# EMA Expert Workshop on Validation of Manufacturing for Biological Medicinal Products

Tuesday 9th April 2013

## Process Validation-Enhanced Approach

# Scale down models

Frank Zettl

EGA
Making Medicines Affordable

EuropaBio™
The European Association for Bioindustries

ebe
european biopharmaceutical enterprises

# Key elements enhanced approach

- Extensive and intensive process knowledge
- Better prediction of scale effects
- Leverage process knowledge into control strategy via continuous process verification

# Scale Down Model (SDM) Lifecycle

**Design**

- Within development
- Continuous improvement

**Qualify**

- Compare outputs
- Assess suitability

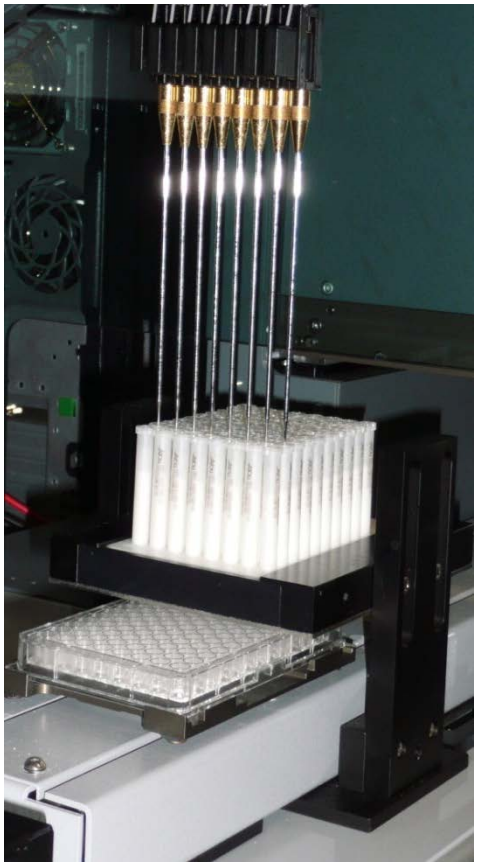
**Maintain**

- Facility changes
- New CQAs

# SDM Design

- SDM useful during design phase
  - Process development and characterization
  - Process validation (e.g. Virus removal)
- Design Options
  - Whole unit operation models
  - Cover specific aspects of a unit operation
  - Worst case model
- Relevant outputs are defined (e.g. CQA)
- Based scientific and engineering principles
- Inputs and environment are considered

# Typical Model Systems Purification



**Robotic system**

Column volume
~ 0.2 – 0.6 ml

**Lab system**

Column volume
~ 15 – 25 ml

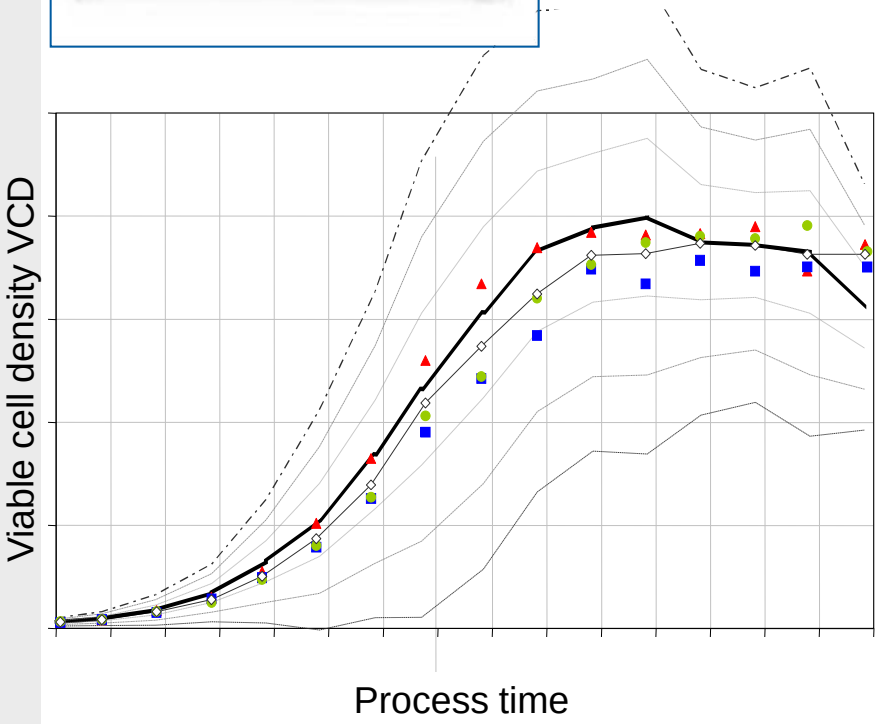
**Production**

Column volume
~ 150 – 400 L

# Typical Model Systems – Cell culture


**10 – 15 mL scale**

**2 L Lab system**



# Benefits of using SDM

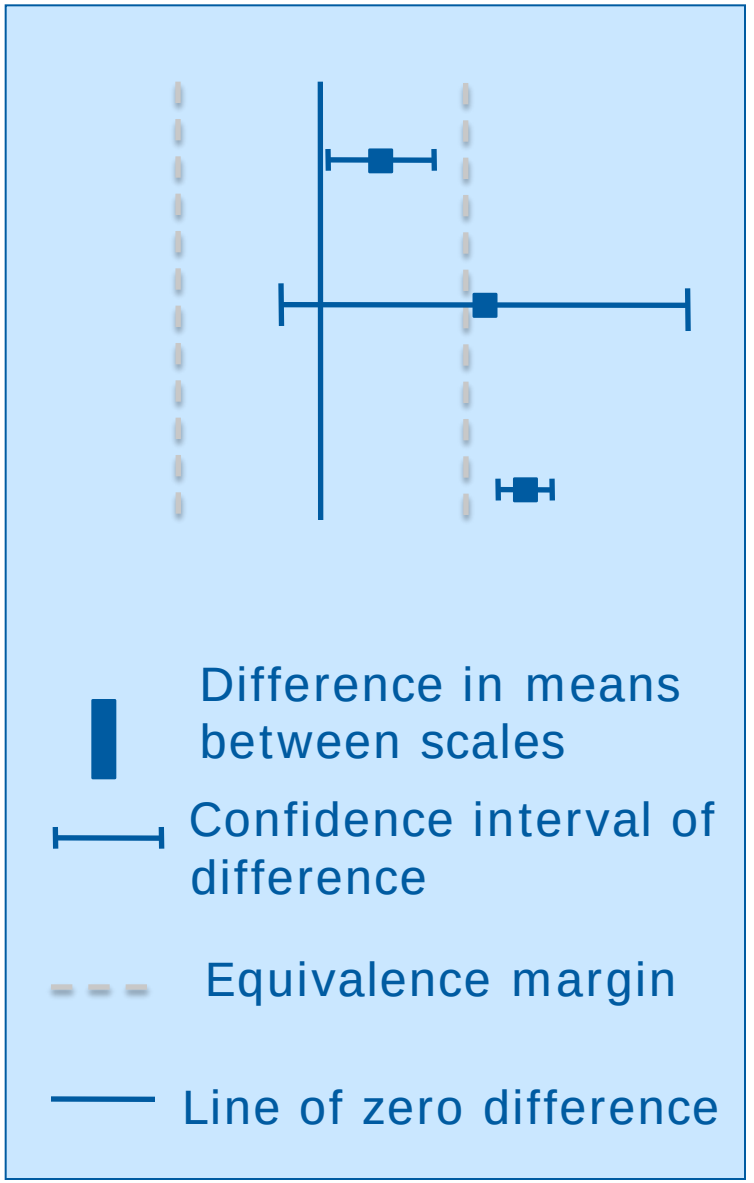
- SDM can be extremely useful even if they do not exactly match large scale performance, provided the differences are understood
- A large number of process parameters can be explored in large ranges
- Several process parameter can be varied independently in a systematic manner
- Interactions and quadratic effects can be identified
- “Categorical variables” (like raw material lots) can be investigated

# Qualification of SDM

- Statistical approach is gold standard
- But effort may vary based on
  - Availability of manufacturing scale batches
  - Applied control strategy
  - Predictions that are made from SDM
- A generic qualification should be possible
  - Depending on understanding of scale effects
  - Depending on control strategy
- Concurrent (re-)validation should be possible

# Equivalence Testing (TOST)

- Contains information about
  - Observed offset between scales
  - Observed variability
- Equivalence margin is defined based on scientific considerations
- SDM containing non-equivalent results may still be suitable



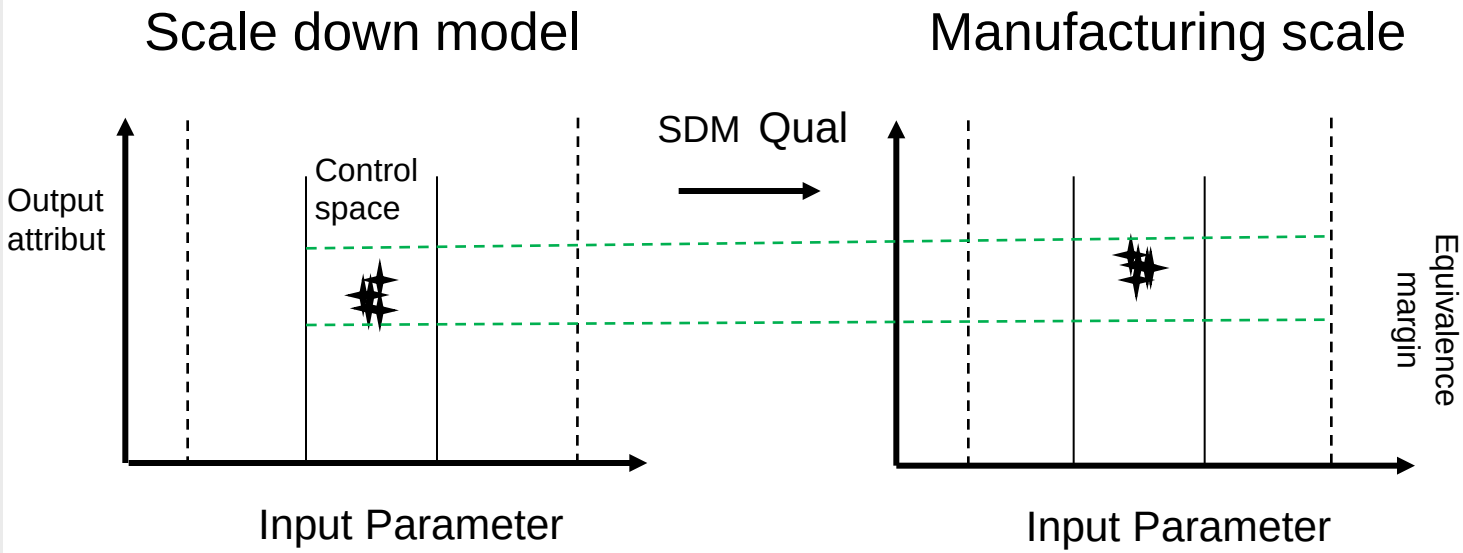
# Suitability of Scale Down Models

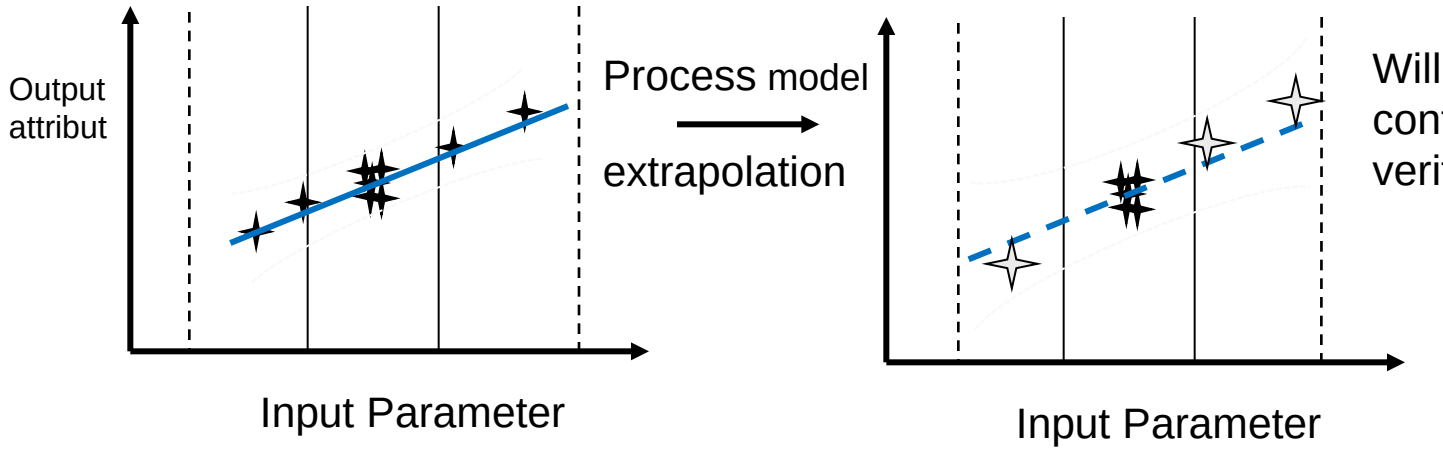
- Even if not statistical equivalent
- Depend on intended use
- Offsets may be applied
  - Scientifically explained
  - Verified with independent data
- Observed variability can be de-risked
  - Worst case studies
  - Control strategy (including in-process testing, specification testing, stability etc.)

# Process Models

- Mathematical description of input/output relationship
- Result from univariate and multivariate experimentation
- Can cover interactions and quadratic effects
- Are assessed with regard to their quality
  - Coverage of data
  - Prediction quality
- Estimate **value** of process outputs and the **confidence** of prediction
- Process models **cannot** be verified over the entire range at scale
- But can be assessed within monitoring program

# The Process Modeling Approach




Will be adressed by continued process verification

# Process Models - Limitations

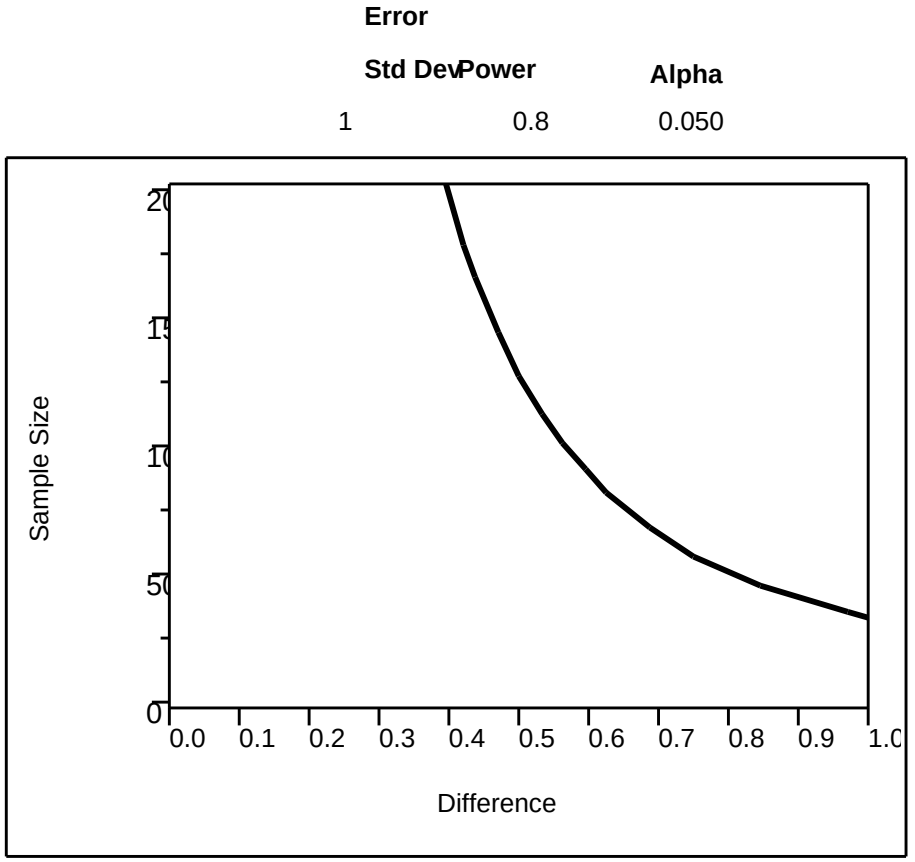
- In many cases not all parameters can be investigated in a single study
- Categorical variables are difficult (if not impossible) to model
- Continued Process Verification and control strategy will overcome potential issues related to this

# At scale verification - Limitations

- Statistical verification is not achievable

- Example IEC- HPLC Peak
- SD (@  scale) = 5%
- Delta model prediction
  = 2%

=> 199/2 batches needed



# The Enhanced Approach Team

| | |
|---|---|
| Deborah Baly | Bayer |
| Bob Kuhn | Amgen |
| Norbert Hentschel | Boehringer Ingelheim |
| Brendan Hughes | BMS |
| Enda Moran | Pfizer |
| Luis Maranga | BMS |
| Frank Zettl | Roche |
| Karl-Heinz Schneider | Bayer |
| Kris Barnthouse | Janssen (J&J) |
| Gilles Borrelly | Sanofi |
| Camilla Kornbeck | Novo Nordisk |
| Markus Goese | Roche |

- THANK YOU