Giornata di Studio

L'applicazione del Quality by Design (QbD) nella produzione dei medicinali

Università degli Studi di Milano

17 Marzo 2014

Uso del QbD nella fabbricazione industriale dei medicinali

Marco Adami – AFI

Pharmaceutical Industry

- Quality cannot be tested into a batch of product but must be built into each batch of product during all stages of the manufacturing process

"… it seems as though industry's objective today is to continue to meet regulatory standards, which are minimal expectations, versus adopting a commitment to high-quality medicines"

Janet Woodcock

Director of FDA CDER

Quality by Design

- Systematic approach to development
- Product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches
- The impact of starting raw materials and process parameters on product quality is well understood
- Emphasizes product and process understanding and process control
- The process is continually monitored, evaluated and updated to allow for consistent quality throughout product life cycle

Quality by Design

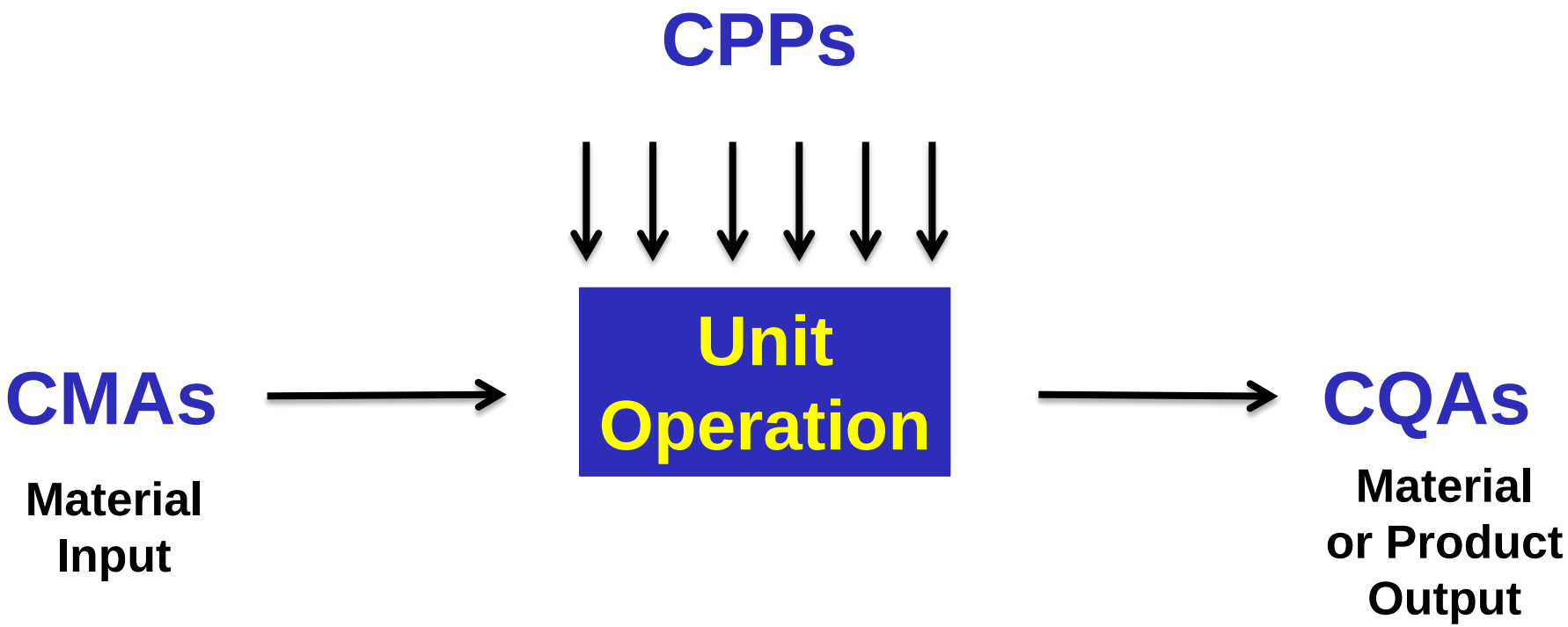
- Specifications should be based on mechanistic understanding of how formulation and process factors interact and impact on the Critical Product Attributes (CQAs) of a product
  - ✓ This understanding should derive from
    - Prior knowledge, both from the literature and personal experience
    - Preliminary data from development activities

(instead, many submissions rely on the empirical determination of the performance criteria based on the analysis of the experimental data)

- ICH Q8: Pharmaceutical Development should include, **at a minimum**, the following elements:
  - ✓ Quality Target Product Profile (QTPP)
  - ✓ Identification of potential critical quality attributes (CQAs) of the Drug Product, so that those product characteristics having an impact on product quality can be studied and controlled
  - ✓ Determine the critical material attributes (CMAs) of the Drug Substance, excipients, etc., and selection of the type and amount of excipients to deliver drug product of desired quality
  - ✓ Selection of an appropriate manufacturing process
  - ✓ Definition of a control strategy
    - a planned set of controls (related to Drug Substance and Drug Product materials and components, facility and equipment operating conditions, IPCs, and finished product specifications) derived from current product and process understanding that ensures process performance and product quality

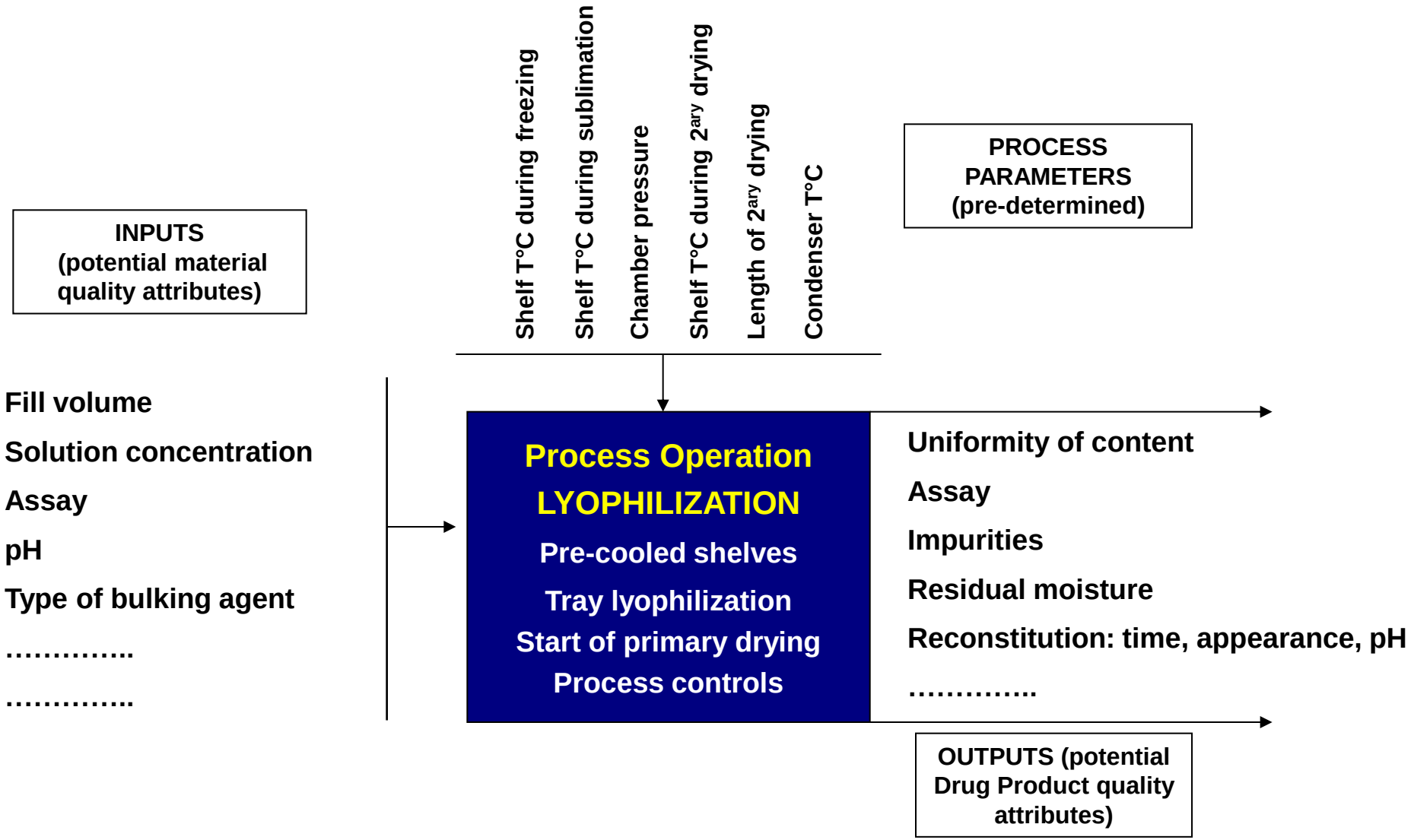
- ICH Q8: An **enhanced**, QbD approach to product development would additionally include:
  - ✓ A systematic evaluation, understanding and refining of the formulation and manufacturing process, including:
    - Identifying, through e.g., prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on product CQAs
    - Determining the functional relationships that link material attributes and process parameters to product CQAs
  - ✓ Using the enhanced product and process understanding in combination with quality risk management to establish an appropriate control strategy which can, for example, include a proposal for a design space and/or real-time release testing

CMA/CPP/CQA Relationship



$$CQAs = f(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$$

Lyophilized Formulation: CMAs/CPPs/CQAs

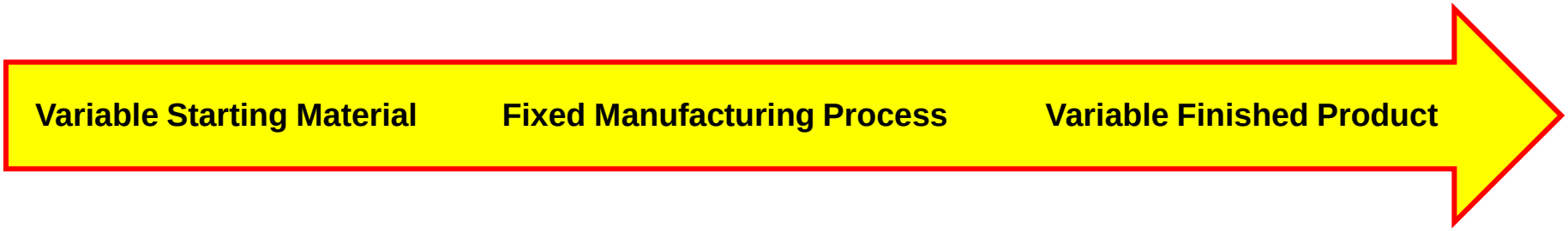


Current *Vs.* QbD Approach to Pharmaceutical Development

Current	QbD
Quality assured by testing and inspection	Quality built into product & process by design, based on scientific understanding
Data-intensive submission	Knowledge-rich submission (showing product knowledge & process understanding)
Specifications based on batch history	Specifications based on product performance requirements
Frozen process – discouraging changes	Flexible process within the design space, allowing continuous improvement
Focus on reproducibility – often avoiding or ignoring variation	Focus on robustness – understanding and controlling variation
Control strategy managed mainly by intermediate and end product testing	Risk-based control strategy, quality controls shifted upstream (possibility for real-time release or reduced end-product testing

"Quality is built in by design, not tested in"

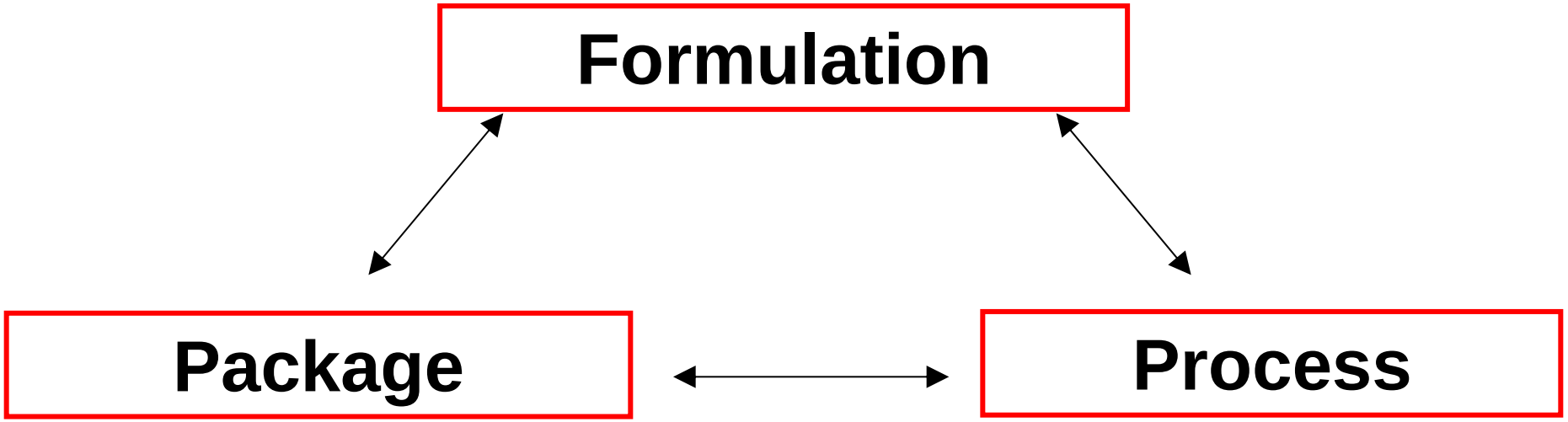
Quality by End Product Testing *Vs.* QbD



Traditional Manufacturing Process

QbD Manufacturing Process

Development of a Drug Product



Ultimate objective: TOTAL QUALITY

- **The formulation, the process and the package must work in unison**

Excipients: Traditional Vs. QbD Approach

- Traditional
  - ✓ Often one source and one lot
  - ✓ “Optimized” formulation and “frozen” processes
  - ✓ Compendial specifications
- QbD
  - ✓ Understanding variation of excipient properties as they relate to product CQAs
  - ✓ Building robustness and flexibility into the manufacturing process
  - ✓ Control of excipients appropriate to ensure product quality

- **Finished product quality influenced by lot-to-lot variability of “impurities” or functionality**
- **ROBUST formulation: ability to accommodate the typical variability seen in API, excipients, and process without the manufacture, stability, or performance of the product being compromised**

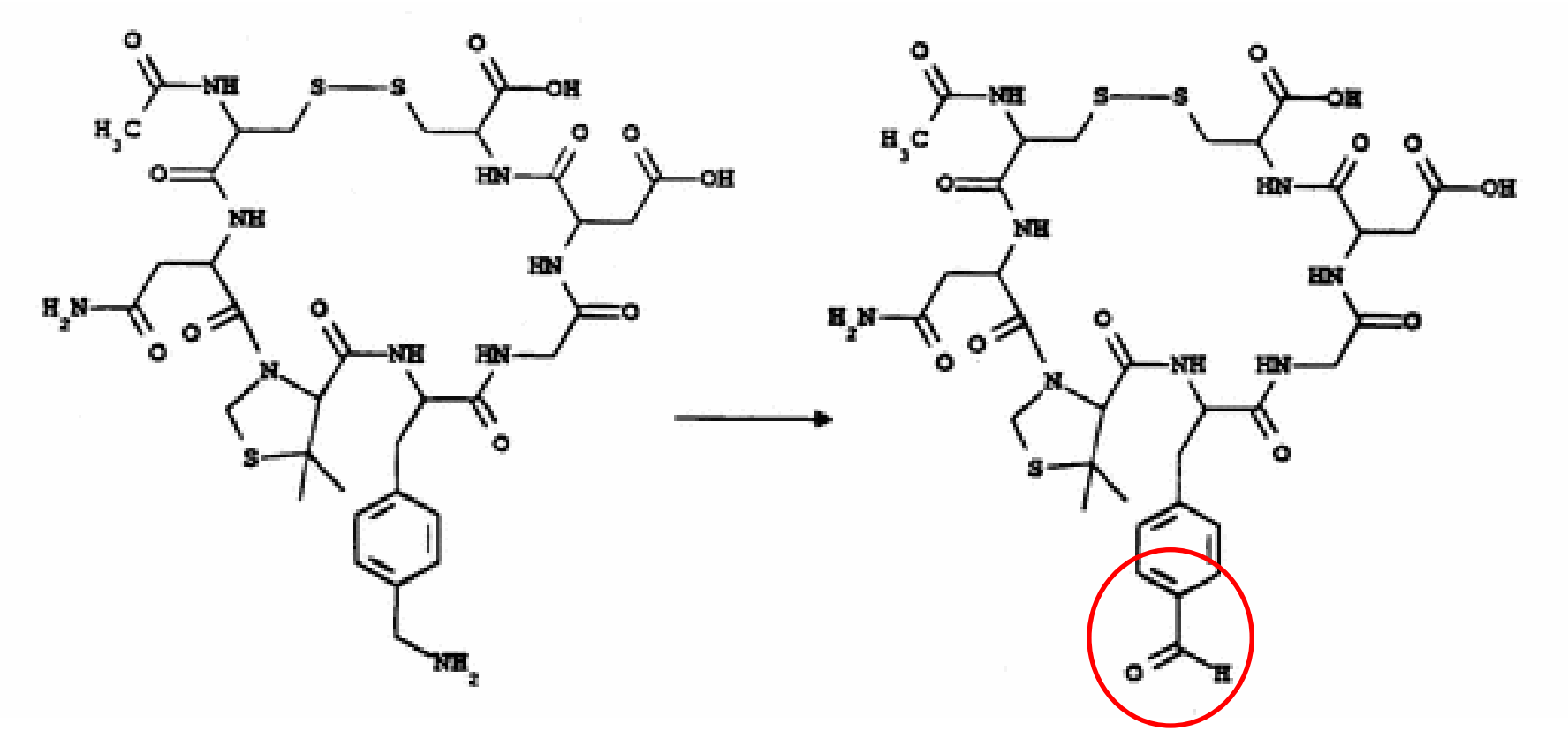
Case Study: Excipient-Induced Oxidation

- Cyclic heptapeptide
- Orally inactive
- IV route
- Optimum aqueous solution stability pH ~ 5
- Insufficient solution stability
- Freeze-dried formulation stable at 30°C, however long-term storage (> 12 months) results in the formation of a RP-HPLC unknown degradation product, **NOT** seen in previuos studies using the drug as solid or in aqueous solution

Pharm. Res., Vol. 13 (1996)

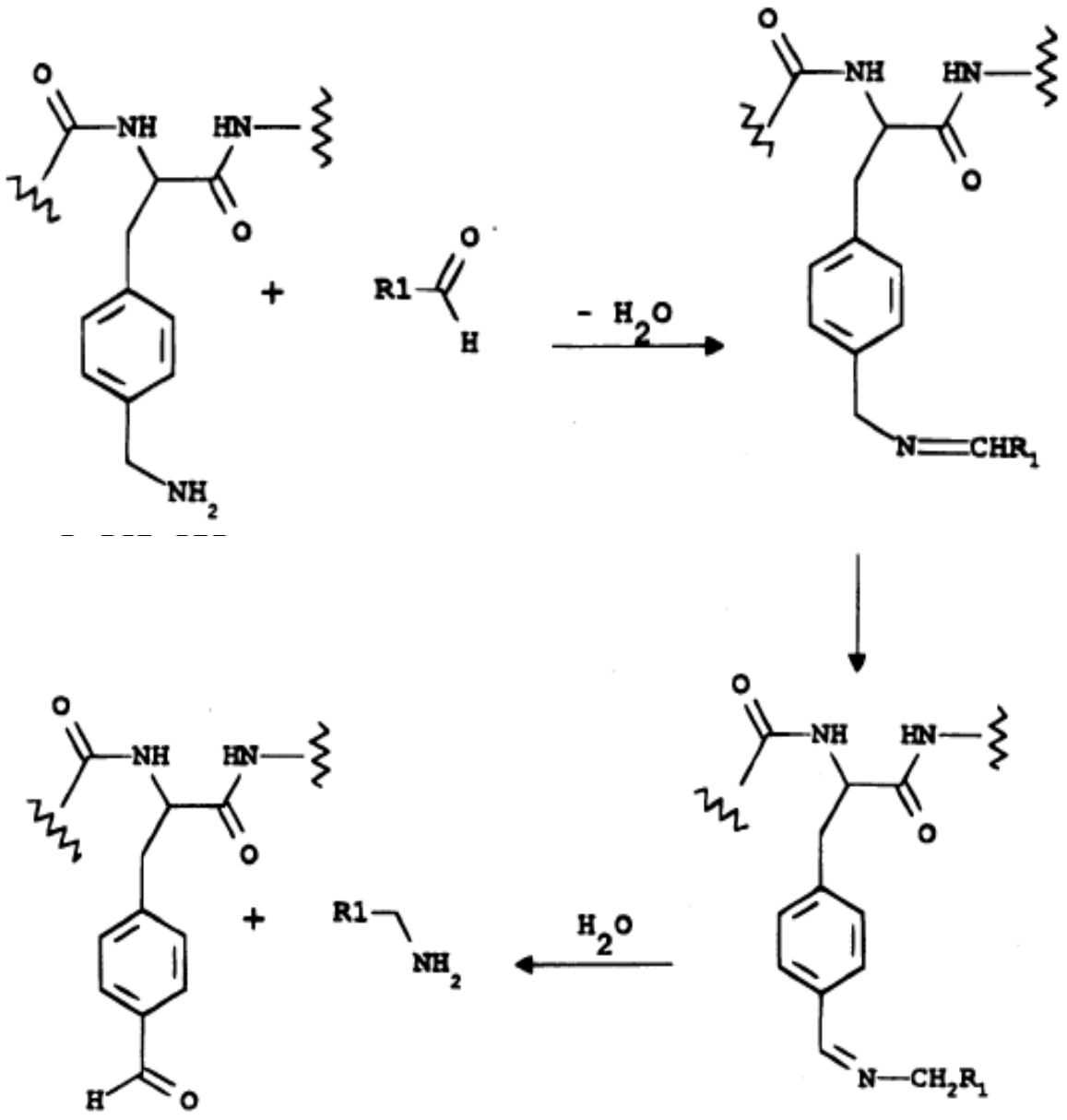
Case Study: Excipient-Induced Oxidation

- Lyophilized Formulation
  - ✓ Peptide, Mannitol, NaOH q.s. to pH 5.0, Wfl q.s.
- Isolation of the degradation product from stressed samples (preparative scale HPLC)
  - ✓ Degradate characterization by UV, MS, Amino Acid Analysis, and ^{1}H NMR
  - ✓ Identification: benzaldehyde derivative arising from oxidative deamination of the drug



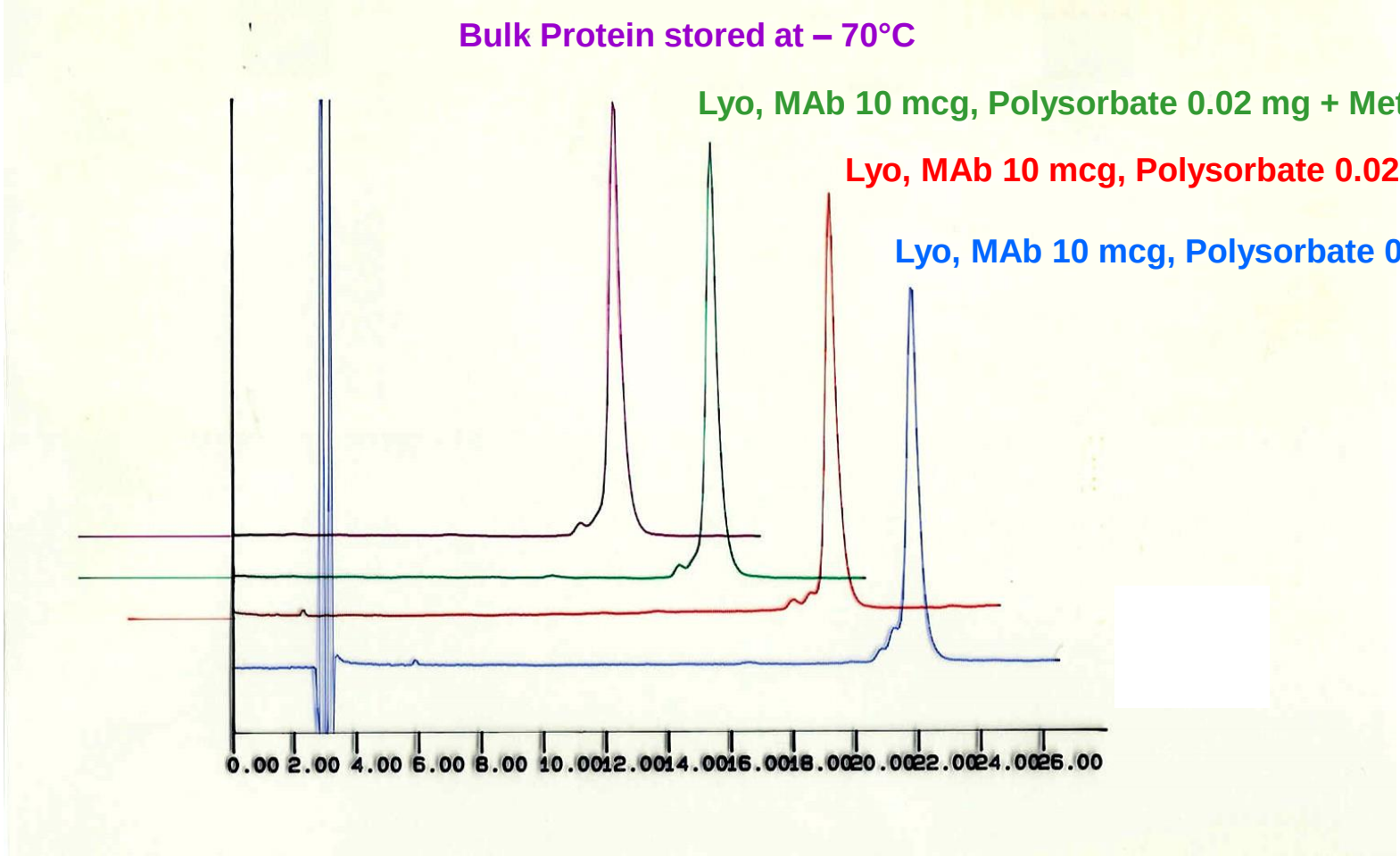
- How does the oxidation of the drug occur in the solid state in a lyophilized product sealed under vacuum? Although the presence of small residues of oxygen cannot be completely ruled out, a free radical mechanism requiring a stoichiometric amount of oxygen does not seem likely
- No such degradation was NOT observed with the drug, either as solid or in solution

⇒ Involvement of Mannitol in the oxidation!



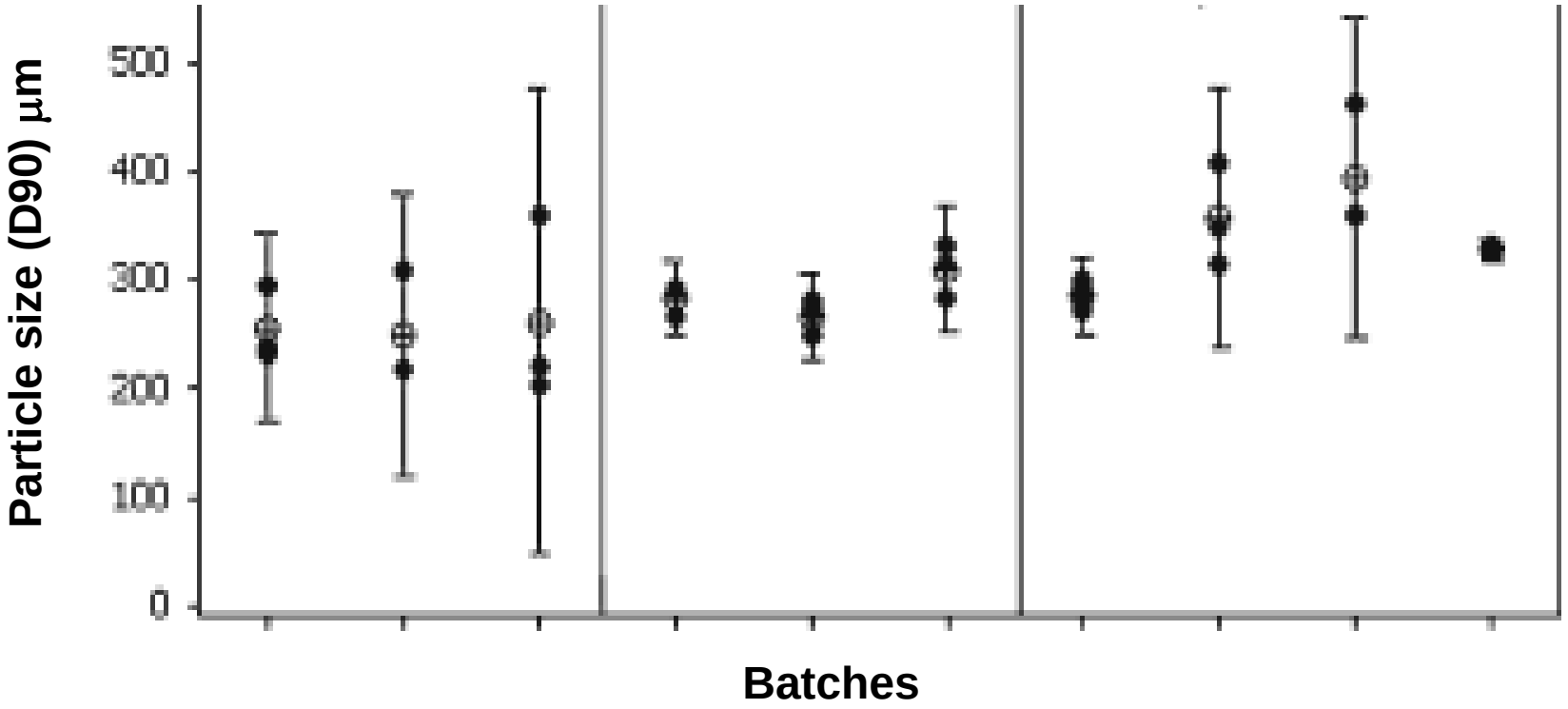
- **Reducing sugar impurities present in Mannitol (~ 0.1%)**
  - ✓ **Schiff base formation between the peptide primary amine and the aldehydic group of the reducing sugar**
  - ✓ **Tautomerization to move the double bond into a more stable configuration (conjugation with the phenyl group)**
  - ✓ **Hydrolytic cleavage to generate the observed degradation product**

Polysorbates contain/may form low levels of peroxides



Direct Compression Anhydrous Lactose

Interval plot of particle size (source and batches)



AAPS PharmSciTech, Vol. 11 (2010)

QbD is a “new” approach. However …

- The holistic and systematic approach of QbD was relatively new to the pharmaceutical industry at the beginning of the twenty-first century. However, elements of QbD were certainly being applied across the industry long before then.

  V. McCurdy – Quality by Design, 2011

- In fact, it is my view that most aspects of QbD have been long practiced, even if not with the current protocol, by at least the best of the scientists/engineers with the best companies. Quality by Accident has never been acceptable.

  M. Pikal – Pharma QbD, Feb 2011

Design Space

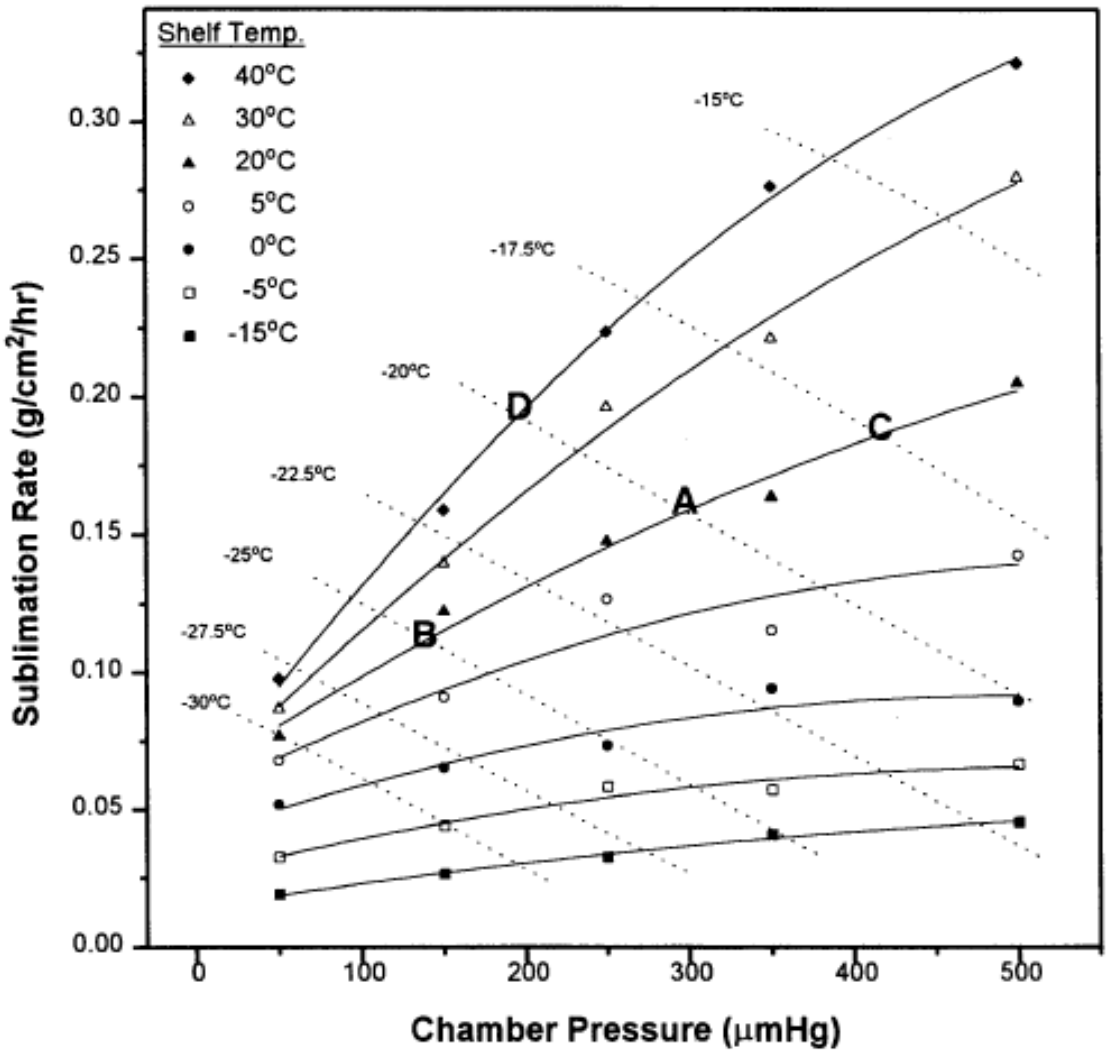
- ICH Q8 emphasizes that one must investigate and characterize the impact of variations in key formulation and process parameters including “interactions” between the parameters
- This emphasis has often resulted in the assumption that Design of Experiments (“DOE”) is the required methodology

Design of Experiments

- Is DOE useful in the design of the primary drying stage of lyophilization?
- "The physics of primary drying can be described by simple heat and mass transfer theory, whereby the impact of variation in the various freeze-drying parameters, including their "interactions" may be quantitatively predicted. Designing processes based on physics is better and more efficient than designing them based on statistics"

M.J. Pikal

Process Control



- **This paper published by Chang and Fischer in 1995(*) , although not the point of the article, suggests an approach to establishing a design space for a lyophilization process: the graph illustrates the functional relationships among sublimation rate (Y axis), product temperature (dotted lines) and the two independently controlled variables in the process: shelf temperature (the solid lines) and chamber pressure (X axis)**

(*) Pharm. Res., 12, 831 (1995)

Process Control

- If we assume that process conditions A, B, C, and D allow product temperature to be maintained below maximum allowable temperature while avoiding condenser overloading, any of them would be acceptable
- To maximize the sublimation rate the combination of highest allowable product temperature and lowest chamber pressure should be found (Point “D”)

Quality by Design

is here to stay!

Milano, March 17, 2014

Thank you for your attention!

m_adami@alice.it