Health Canada / Santé Canada

Product Development by Quality by Design (QbD)

Krishnan R. Tirunellai, Ph. D.
Bureau of Pharmaceutical Sciences
TPD, Health Canada
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krishnan_tirunellai@hc-sc.gc.ca

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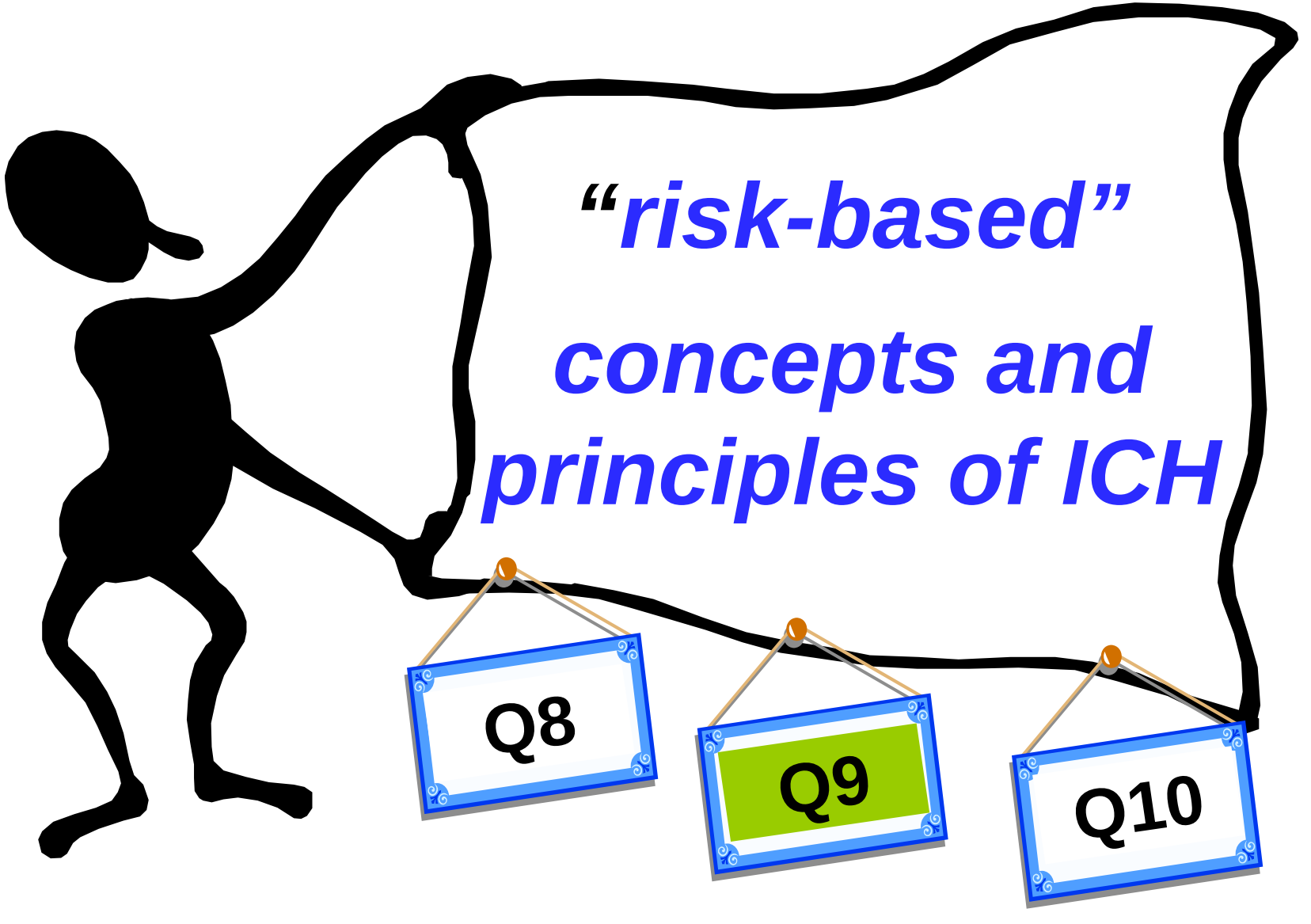
Health Products and Food Branch
Direction générale des produits de santé et des aliments

Concepts

- ICH Q8, 9 & (10)
- Q9 - Quality Risk Management
- Q8 - QbD
  - Design of Experiment (DOE)
  - PAT tools
  - Design space

Focus on a New Paradigm in Quality



Ref: ICH

Drug Life-cycle Management

- Drug Life-Cycle begins with the early stage of discovery and leading through the development stages, regulatory review, market authorization, and post-market activities until it is no longer on the market.
- **HC's Progressive Licensing initiative will address** drug regulatory system for the future:
  - **Safety & Efficacy:** Therapeutic Effectiveness, Pharmacovigilance, *Post Approval Changes*, etc.
  - **Quality:** Improvement & Innovation

Reasons for ICH Q8 & Q9

- **Situation today for both regulators and industry**
  - Increasing external requirements
  - Increasing efforts and costs
  - Growing complexity and scope of risks
- **Empowerment & Flexibility is needed**
  - Master complexity and streamline decision making
  - Proactive disclosure **build trust and understanding**
  - Improve communication through **sharing best practice and science based knowledge**
  - **Convert data into knowledge**

Ref: ICH

New Paradigm has Incremental Steps

Pharmaceutical Development (Q8)

Past: Data transfer / Variable output

Present: Knowledge transfer / Science based / Consistent output

Quality Risk Management (Q9)

Past: Used, however poorly defined

Present: Opportunity to use structured process thinking

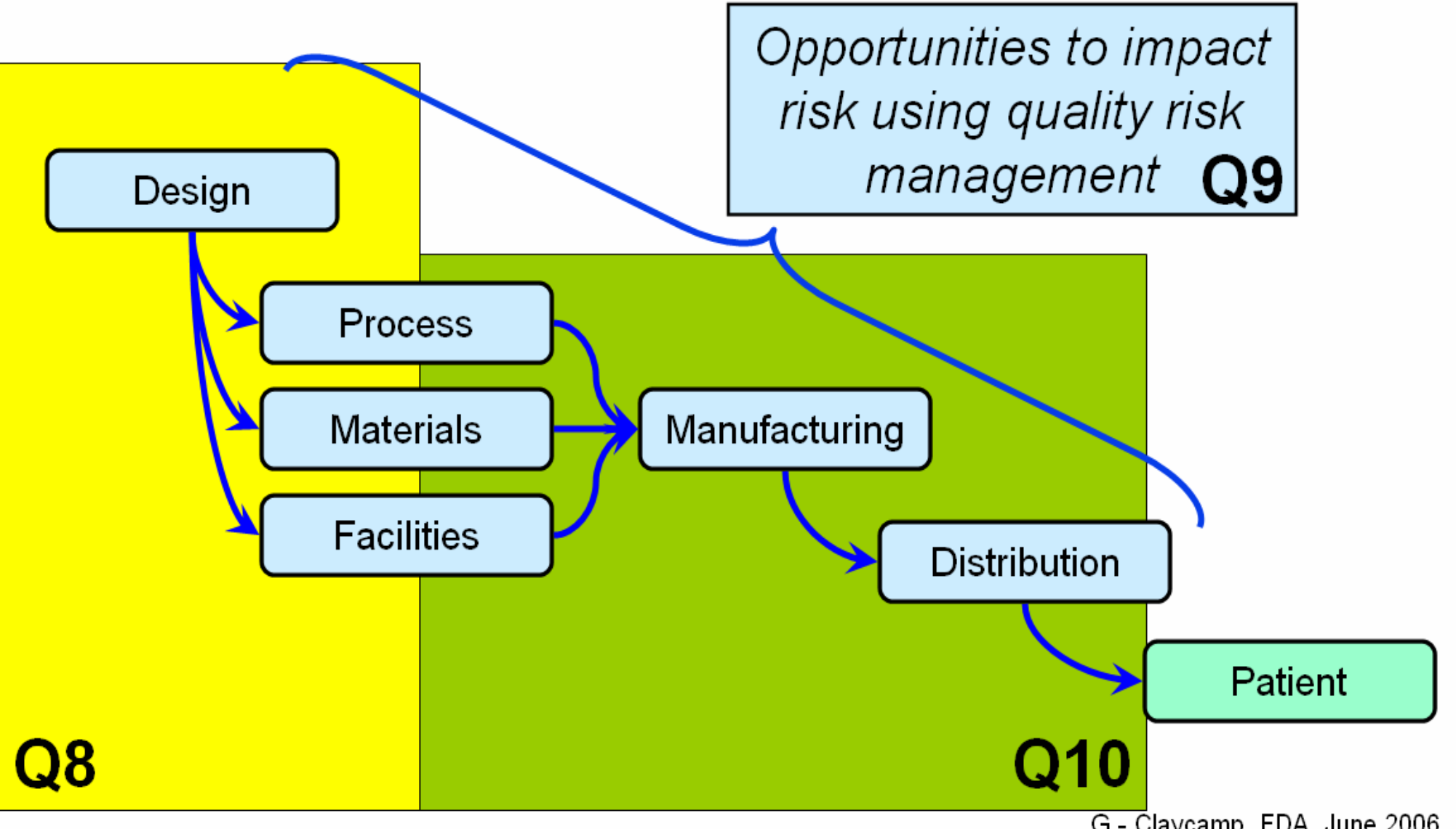
Pharmaceutical Quality Systems (Q10)

Past: GMP checklist

Future: Quality Systems across product life cycle

Ref: ICH

ICH Q's link to Patient Wellbeing



G.- Claycamp, FDA, June 2006

Vision of the Future Becomes Fact

	Old Approach	New Approach	Remarks
Broad Concept	Quality decisions divorced from science and risk evaluation. Adherence to **filing commitments**.	Quality decisions and filing committments based on **Process Understanding** and **Risk Management**. Quality by Design.	**Design Space** concept introduced to integrate process knowledge with regulatory evaluation.
Quality	**Post-factum** sampling and quality testing. **Process Validation**.	Management of variability Process control focused on critical attributes. **Continuous Quality Verification**.	**Quality by design** definition applied. Measure critical process parameters to control output product quality.
Systems	Systems designed to inhibit changes & minimize business risks. **Discourages improvement & innovation**.	Changes managed within company's quality system. **Real time batch release** feasible.	Regulators and industry place higher **reliance / trust / understanding** on systems. Multidisciplinary evaluation and decision making.
Regulatory	**Compliance focus**. Changes require prior approval.	Regulatory scrutiny adjusted to level of Process Understanding. **Continuous improvement allowed within Design Space**.	Requires mechanisms to **communicate Process Understanding** data *("inspectable rather than reviewable")* .

Based on EFPIA, PAT Topic Group, 2005

The Vision is Driven by ICH Q9

- **Manage risk to patient, based on science:**
  - **Product, process and facility**
  - **Robustness of Quality System**
  - **Relevant controls to assess & mitigate risk**
- **Level of oversight required commensurate with the level of risk to patient for:**
  - **Marketing authorization applications**
  - **Post-approval change review**
  - **GMP inspections**

Ref: ICH

Pharmaceutical Industry and Quality Risk Management

- **Pharmaceuticals have lagged behind related industries in adopting structured risk management in the quality area; e.g.**
  - Medical devices make reference to ISO 14971
  - Food industry uses HACCP **Hazard Analysis Critical Control Point**
- **In pharmaceuticals quality risk management is used but its implementation is patchy, and there is scope for improvement.**

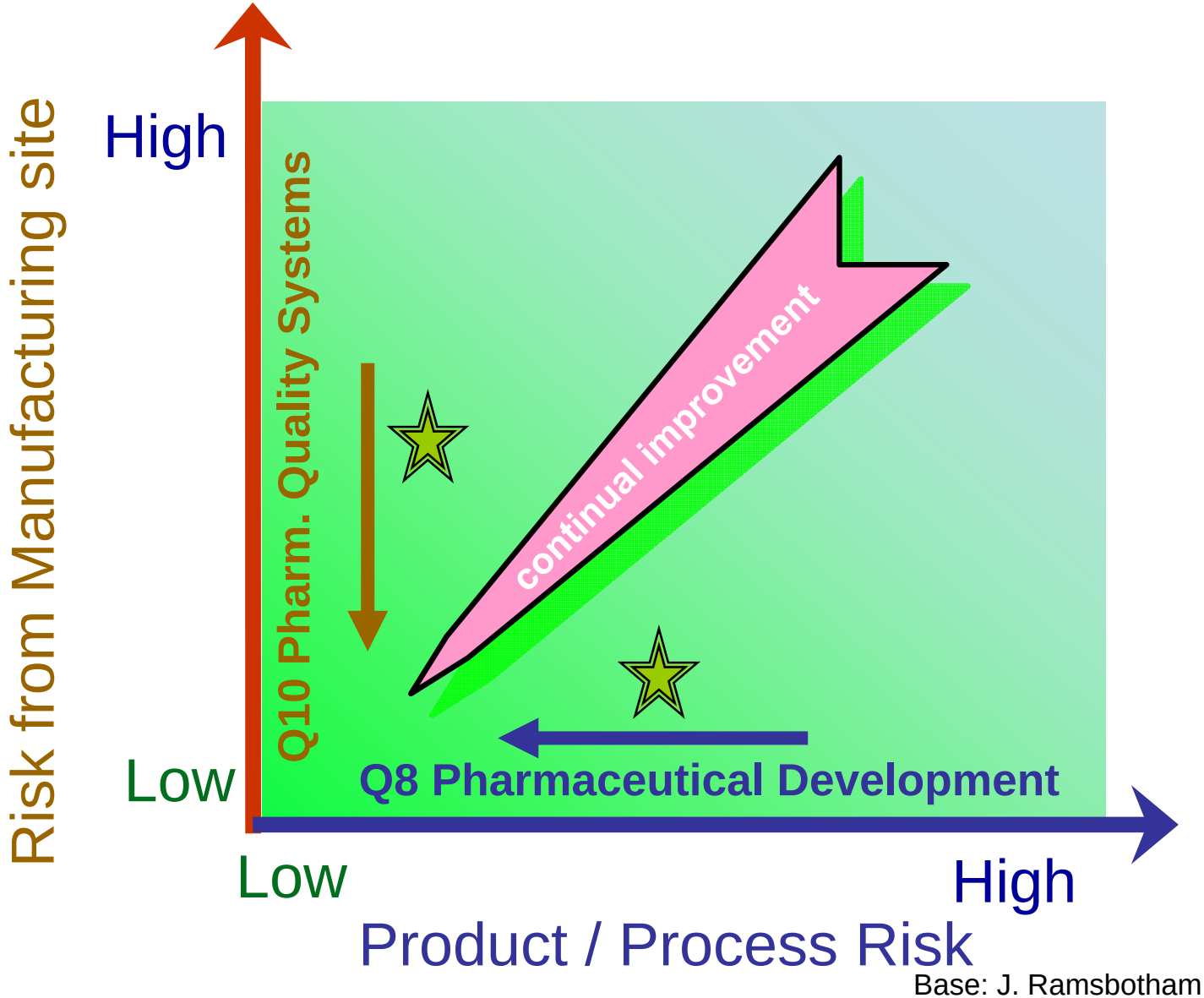
ICH Q9 – Quality Risk Management

- ***Quality:*** Degree to which a set of inherent properties of a product, system or process fulfills requirements.

- ***Risk:*** defined as the combination of the ***probability* of occurrence** of harm and the ***severity*** of that harm.

- ***Management:*** Systematic process for the **assessment**, **control**, **communication** and **review of risks** to the quality of the drug (medicinal) product across the **product lifecycle**.

How Q9 interacts with Q8 and Q10

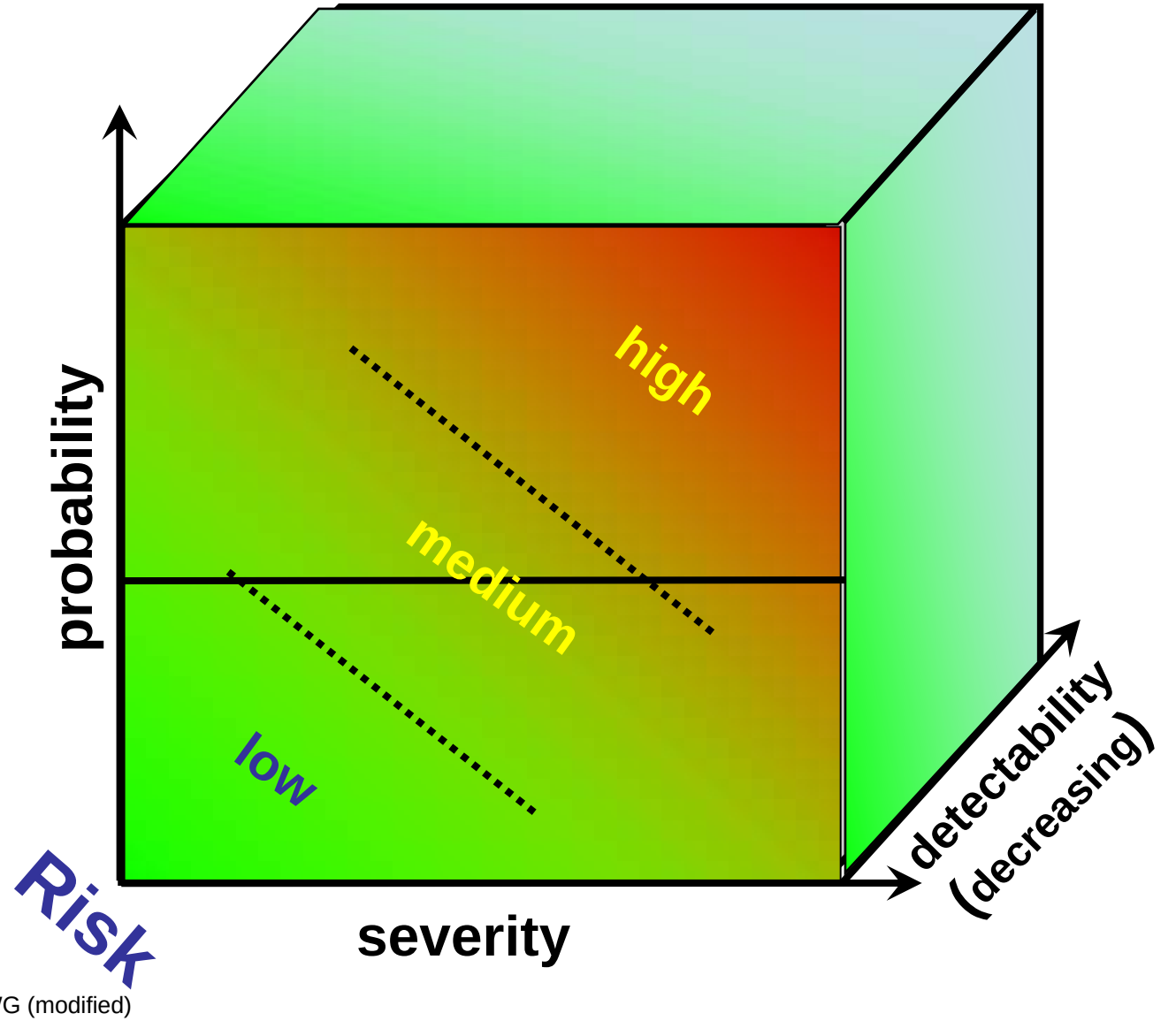


Using Q9 Quality Risk Management principles

Base: J. Ramsbotham, Solvay Pharm. NL / EFPIA

The “risk-based approach”

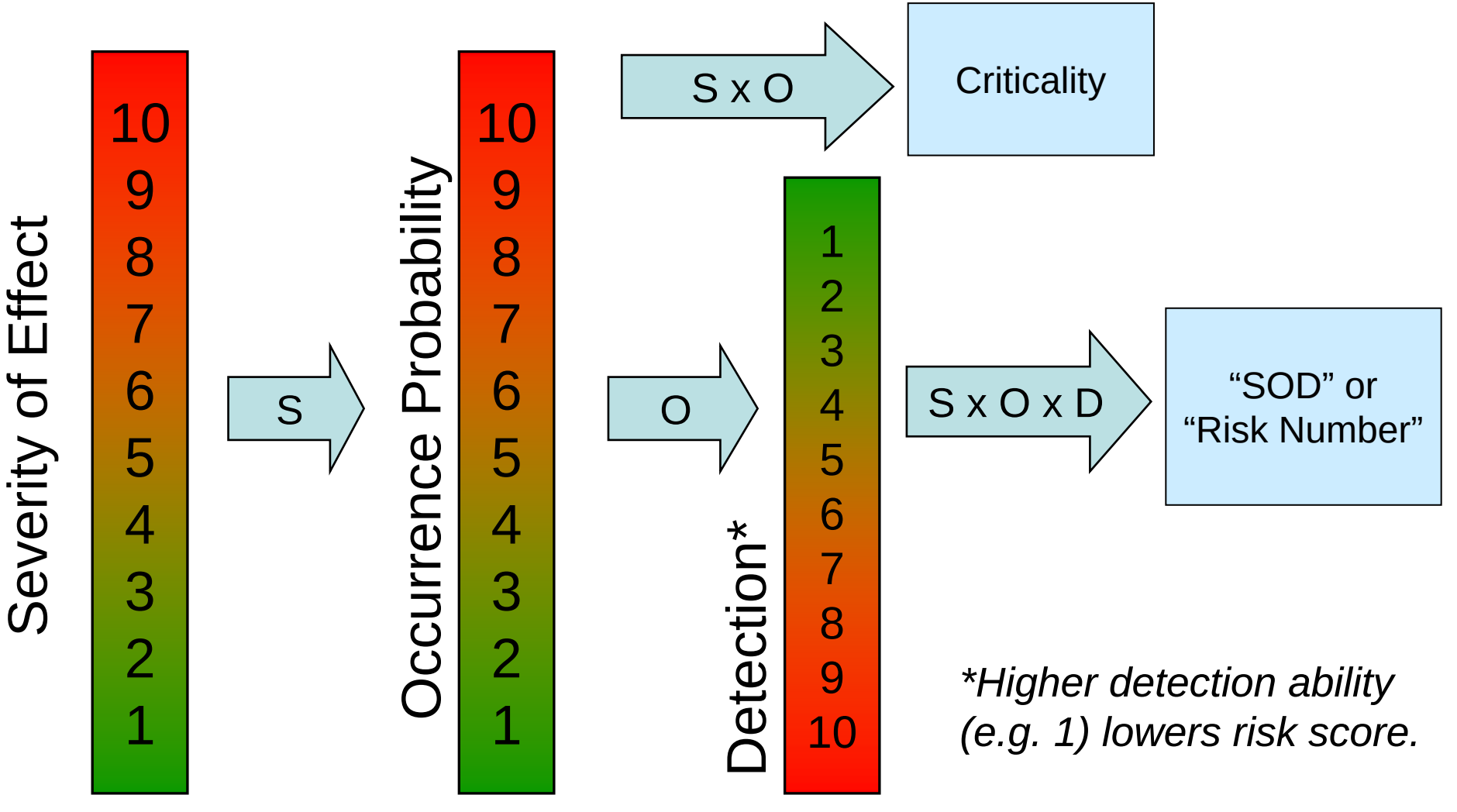
Parameters for evaluating risks



Ref: Prepared by the members of ICH Q9 EWG (modified)

Failure Mode Effects (control) Analysis

FME(C)A

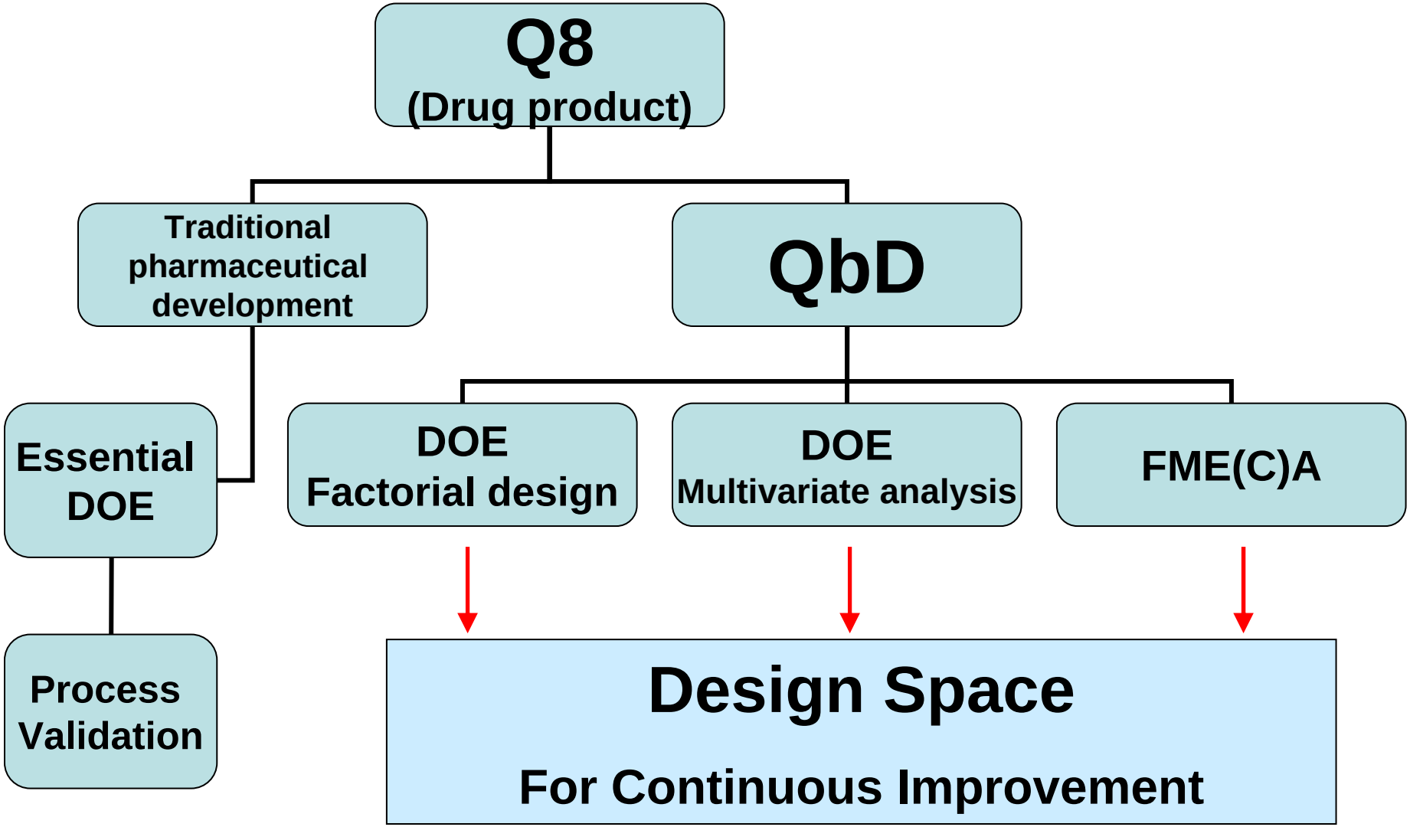


Ref: Claycamp 2006

E.g., FME(C)A Chart

					Traditional						
ID #	Process step	Equipment	Cause for failure	Potential effect	Effect on entire system	Severity	Occurance Probability	Criticality	Detection	SOD	Control
1	DS Milling	Jet Mill	Overloading	Large particle size	Dissolution failure	9	5	45	2	90	Particle size
2	Dry blending	High shear	Excipient quality	Homogeniety	Content U failure	8	3	24	5	120	Blend Homo
3	Wet massing	Hign Shear	Excipient quality	Over/under gran.	Tableting problem	8	8	64	8	512	Time
4	Lubrication	V Blender	Load	Flow/Dissolution	Content U, dissolution	9	4	36	8	288	Time
5	Compression	Tablet Press	Speed	Weight, hardness	Variations	8	6	48	8	384	Release test

Pharmaceutical Development Paths



QbD- a well known concept of the 50's

Ref: Out of Crisis (1986): W. EDWARDS DEMING

- Depending on inspection is like treating a symptom while the disease is killing you. The need for inspection results from **excessive variability** in the process. The disease is the variability. Ceasing dependence on inspection means you must **understand your processes** so well that you can **predict the quality** of their output from upstream activities and measurements. To accomplish this you must have a thorough understanding of the sources of variation in your processes and then work toward reducing the variation. Ceasing dependence on inspection forces you to reduce variability.

Ref: http://deming.eng.clemson.edu/pub/den/files/varman.txt
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Quality by Design (QbD)
- a component of Q8

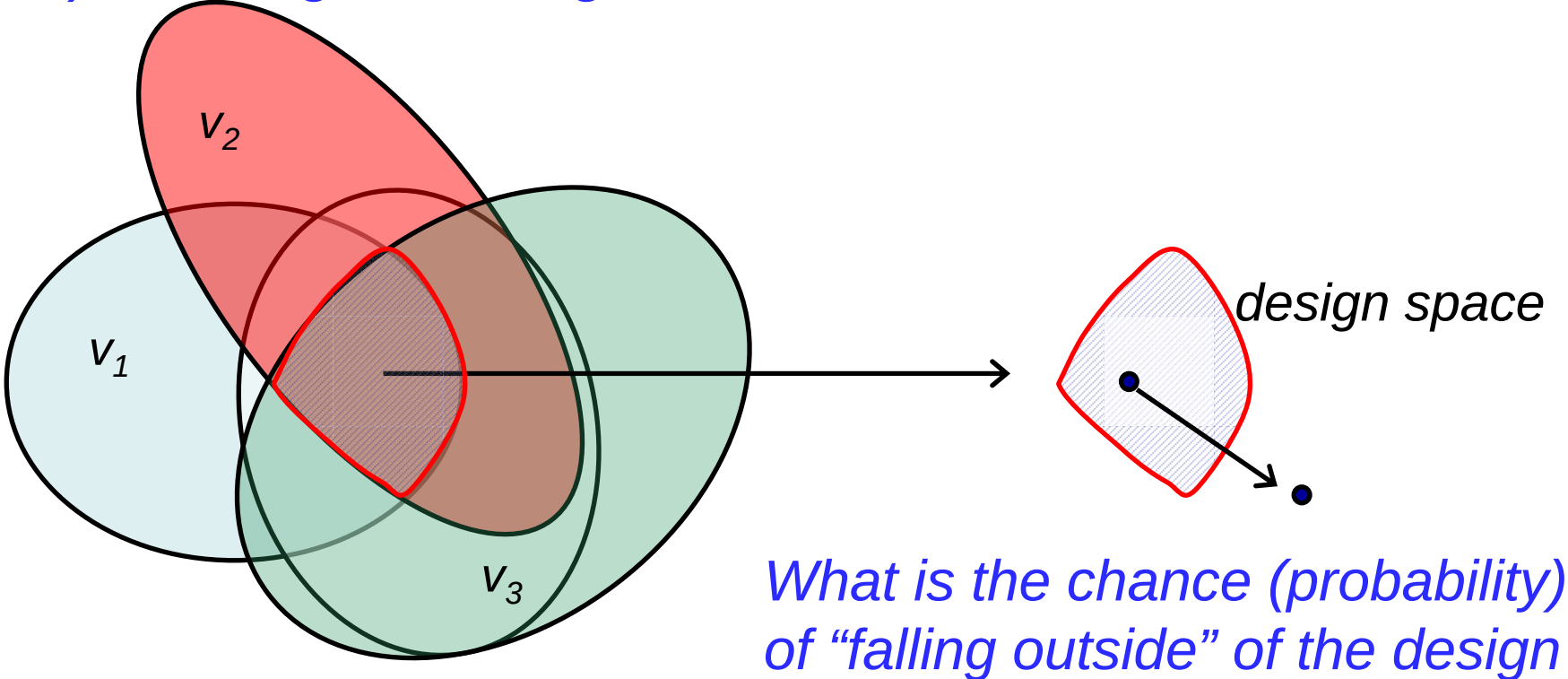
- The design of manufacturing processes using principles of pharmaceutics, engineering, material science, and quality assurance to ensure acceptable and reproducible product and performance throughout a product's shelf life.
- **QbD** assumes complete understanding and control of manufacturing process.
- At present QbD applies only to drug product.

Essential Elements of QbD

1. Complete **understanding** of product development and manufacturing process.
2. Identification of critical factors (e.g., FMEA), and use of control tools (e.g., PAT) to monitor, and **control critical** factors to **reduce variability** & **avoid failure**.
3. Develop **design space** based on **DOE**.
4. **Operate within a design space** which could be independent of:
    1. batch size
    2. equipment (size etc.)
    3. manufacturing site
5. **Design space** created would dictate the degree of regulatory **flexibility** that could be obtained.

QRM and the Design Space

Risk analysts estimate probabilities of being outside (or inside!) of design limits, given various scenarios.



Design parameters and their intersection in a “design space” concept

What is the chance (probability) of “falling outside” of the design space per unit time?

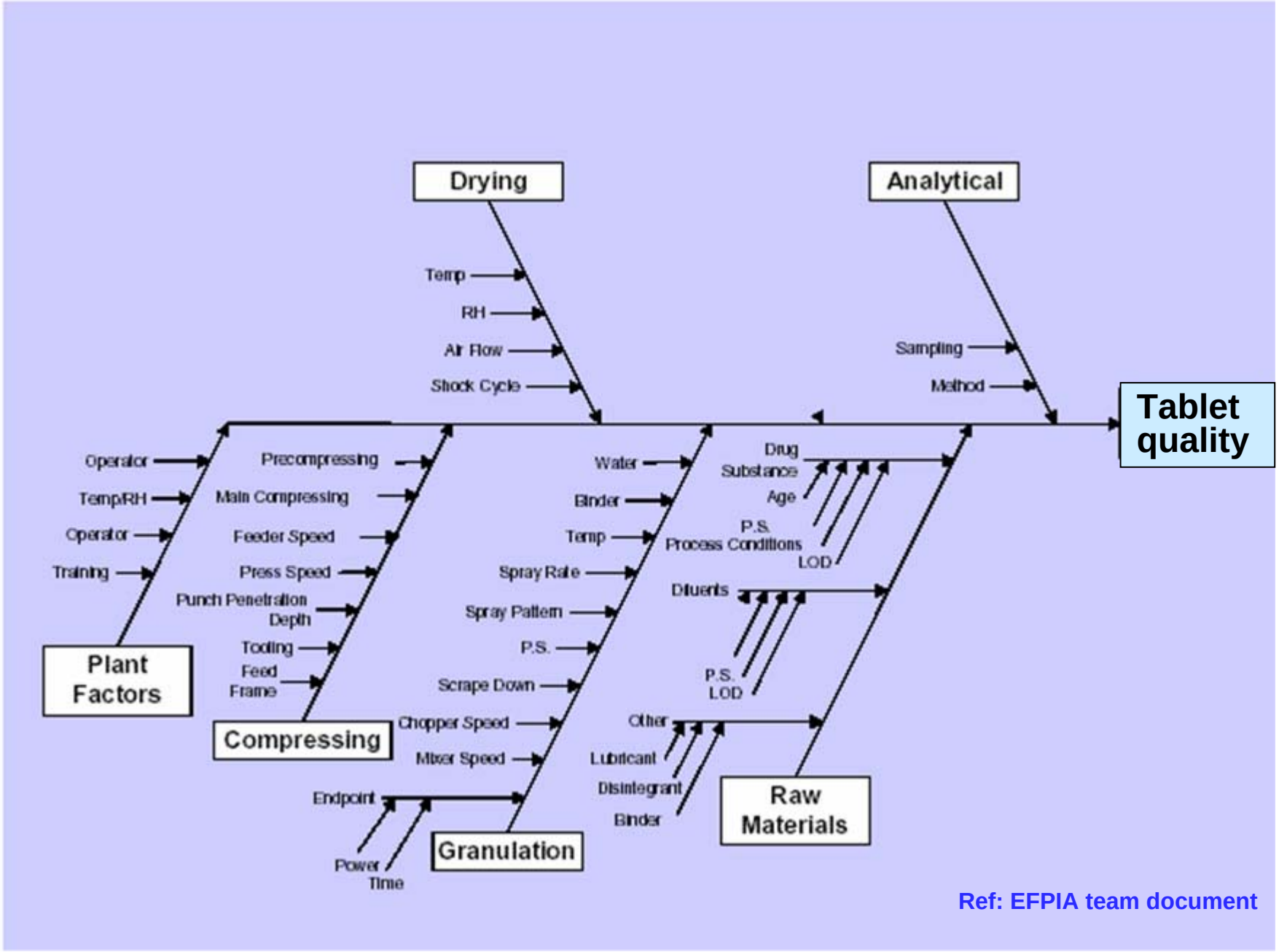
Ref: Claycamp 2006

Design of Experiments (DOE)

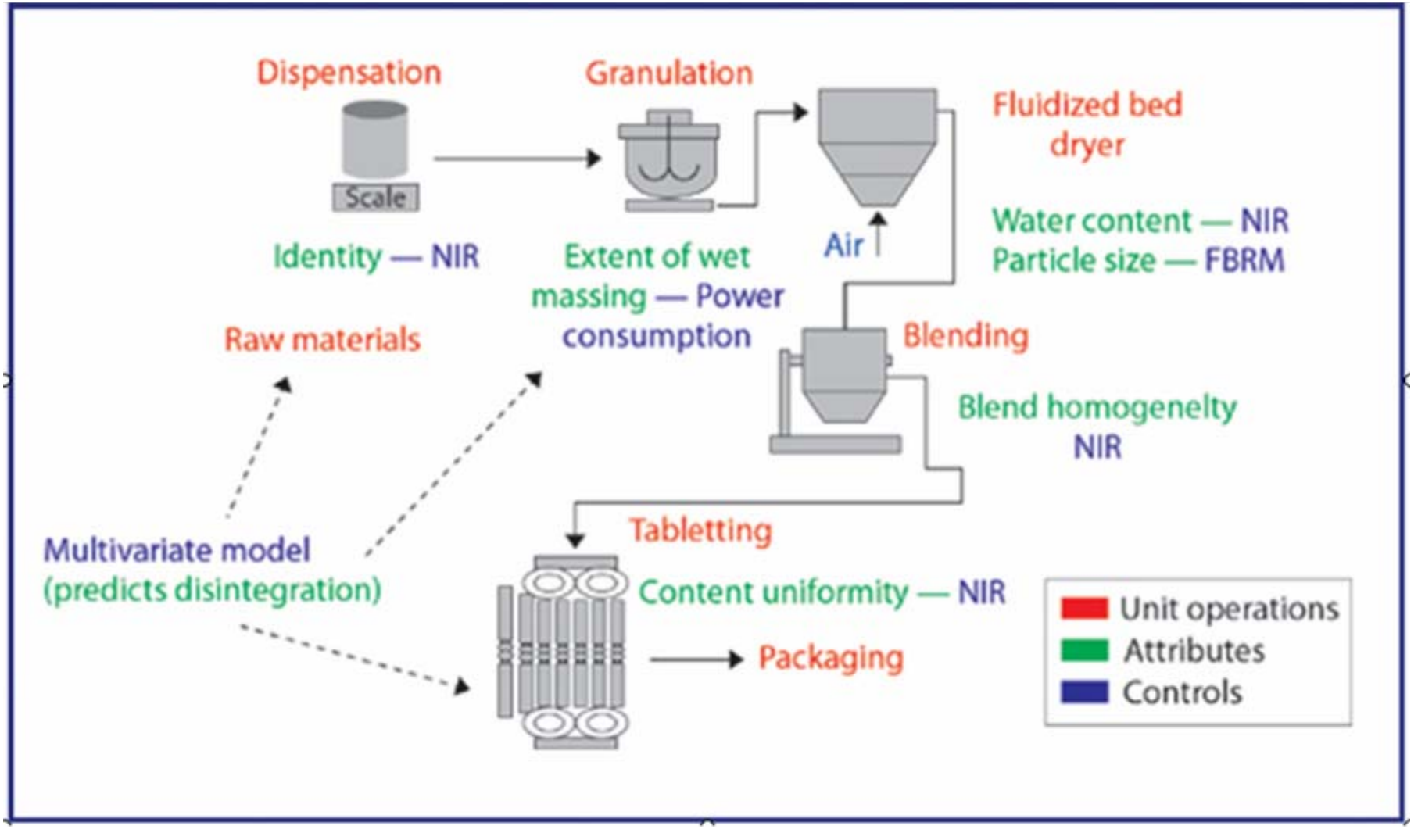
- **DOE** is a systematic planned approach to solving problems by gaining information through **carefully planned experiments** or studies.
- These studies should have **adequate statistical** properties to be able to measure effects of **formulation and process factors** on key **response variables** (e.g., Content U, dissolution) to be able to determine **if** these effects are **real**, and **accurately quantify** them.
- Term such as **process challenge study** describe similar concept used in a traditional approach, and has limited scope.

Cause & Effect Diagram

(a basis for DOE)



Ref: EFPIA team document


Dispensation
Granulation
Fluidized bed dryer
Scale
Identity — NIR
Extent of wet massing — Power consumption
Air
Water content — NIR
Particle size — FBRM
Raw materials
Blending
Blend homogenelty NIR
Tabletting
Multivariate model (predicts disintegration)
Content uniformity — NIR
Packaging
Unit operations
Attributes
Controls

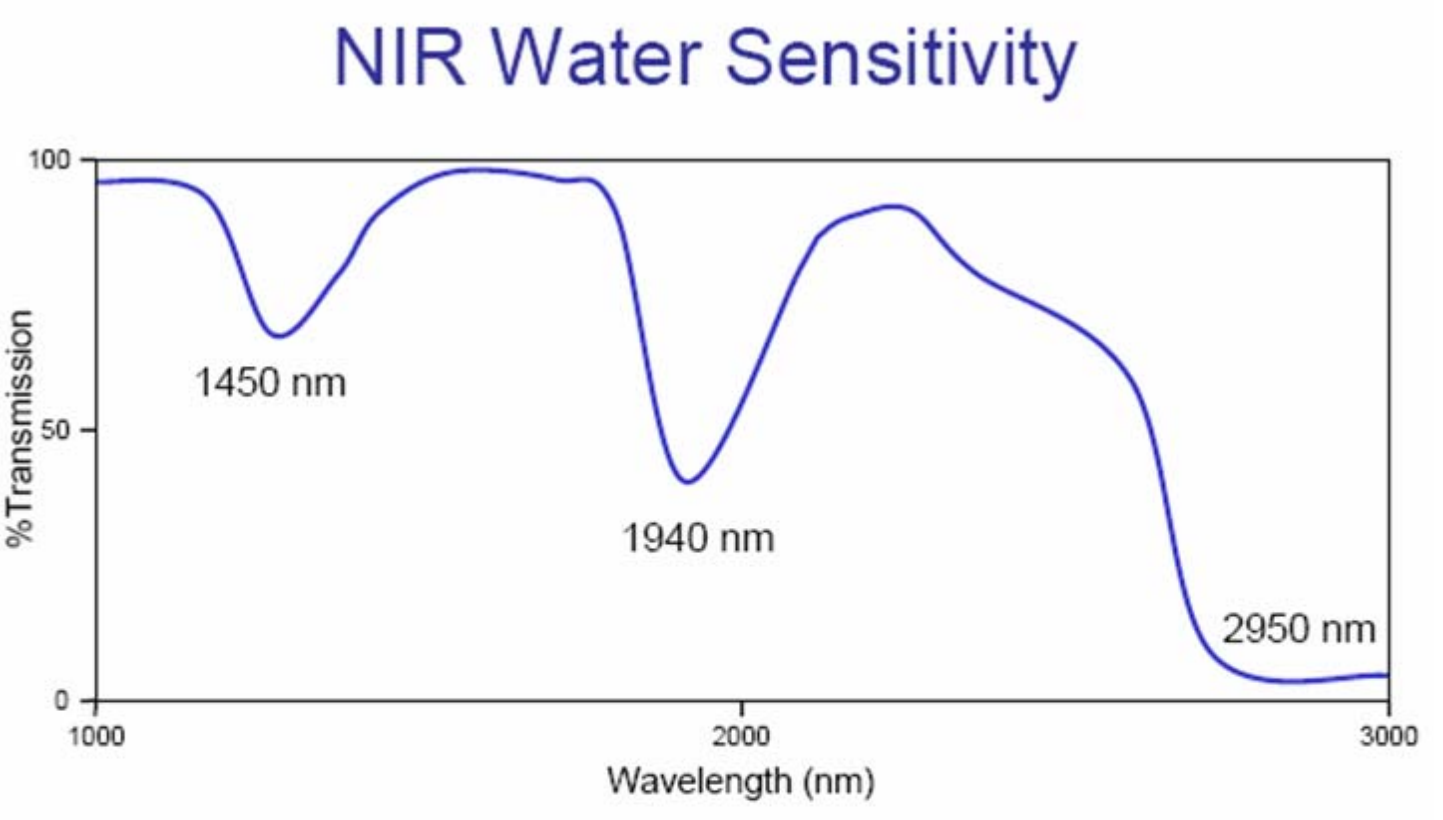
Use of Process Analytical Technology (PAT) in QbD: It helps

- To understand critical manufacturing process parameters
  - Incorporated from development stage
- To monitor and feedback during processing
  - In-process real time control
- Continuous evaluation of conformance to specifications
  - To reduce variability
  - Ensure required quality in the whole batch
- E.g. of PAT tools: **NIR**, Raman spectra

Near Infra Red (NIR) basics

- NIR region is 780–2500 nm (12820–4000 cm–1)
- NIR bands are due to overtones and combinations of fundamental vibrations of mainly hydrogen bonds.
- In most cases several wavelengths, even entire spectrum is used to build models for qualitative or quantitative analysis.
- Types:
  - Transmittance probes for clear transparent fluids.
  - Reflectance probes for slurries and powders.
  - Combination of both also used.
- Several factors, e.g., particle size, packing, etc. can affect results
- **The pattern in which the end point is reached** (e.g., shape of the curve) **is important**.

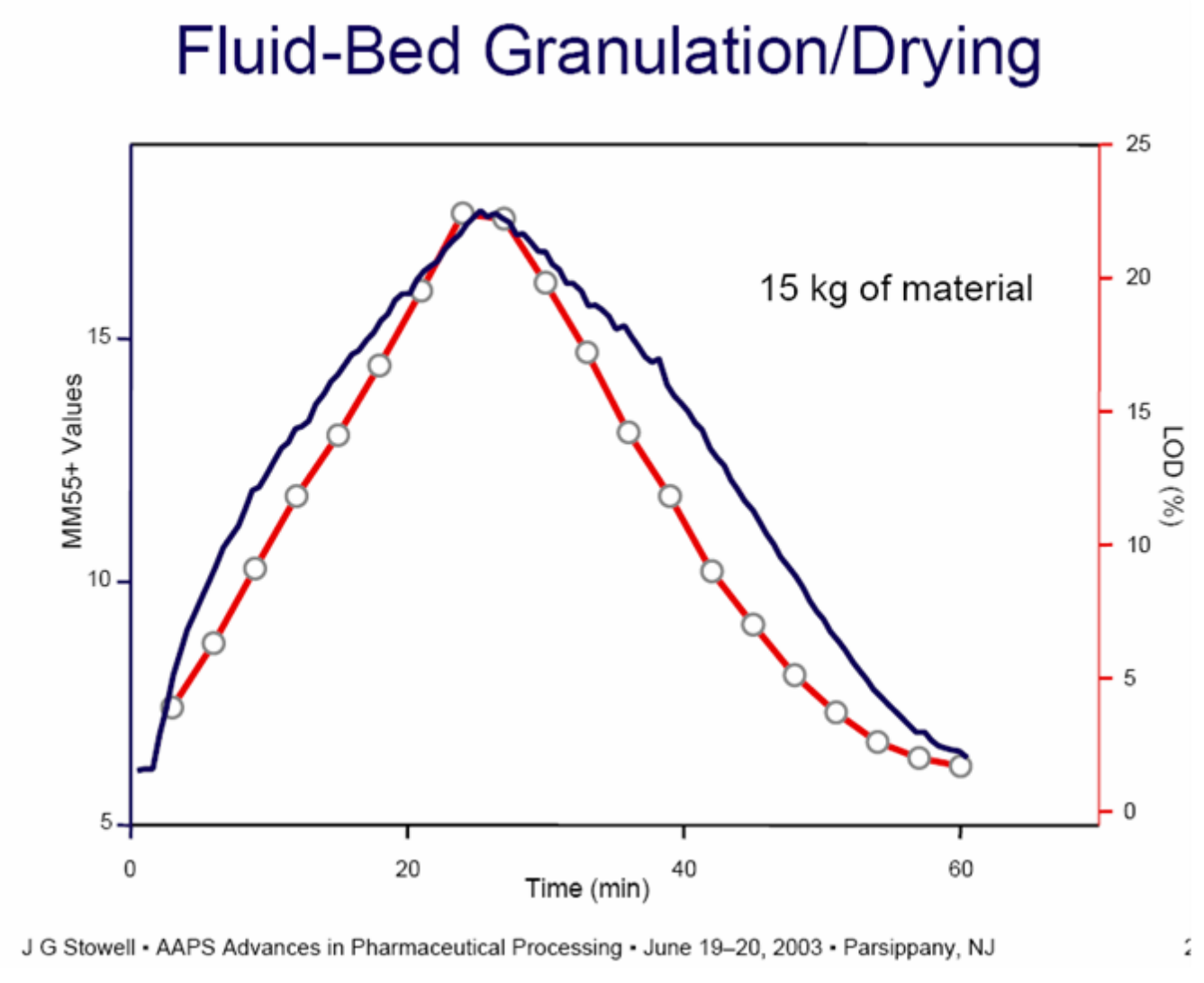
Water's NIR



- Band at 1940 nm (5155 cm^{-1}) is combination band of fundamental water vibrations of O—H stretch (3500 cm^{-1}) and O—H bend (1655 cm^{-1}).
- Band at 1450 nm (6900 cm^{-1}) is first overtone of O—H stretch (3500 cm^{-1}).

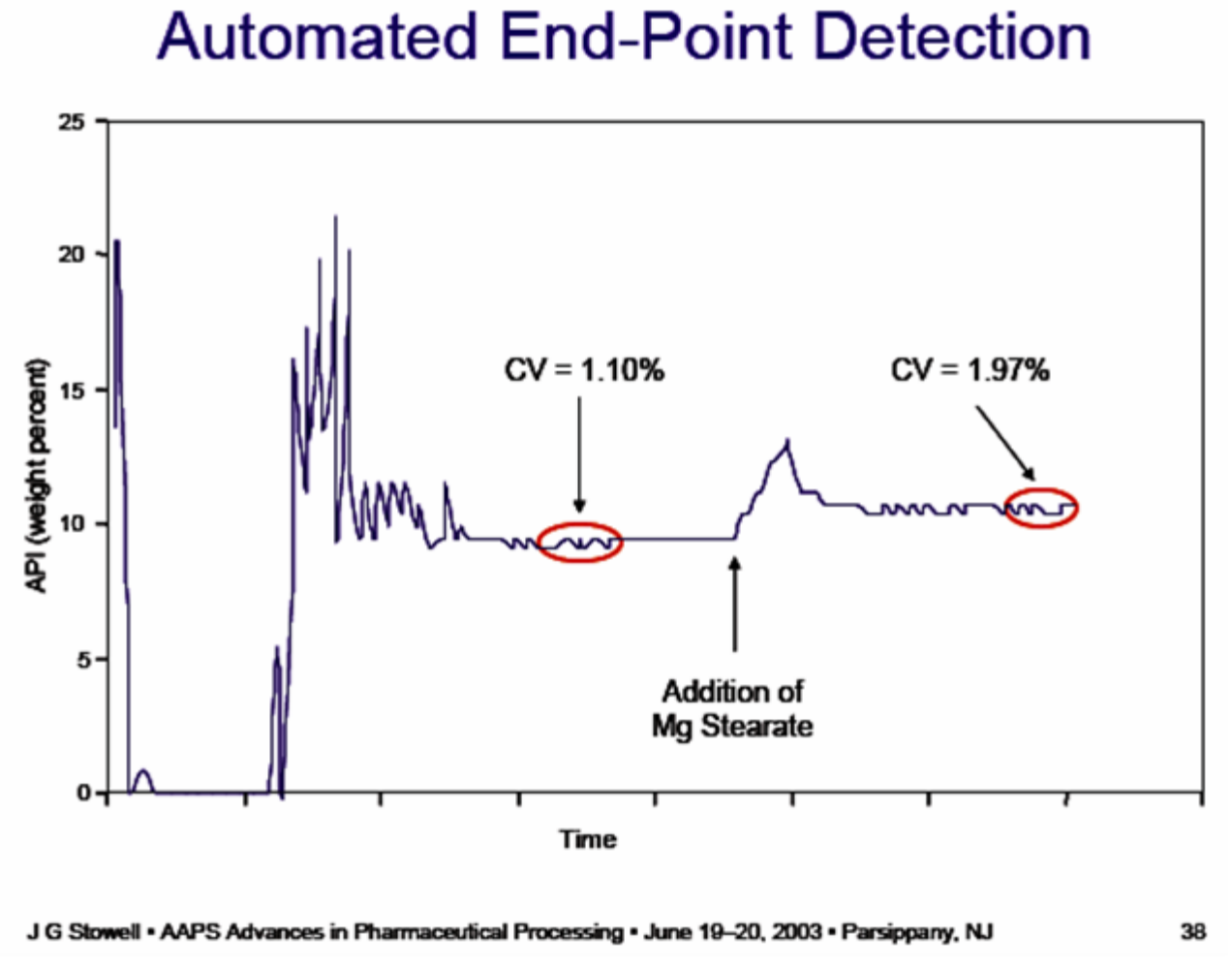
NDC–Infrared Engineering, Irwindale, CA

Use of NIR in process optimization



Use of NIR in process optimization

- The end point of mixing is more definite
- Sampling errors and multiple analysis is avoided
- On-line analysis using NIR data can pin point end of a mixing step



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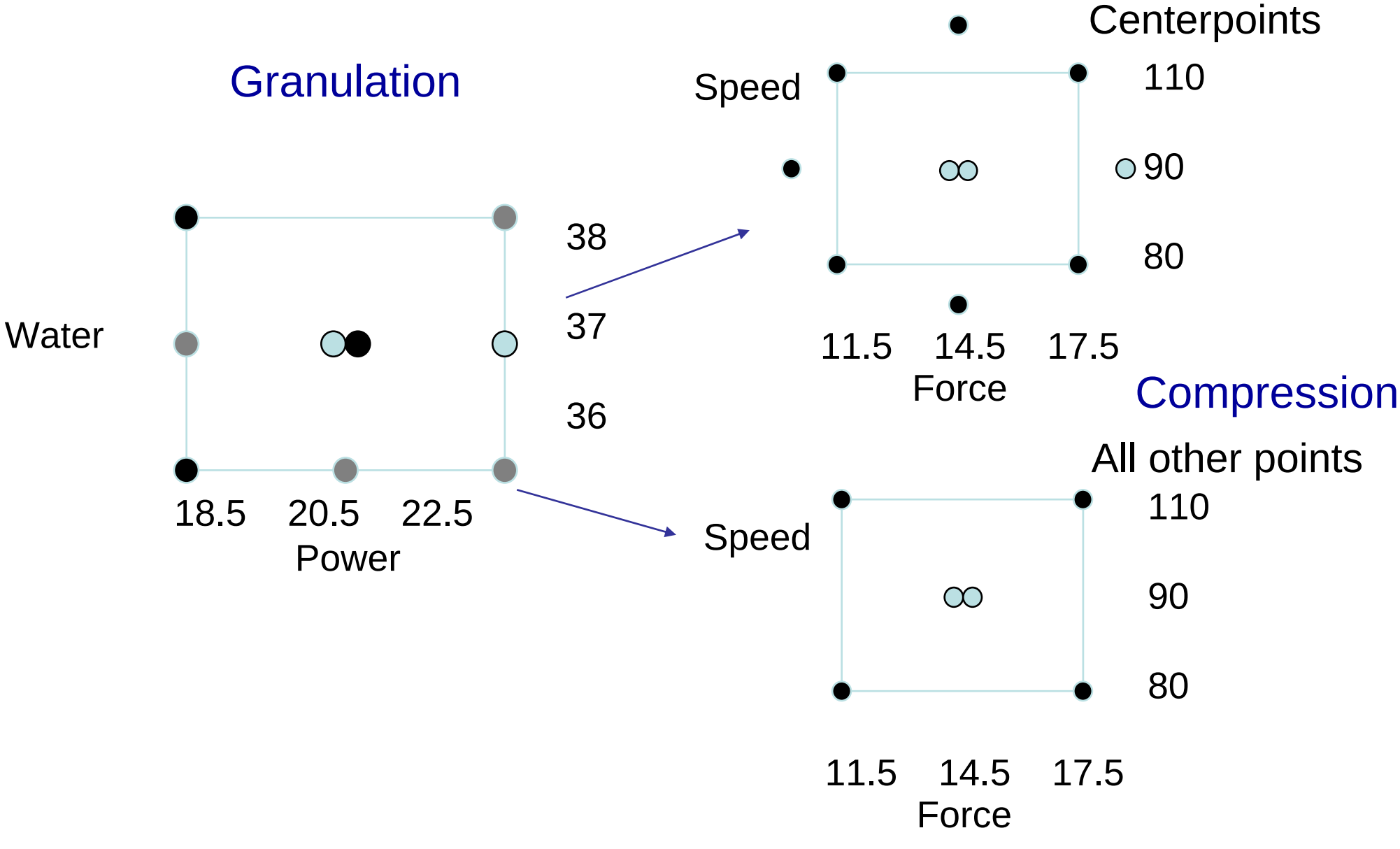
3	Wet massing	Hign Shear	Excipient quality	Over/under gran.	Tableting problem	8	8	64	3	192	Time, Power
4	Lubrication	V Blender	Load	Flow/Dissolution	Content U, dissolution	9	4	36	2	72	NIR
5	Compression	Tablet Press	Speed	Weight, hardness	Variations	8	6	48	4	192	Statistical
											in-process

Granulation & Compression DOE Studies



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Conclusions

- QbD requires **complete understanding** of product and manufacturing process to control the critical steps to avoid batch failure.
- **Design space** developed through a proper study would reflect the **degree of confidence** in the process and the possible **regulatory flexibility**.
- Industry and regulatory agencies have to build **mutual trust** to share vital information.
- Ultimately, if the patients are assured of good quality products, **everybody is a winner!**

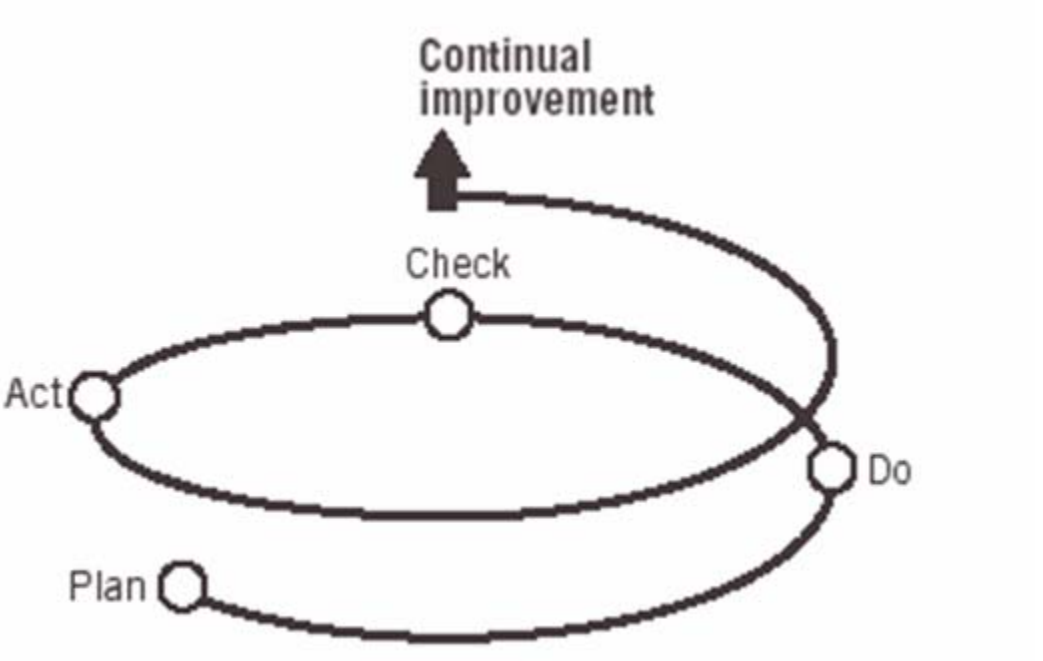
Fear factor !


EXPECTATIONS
REGULATIONS
REQUIREMENTS
COMPETITION
IT'S GAINING ON US!
NOW YOU UNDERSTAND WHAT CONTINUAL IMPROVEMENT IS ALL ABOUT!
ISO 9000
ISO 14000
PK 2002

Working together

Process as defined by Dr. W. Edwards Deming, should have four steps

Ref: Natural Resources Canada



Thanks!