Considerations for a Science and Risk based Scale up and Technology Transfer

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Outline

- Overview of scale up approaches
- Considerations for scale up
- Considerations for technology transfer
- Communication of scale up information in a regulatory submission
- Conclusions

What Do We Understand as QbD?

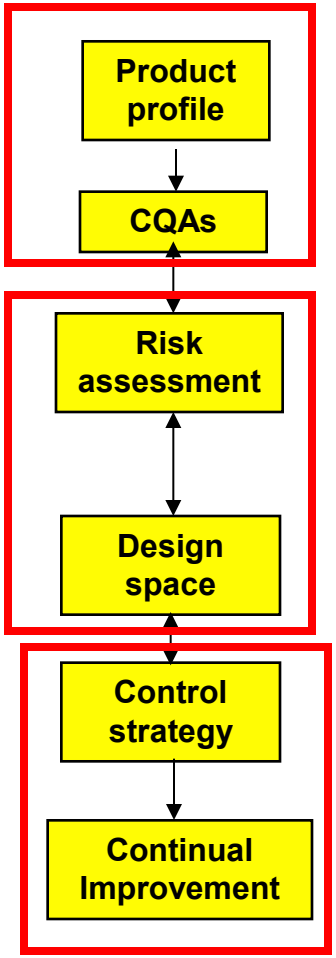
- From ICH Q8(R2), '*A systematic approach to development that begis with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management*'.

- The premise of Quality by Design (QbD)
  - **Patient focused development approach**
  - A **science and risk based** approach

- Companies do not manufacture QbD, FDA does not approve QbD, and patients do not receive QbD
  - However, all benefit from implementation of the QbD approach

- QbD is made up of data the way a house is made up of bricks!

Where Scale-up fits in the QbD paradigm



PRODUCT UNDERSTANDING

PROCESS UNDERSTANDING

SCALE UP &
TECHNOLOGY TRANSFER

PROCESS CONTROL

Approaches for Scale up

- Empirical
  - Defining process parameter ranges at commercial scale based on experiments
  - Establishing scale independent region of operation at pilot scale
    - In terms of scale independent variables
    - In terms of material attributes
- Hybrid (Experimental + Model)
  - Establishing process parameter ranges at pilot scale and then scaling to commercial scale using:
    - Vendor provided correlations/ scaling factors
    - Models available in literature
    - Dimensionless numbers
- Mechanistic
  - Physico-chemical models of individual unit operations based on first principles

Example #1: Empirical Approach

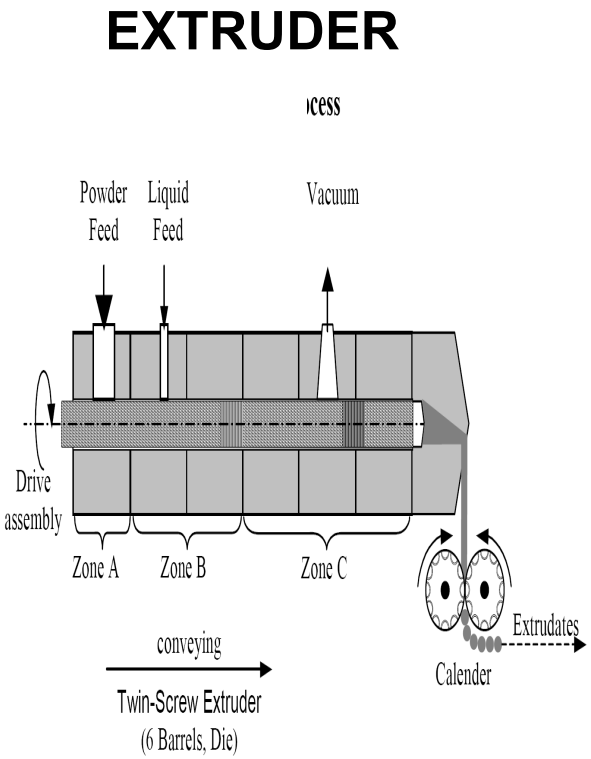
1. DOE performed for the hot melt extrusion at laboratory scale.

2. DOE data analyzed to define design space in terms of a critical parameter e.g.
Screw speed / feed rate

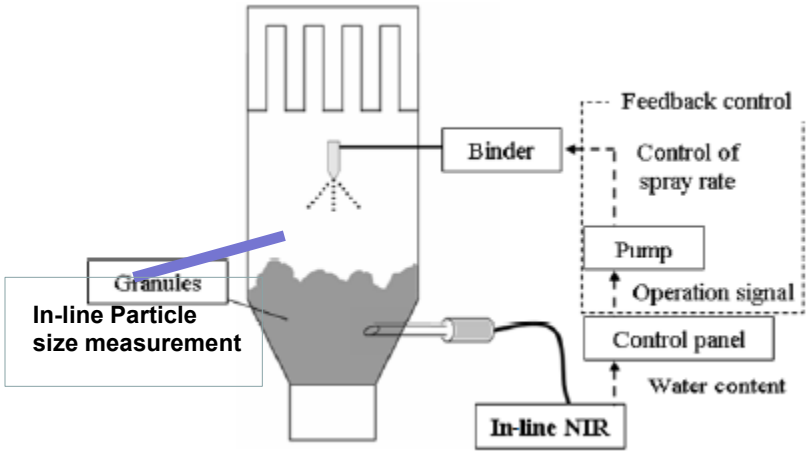
3. Process scaled up to an extruder at commercial scale that is geometrically similar to the laboratory extruder.

4. Screw speed to feed rate ratio scaled using ratios of screw diameters, and design space re-defined.

5. Then design space is experimentally verified at commercial scale.



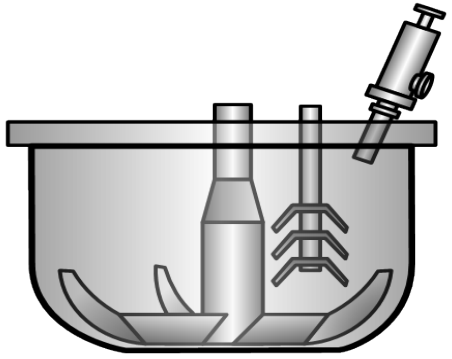
Example #2: Empirical (Material Attribute based)



- Fluid bed granulation
- Water content of granules and particle size of granules identified as CMA* (critical material attributes)
- Acceptance values for CMA identified during development that would meet the desired finished product CQA (Critical Quality Attributes)
- Goal of scale up is to keep the same values of CMA
- Presence of on-line monitoring tools facilitates enhanced measurement and reduces scale up risks

* CMA is not an ICH term, term used here for the purpose of this presentation

Example #3: Hybrid Approach (Dimensionless Numbers)



High Shear Granulator (HSG)

Process parameters for high shear granulation represented by a dimensionless number:

Spray Flux: Measure of area wetted by drops from spray nozzle to powder flux through spray zone

↓

Multivariate DOE to study granulation at pilot scale:

Inputs: amount of granulation liquid, impeller speed, granulation time

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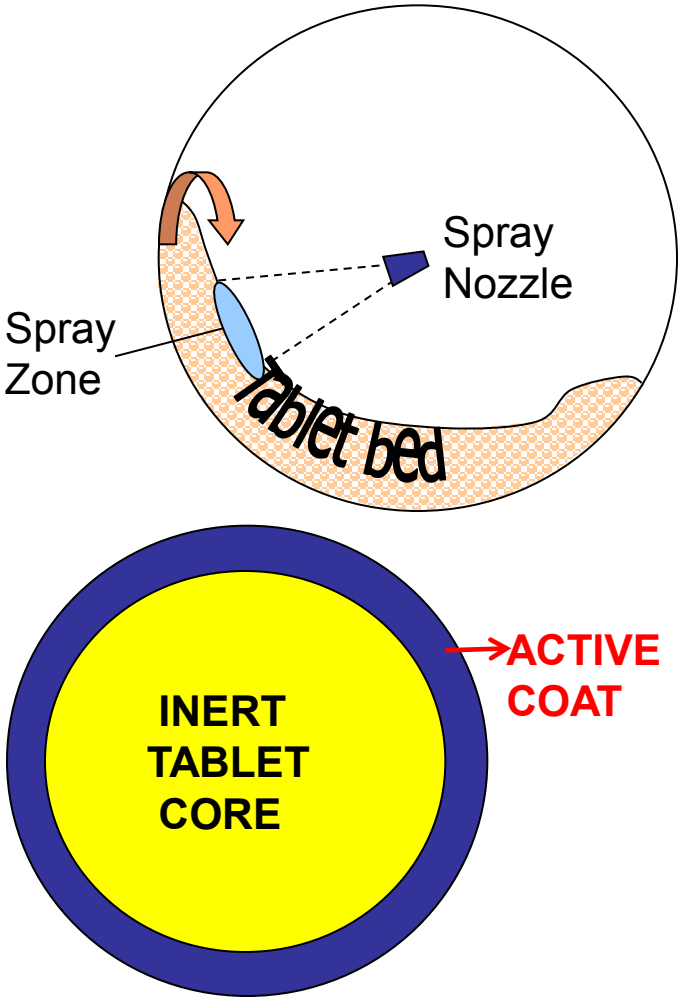
Analysis of DOE data used to define a **scale invariant design space** in terms of range of **Spray Flux**

Example #4: Mechanistic Model



- Active coating of tablets in a pan coater
- Mechanistic model to predict tablet coating uniformity
- Model is a function of spray zone size, tablet "velocity" & bed loading
- Model developed using DOE data at pilot scale
- Model verified by comparing model predictions with actual experimental data
- Model used to select operating conditions at large scale
- Verify model predictions by manufacturing one or batches at the determined operating conditions

Considerations for Scaling up Design Space (I)

- Ensuring significant **intermediate material attributes** remain unchanged across scales
- Consider impact of variability of in-coming material (e.g. due to change in supplier)
- Typically limited design space verification at the time of submission
  - Verification typically occurs at or near target operating ranges
- When scaling up a **scale dependent** design space
  - Not necessary to repeat at commercial scale all the experiments that were conducted at pilot scale to define the design space
  - Movements to commercially unverified areas can pose risks to quality due to potential scale up effects or model assumptions
  - Verification approach guided by **risk assessment**
    - Management of risk can include additional monitoring that is not included in the routine control system
  - Plans for design space verification included in design space verification protocol within the firms internal Quality System

Considerations for Scaling up Design Space (II)

- If a design space is demonstrated as **scale independent**, then additional mitigation steps may not be necessary
- Consider potential risk to stability for change in scale
- Refer Q&A #2 on Design Space Verification, from FDA-EMA QbD pilot

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/11/WC500153784.pdf

Considerations for Models for Scale-Up

- For empirical models (e.g. regression models)
  - Understand impact of multivariate interactions
  - Incorporate process and/or method uncertainty in the model
- For mechanistic models
  - Understand applicability of model assumptions at commercial scale
- Verify model predictions at commercial scale
  - Understand model limitations
  - Provide additional evaluations when moving to areas of uncertainty

Considerations for a Continuous Manufacturing Process

- Typical batch process scale up considerations often don't apply
  - No change of scale needed for a continuous manufacturing process
- Offers flexibility to change batch size to accommodate supply needs
  - Same equipment can be used
- Various options for increasing batch size
  - Scale out (i.e. adding identical multiple lines manufacturing the same product)
  - Increase in line rate
  - Increase in duration of operation
- Ways to define a batch/lot at the product collection step
  - Production time period
  - Production variation (e.g., different lots of feedstock)
  - Dependent on equipment cycling capability
- Consider potential risk to stability for change in scale

What is Technology Transfer

- Technology Transfer (ICH Q10)
  - o New product transfers during development through manufacturing
  - o Transfers within or between manufacturing and testing sites for marketed products

- The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization. This knowledge forms the basis for the manufacturing process, *control strategy*, process validation approach, and ongoing continual improvement.

Considerations for Technology Transfer

- Requires efficient systems for knowledge management
- Enhanced monitoring during technology transfer can provide preliminary indication of process performance
- CAPA can be used as an effective tool during technology transfer to optimize the control strategy
- Understand impact of potential variability in raw material properties (e.g. change in supplier)
- Technology transfer is typically a component of PPQ (Process Performance Qualification) stage (i.e. Process Validation stage II)

Example: Considerations for Transfer of PAT tools (e.g. NIR)

- Maintaining similarity in placement of NIR probe, and sample size for measurement
- If known *apriori* that NIR tool at the commercial site would be from a different manufacturer than that at scale up site
  - Suggested to include data from both these instruments to build calibration model
  - Re-verification of model is typically not necessary at commercial site
- If necessary, revise and revalidate the calibration model as needed
  - Validate using acceptance limits equivalent to those used for the original procedure
- Revising of calibration model may be needed if there is change in excipient material properties (e.g. change in supplier)

Review Consideration (I)

Scale up related question in QbR (Question based Review)

2.3.P2.3 Manufacturing Process Development

16. For each of the potentially high risk manufacturing unit operation:

a) What input material attributes and process parameters were selected for study and what are the justifications for the selection?
b) What process development studies were conducted? Provide a summary table listing batch size, process parameter ranges, equipment type and estimated use of capacity.
c) What process parameters and material attributes were identified as critical and how do they impact the drug product CQAs?
d) How were the process parameters adjusted across lab, pilot/registration and commercial scale? What are the justifications for any changes?

Review Consideration (II)

Points to consider for inclusion of scale up information:

- A discussion of the theory, scale-up factors, first principles and/or other approaches used to adjust process parameters across scales should be provided
- Summarizing changes made to process parameters in a table

Table 52. Scale-up of the roller compaction and integrated milling process

Scale	Batch Size		Alexanderwerk model	Roller width	Roller diameter	Roller gap	Roller pressure	Mill screen orifice size
--	(kg)	(units)	--	(mm)	(mm)	(mm)	(bar)	(mm)
Lab	5.0	25,000	WP120	25	120	1.2-2.4	20-77	1.0
Pilot	50.0	250,000	WP120	40	120	1.8	50	1.0
Commercial (Proposed)	150.0	750,000	WP200	75	200	2.0-4.0*	31-121*	1.0

- *The range is based on the scale-up equation and needs to be verified.

Ref: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM304305.pdf

- If applicable, rationale for change in equipment type from pilot to commercial scale
- If models are used to support scale up, a discussion of how model predictions were used to make decisions

Some Common Scale up / Tech Transfer Related Concerns

- Inadequate data to support proposed process parameter ranges upon scale up
- Overlooked difference in equipment capacity utilization between pilot and commercial scale
- Potential raw material variability upon scale up or tech transfer not addressed
- Incorrect implementation of known scale up principles
  - Examples: Indicating same shaft speed and blending time when scaling up a V-blender; use of same agitator speed to scale up a high shear mixer granulator (i.e. would result in different tip speed)
- Lack of understanding of scale up risks and inclusion of appropriate detection and mitigation techniques in the control strategy

Conclusion

- Regulators have been steadfast in encouraging industry to adopt science and risk based principles for scale up and technology transfer
- Implementation of a control strategy that mitigates any potential scale up risks
- Providing supporting scale up information in the submission facilitates thorough evaluation of the proposed manufacturing process and minimizes IR (Information Request) cycles

Successful scale-up and technology transfer assures consistent manufacture of desired quality product and ***minimizes risk to the patient***

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Thank you!

Questions, comments, concerns:

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