21st EAFP Annual Conference, Quality Assurance in Pharmacy Education, May 14-16, 2015

"Application of Quality by Design in formulation and process Development"

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Quality by Design

The “new” Concept:

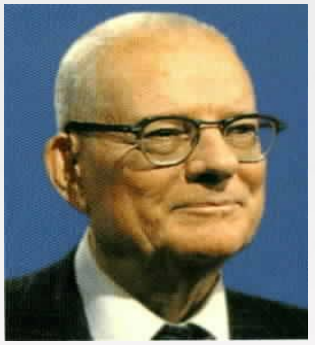
- Is it actually new?
- The actual status of the Pharma industry.
- The framework - Quality by Design and pharmaceutical product life-cycle.
- Application in product and process development

Is it actually new?

Knowledge

Focus on the process
Variability reduction
Discrimination of causes

Team work
Company wide – TQM
Quality by Testing Vs Quality by Design



W.E. Deming

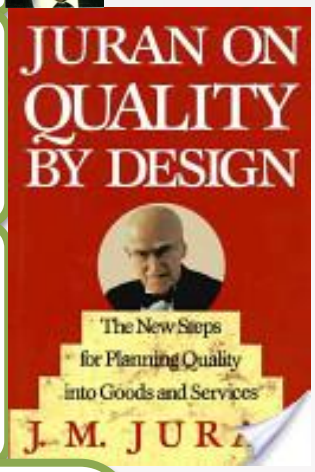
"**Lack of knowledge . . . that is the problem.**"
"Does experience help? **NO! Not if we are doing the wrong things**."
"If you **can't describe what you are doing as a process**, you don't know what you're doing."
"We must **understand variation**."
"Quality is **everyone's** responsibility."

Is it actually new?

J.M. Juran

Knowledge

Focus on the process
Variability reduction
Discrimination of causes



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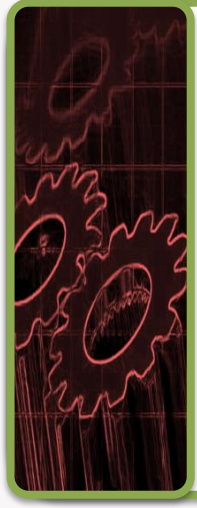


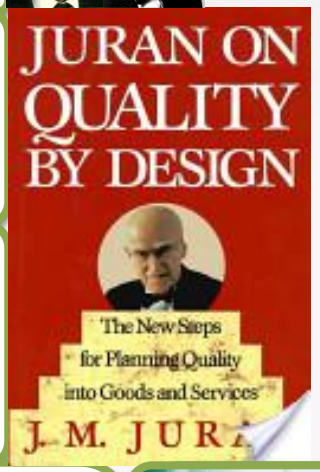
Built-in quality
Continuous monitoring and **improvement**
Different "Factors" have different **impact** – **identification** and **prioritization**
Risk based approach

- **"Staple yourself to the process."**
- **Juran's Trilogy**
- **Pareto principle**

Is it actually new?

Knowledge

Focus on the process
Variability reduction
Discrimination of causes

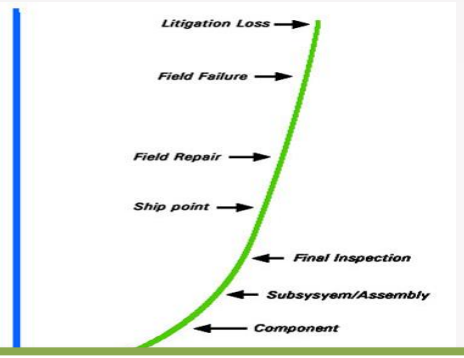


Team work
Company wide – TQM
Quality by Testing Vs Quality by Design

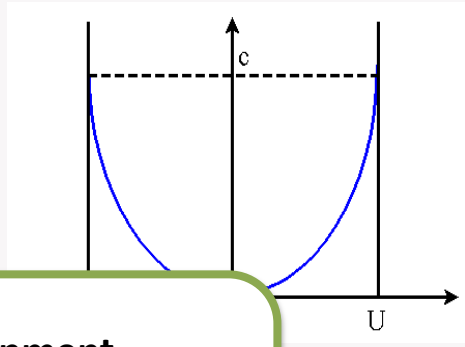
A. Feigenbaum

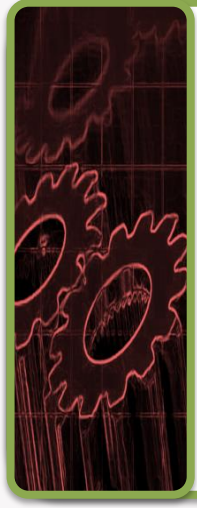
G. Taguchi

Failure Cost



Taguchi's Quality Loss Function
Loss to the SOCIETY





Built-in quality
Continuous monitoring and **improvement**
Different "Factors" have different **impact** – **identification** and **prioritization**
Risk based approach

Focus on **development**
Internal and external **failures**
Early identification of failure modes
Pre-active approach
Quality loss is loss to **Society** (Patients)
Development of **robust** processes and products

Is it actually new?

Knowledge

Focus on the process
Variability reduction
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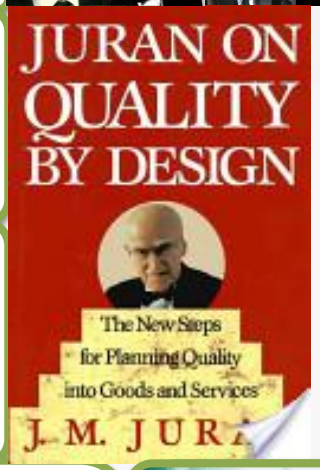

Team work
Company wide – TQM
Quality by Testing Vs Quality by Design

Dr W. Shewhart

K. Ishikawa

- Outlining of the Magnificent Seven (Check Sheets, Stratification, Histograms, Pareto Charts, **Cause and Effect diagrams**, Scatter Diagrams and graphs/Control charts.
- Company Wide Quality Culture and Continual Improvement (KAIZEN)

Built-in quality
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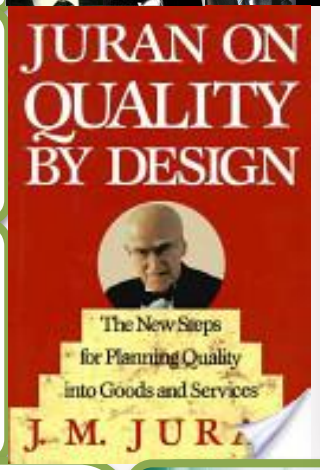

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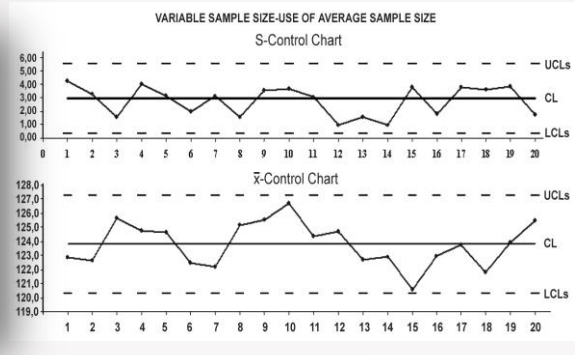

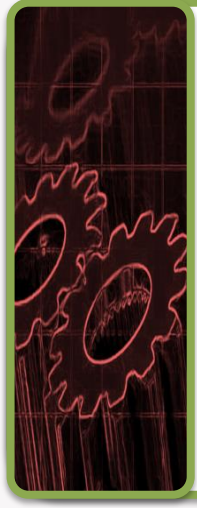

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Risk based approach

Focus on **development**
Internal and external **failures**
Early identification of failure modes
Pre-active approach
Quality loss is loss to **Society** (Patients)
Development of **robust** processes and products

Is it actually new?

Knowledge	QUALITY
Focus on the process **Variability reduction** **Discrimination of causes**	Use of **statistical tools** and effective Data Collection and Analysis Identification of **relationship between causes and effects** **Effective process monitoring**
Team work **Company wide – TQM** **Quality by Testing Vs Quality by Design**	Focus on **development** Internal and external **failures** **Early** identification of failure modes **Pre-active** approach **Quality loss** is loss to **Society** (Patients) Development of **robust** processes and products
Built-in quality **Continuous monitoring** and **improvement** Different "Factors" have different **impact** – **identification** and **prioritization** Risk based approach	

Wrap-Up:

- For **all process industries** (Focus to Pharmaceuticals):

Development

Process knowledge

Identification, allocation and reduction of variability

Prioritization of risks

Risk identification, prioritization and mitigation

Scale up and product realization

Process robustness and stability

Company wide culture

Infrastructure, resources, inputs, management support etc.

Risk identification and mitigation

Process verification – assurance of process stability over time – control and release strategies

Quality

Product proof of concept:

Clinical trials

Continual improvement through out life cycle

Company wide culture – PDSA cycles

Continuous fight against variability

Infrastructure, resources, inputs, management support etc.

Quality

Development

ICH Q8 Pharmaceutical Development

ICH Q9 Risk Management

ICH Q10 Pharmaceutical Quality System

ICH Q11 On development and manufacturing of APIs

Scale up and product realization

Process robustness and stability

ICH Q8 Pharmaceutical Development

ICH Q9 Risk Management

ICH Q10 Pharmaceutical Quality System

Guideline on process validation for finished products

ICH Q7A: GMPs

ICH Q11 On development and manufacturing of APIs

Product proof of concept:

Reflection paper on risk based quality management in clinical trials

Continual improvement through out life cycle

ICH Q10 Pharmaceutical Quality System

ICH Q7A: GMPs

ICH Q9 Risk Management

Current status of pharmaceutical industry - criticism:

Two categories of symptoms

Technical

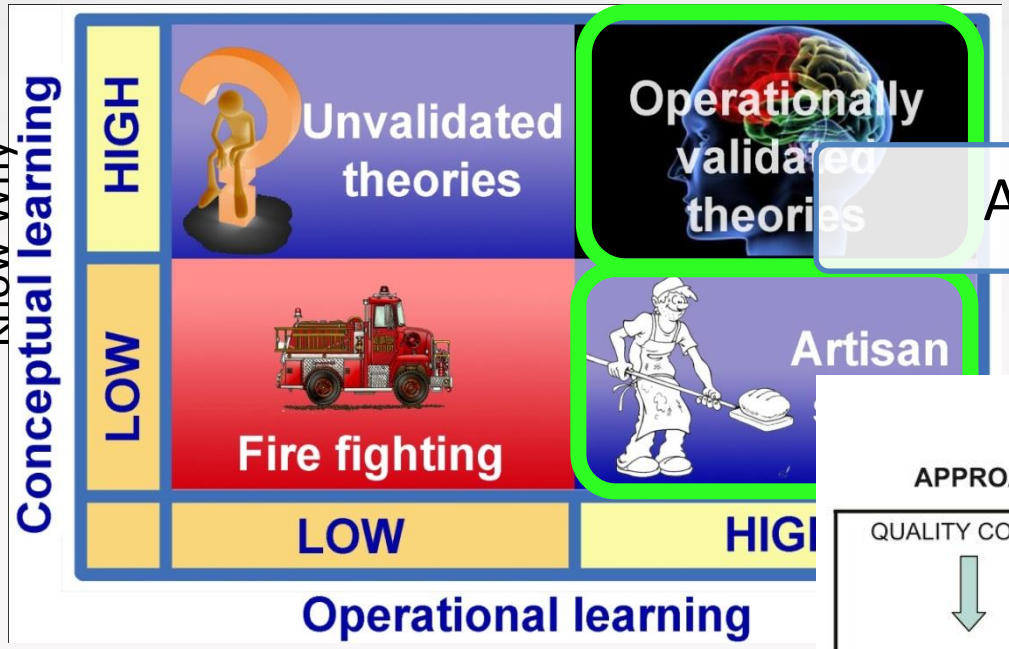
- Obsolete production methods, slow adoption of new technologies
- Estimation of annual cost of production deficiencies US$90b/y
- Functions at 2,5-3,0 sigma with average manufacturing capacity of 20-30%
- Lags behind other industries

Ethical

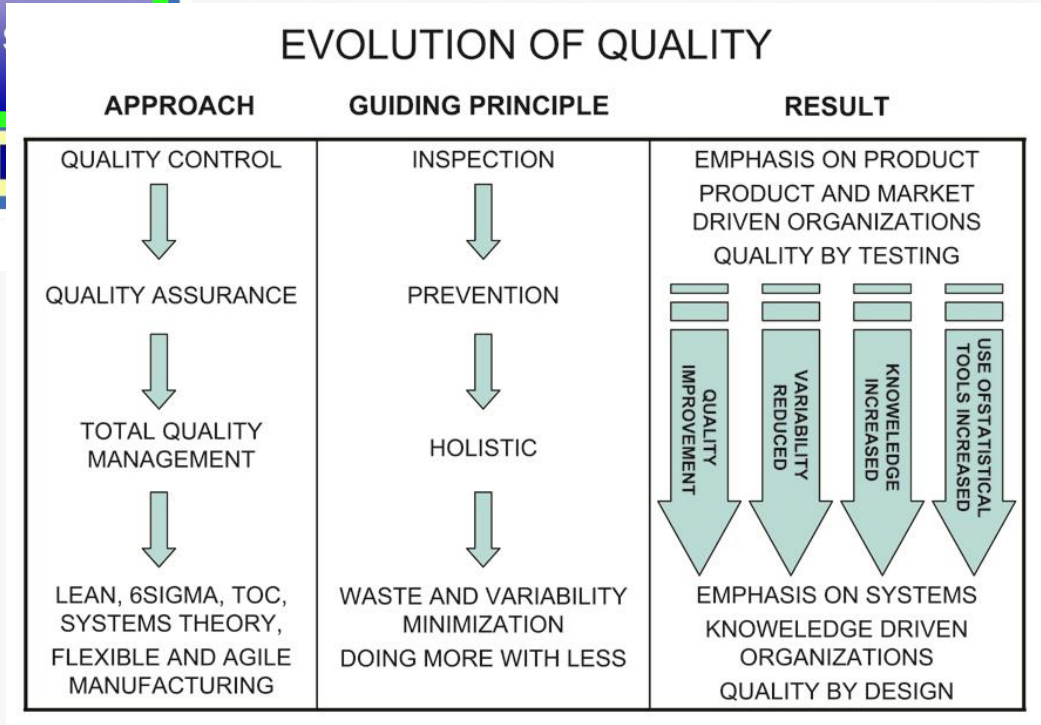
- Safety
- Clinical trial design
- Promotion methods
- Others

Politis S.N., Rekkas D.M., 2011, The Evolution of the Manufacturing Science and the Pharmaceutical Industry, Pharmaceutical Research, 28, 7, 1779-1781

Current status of pharmaceutical industry - change:



A transition was required…



Beginning from the obvious…

Korakianiti E., Rekkas D.M., 2011, Statistical Thinking and Knowledge management for Quality-Driven Design and Manufacturing in Pharmaceuticals, Pharmaceutical Research, 28, 1465-1479.

The framework – QbD and product life cycle:

Beginning from the obvious…

The framework – QbD and product life cycle:

Beginning from the obvious…

June 20, 1963:
FDA announces three sets of regulations governing the manufacture, effectiveness and promotion of drugs.

tion. Any drug limited to prescription use under section 503(b)(1)(C) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling. A

GEO. P. LARRICK,
Commissioner of Food and Drugs.

[F.R. Doc. 63-6337; Filed, June 19, 1963; 8:45 a.m.]

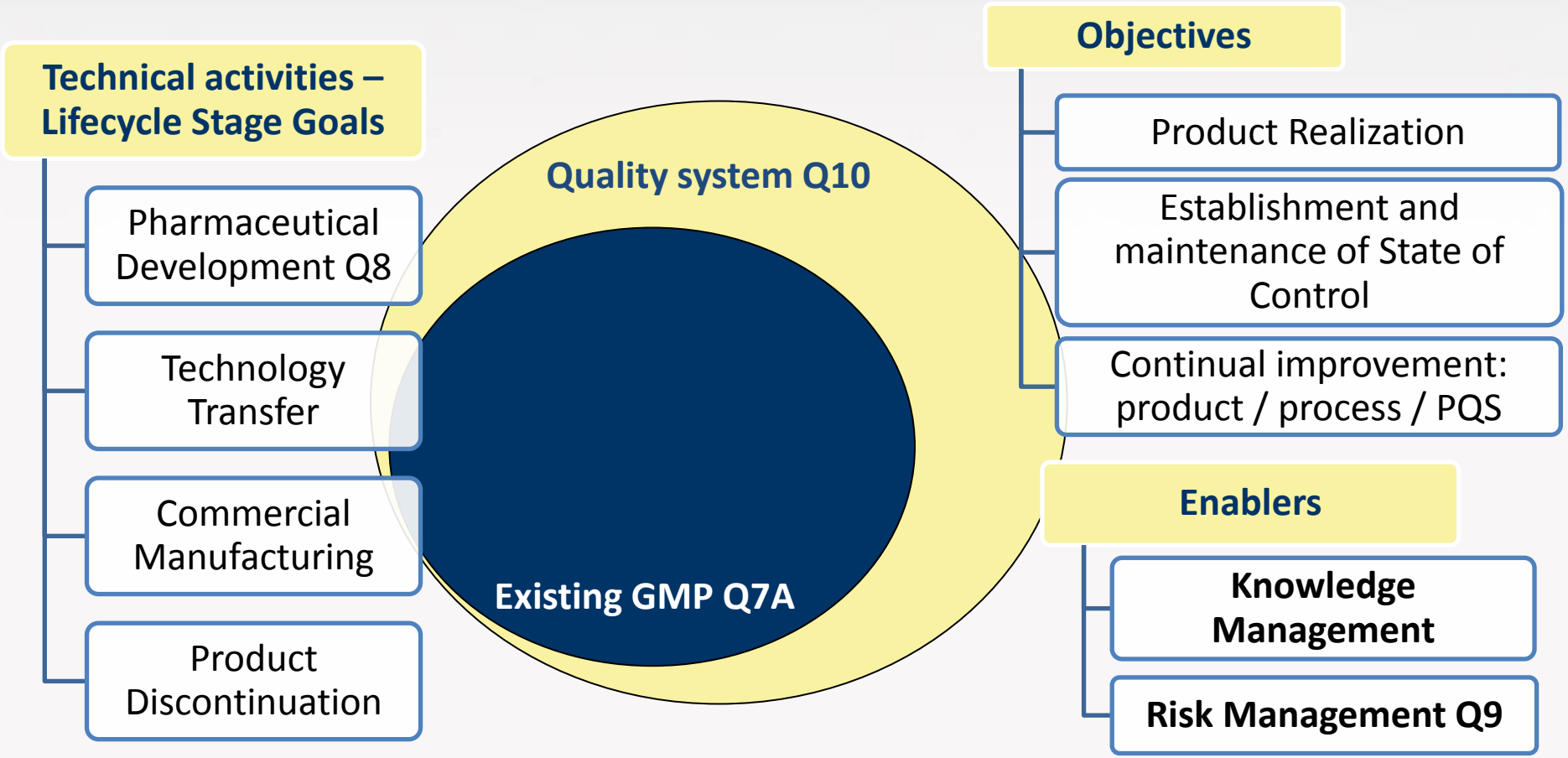
PART 133—DRUGS; CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURE, PROCESSING, PACKING, OR HOLDING

In the FEDERAL REGISTER of February

good manufacturing practice to assure that a drug meets the requirements of the act as to safety, and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess, as required by section 501(a)(2)(B) of the act. The regulations in this Part 133 permit the use of precision automatic mechanical or electronic equipment in the production of drugs when adequate inspection and checking procedures are used to as-

The framework – QbD and product life cycle:

Moving from Compliance to an integrated QMS covering overall product lifecycle



ICH consensus vision on Quality: "Develop a **harmonized pharmaceutical quality system** applicable across the life cycle of the product **emphasizing an integrated approach to risk management and science**"

E. Korakianiti: Quality by Design Event Athens, 2010

The framework – QbD and product life cycle:

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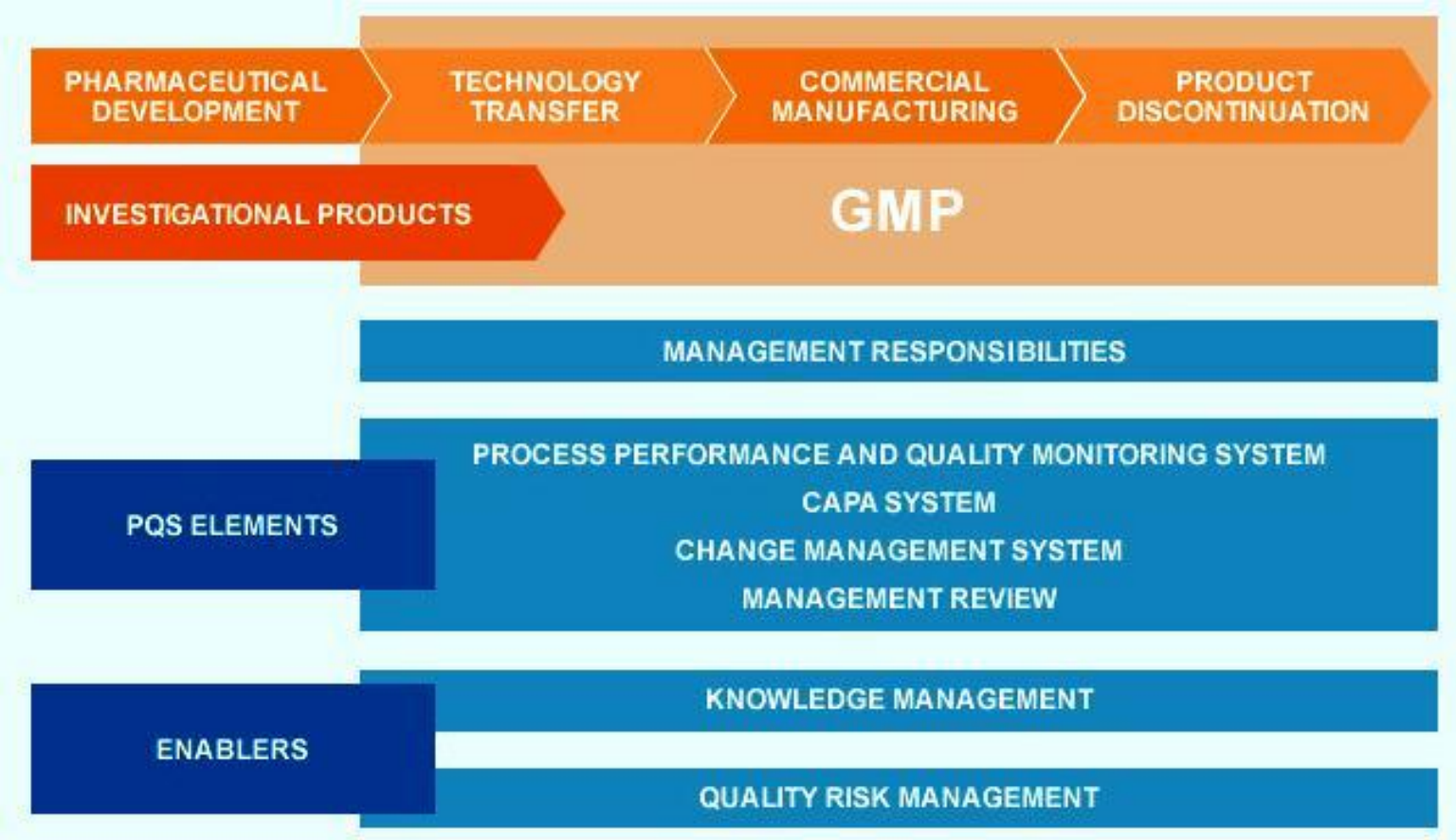

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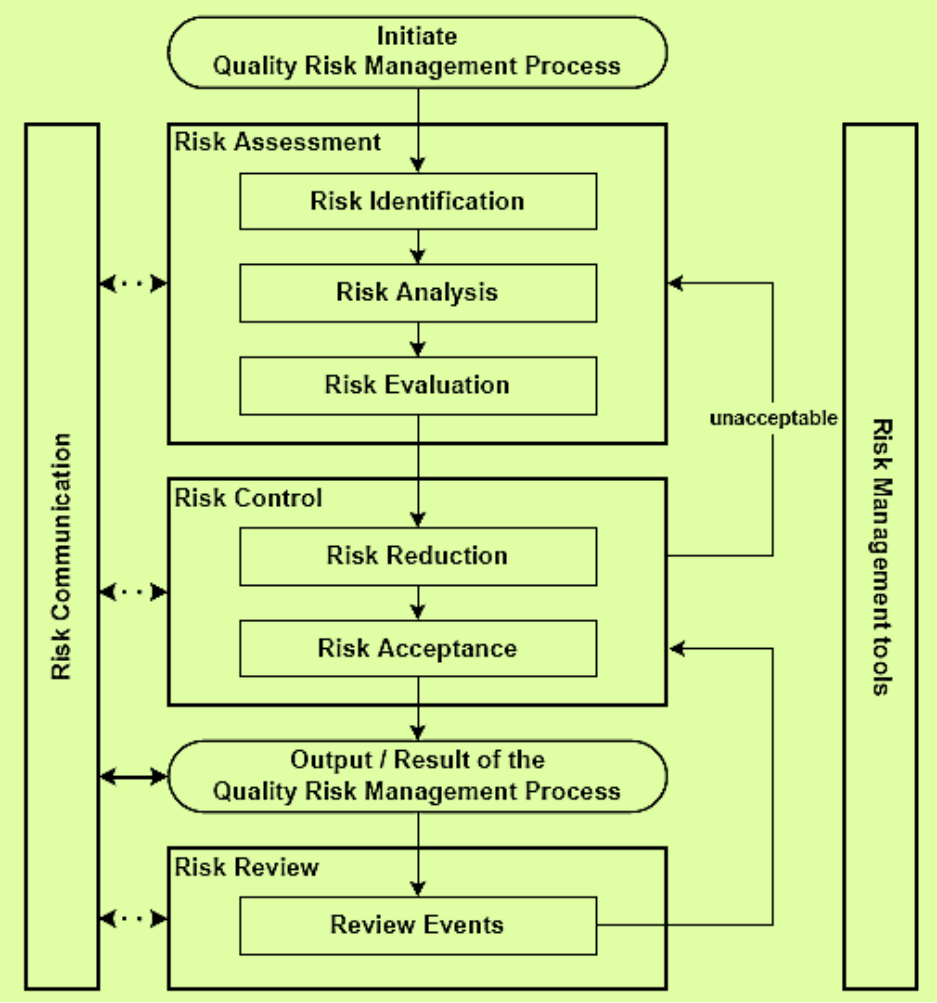
The framework – QbD and product life cycle:

Risk analysis and mitigation throughout product lifecycle



- The link between the product realization steps (technical level)
- The link between reality and statistics
- The link between experience and statistical thinking

The framework – QbD and product life cycle:

Risk analysis and mitigation throughout product lifecycle

Quality Risk Management:
a **systematic process** for the **assessment, control, communication** and **review** of risks to the quality of the drug product across the product lifecycle

Risk:
the **combination** of the **probability** of occurrence of harm and the **severity** of that harm. **Detectability** is important to be also considered.

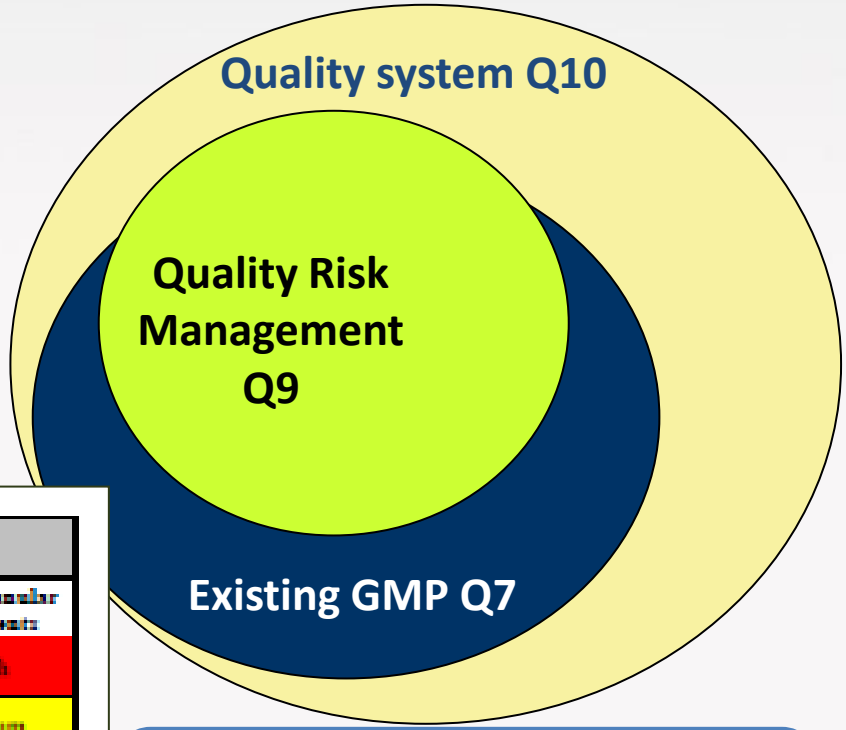


Table 20. Initial risk assessment of the formulation components

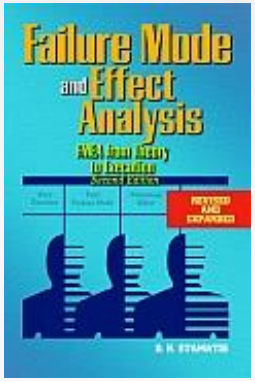
Drug Product CQAs	Formulation Components: IR Granules	ER Beads: layered beads	ER Beads: coated beads	Extragranular Excipients
Physical Attributes (size and splitability)	Low	Low	Low	High
Assay	Low	High	Low	Medium
Content Uniformity	Low	Medium	Low	High
Drug Release – whole tablets	Medium	High	High	High
Drug Release – split tablets	Medium	High	High	High
Drug Release – alcohol-induced dose dumping	N/A	N/A	High	Medium

Risk Priority Number (RPN)
=S x O x D
S: Severity
O: Occurrence (probability of)
D: Detectability

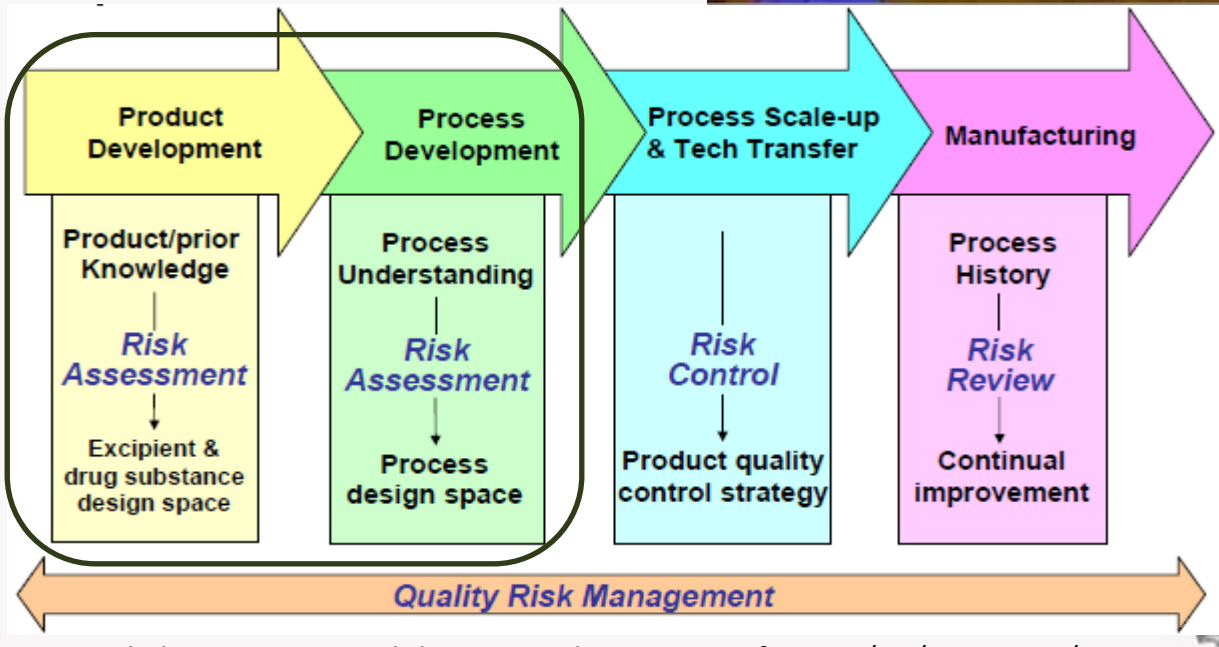
ANDA (Abbreviated New Drug Application) Mock Example QbD MR Tablet, 3.2.P.2 Pharmaceutical Development

The framework – QbD and product life cycle:

Risk analysis and mitigation throughout product lifecycle

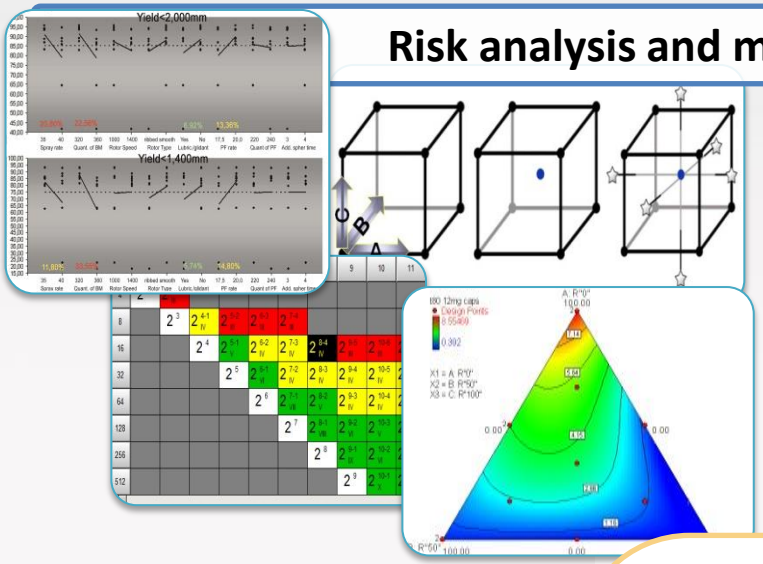


Initial product and process assessment
Brainstorming – Previous experience
QTPP determination
Candidate CQAs CPPs



Moheb Nasr, 2008, Workshop on implementation of ICH Q8/Q9/Q10, CDER/FDA.

The framework – QbD and product life cycle:



Risk analysis and mitigation throughout product lifecycle

Optimum Development through
cycles of risk identification and mitigation
CPP CQA relationship
Design Space
Justification of specs and control strategy
Predictable, robust and repeatable

ICH Q8
(ICH Q11)
QbD

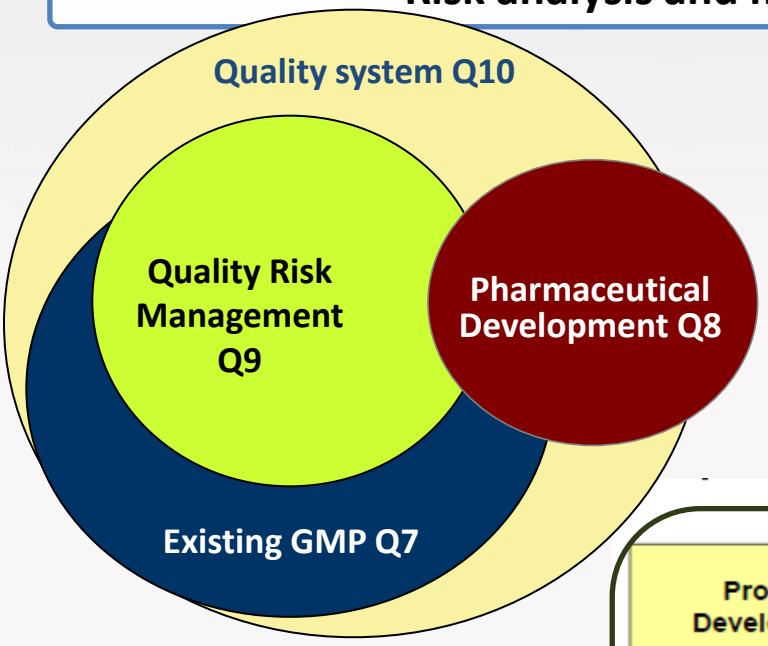
Sequential experimentation

QTPP & CQAs → Process Variables → QRM

Design of Experiments → Design Space → Control Strategy

The framework – QbD and product life cycle:

Risk analysis and mitigation throughout product lifecycle

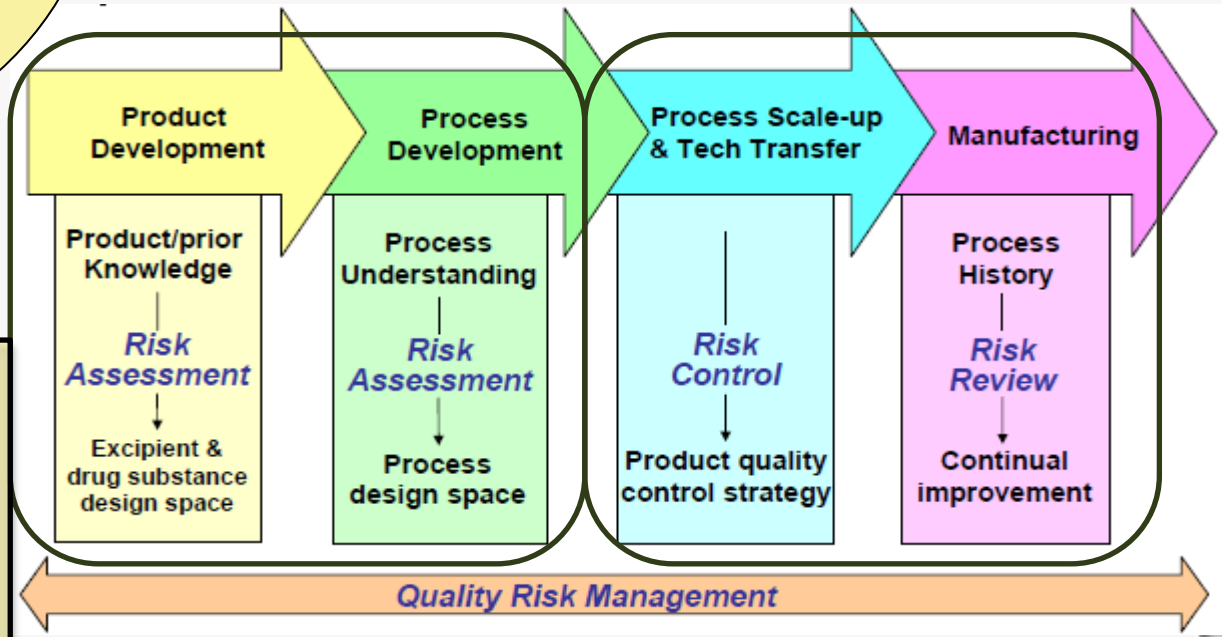


Process Verification-PAT

”Validation offers assurance that a process is reasonably protected against **sources of variability** that could affect production output, cause supply problems, and **negatively affect public health**”

ICH Q8 QbD

Optimum Development through cycles of risk identification and mitigation
CPP CQA relationship
Design Space
Justification of specs and control strategy
Predictable, robust and repeatable process



Moheb Nasr, 2008, Workshop on implementation of ICH Q8/Q9/Q10, CDER/FDA.

The framework – QbD and product life cycle:

Risk analysis and mitigation throughout product lifecycle

Process validation

Assurance that scale up, tech transfer and manufacturing risks are properly addressed

Traditional approach (with enhanced control strategy): 3 batches…

Continuous Process Verification (CPV):
Manufacturing process performance is continuously monitored and evaluated
Science and risk based approach
Process operates always within its predefined parameters and product consistently meets all its CQAs
PAT (see right)
Statistical support tools (SPC)

Hybrid
Justified Use

Process Analytical Technology-PAT

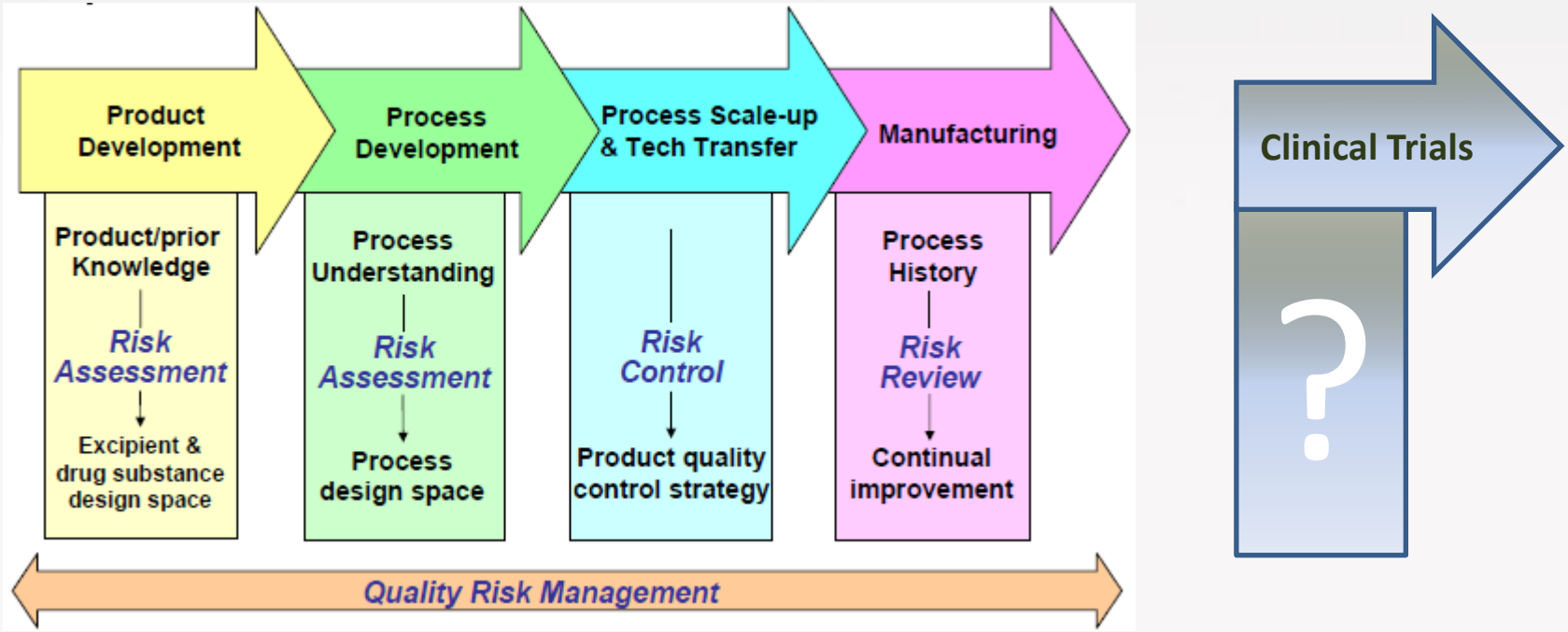
A system for **designing, analysing** and **controlling** manufacturing through **timely** measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of **ensuring final product quality**

PAT tools:
Multivariate tools for design, data acquisition and analysis, Process analyzers, Process control tools, Continuous improvement and knowledge management tools
Continuous **real time** verification of CPPs,CQAs and their trends - RTRT

The focus is on Process/ Product Understanding not on advanced online monitoring of the process

The framework – QbD and product life cycle:

Risk analysis and mitigation throughout product lifecycle



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The framework – QbD and product life cycle:

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 4 August 2011
2 EMA/INS/GCP/394194/2011
3 Compliance and Inspection

4 Reflection paper on risk based quality management in
5 clinical trials
6 Draft

7

Draft Agreed by the CTFG[1] for release for consultation	31 May 2011
Draft Adopted by the GCP Inspectors Working Group for consultation	14 June 2011
End of Consultation (Deadline for Comments)	15 February 2012

EMA, Reflection paper on risk based quality management in clinical trials, Draft, 4 August 2011.

The framework – QbD and product life cycle:

With the planning and conduct of clinical trials, we understand that there can be issues with the following:

- Poor design of studies, study processes in themselves, often being much more complicated than necessary to achieve what is required, but in so doing diminishing focus and resource available to achieve the quality necessary for the more important objectives.
- Failure to identify priorities. Both study and process design is often cluttered by data collection requirements or quality control activities (e.g. monitoring etc.) of limited importance that distract greatly from the most important issues.
- Poor risk identification and poor risk mitigation – a lack of use or understanding of risk management tools and techniques, is often associated with a reactive, fire-fighting approach to problem management. This results in processes largely based on corrective rather than preventive action.
- Lack of proportionality (one size fits all) in the implementation of quality control activities (e.g. monitoring etc.) often related to a lack of understanding of the impact of variability in trial conduct and measurement or data collection on the study results and their reliability.
- Lack of knowledge or more particularly real understanding of the goals of the legal framework and guidelines, and the flexibility that they currently present.

EMA, Reflection paper on risk based quality management in clinical trials, Draft, 4 August 2011.

The framework – QbD and product life cycle:

Pharmaceutical Development	Clinical Trial
Critical Quality Attributes	Critical Success Factors
Process Measures and Controls	Proactive Design, Training and Tracking
Design Space	Risk-Based Targeting
Continuous Improvement	Corrective Action Plans

Seely L. Clinical Trial Quality-By-Design Case Study – A Small Company Experience , Workshops on Quality by Design Clinical Trials Transformation Initiative (CTTI), February 2012

- European Science Foundation (ESF): Forward look: Investigator Driven Clinical Trials

(http://www.esf.org/fileadmin/links/EMRC/FL_IDCT.pdf)

- Organization for Economic Cooperation and Development (OECD): Facilitating International Cooperation in Non-Commercial Clinical trials

(http://www.oecd.org/dataoecd/31/8/49344626.pdf)

- BfArM and academia – the ADAMON project.

Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials, Clin Trials 2009 6: 585

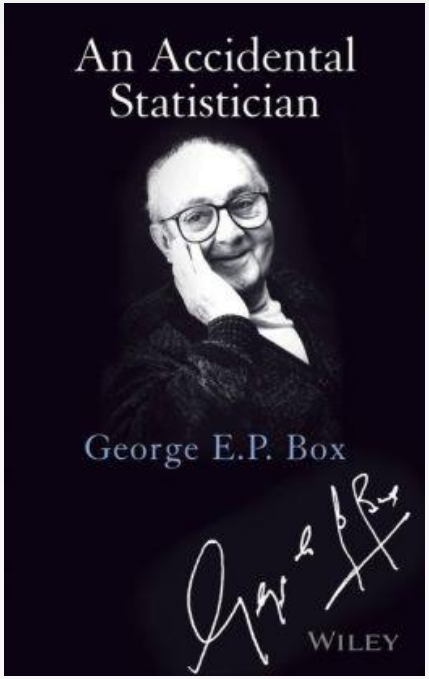
(http://ctj.sagepub.com/content/6/6/585.full.pdf)

- MRC/DH/MHRA Joint Project: Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products

(http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf)

Design of Experiments:

The "new" Concept:



GEP Box
"Statistics for Experimenters"
(Hunter)
RSM, Box Behnken, CCDs
etc etc


The
Design of Experiments

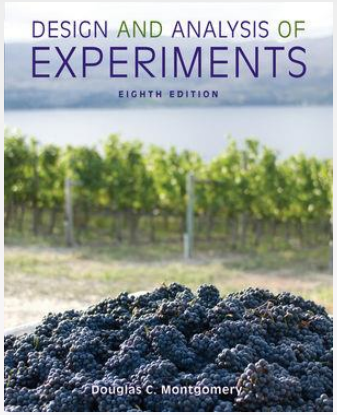
By

Sir Ronald A. Fisher, Sc.D., F.R.S.

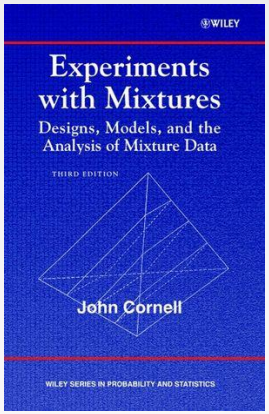
Sir RA Fisher
Statistical Methods for ***Research Workers*** (1925)
The design of experiments (1935)

H. Scheffe
Mixture Designs

Design of Experiments:

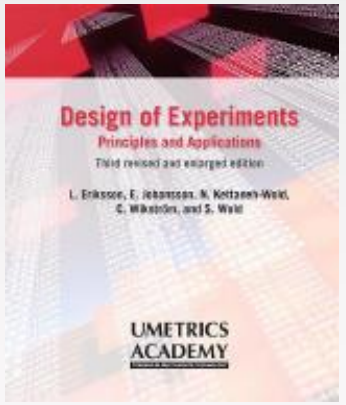


D.C. Montgomery



J. Cornell

W. Smith



Umetrics
E. Johansson
et al

Design of experiments is the ***key*** to the ***magic*** kingdom of quality

(Bhote, 1991)

Direct pelletization technologies

I. FAST, LEAN AND AGILE DIRECT PELLETIZATION PROCESS FOR THE PRODUCTION OF MODIFIED RELEASE SPHEROIDS

II. LEAN DIRECT PELLETIZATION PROCESS FOR THE PRODUCTION OF IMMEDIATE RELEASE PELLETS UTILIZING EFFERVESCENCE MIXTURES

III. FAST DIRECT PELLETIZATION PROCESS FOR THE PRODUCTION OF FAST DISSOLVING PELLETS

D.M. Rekkas, S.N. Politis, A. Karatzas, T. Katsiveli
Faculty of Pharmacy, University of Athens
Greece

I.FAST, LEAN AND AGILE DIRECT PELLETIZATION PROCESS FOR THE PRODUCTION OF MODIFIED RELEASE SPHEROIDS

(Politis & Rekkas)

Hot melt direct pelletization process
Lean and fast
High yields
Customized solutions – Agility
Patented

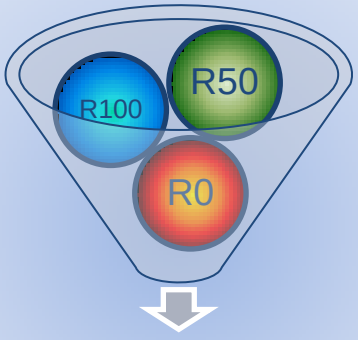
Simple formulation (2-3 constituents):

- Carnauba Wax
- Gelucire 50-13
- HPMC K100M

I.FAST, LEAN AND AGILE DIRECT PELLETIZATION PROCESS FOR THE PRODUCTION OF MODIFIED RELEASE SPHEROIDS

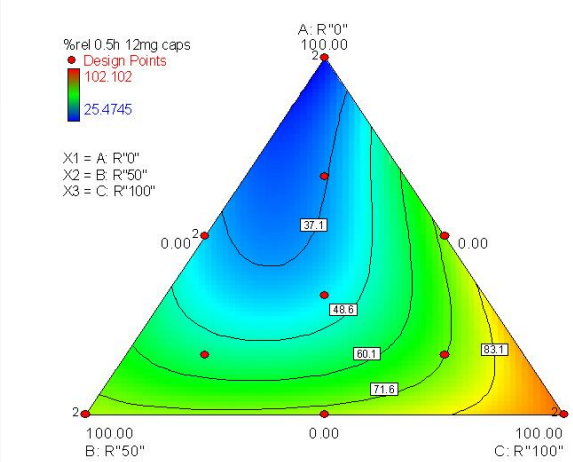
I.FAST, LEAN AND AGILE DIRECT PELLETIZATION PROCESS FOR THE PRODUCTION OF MODIFIED RELEASE SPHEROIDS

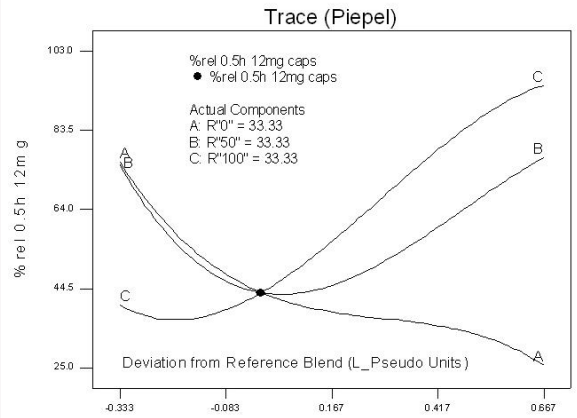
Release profiles – agility deriving from pellet combinations

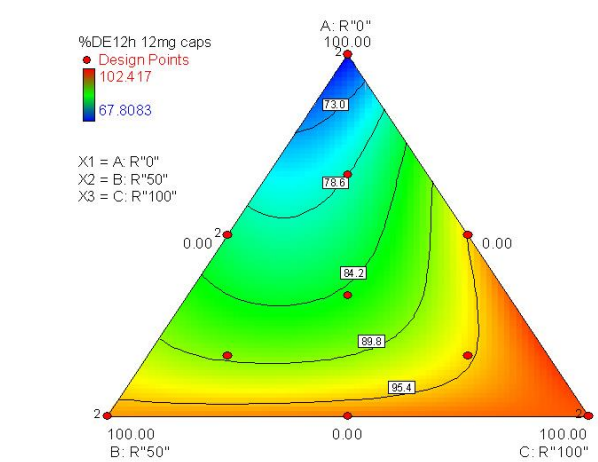


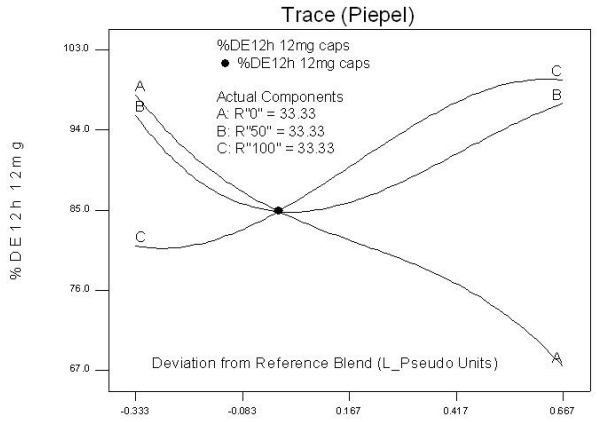
Pellet mixing

Customized release profiles









II. LEAN DIRECT PELLETIZATION PROCESS FOR THE PRODUCTION OF IMMEDIATE RELEASE PELLETS UTILIZING EFFERVESCENCE MIXTURES

(Katsiveli, Politis & Rekkas)

Direct pelletization process utilizing aqueous media

Lean process – simple formulation

High yields

Immediate release pellets

Patented

Mechanism(s):

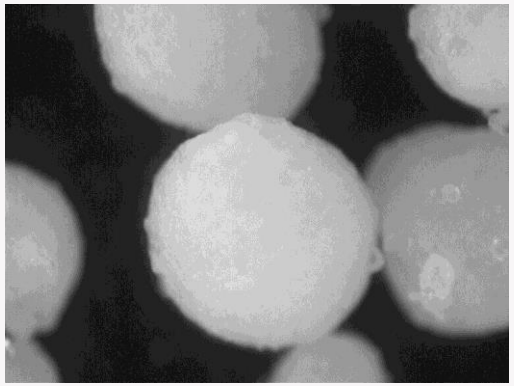
- **"In situ CO_2 release during the process"**
- **"Active residual effervescent mixture"**

Incorporation of Ibuprofen as a "model drug"

- Practically insoluble in water

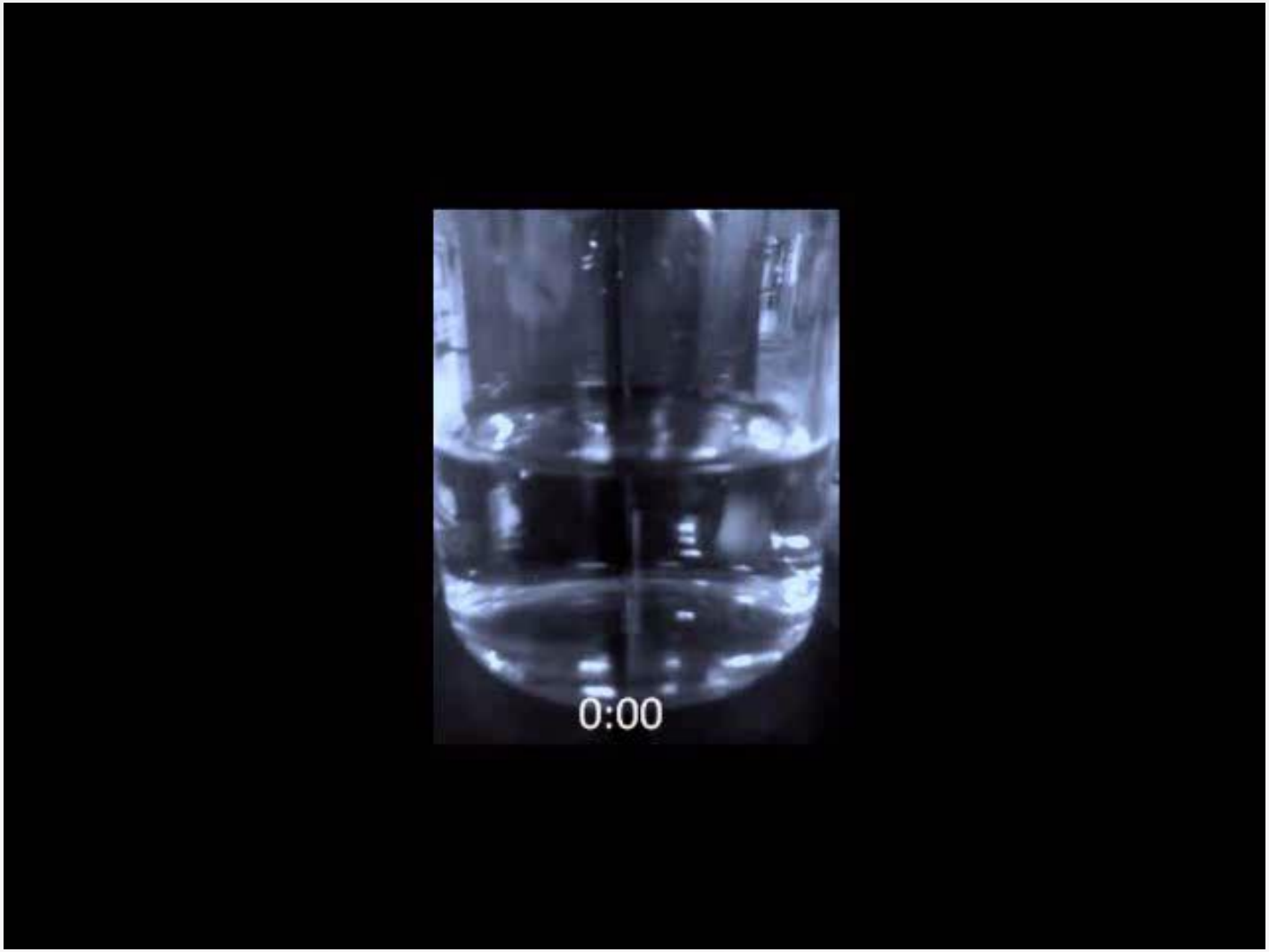
III. FAST DIRECT PELLETIZATION PROCESS FOR THE PRODUCTION OF FAST DISSOLVING PELLETS (Karatzas & Rekkas)

Direct pelletization process
Completely dissolving formulation - Clear solutions
High yields
Acceptable inherent taste
Appropriate for orally dispersible formulations
Patented



•Use of effervescent mixture in combination with water soluble excipients
•Non – aqueous process

III. FAST DIRECT PELLETIZATION PROCESS FOR THE PRODUCTION OF FAST DISSOLVING PELLETS

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Thank you very much for your attention

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