Understanding Process Dynamics: the route to continuous improvement

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Understanding Process Dynamics: the route to continuous improvement

- **Introduction: the languages we speak**
- **Chemistry**
- **Engineering**
- **Batch processing**
- **Continuous processing**
- **Steady state *vs* controlled state**
- **Perturbations *vs* Deviations**
- **Regulatory impact of continuous improvement**

How to translate between related languages

- **Process dynamics for the chemist:**
  - **Kinetic measurements – precise, empirical,**
  - **Equilibrium constants – empirical**
  - **Strict demarcation between kinetics and thermodynamics**
  - **Scale of scrutiny generally small**
  - **Chemists like reactions that proceed to completion**
  - **Chemists almost always start with a round bottomed flask**

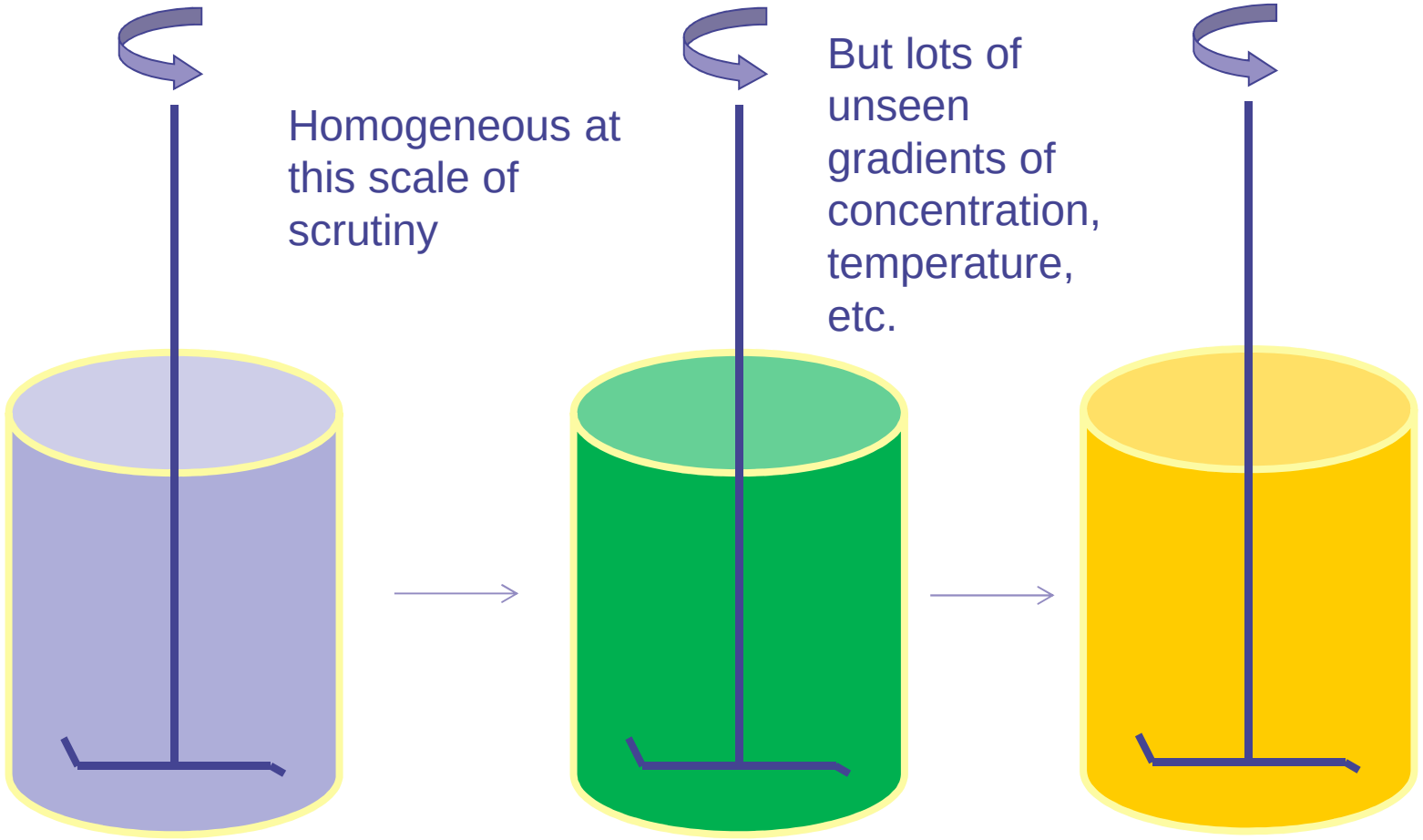
- **Process dynamics for the engineer**
  - **Mass transfer *vs* heat transfer**
  - **Descriptors often not precise**
    - Reynold's Number (or other dimensionless numbers) large or small
  - **Engineers generally look at whole systems**
  - **Chemical engineers outside pharmaceutical industry like continuous processes**

- **Both approaches are needed**
- **Neither group traditionally strong in statistics, especially Bayesian**
- **Further translations for regulatory submissions and inspections needed!**

Batch processing

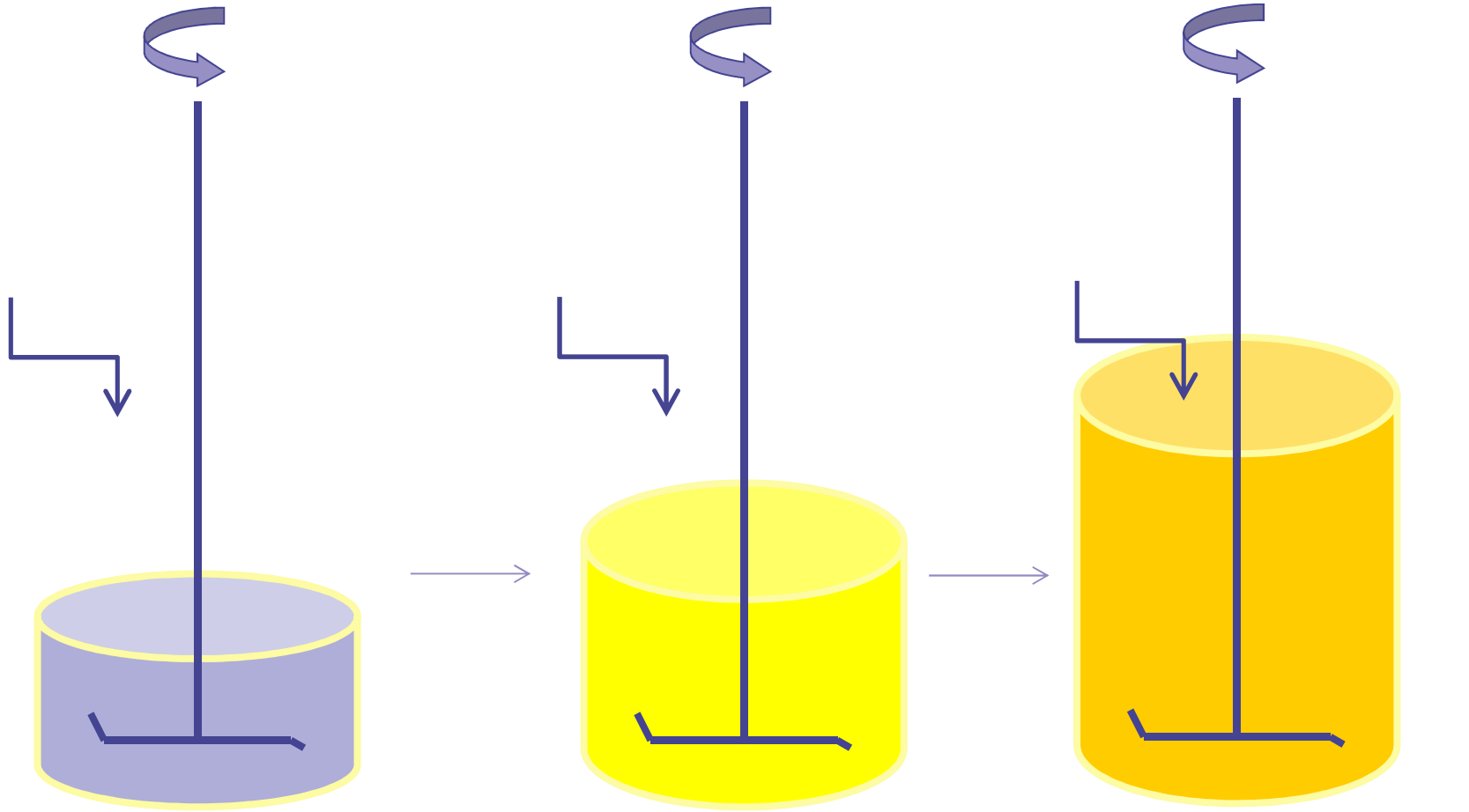
- **Has been the preferred *modus operandum* for pharma industry for decades**
- **API**
  - **Use of glass lined or 316 SS/Hastelloy stirred tanks with 3 blade retreat curve impellors or anchor stirrers for reactions**
  - **Larger stirred tanks for extractions**
  - **Dedicated crystallisation vessels**
  - **Basket centrifuge or Nutsche filters for solid isolation**
  - **General purpose dryer (or filter dryer)**
  - **Milling**
- **DP (oral solid dose)**
  - **Blending**
  - **Wet granulation**
  - **Drying**
  - **Blending?**
  - **Tablet compression (or capsule filling)**
  - **Tablet coating**
  - **Printing**
  - **Packaging**

Batch Reaction



Does not operate at steady state

Semi-batch (fed batch for biotech) processing

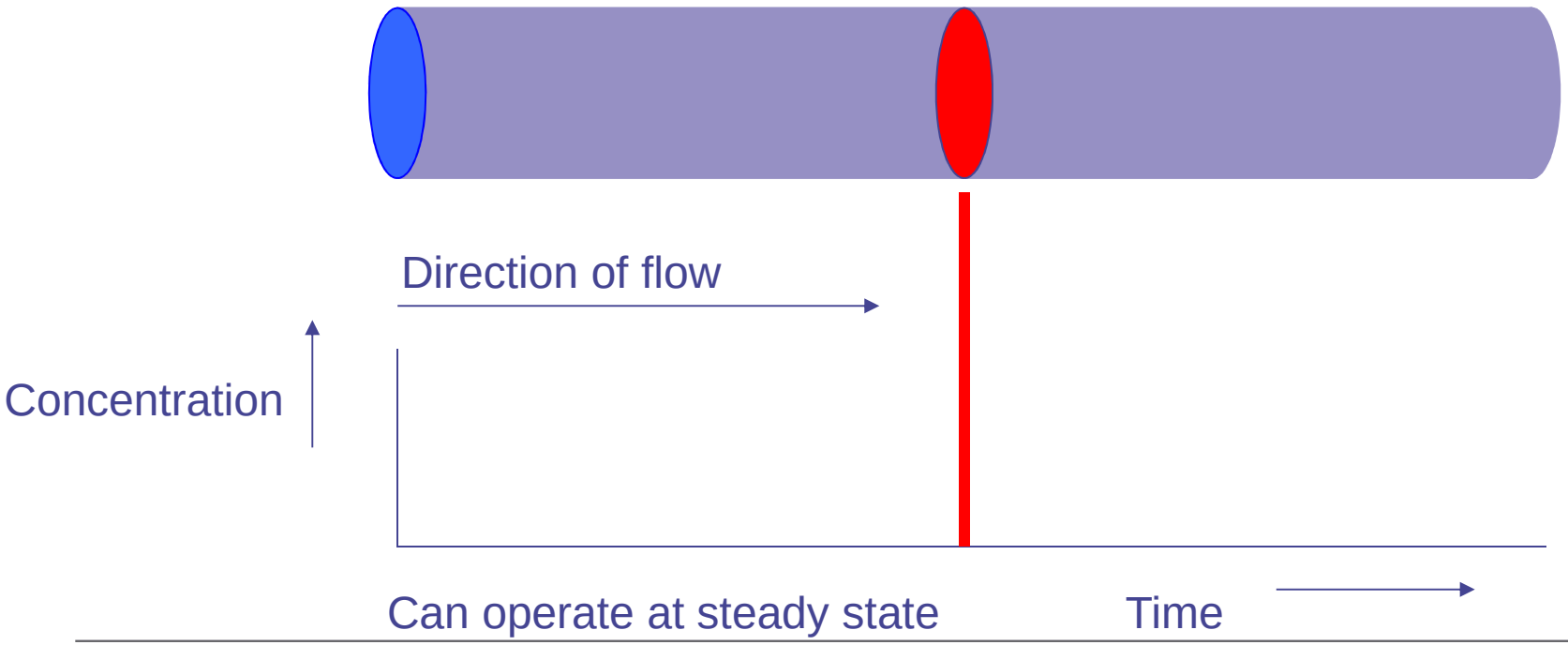


Does not operate at steady state

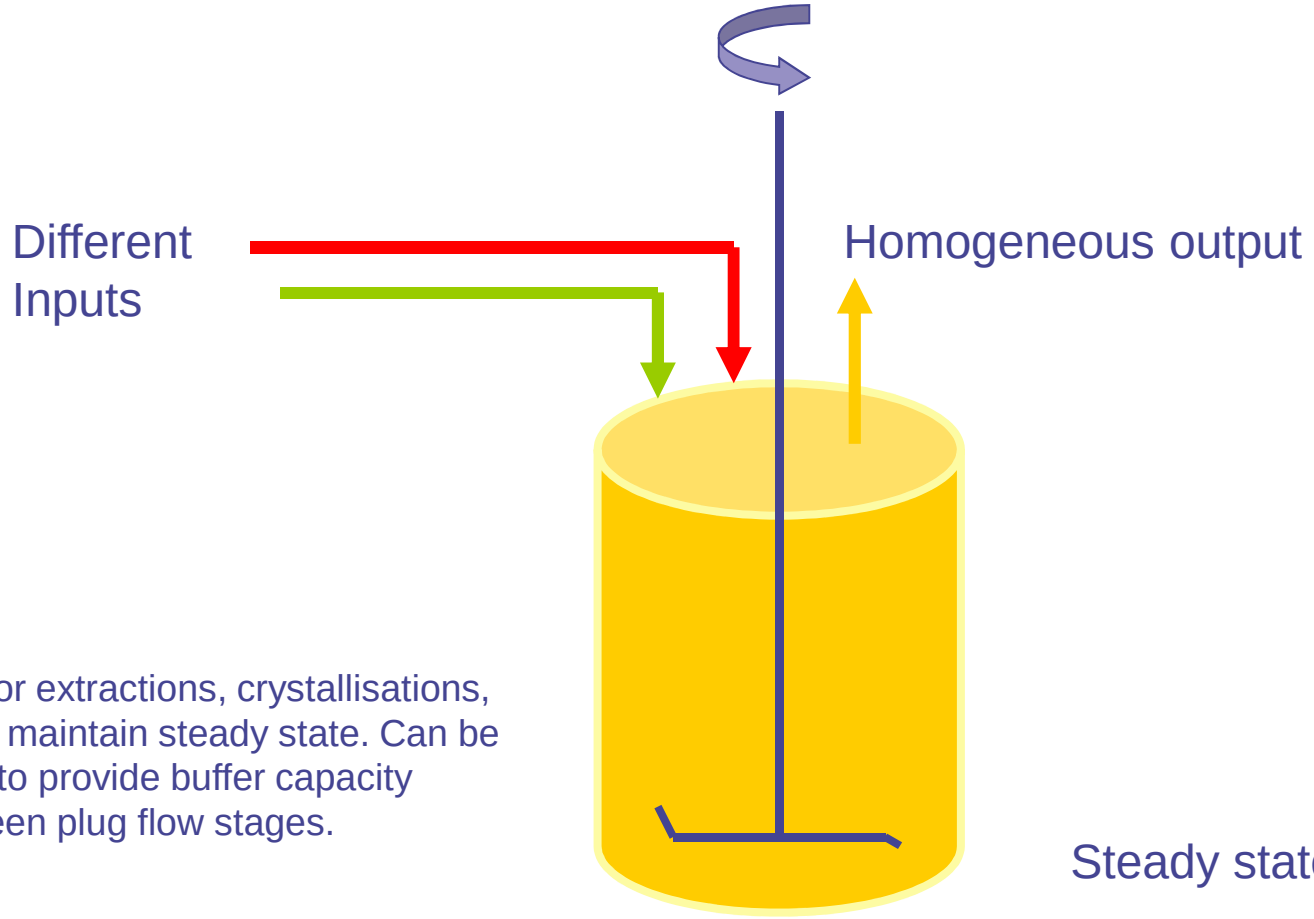
Idealised plug flow

Discrete slice of material with zero axial mixing and perfect radial mixing

Use for faster reactions, highly exothermic reactions, low temperatures or high temperatures, high pressures



Idealised CSTR (perfusion for biotech) regime



Use for extractions, crystallisations, etc to maintain steady state. Can be used to provide buffer capacity between plug flow stages.

Steady state operation

Flow regime characteristics

- **Plug flow**
  - **Used for fast reactions, *etc.* Kinetic control predominates.**
  - **Highly dynamic and responsive to change**
  - **Susceptible to process “spikes”**
  - **Needs PAT that is fast**
- **CSTR behaviour**
  - **Equilibrium (thermodynamic) control**
  - **High buffering capacity and slow response time**
  - **Insensitive to process “spikes”**
  - **PAT needs to be stable**

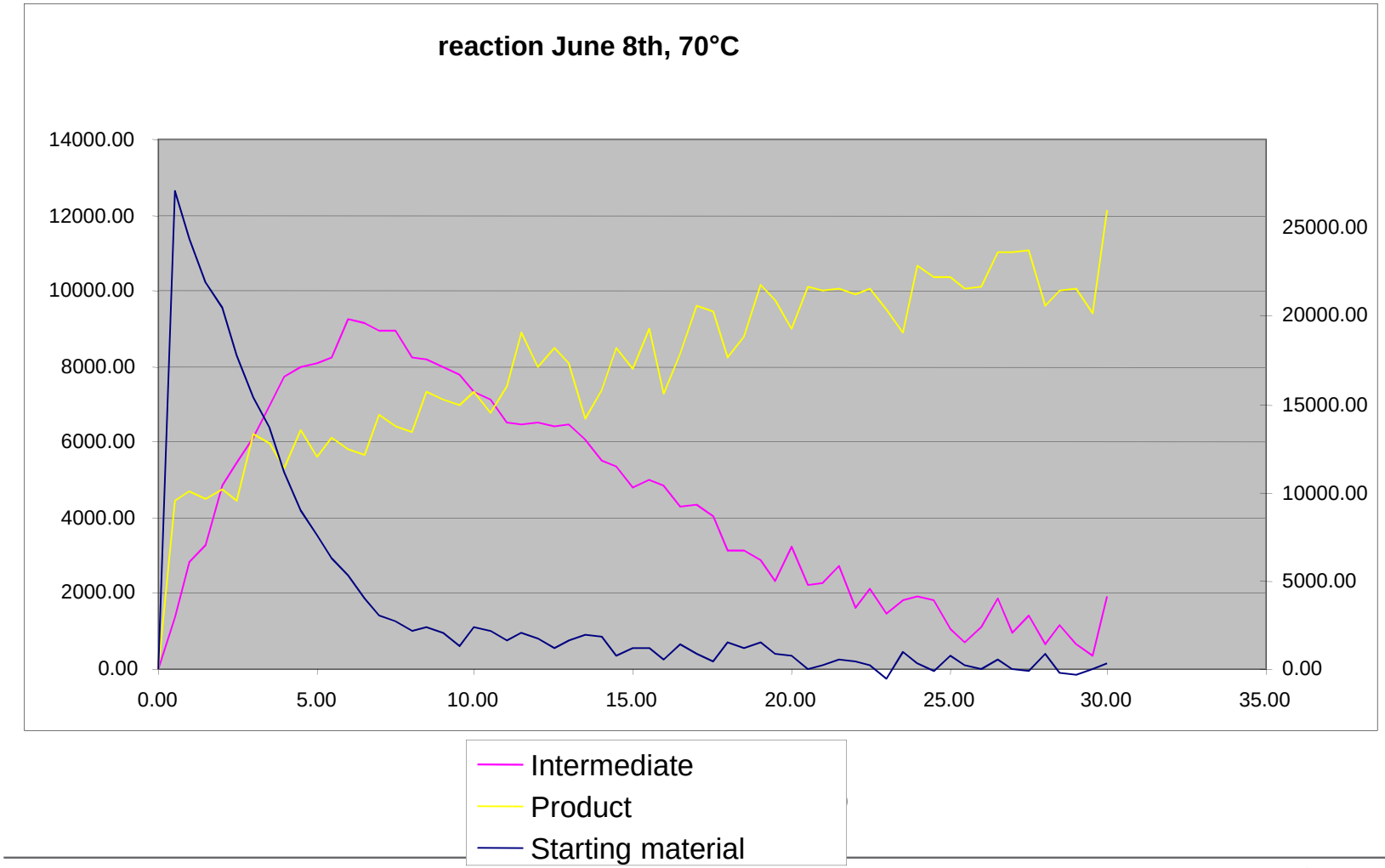
System dynamics and measurements

- **Which regime requires rapid measurement and response?**
  - **Dynamic systems**
    - Plug flow
    - Semi-batch
- **Which regime needs accurate, but possibly imprecise measurement?**
  - **Less dynamic systems**
    - CSTR
- **Which regime can use less accurate, but precise measurement?**
  - **Systems which need batch to batch variation managed**
    - Batch processes

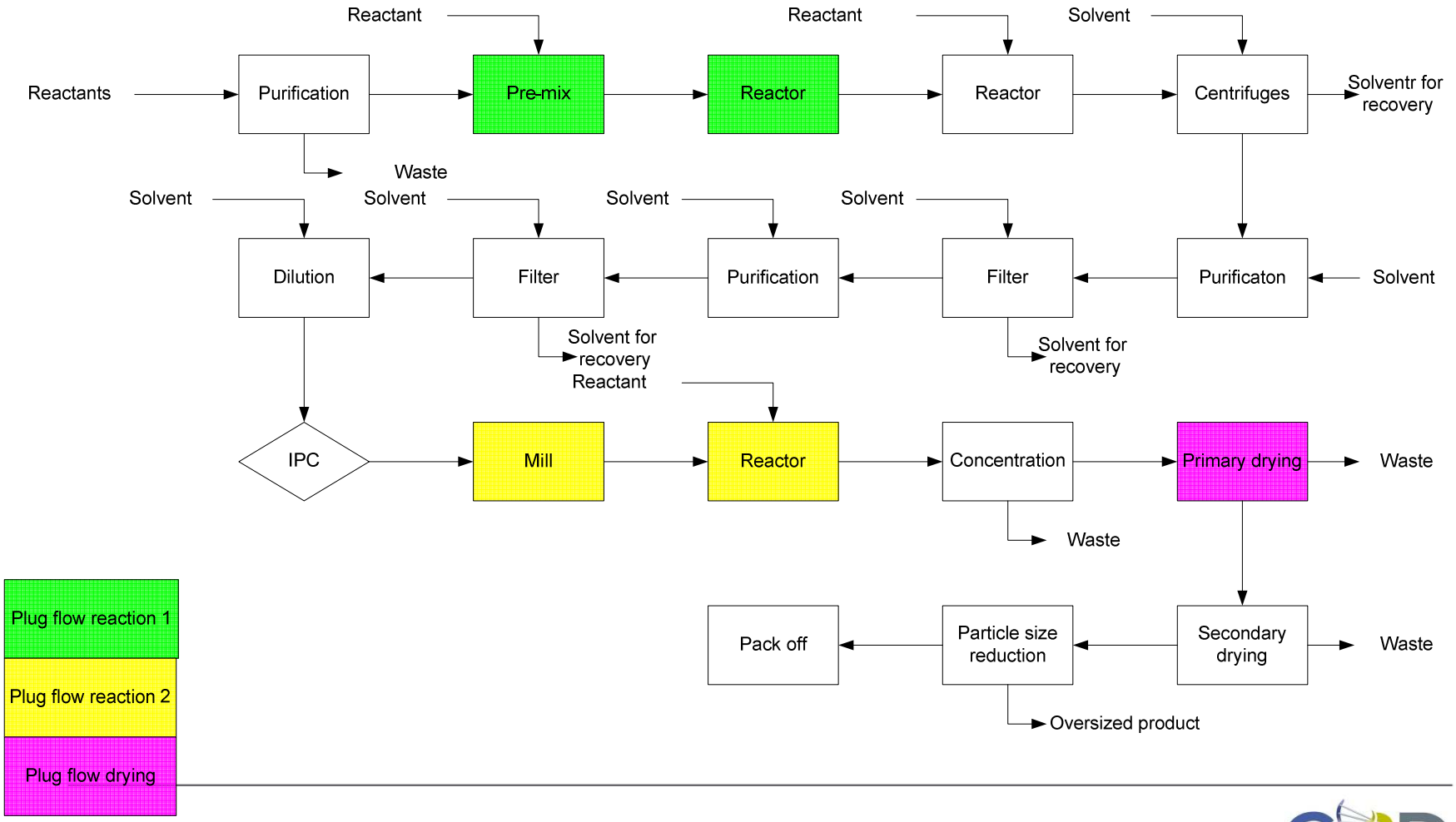
What do you do with process measurements?

- **Do you make decisions based upon them?**
- **Do you make nice graphs?**
- **Are they made to tell you that everything is as it was before?**
- **Are they used for predictive maintenance?**
- **Do they add to process understanding?**
- **Are they used for continuous improvement?**
- **Are they made because you filed them?**
- **Do you believe them?**
- **How do they serve your business?**

Process understanding is needed



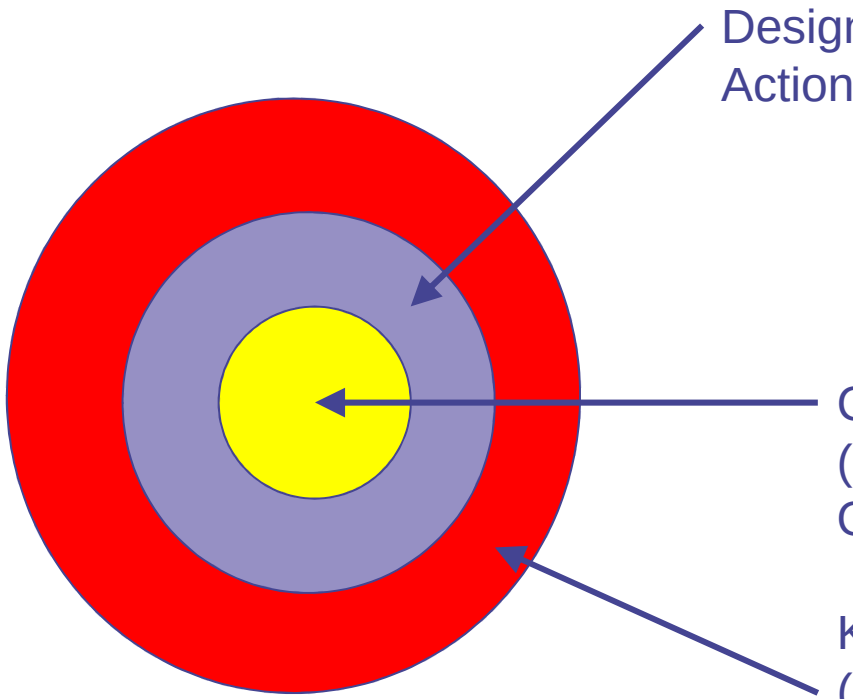
Manufacturing Process Flow – real example operated at multi hundred TPA



Design space and alerts/alarms

Current thinking has moved from maintaining steady state to maintaining control state.

You would like to be able to drive your car at different speeds wouldn't you?



Managing deviations

- **Perform risk assessment on unit operations**
  - **Without necessarily considering the reason for a deviation consider what should happen to the product affected**
    - Stop
    - Keep going
    - Divert affected product to waste
  - **Do this during design phase!**

Deviations

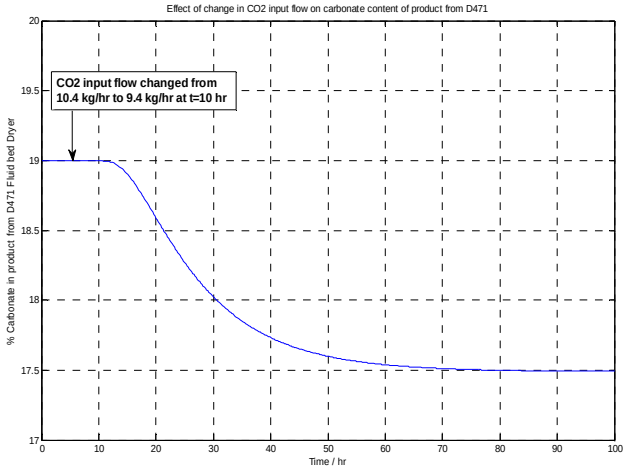
- **Use risk assessment techniques prior to event if possible**

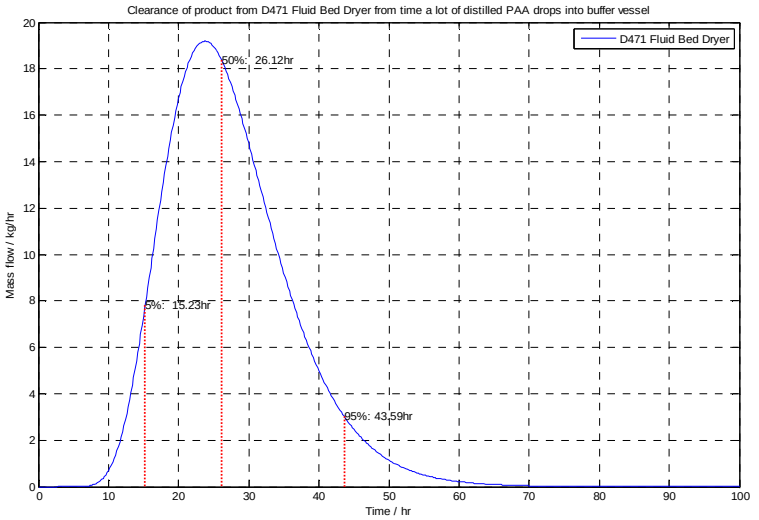
- **Write regulatory filings carefully to avoid regulatory non compliance which would have no adverse patient affect**
  - **Example:**
    - A spray dryer indicates an outlet temperature of 123°C for 1 minute 17 seconds. The NDA/MAA filings state that the product is dried below 110°C. What do you do?

    - What temperature is the product?
    - Is primary drying over?
    - How long is the exposure?
    - What is the effect of the exposure?
    - Each particle is exposed for a very brief time – however long the excursion lasts.
    - When does a dryer ever show the actual product temperature?

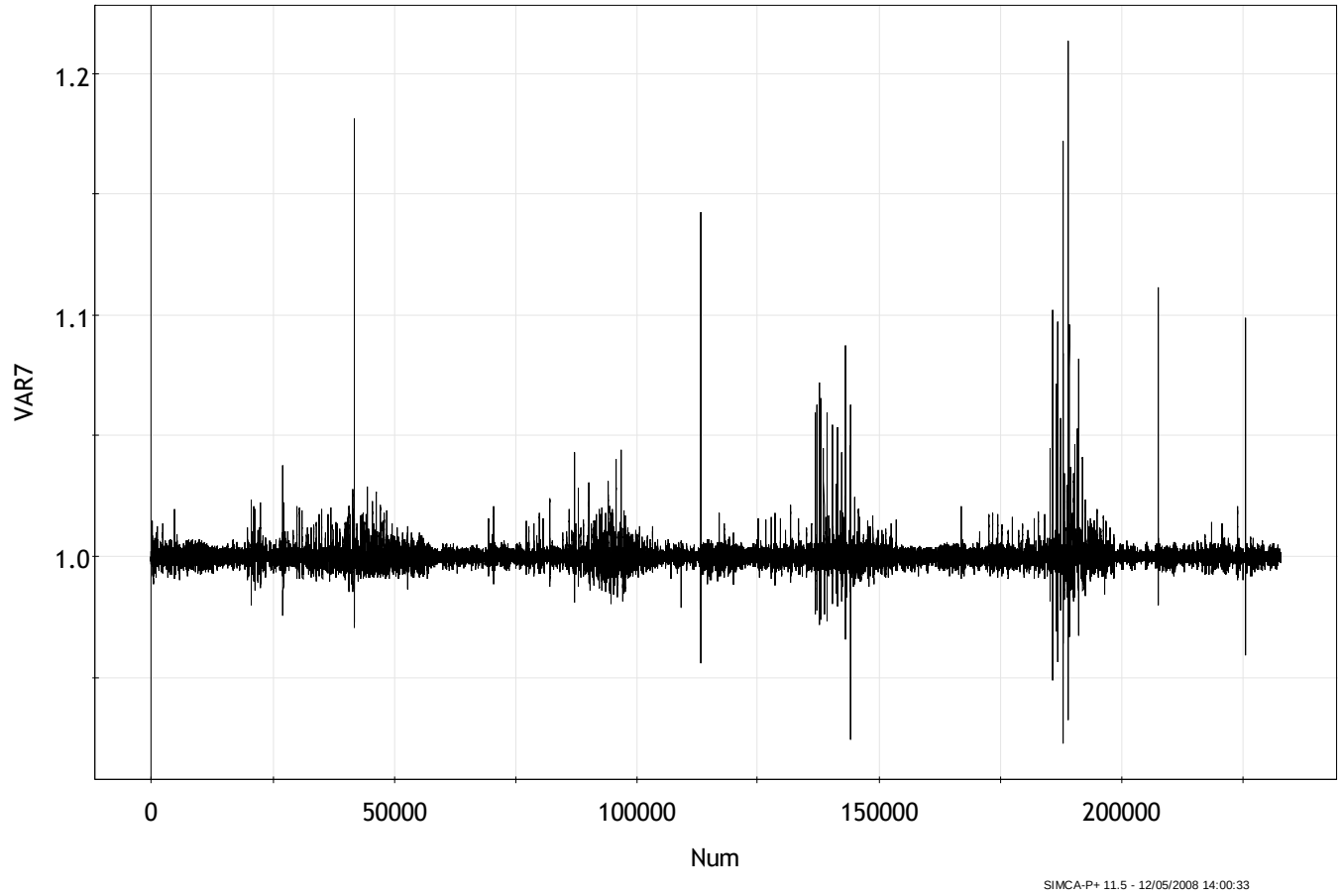
Coping with perturbations

- **Almost impossible to detect change once product enters CSTR stage**
- **Need to wait for equilibrium to be attained before the process change is possibly identifiable**
- **Use development data to confirm that the new conditions have the effect that you anticipate**



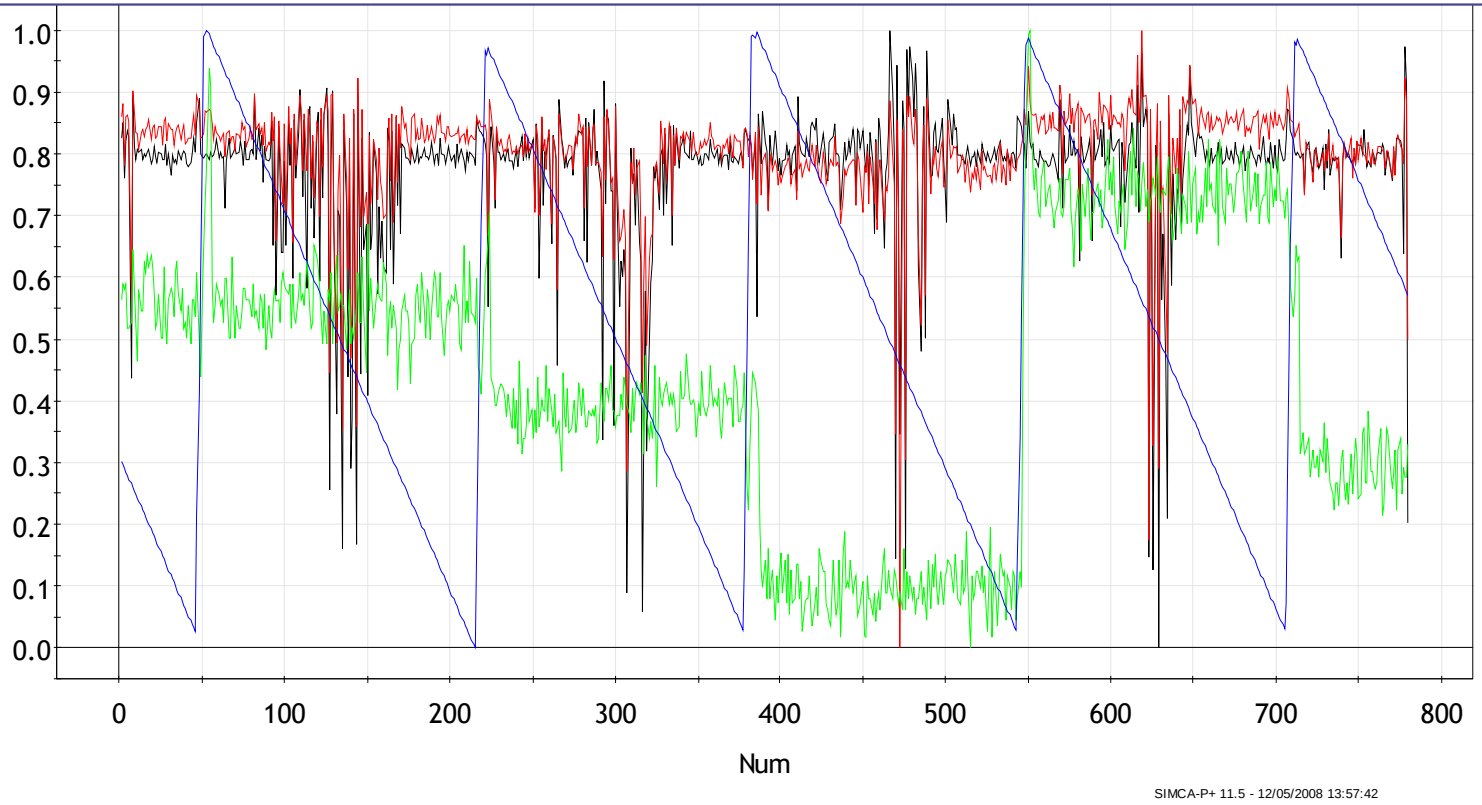


Example from commissioning (feed rate of a reactant with time) – raw data



The explanation

Black = Feed rate reactant #1; Red = feed rate reactant #2; Green = Concentration (NIR) of reactant #1; Blue = fill level of vessel feeding reactant #1



Regulatory impacts of continuous improvment

- **Write down your intention, not the way you have done it to date**
  - **A is added to B to give at least 80% C with no more than 2% D**

  vs

  - **Concentration X of A is added to concentration Y of B at Z litres/min maintaining the temperature between 5 and 10°C**

- **State criteria that you will use to implement improvement**
  - **Statistical methods, acceptance limits (not timelines) and how you will report them (Annual update, CBE0, *etc.l*)**