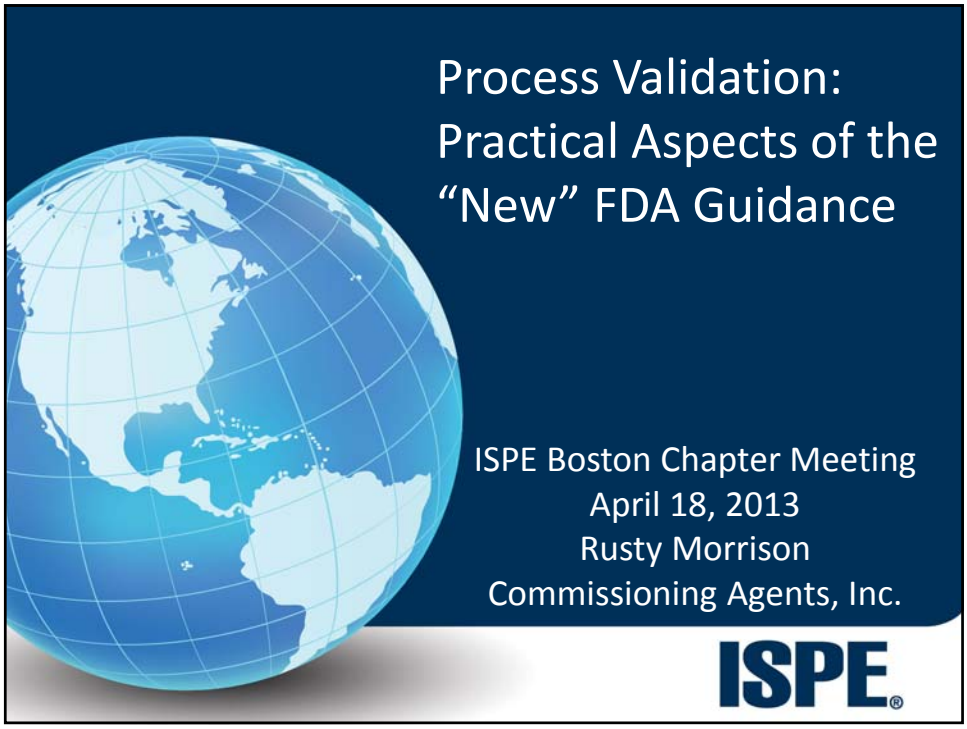

Objectives / Summary

- What is Process Validation?
- Regulatory Basis and Guidance Documents
- Definitions
- Review of the FDA 2011 PV Guidance
- Applying New Guidance to Old Products

2

Regulatory Basis

21CFR 211.110 a:

"... control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product."

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Process Validation – Old Definition

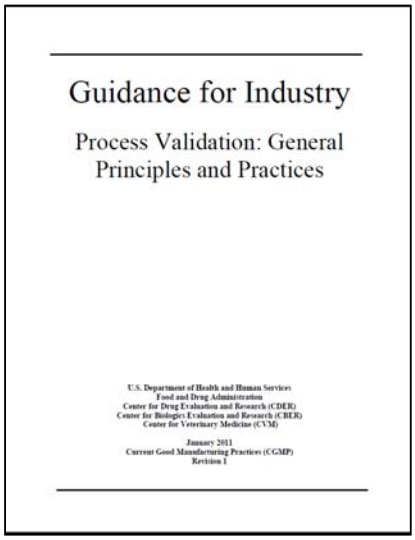
"Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

Guidelines on General Principles of Process Validation, FDA (1987)

4

"New" FDA Process Validation Guidance

In January, 2011 FDA issued new guidance for industry regarding process validation


Guidance for Industry

Process Validation: General Principles and Practices

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

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Process Validation - Today

New FDA guidance focused on product quality through process understanding and control:

"Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production which establishes scientific evidence that a process is capable of consistently delivering quality product."

(emphasis added)

Guidelines for Industry - Process Validation: General Principles and Practices
FDA (January 2011)

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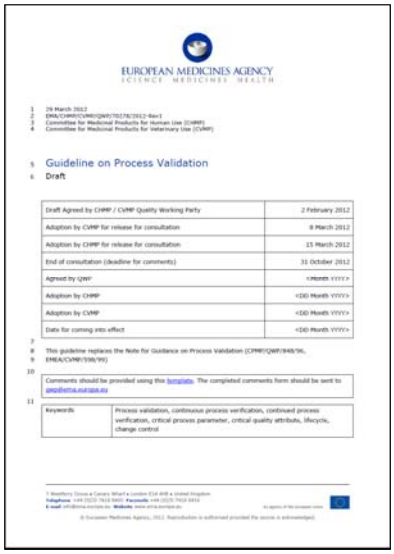
Process Validation - Today

- Summary of significant changes:
  - Add emphasis to process design
  - Includes discussion of risk
  - Involve activities over entire process lifecycle (ongoing program, in three defined stages)
  - Emphasizes role of objective measures and statistical tools
  - Emphasizes knowledge, detection and control of variability
- As always, new guidance will take time to work its way down to “traditional” process validation
  - How to apply new guidance for legacy products?

EMA Draft Process Validation Guidance

In March 2012 FDA issued a draft guideline for process validation



EUROPEAN MEDICINES AGENCY

29 March 2012

Guideline on Process Validation

Draft

Draft Agreed by CHMP / CVMP Quality Working Party	2 February 2012
Adoption by CVMP for release for consultation	8 March 2012
Adoption by CHMP for release for consultation	15 March 2012
End of consultation (deadline for comments)	31 October 2012
Agreed by QWP	<Month YYYY>
Adoption by CHMP	<DD Month YYYY>
Adoption by CVMP	<DD Month YYYY>
Date for coming into effect	<DD Month YYYY>

This guideline replaces the Note for Guidance on Process Validation (CPMP/QWP/848/96, EMEA/CVMP/598/99)

Comments should be provided using this template. The completed comments form should be sent to qwp@ema.europa.eu

Keywords	Process validation, continuous process verification, continued process verification, critical process parameter, critical quality attribute, lifecycle, change control

US FDA vs. EMA

- Significant differences exist between the issued FDA guidance and draft EMA guideline
- The remainder of this presentation will be based on the FDA guidance.

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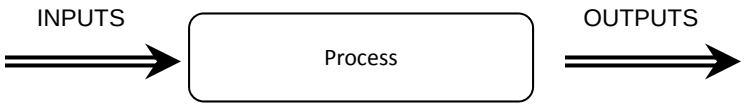
Definitions

Manufacturing Process

– "The sequence of activities, people, and systems involved in carrying out some business or achieving some desired result."



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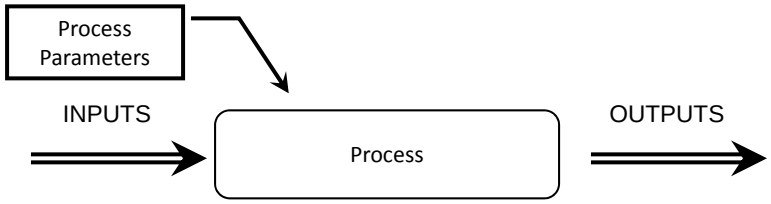
Definitions

Process Parameters (aka Operating Parameters)

- The conditions under which a process is performed
- Can be physical or chemical
  - pH, temperature, pressure, agitator rpm, flow rate, etc.
- Process parameters are usually **controlled** within defined operating ranges to setpoint values



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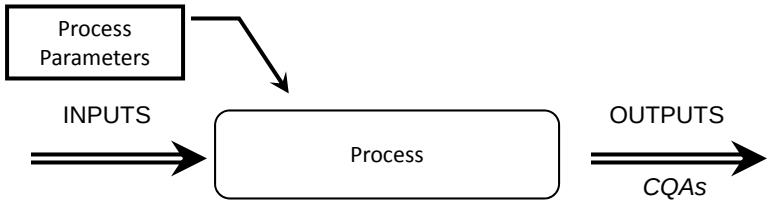
Definitions

Critical Quality Attributes (CQAs)

- A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8)
- Not all outputs are CQAs



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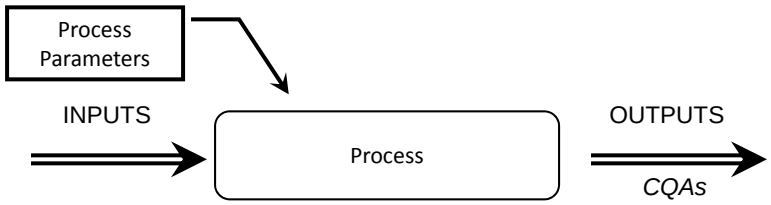
Definitions

Critical Quality Attributes (CQAs)

- Acronyms for "appropriate limit, range, or distribution"
  - Acceptance Criterion (plural: Criteria)
  - Specification



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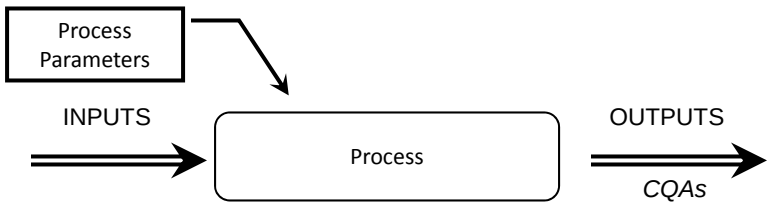
Definitions

Critical (or Key) Process Parameters – (CPPs)

- A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (ICH Q8)
- Example: pH during ion exchange chromatography steps



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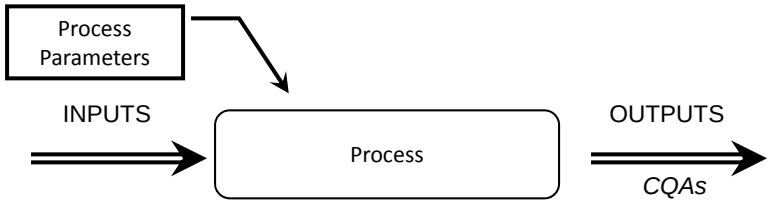
Definitions

Non Critical / Non Key Process Parameters

- Those process parameters which do not have a direct impact on product quality
- Example: Flow rate during bioreactor inoculation



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CPPs and CQAs

CPPs	CQAs
Typically, setpoint with an operating range	Acceptance Criteria / Specifications
"Inputs"	"Outputs"
Controlled to achieve consistent, repeatable, reliable results	Used to demonstrate process control, repeatability, and reliability

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Process Validation – New Guidance

- Key Concepts:
  - Understand the sources of variation
  - Detect and measure sources of variation
  - Understand the impact of variation on the process and final product attributes
  - Control the sources of variation commensurate with the risk they represent to the process and final product attributes

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Process Validation – New Guidance

- Process validation involves a series of activities taking place over the lifecycle of the product :
  - Stage 1: Process Design
  - Stage 2: Process Qualification
  - Stage 3: Continued Process Verification
- Many activities occur in more than one stage (think lifecycle…)

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Stage 1: Process Design

- The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities

Stage 1: Process Design

Element 1: Building / Capturing Process Knowledge

- Quality Target Product Profile (ICH Q8)
  - Intended dosage form
  - Route of administration
  - Expected drug product quality attributes
  - General manufacturing pathway

Stage 1: Process Design

Element 1: Building / Capturing Process Knowledge

- Activities (Characterization)
  - Design of Experiments
    - Design Space / Control Space
  - Risk Assessments
  - Lab or pilot scale experiments
  - Computer modeling
- Documentation of results is essential

Stage 1: Process Design

Element 2: Establish Process Control Strategy

- Control sources of variation
  - Reduce input variation
  - Adjust for input variation during manufacturing
  - Combination of both
- Process Analytical Technology (PAT) implementation

Stage 2: Process Qualification

The process design is evaluated to determine if the process is capable of reproducible commercial manufacturing

Stage 2: Process Qualification

Element 1: Utility / Equipment Qualification

Demonstration that utilities and equipment are suitable for their intended use, and perform properly.

- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

Stage 2: Process Qualification

Element 2: Process Performance Qualification (PPQ)

- This stage has traditionally been known as "conformance runs" or "demonstration batches"
- A manufacturer must successfully complete PPQ before commencing commercial distribution of the drug product
- Approach to PPQ should be based on
  - Overall product & process understanding
  - Demonstration of control
  - Use of objective measures (statistics) to provide assurance of control

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Stage 2: Process Qualification

Element 2: Process Performance Qualification (PPQ)

- In most cases, PPQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance than would be typical of routine commercial production
- The increased level of scrutiny, testing, and sampling should continue through the process verification stage as appropriate, to establish levels and frequency of routine sampling and monitoring for the particular product and process.

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Stage 2: Process Qualification

Element 2: Process Performance Qualification (PPQ)

How many PPQ runs?

- Considerations for the duration of the heightened sampling and monitoring period:
  - volume of production
  - process complexity
  - level of process understanding
  - experience with similar products and processes
- More variability → more runs
- More uncertainty → more runs

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Stage 2: Process Qualification

Element 2: Process Performance Qualification (PPQ)

PPQ Protocol

- Manufacturing conditions
- Data collection and evaluation
- Testing, including acceptance criteria
- Sampling plan
  - Intra- and inter-batch quality

PPQ Report

- Summarize data / results from PPQ runs
- State a clear conclusion regarding state of control

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Stage 2: Process Qualification

Element 2: Process Performance Qualification (PPQ)

Release of PPQ Batches

- Normally, completion of all PPQ batches and approval of PPQ reports is required for commercial distribution of a product
- Under special circumstances, concurrent release of PPQ batches may be acceptable
  - Infrequently manufactured (orphan drugs)
  - Short half lives
  - Drug shortage

Stage 3: Continued Process Verification (CPV)

Goal of CPV: Continual assurance that the process remains in a state of control (the validated state) during commercial manufacture

Stage 3: Continued Process Verification (CPV)

How is this accomplished?

- System(s) for detecting unplanned departures from the process as designed
- Ongoing program to collect and analyze product and process data that relate to product quality
  - Process trends
  - In-process material
  - Finished products
- Statistical trending with review
  - Statistician or person with SPC training

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Stage 3: Continued Process Verification (CPV)

- Other means to detect variation
  - Deviations / non-conformances
  - Out-of-Specification results
  - Batch records
  - Defect complaints
  - Adverse event reports
  - etc.

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Stage 3: Continued Process Verification (CPV)

- FDA recommends continued monitoring and sampling of process parameters and quality attributes at the level established during PPQ until sufficient data is available to generate variability estimates.
- These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process.
- Monitoring can then be adjusted to a statistically appropriate and representative level.

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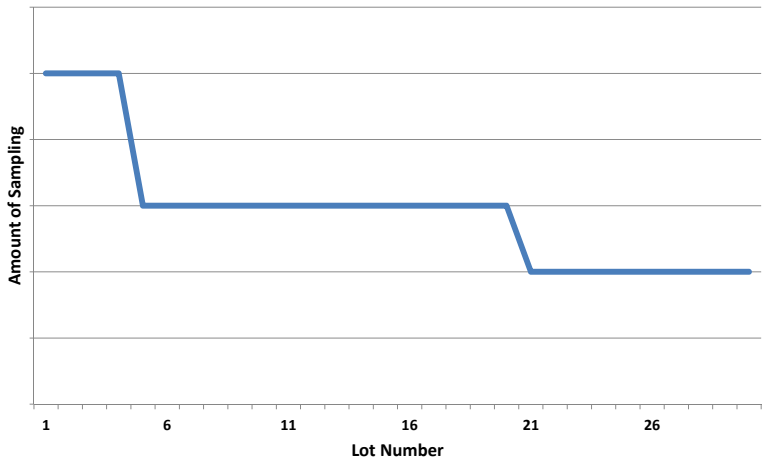
Process Validation Sampling



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Applying New Guidance to Old Products

- Approved product implies that Stages 1 and 2 complete
- How to implement Stage 3

  "The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture."

  "A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal."

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Applying New Guidance to Old Products

- Theory: Continue to gain knowledge throughout product lifecycle
  - Manufacturing experience should yield increased knowledge and process improvements
  - Lack of process improvements indicates lack of process understanding and failure to learn (implement learning)

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Applying New Guidance to Old Products

- Practice: Don't fix it if it's not broke
  - Traditionally manufacturers are reluctant to change a process once validated
  - Reluctance to look backward at released lots (what will we find?)
  - Analysis, trending, and assessing variability are typically ad-hoc
  - Only impetus for change were deviations / OOS results

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Applying New Guidance to Old Products

Challenge: Identifying CPPs and CQAs

- Sources:
  - Original process validation
  - Specifications
  - Batch records / SOPs
  - Deviations / CAPAs / Change Controls

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Applying New Guidance to Old Products

Challenge: Obtaining Data

- Executed batch records
- Annual product review

Applying New Guidance to Old Products

Challenge: Establishing a CPV Program

- How will the program be set up?
- Who will implement it?
  - What are the required qualifications?

Applying New Guidance to Old Products

Recommendations

- Assemble a multi-disciplinary team
  - Validation, PD, Manufacturing, QA, QC
- Get a basic program in place (SOP or Validation Plan?)
  - Data collection / recording
  - Plotting
  - Analysis
  - Response to out-of-control results
  - Reporting Frequency (review & approval)?
  - Pathway for process improvements

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Applying New Guidance to Old Products

Recommendations

- "Small Steps"
  - Obtain data, either retrospectively or prospectively
  - Plot data with specification limits
  - Look for obvious issues:
    - Trends
    - Visual mean value offset from target or specification centerline
    - Bi-modal results
    - Insufficient resolution (pH only recorded to 0.1 unit)

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Applying New Guidance to Old Products

Recommendations

- "Small Steps", continued
  - Assess normality of data
  - Establish control limits (20-30 data points needed)

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Applying New Guidance to Old Products

Other Challenges

- SPC assumes process is in a state of statistical control. However, not every element of every process will be.
- Data is not normally distributed
  - Observed variation well within specification limits
- Data indicates specification limit excursions are likely

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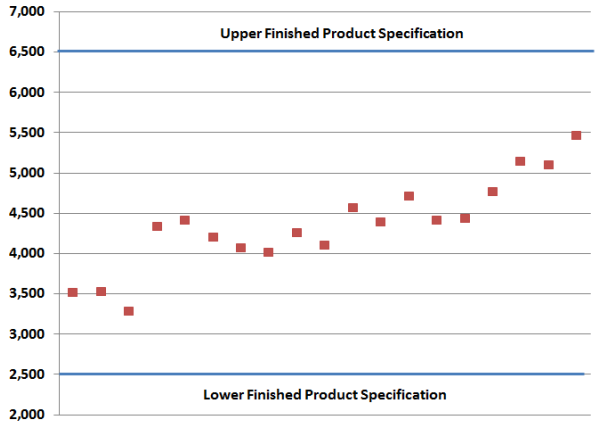
Applying New Guidance to Old Products

Challenges: Artifacts are found in data review: Trends



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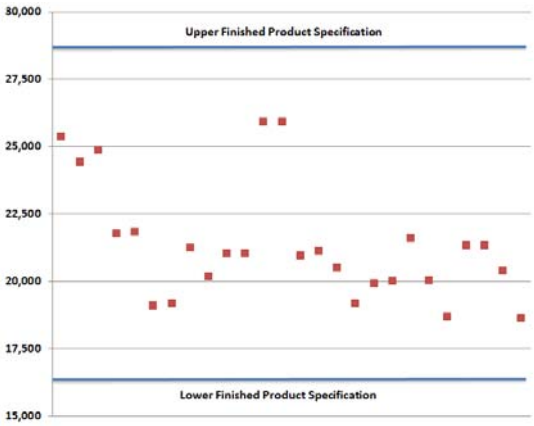
Applying New Guidance to Old Products

Challenges: Artifacts are found in data review: Bimodal Results



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References

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- EMA Draft Guideline on Process Validation (March 2012)
- ICH Q8:Pharmaceutical Development (QBD)
- ICH Q9: Quality Risk Management
- ICH Q10: Pharmaceutical Quality System
- ASTM E2500: Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment
- PDA Tech Report 60: Process Validation - A Lifecyle Approach
- PDA Tech Report 59: Utilization of Statistical Methods for Production Monitoring

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Other Resources

- ISPE Process Validation Discussion Papers (http://www.ispe.org/publications/discussion-papers)
- ISPE Product Quality Lifecycle Implementation (PQLI) Guides
- ISPE Communities of Practice

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Questions / Conclusions