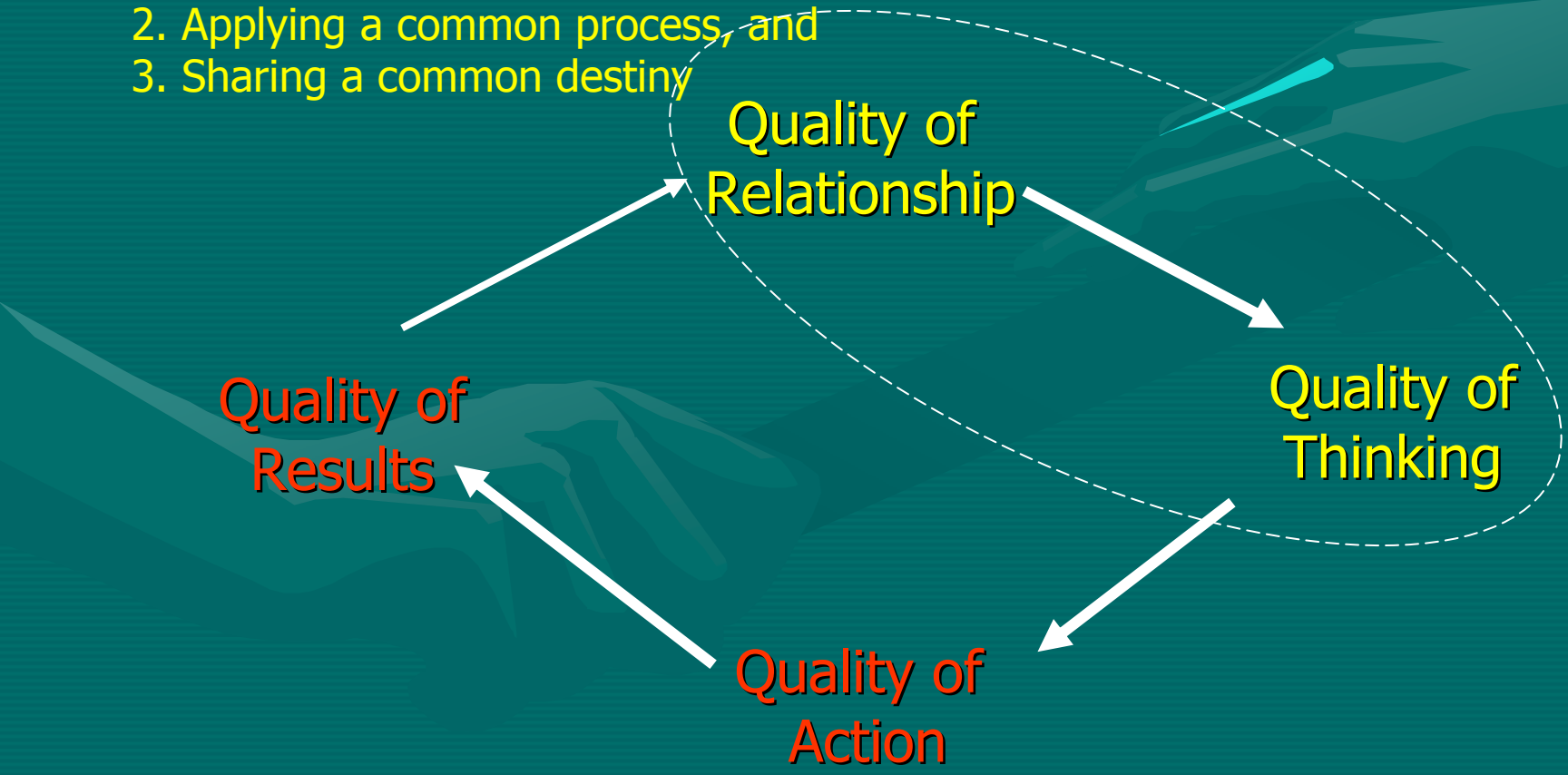
Bryan Riley (CDER)

The PAT Team: The Engine of Success

A team is a group of interdependent individuals with complimentary skills who are organized and committed to:

1. Achieving a common purpose
2. Applying a common process, and
3. Sharing a common destiny




Group

MAKE GOOD GREAT.™

acknowledge it. embrace it. champion it.

ASQ

"When we stop improving, we start to slip backward." -

H. James Harrington