The Importance of Properly Designed Experiments for Comparative Studies

Robert Shaw

Principal Scientist Statistics

Global Product Development AstraZeneca Macclesfield UK

With acknowledgement to Marie South

EMA Workshop " Draft Reflection Paper on statistical methodology for the comparative assessment of quality attributes in drug development"

3-4 May 2018

ebe
european biopharmaceutical enterprises

Vaccines Europe
An industry for healthy lives

This is a joint industry presentation on behalf of the trade associations shown

The Importance of Properly Designed Experiments for Comparative Studies

- **Background and motivation**

- Design considerations:
  - Randomisation and blocking
  - Case study – instrument comparison
  - Analytical and sampling variability

- Summary
  - Properties of well-designed experiments
  - Steps in planning experiments

Background / Motivation

- With regard to Design of Experiments, the paper includes considerations of random sampling, choice of sample size and experimental unit.
- However these and other important aspects of DoE deserve more in-depth coverage and increased clarity.
- Investing effort in the design of the comparative study is crucial to the quality of the data generated and the efficiency with which resource is applied.

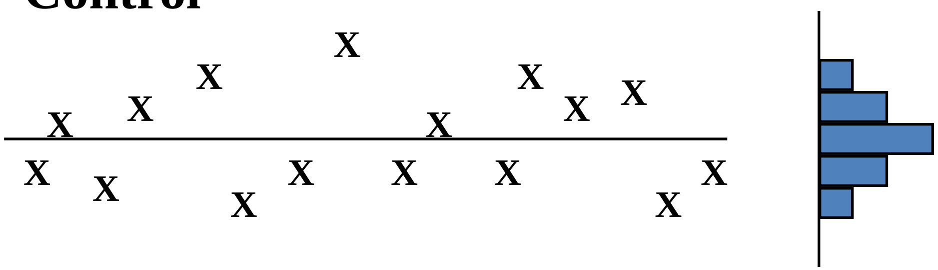
Design of Comparative Experiments

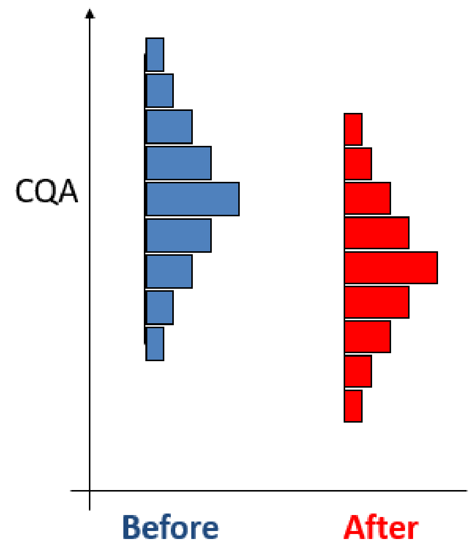
- Clearly define objectives of the experiment. What question(s) is the experiment aiming to address?
- Can the experiment be designed such that the questions posed will be answered unambiguously? An important issue is ***bias***.
- How can the experiment be designed so that it is ***efficient?***

Variability – Common Cause vs Bias

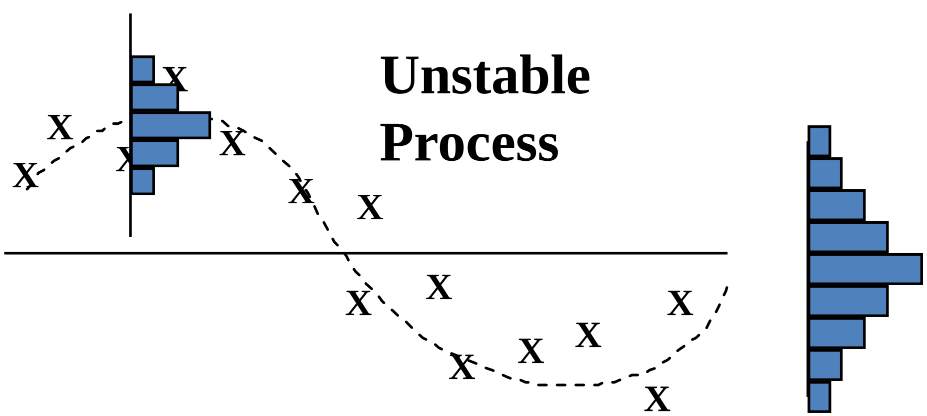
N.B. Applies to both manufacturing and analytical processes.

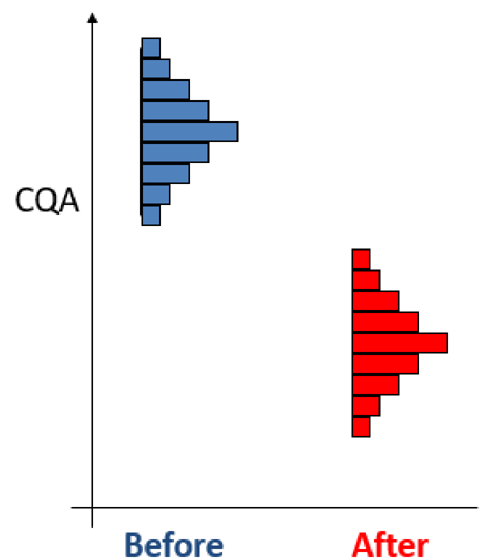
Stable Process - In Statistical Control





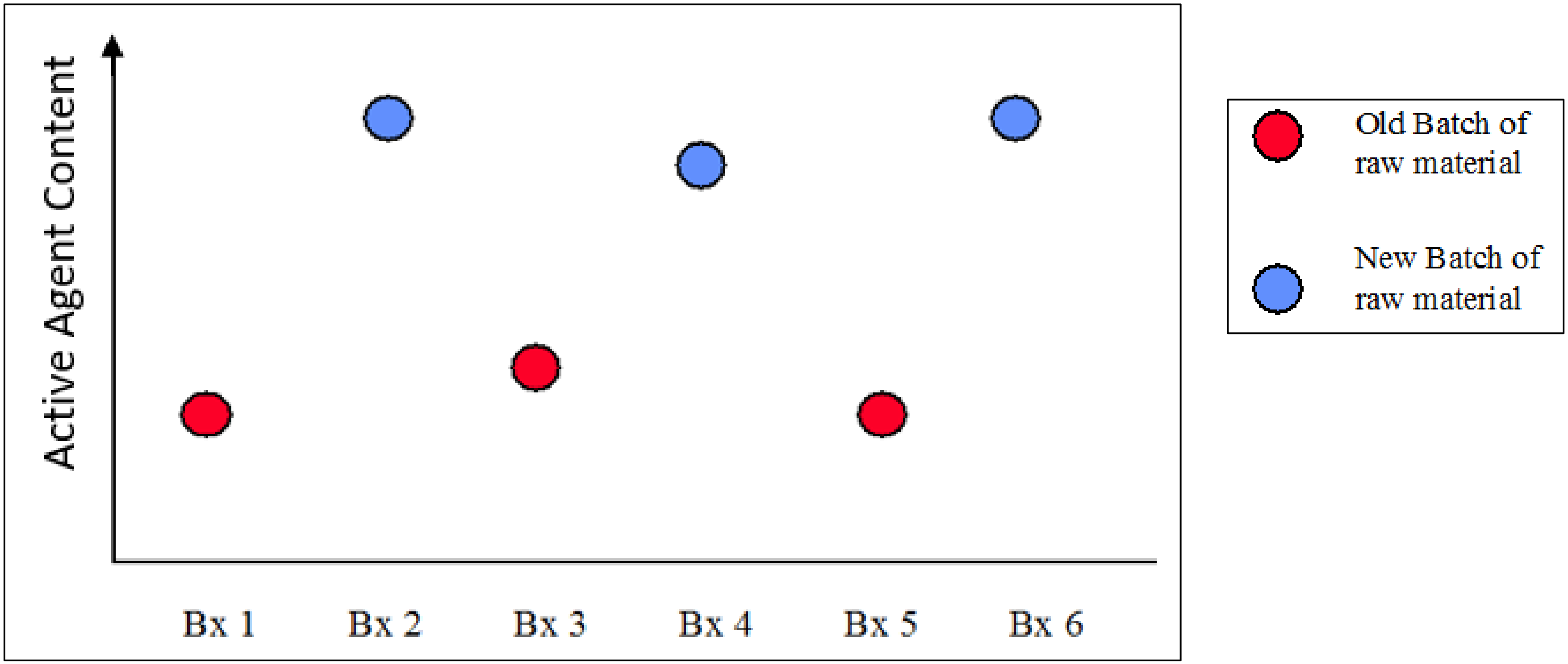
If common cause variability high, then this can obscure a real before/after effect.





If production process out of control, then an apparent before/after effect may be due to some other cause, i.e. conclusion *biased*.

“Leapfrog” Design



Simple experimental design can be introduced to help assess the impact of changing batches of raw material & reduce risk of bias from other sources of variability.

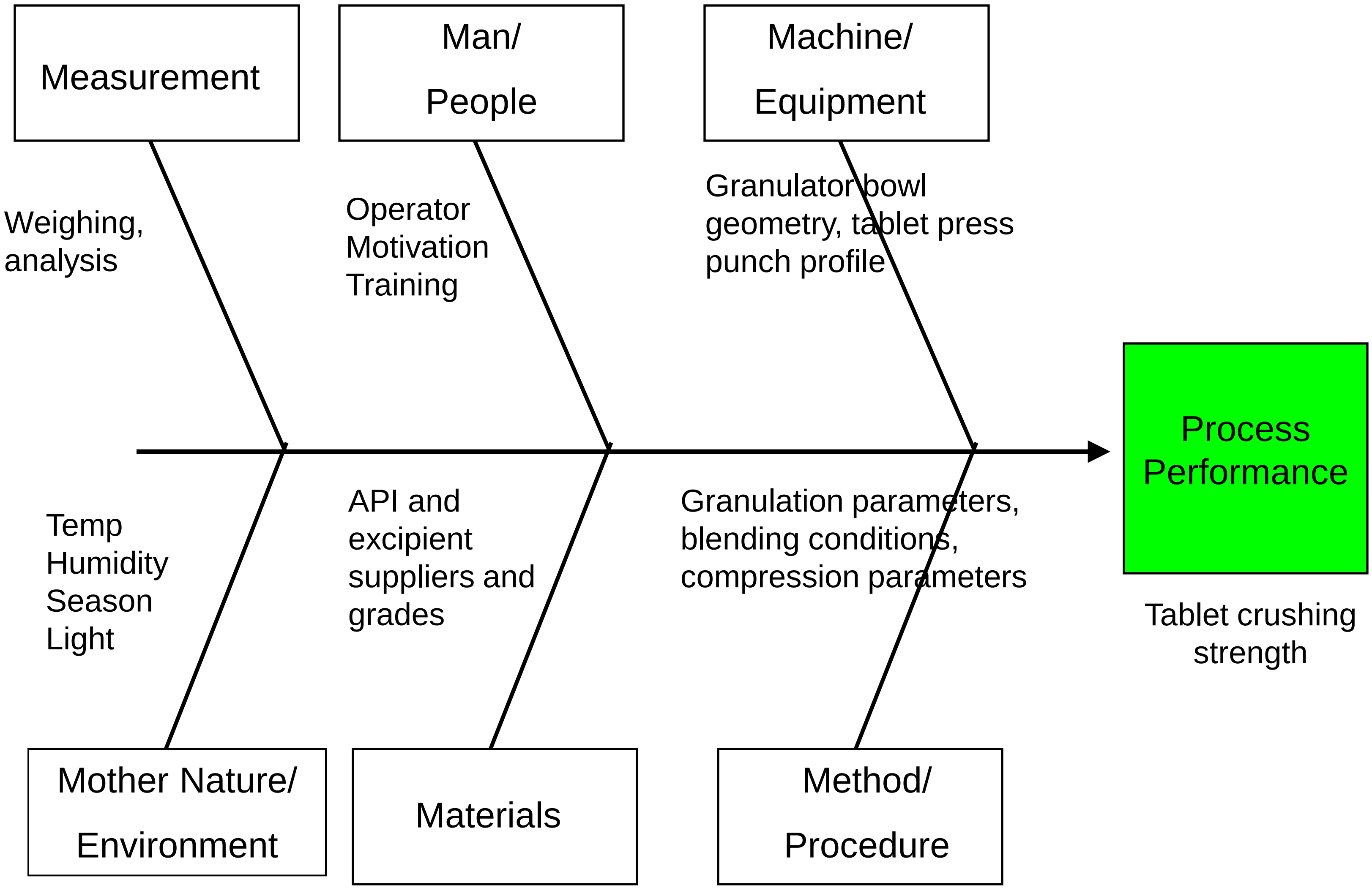
The Importance of Properly Designed Experiments for Comparative Studies

- Background and motivation

- **Design considerations:**
  - **Randomisation and blocking**
  - Case study – instrument comparison
  - Analytical and sampling variability

- Summary
  - Properties of well-designed experiments
  - Steps in planning experiments

Fishbone Diagram



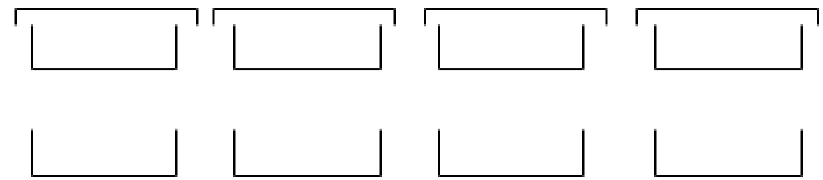
Simple Blocking Example
Effect of Lidding in Freeze-Drying Process

Drum freezer –
Material splits into 4 trays or sub-parts.

An experimental program is proposed to investigate the impact of running the freeze drier stage with and without lids on the trays.

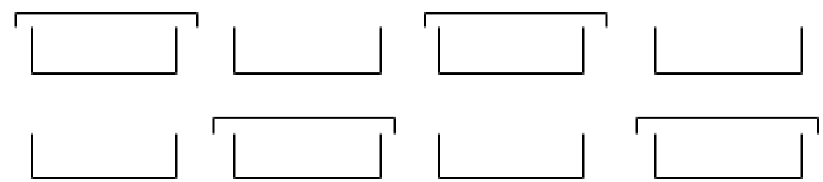
2 alternative options are shown here. Option 2) is an example of a *blocking design*.

1. Bx 1
   Bx 2



+ Simple to organise - little chance of mistake
- Any difference between batches may be due to other factors, not just lids e.g. environment, equipment

2. Bx 1
   Bx 2



- More scope for human error
+ Reduced potential for bias when estimating the effect of lidding

"Block what you can, randomise what you cannot" – George Box

The Importance of Properly Designed Experiments for Comparative Studies

- Background and motivation

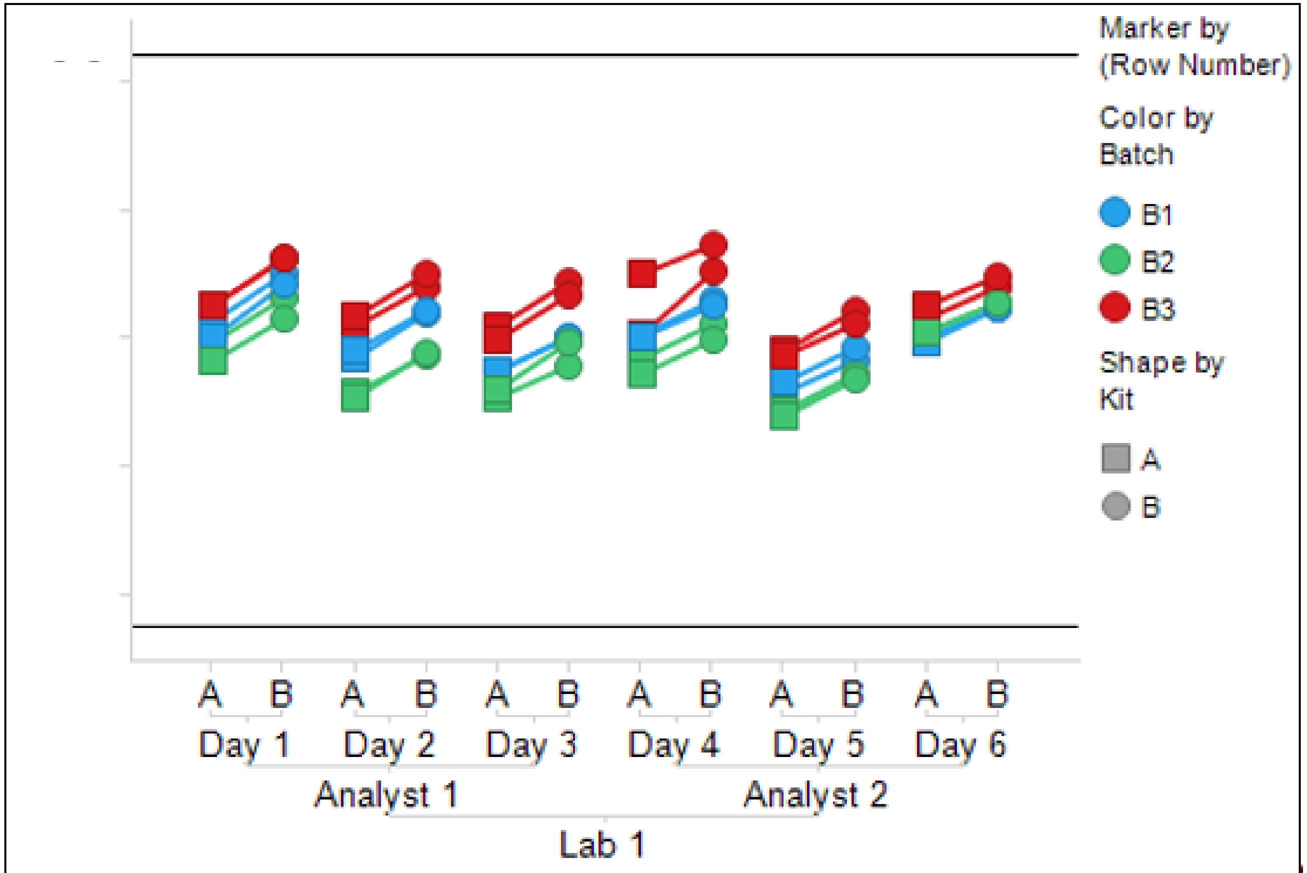
- **Design considerations:**
  - Randomisation and blocking
  - **Case study – instrument comparison**
  - Analytical and sampling variability

- Summary
  - Properties of well-designed experiments
  - Steps in planning experiments

Instrument Comparison – Matched-Pairs Design

Impact - This design led to much greater statistical power than would have been possible with a randomised design. A much greater sample size would have been required to achieve the same precision.

- 2 sets of equipment explored in a designed experiment to assess if they could be used interchangeably for an analytical method.
- Blocking factors are analyst, day and batch.
- 2 samples prepared for each batch and each sample tested on both sets of equipment. This is an example of a matched-pairs design.



Components of Variance -> Experimental Design

FACTOR: any aspect of the experimental conditions which can affect the data obtained from an experiment.

experimental | nuisance

THE PROCESS

- Identify the factors which may affect the result of an experiment
- Design the experiment so that the effects of nuisance factors are minimised
- Use statistical analysis to separate out the effects of the various factors involved

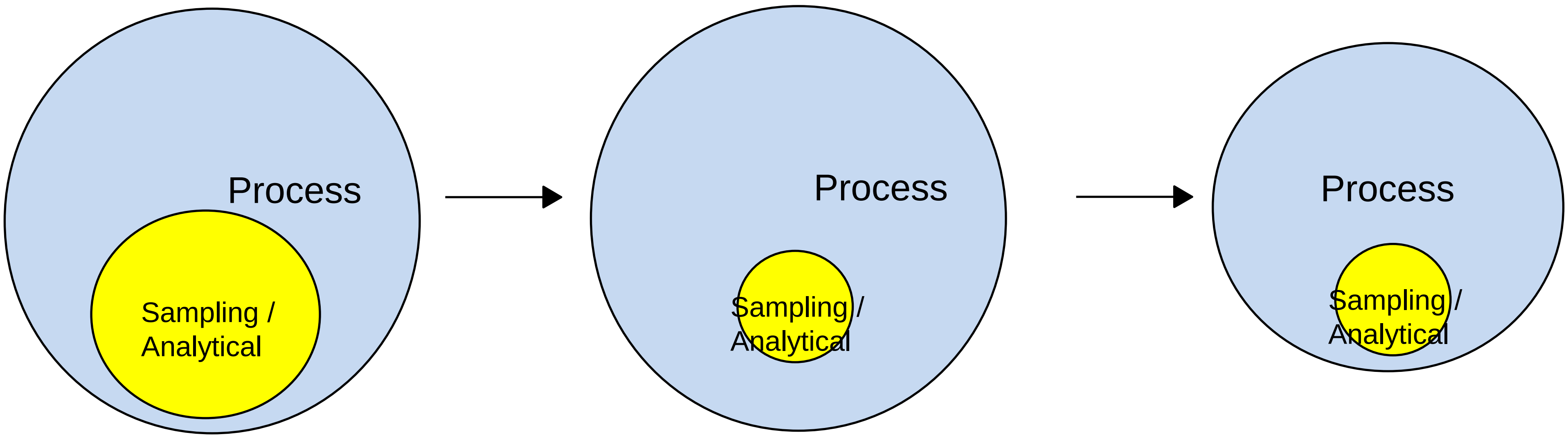
The Importance of Properly Designed Experiments for Comparative Studies

- Background and motivation

- **Design considerations:**
  - Randomisation and blocking
  - Case study – instrument comparison
  - **Analytical and sampling variability**

- Summary
  - Properties of well-designed experiments
  - Steps in planning experiments

Components of Variability



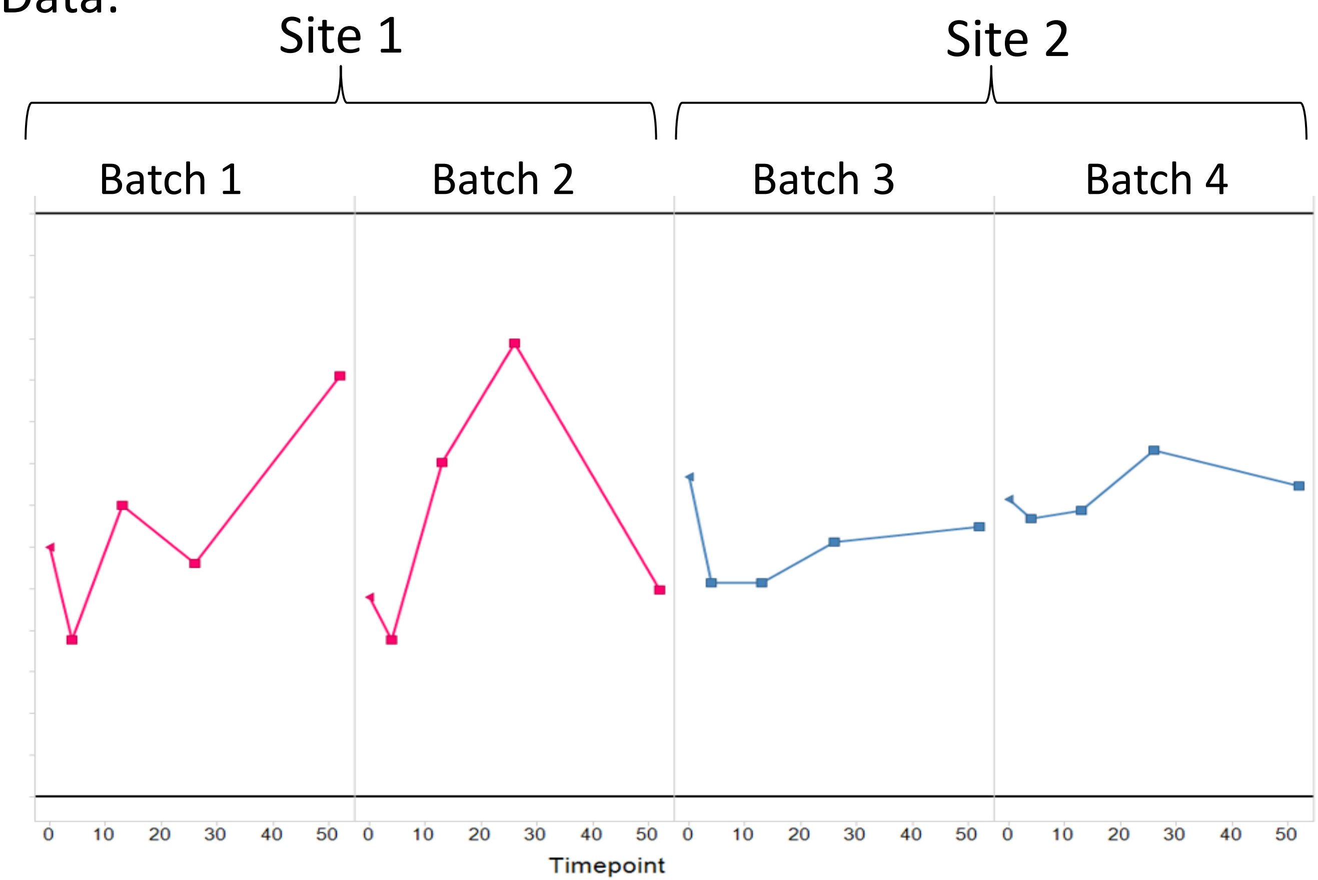
Variance is proportional to area of circle with radius equal to standard deviation

Total variance = analytical variation + sampling variation + process variation = A + S + P

If analytical variation + sampling variation is high then this will obscure any change made to the manufacturing process.

Contribution of Analytical Variability

Stability Data:



General Comments / Learning:

- Manufacturing variability comprises different components
- High analytical variability can:
  - lead to misleading conclusions about product quality
  - mask desired improvement to processes.

The Importance of Properly Designed Experiments for Comparative Studies

- Background and motivation

- Design considerations:
  - Randomisation and blocking
  - Case study – instrument comparison
  - Analytical and sampling variability

- **Summary**
  - Properties of well-designed experiments
  - Steps in planning experiments

Properties of Well-Designed Experiments

- Able to meet specific objectives
- Proposed approach pre-tested (pilot studies)
- As simple as possible
- Sample size justified (taking account of purpose of study and planned data analysis)
- In-built estimate of error (replication)
- Good use of randomisation and blocking
  - manufacturing / processing
  - analytical testing
- Hold back some resource for confirmation of conclusions

Steps in Planning Experiments

- Step 1: Clearly define goals and objectives
- Step 2: Consider measurement of response factor(s)
  - Beware qualitative response (e.g. Pass/Fail)
  - Consider blinding particularly for subjective assessment
- Step 3: Consider all factors affecting the response
  - Raw materials, processing factors, measurement, nuisance factors
- Step 4: Identify the appropriate type of design
- Step 5: Detailed design and plan for analysis

Questions…