

Technical R&D/CHAD
CM Unit



Continuous Manufacturing

We change the way medicines are made

Novartis E2E CM case study

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Continuous Manufacturing at Novartis Basel



~300 m² productive area, 2 upstream trains, 1 downstream train, in total 21 modules, plant-wide process control system, development and operational scale

Major aspirational goals for our CM implementation

- Effectively risk-based 100% control for most relevant dimensions
- Controls as fast as needed, as slowly as possible
- Modular, multipurpose, universally applicable principles
- Low end throughput
- Plant wide process control
- Real-time release is enabled, but not mandatory

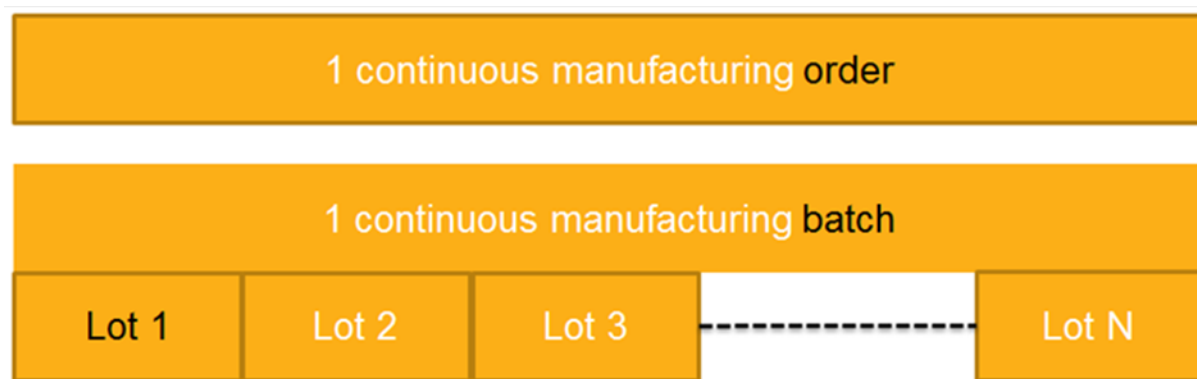
Principles relevant to long chain CM (E2E)

- Traceability is built backwards, not forward
- Push vs. pull concept
- Traceability is based on probability distributions
- Area of Impact needs to be defined for unit op network
- Avoid interrupts, keep process alive
- Release decision based on quality attributes AND process history
- **Main challenge: alignment/integration of chain in terms of transformation kinetics, traceability and control dynamics**

1) How did you define the boundaries of the material that is subjected to a release decision?

2) *Batch* means a specific quantity of a drug or other material that is **intended to have uniform character and quality, within specified limits**, and is produced according to a single manufacturing order during the same cycle of manufacture.

(10) *Lot* means a batch, or a specific identified portion of a batch, **having uniform character and quality within specified limits**; or, in the case of a drug product produced by continuous process, it is a specific identified amount **produced in a unit of time or quantity** in a manner that assures its having uniform character and quality within specified limits.

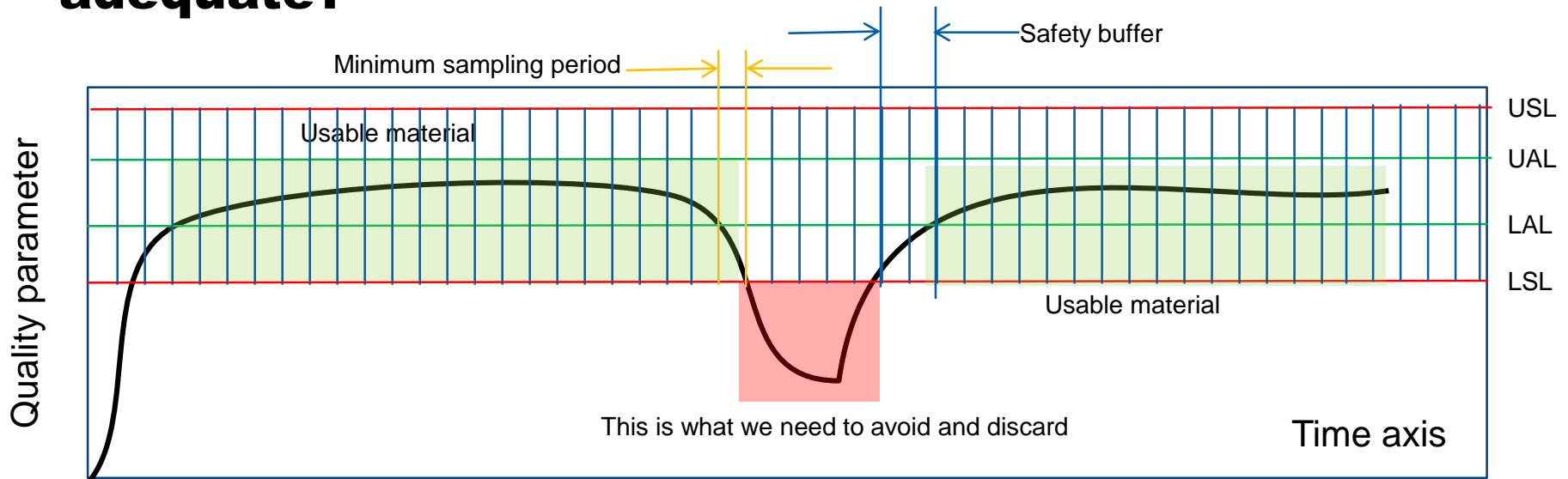


Defined by order size,
not by equipment or
source lot

2) How do you identify material that has questionable quality and how do you deal with it?

- Determine process dynamics for complete process chain (network)
- Monitor state of control per unit operation in real time for the entire process chain and follow the state of all unit operations electronically, reflecting the propagation kinetics
- If nonconforming material is detected somewhere, flag it electronically, trace propagation in real time, segregate at the end of the process and optionally investigate segregated material for final disposition
- Special case: In case of big reservoirs inside the chain, a salvaging of in-spec material and restarting is possible

3) How do you justify that the proposed sample rate of the CPPs or the CQAs and IPC reflects the inherent material characteristics and process dynamics is adequate?



- Define, how much sooner do we need to know before an unstable process can leave the spec limit (**pre-warning time leads to action limits**)
- Determine maximum rate of change of the process and align measuring (sampling) frequency with maximum rate of change such that no process change exceeding suitable ranges can be missed
- Link action limits with sampling=measuring period and rate of change
- Measure constantly at this sampling rate=system update rate

- Effectively 100% controls of product quality, as process can not deviate undetected

4) How do you assure that materials are collected while the process is in a state of control? How do you track the state of the process?

- By tracking state of process and material in real time and diverting suspect material at the end.
- Have an **electronic monitor of good/bad flags** for the entire network in **real time**, monitoring state and material propagation (wave-like propagation) per unit op
- The **good/bad flags are updated at high frequency** (1 sec) per unit operation and forward into next unit op and so on
- When the **last step indicates good material** coming off the line, **collect**, else segregate.
- We call this real time monitor a “virtual pipe” in-silico, and the monitor “material and event propagation”

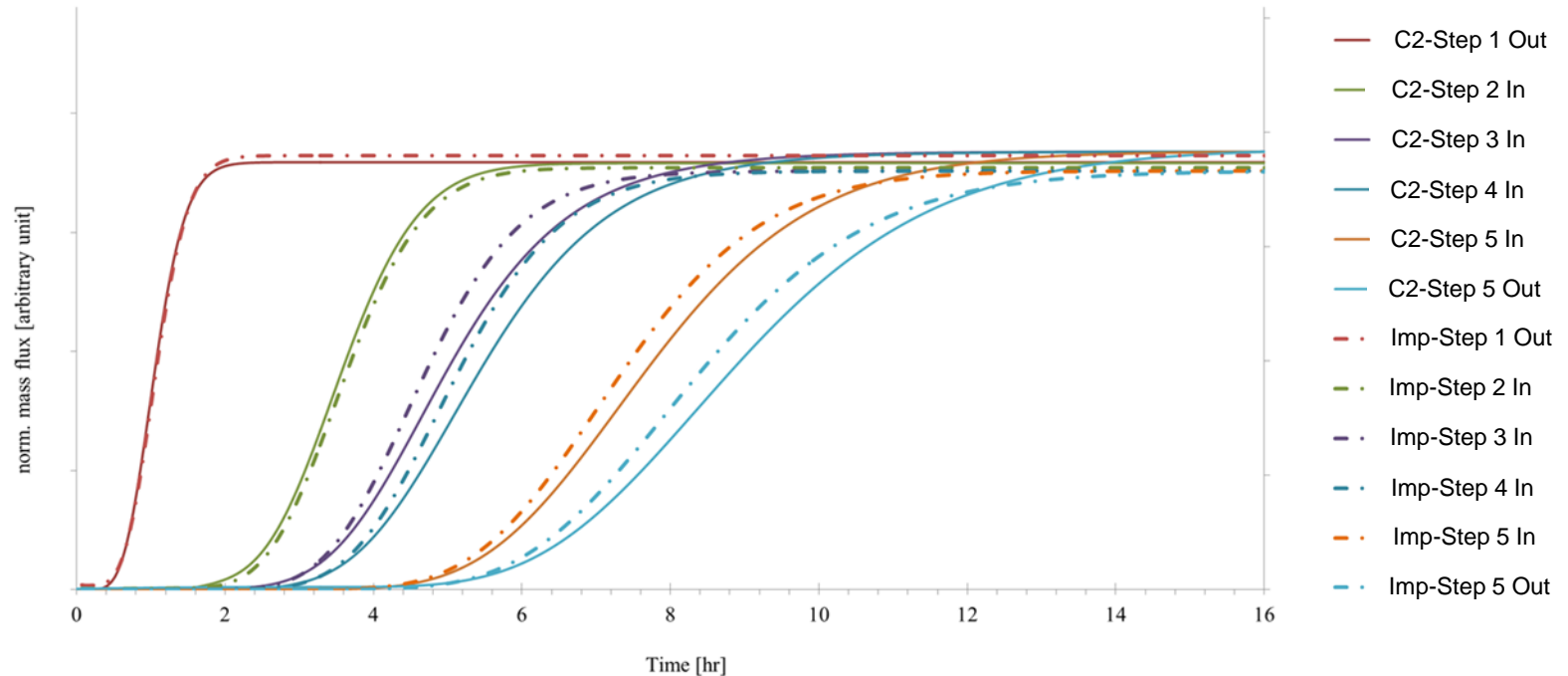
Excursion: How to solve the traceability question?

3 different approaches

- **1st option: 1st principles model**
 - Thorough, exact, powerful, ab initio simulations for dynamics and equilibrium
 - expensive, not realtime capable, computationally sensitive
- **2nd option: empirical model with experimental verification**
 - Verified experimentally, precise enough, realtime capable, robust
 - Models dynamics only, no ab initio simulations, medium cost
- **3rd option: model-free approximation**
 - No assumptions on model validity needed, good enough with safety margins, practical, computationally very cheap and hence realtime, only for dynamics, capable on DCS

Option 1: 1st principles model for chemical steps

Shown for main raw material and very different impurity



- Process and equipment design dominate over material characteristics
- Network analysis allows to derive full traceability AND system dynamics
- Network analysis can serve as the engineering basis for advanced technical control strategy, but is not relevant for regulatory control strategy

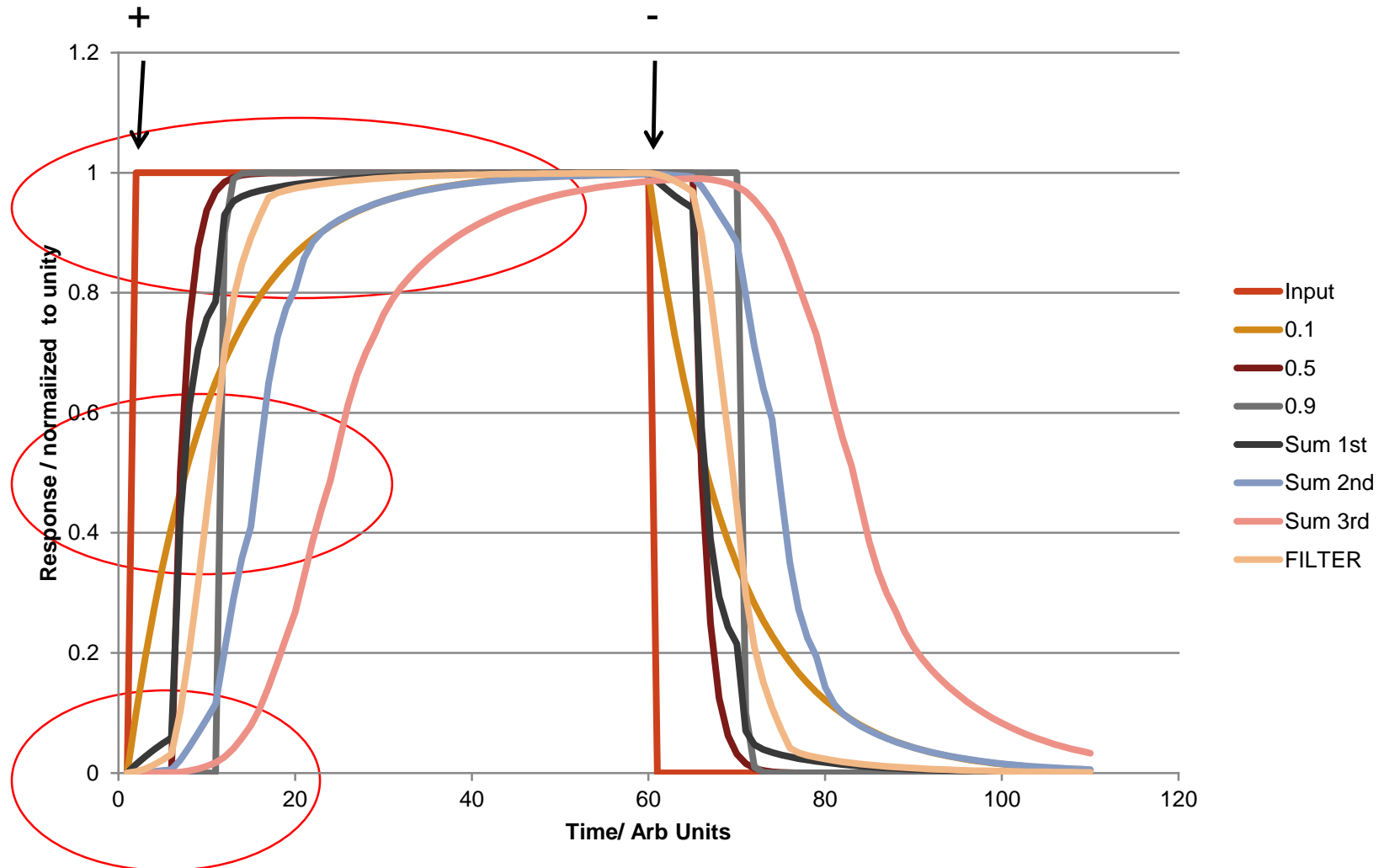
Conclusions on 1st principles model

High Science, but expensive

- Requires ultimate process understanding
- Requires lots of experimental determination of ingoing parameters
- Computationally expensive
- Not realtime capable, at least not practical
- Can serve as basis for sensitivity analysis=risk analysis in silico
- Can serve as the ultimate tool to find the ideal control strategy
- Require highly specialized experts (vertical skill set)

Option 2: Empirical Step response model

Demonstration of flexibility by superposition of 3 material streams



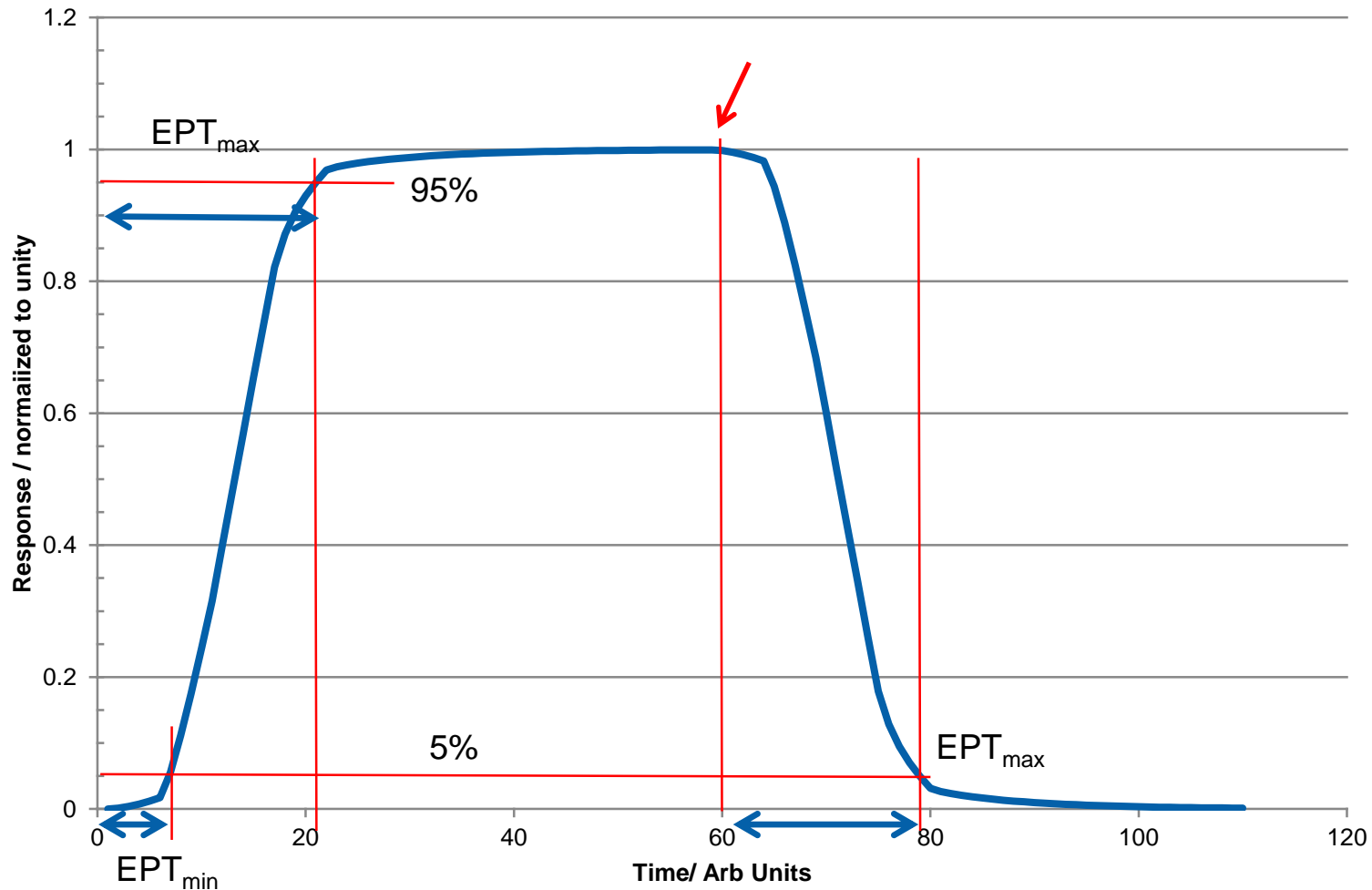
Conclusions on empirical model

models dynamics only, but is more practical to use

- Requires experimental verification of hybrid parameters
- Requires more macro level experiments
- Does not require full process understanding at the micro level
- Computationally cheap
- realtime capable
- Can not serve as ab initio simulation
- Can serve as as reasonable tool to tune control strategy
- Require highly specialized experts (vertical skill set)

Option 3: Model-free dynamic characterisation

Practical and robust to implement on a unit operation basis



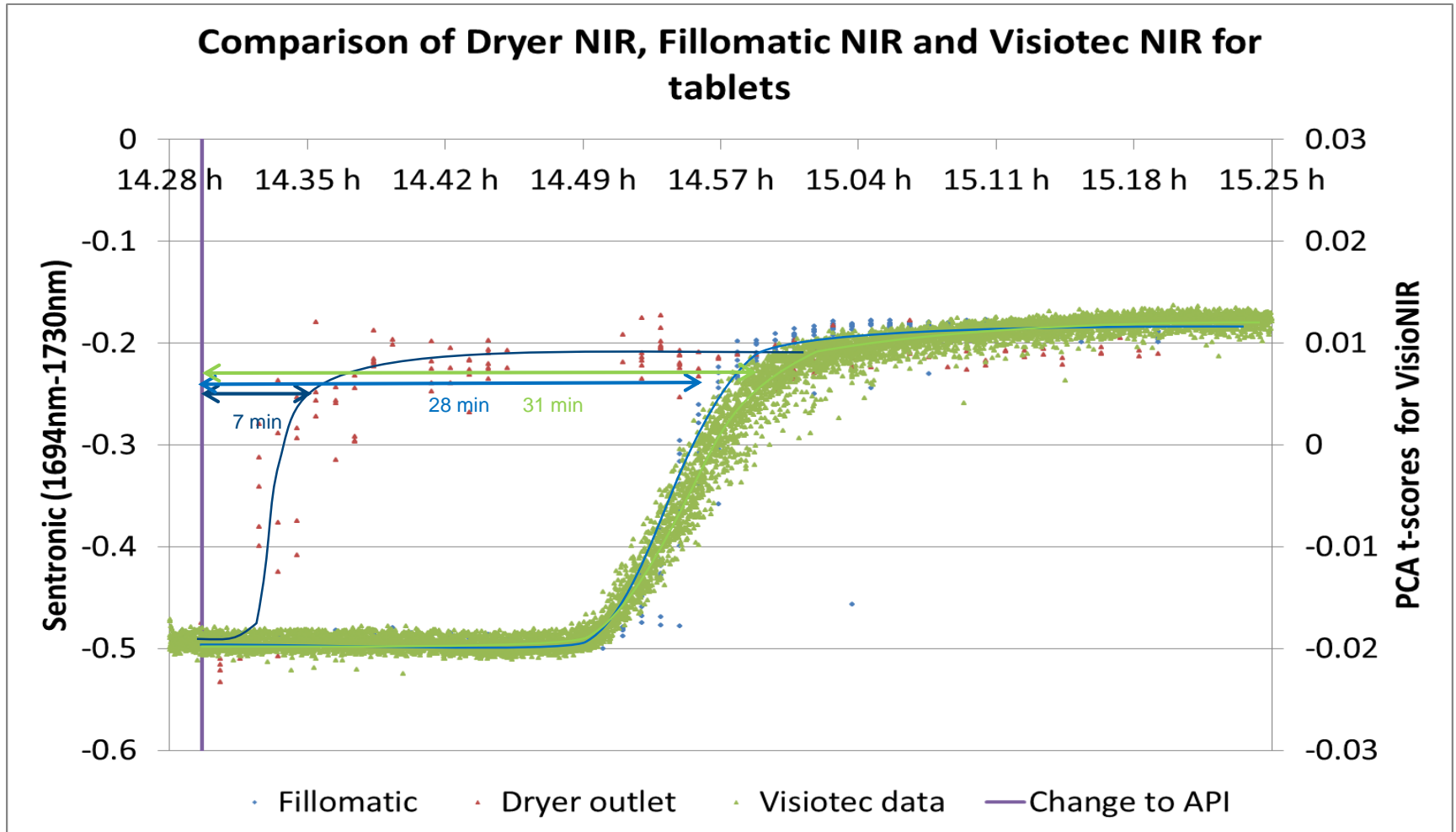
Conclusions on model-free approach

models dynamics only, but is more practical to use

- Requires straight forward experimental determination
- Requires few macro level experiments
- Does not require full process understanding at the micro level
- Computationally very cheap
- realtime capable on a DCS
- Intuitive and practical for operator plausibility check in plant, like a train schedule
- Inherent safety margin

Experimental verification of network dynamics

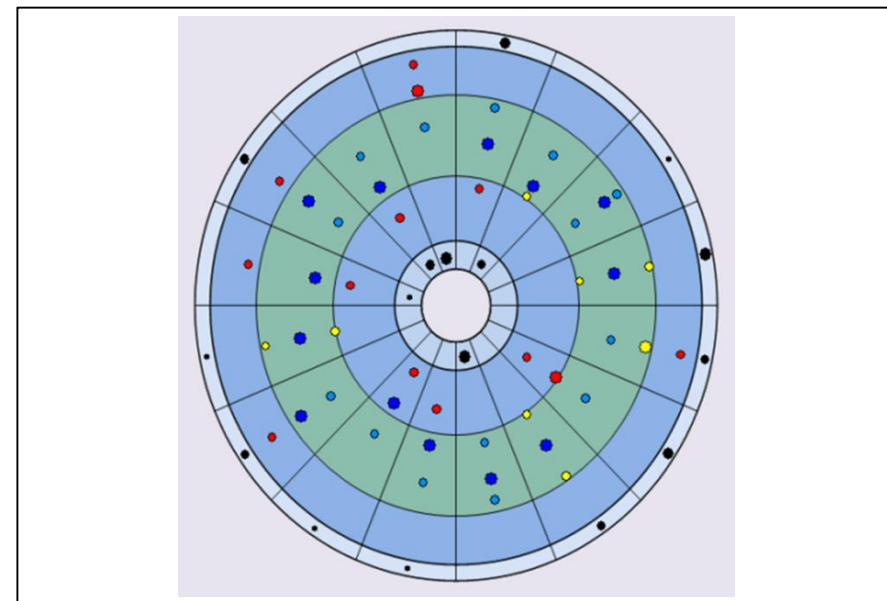
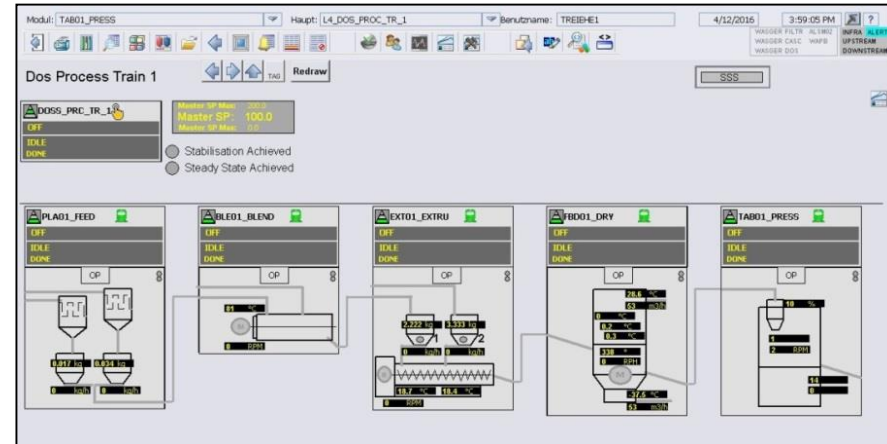
Shown here for secondary sequence



5) How can the operator stay informed, in real time, about the state of the process?

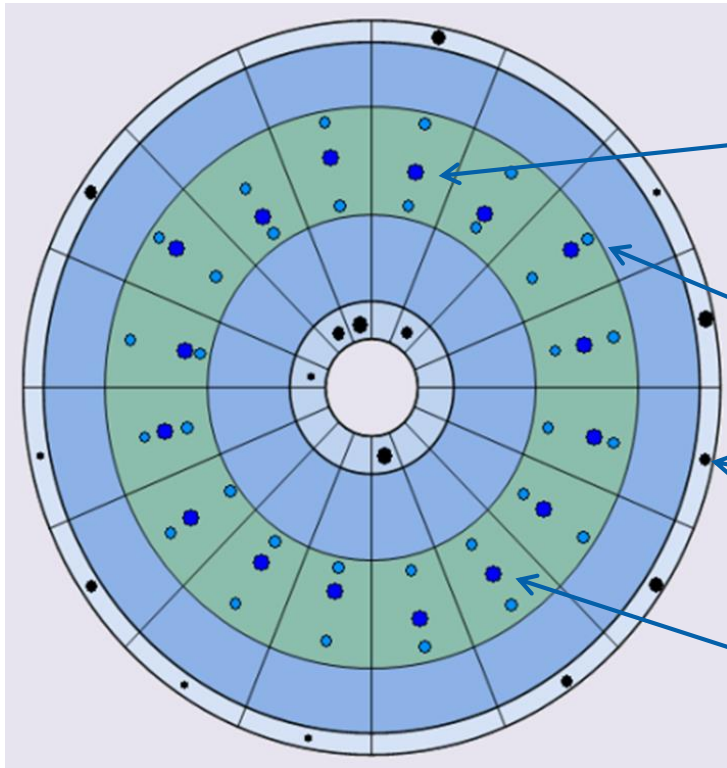
Human interface design

- Ergonomy
 - Digest complex information in real time
 - If it is not practical and easy for the operator, quality suffers
- Control cockpit
 - Monitoring & trending
 - Alarming
 - Reporting Q-relevant tags
- Automation
 - Process control & adjustment



Process health criteria

The Novartis Model = the eye on the process



Process is inside quality band, ideally centered in ranges

Process extremes do not violate ranges

Process change rates are not exceeding certain thresholds (process does not jump) (dynamically identifying systematic deviations)

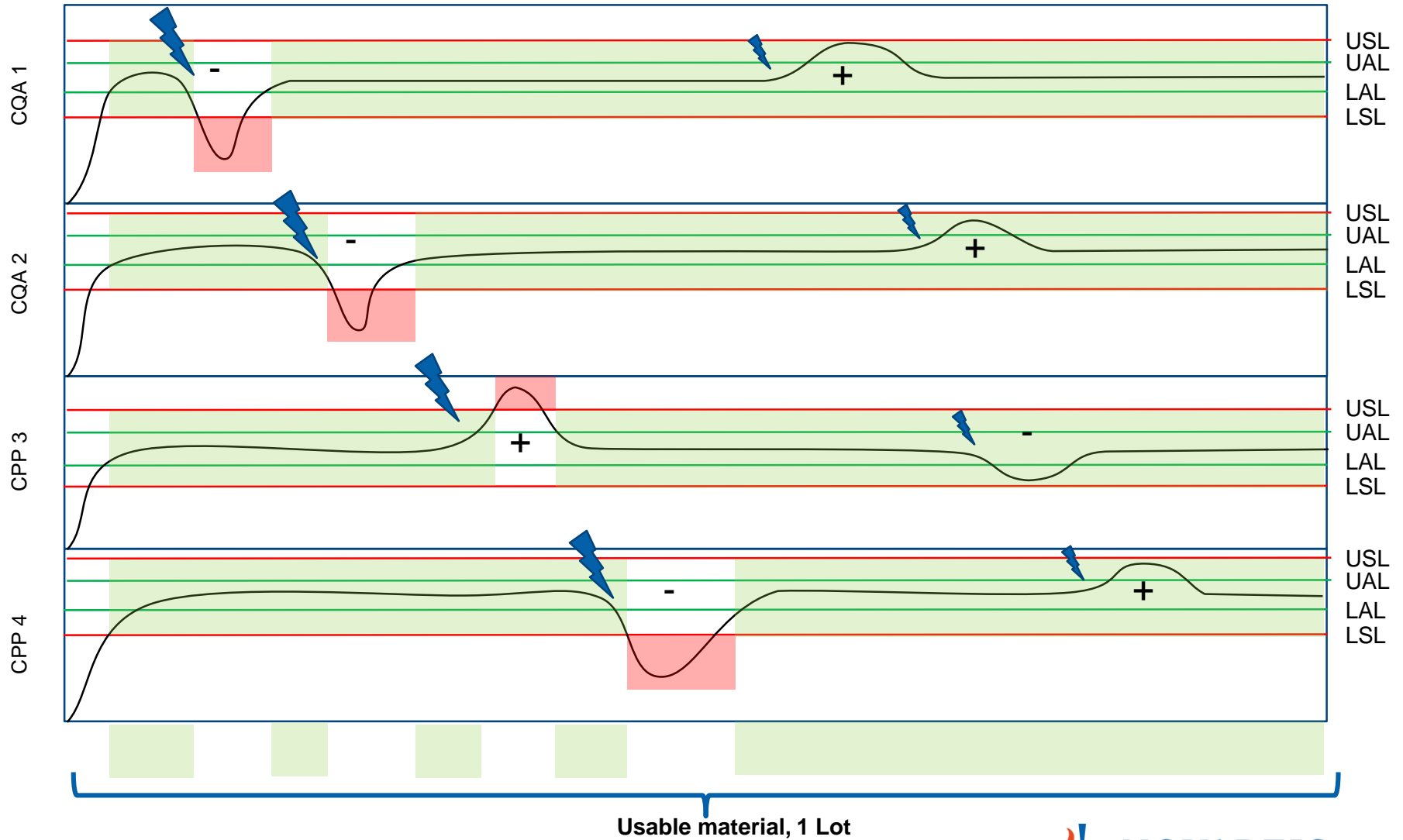
Process current status is ideally centered between its extremes

Process is stable, centered, unbiased and performs! (= Healthy)

6) How do you assess and demonstrate the reliability of the process for the intended commercial runtime?

- Follow the state of the process in real time as discussed before in terms of state of each unit operation, material states and propagation
- Verify process behaviour at extremes, and verify operation of material diversion (cut-outs) (level 1)
- Demonstrate by superposition with small disturbances that the process is still healthy and able to detect those (level 2) (“pulse check for system health”)
- Use level 1 and level 2 to demonstrate system health and dynamically extend runtime as long the process is in state of control and healthy

System Performance Verification (level 2)



The take home message

Integrated thinking
<Process design, process control, process dynamics> is key!

- **Batch definition** (with proper interpretation same as batch)
- **System dynamics** (process and control dynamics need to be matched) is a must know for:
- **Material traceability in CM train** (everything is in motion, always)
- **Release decision** (can be same as batch, Realtime Release optionally)
- **Runtime verification** (Continuous Performance Verification level 1 and 2)

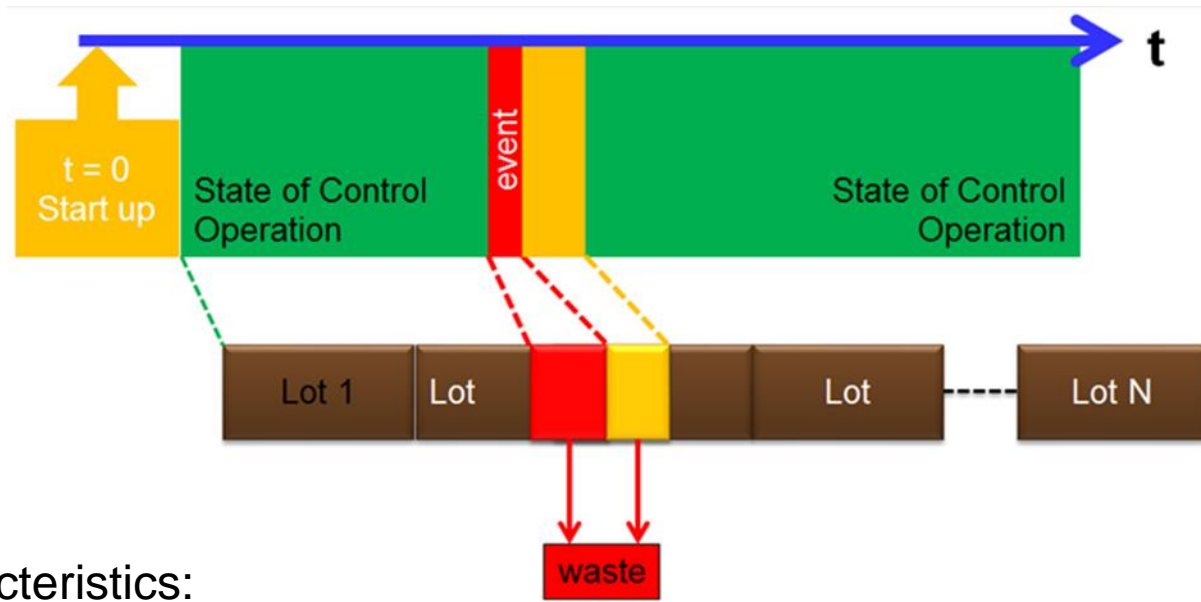


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Backup

Material Traceability and Event Handling



Key characteristics:

- State of control matters, not steady state
- Events (reach or lose state of control) will propagate through system following similar principles like materials
- Events are basis for flagging and diversion decision
- Divert material at end of process to minimize disturbance

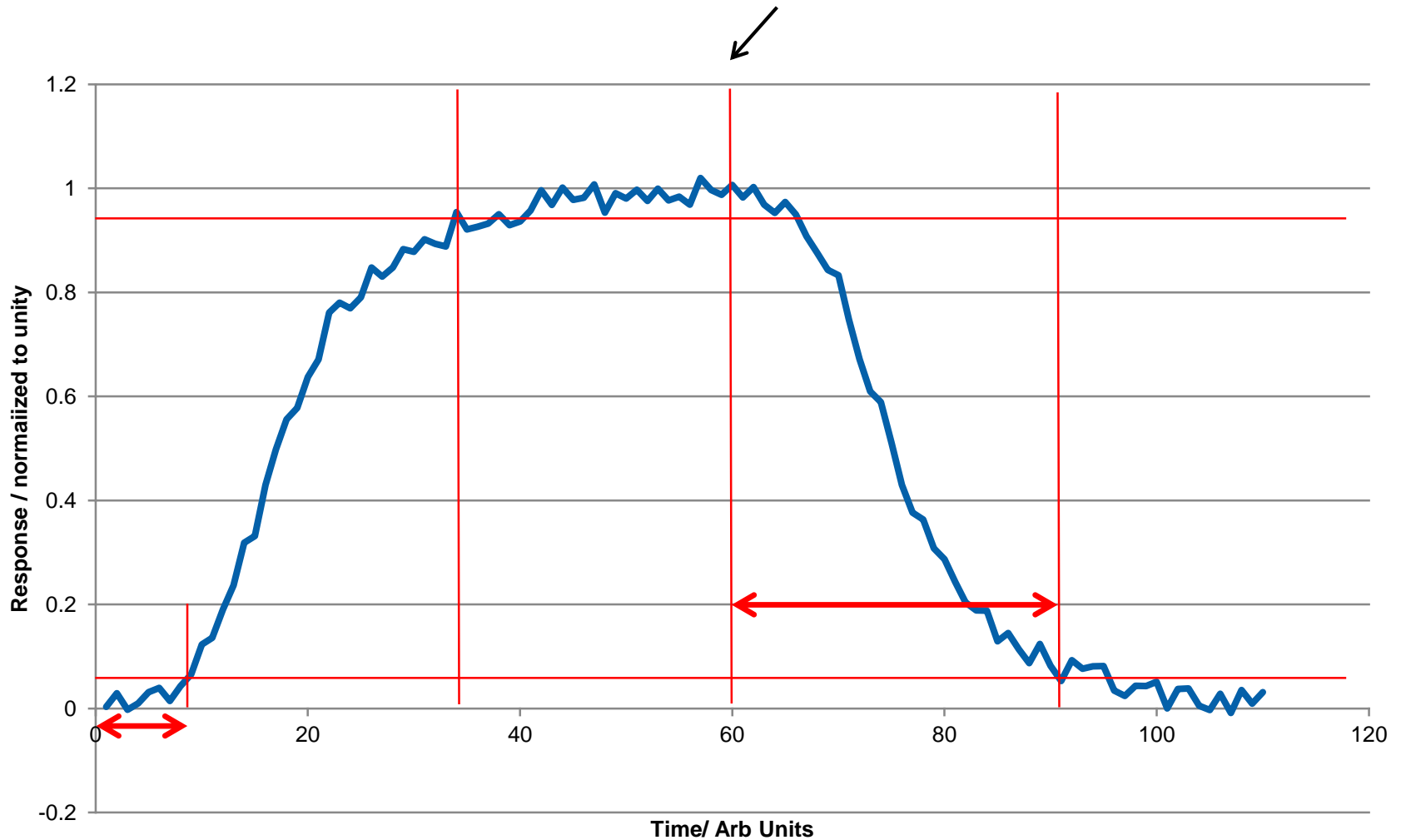
Release decision would be based on quality attributes AND process history with time-stamped data

2) Detailed procedure

- 1) monitor state of control per unit operation, incl. feed(!)
- 2) allow priming (pre-loading) of the unit operations with in-spec material to reach state of control fast
- 3) start collection at the end of the chain, once last unit operation has reached state of control (track S of C...)
- 4) as soon as a unit operation triggers a Q relevant alarm (loss of state of control), **flag the material and divert at the end of the chain** (material propagates as wave)
- 5) in case of a big hold-up (long RT) in the chain and loss of control upstream thereof, disconnect and hold the line downstream of that and divert before feeding into hold-up

Practical aspects in determination of EPT's

3% noise, analytical range



6) How do you assess and demonstrate the reliability of the process for the intended commercial runtime?

- Detailed procedure:
 - Identify the most critical CPPs of the train via FMEA (risk-based)
 - Determine technical capability of the equipment for these CPPs and proposed ranges (DoE etc.) (risk-based)
 - Verify CQAs and verify performance of cut-outs. (can be classical or PAT or Model-based)
 - **Demonstrate adherence of process in short term and long term (PAT, SPC, short and long term variations)=level 1**
 - Operate equipment train at set points and add programmatically **disturbances** (not set-point changes) to the CPPs, one causing the system to exceed the range, one to stay inside the range, one positive, one negative (new)
 - Rotate sequentially, but only one at a time.(new) = level 2
 - **Classical verification (sample and test) is the reference standard**