Pharmaceutical Quality System (ICH Q10) Conference
October 4-6, 2011 | Crystal Gateway Marriott | Arlington, Virginia
November 14-16, 2011 | Sheraton | Brussels, Belgium

Scale-up & Technology Transfer as a Part of Pharmaceutical Quality Systems

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Outline

- Introduction
- Key aspects of product Robustness
- Review essential elements of Scale-up/Technology Transfer
- Key Development Principals Leading to a robust Scale-up/Technology Transfer
- Scale-up/Technology Transfer Leading to Successful Validation and Robust Commercialization
- Review of several Studies
- Advantages of Using a Holistic QBD Approach to Product Development/Technology Transfer

Manufacturing Science Definition:

The body of knowledge available for a specific product and process, including critical-to-quality product attributes and process parameters, process capability, manufacturing and process control technologies and quality systems infrastructure.

(Source: PhRMA Quality Technical Committee, 2003)

"Robustness"

- ✓ Is the ability of a process to demonstrate acceptable quality and performance, while tolerating variability in inputs.
- ✓ Is a function of formulation and process design
- ✓ Control capability when processing at Pilot vs. Manufacturing scale must be understood.
- ✓ Experimentation In manufacturing is limited vs Research and Development but the state of robustness can be determined via Proactive process monitoring.

Goals of Technology Transfer

- Is a valuable step in the developmental life cycle leading to successful commercial manufacturing
- To take all the gathered knowledge and use it as the basis for the manufacturing control strategy, the approach to process qualification and on-going continuous improvement
- The transition of the product/process/analytical method knowledge between development and manufacturing sites
- To ensure variability of process and parameters are controlled and sufficient in the face of the rigors of a commercial production environment
  To verify parameters established during development are still within the determined design space and/or adjusted at scale-up

ICH Q10
"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 realisation. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement."

Utilization of a QBD Approach Ensures a Robust Technology Transfer

- Form a diverse/skilled and collaborative development team
- Review process flow diagram for key inputs/outputs that could impact quality (QRM)
- Uni/multi variant experiments should have been completed to study relationships and gain information on potential sources of variability. (Need to know where quality could be impacted)
- Make sure you understand your measurement capability (i.e. repeatability, precision)
- Critical Process Parameters (CPPs), Critical Quality Attributes (CQAs) and other important parameters are identified
- Design space should be defined and understood consisting of a set of input ranges (CPPs) that provide high probability that CQAs will meet specification.
- A control strategy needs to be in place to assure focus on critical points

Pharmaceutical Quality Systems
"A Common Thread to Tech Transfer"

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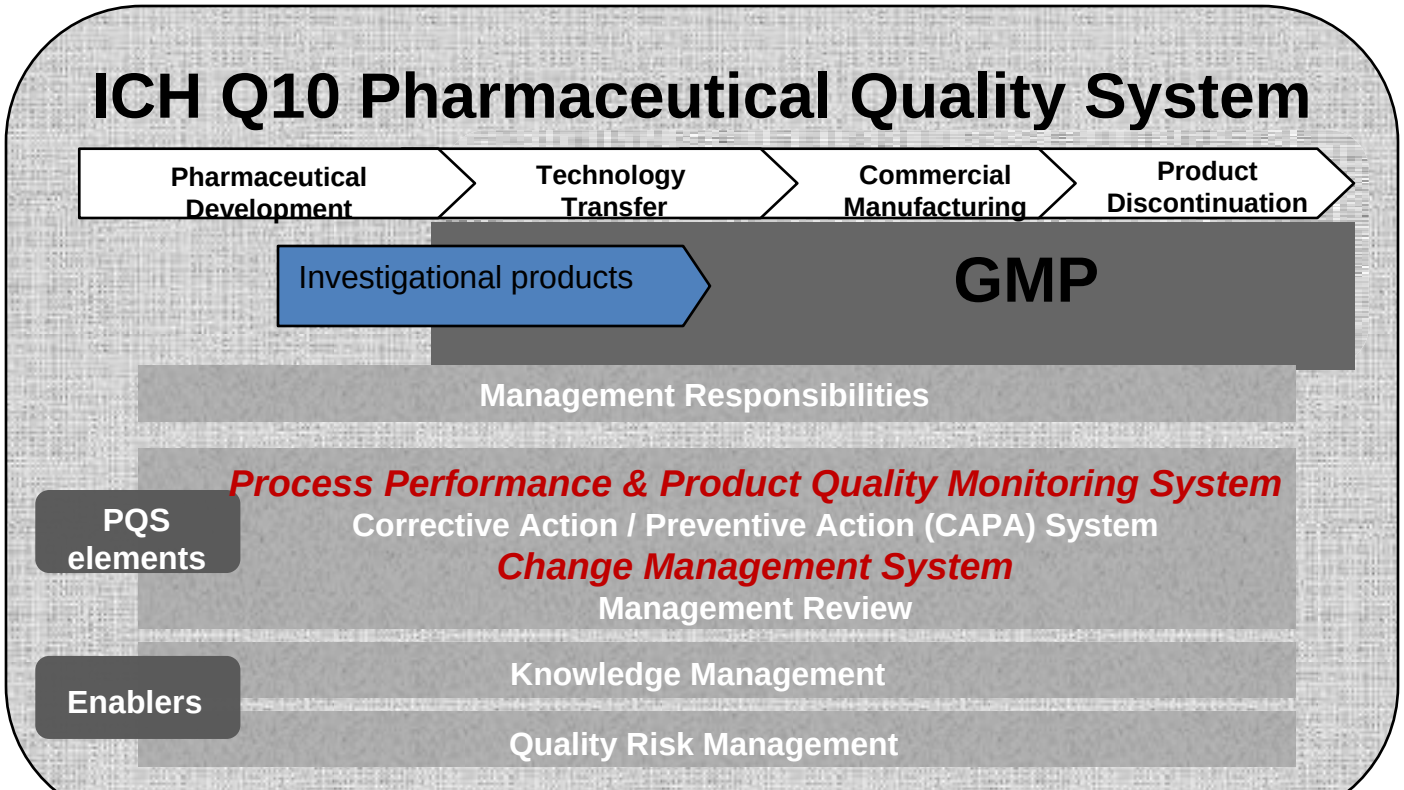
ICH Q10

"The change management system should provide management and documentation of adjustments made to the process during technology transfer activities."

"Aspects of management review should be performed to ensure the developed product and process can be manufactured at commercial scale."



Key Elements of Technology Transfer

Documentation/Information:

- Consistent and controlled procedures for Technology Transfer and for running your process
- Assurance of clear documentation of all process/product knowledge
- Understanding of prior knowledge from similar products

Personnel:

- The integrated interdisciplinary team of cross functional experts: Operations, Tech Operations, CMC, Supply Chain, Analytical, Quality, R&D etc.
- Roles and responsibilities of development group and the site are defined

Technology Evaluation/Development:

- Assure have well understood, robust process, and corresponding analytical methods
- Well designed and well understood equipment train
- Utilize principals in ICH Q8, Q9 QRM, and Q10
- Uni/Multivariant Design of experiments
- Identification/verification of CPPs and CQAs and other important parameters.

Key Elements of Technology Transfer (Continued)

Execution:

- Successful manufacture of demonstration batches

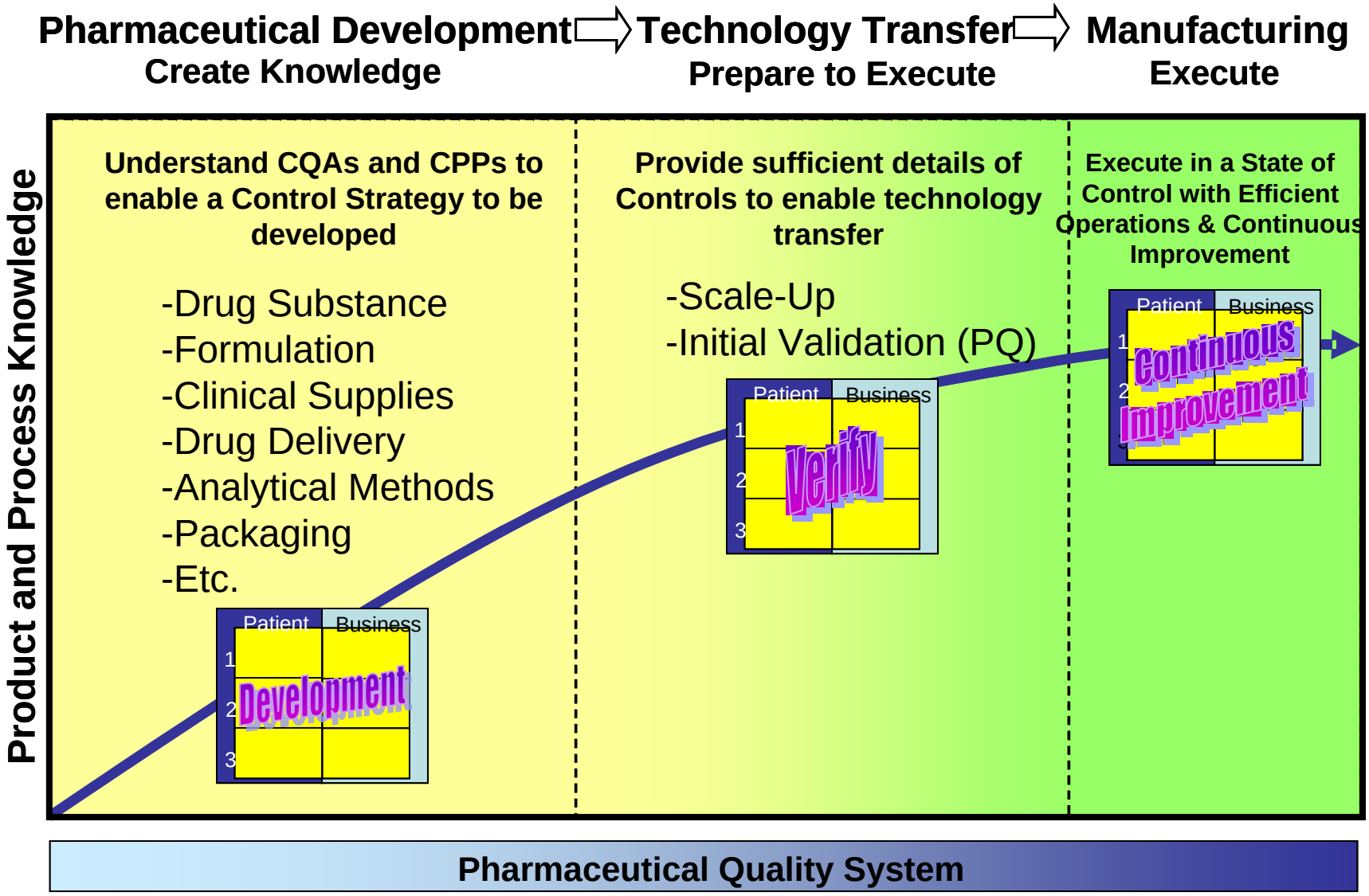
  Note: This aids in site training and demonstrates that the receiving site has the ability to perform the process adequately and is the basis for Process Validation
- Understand validation requirements/strategy
- Continuous monitoring (i.e. PAT, Pi Data acquisition, Proactive process Analysis etc.)

Pharmaceutical Quality System:

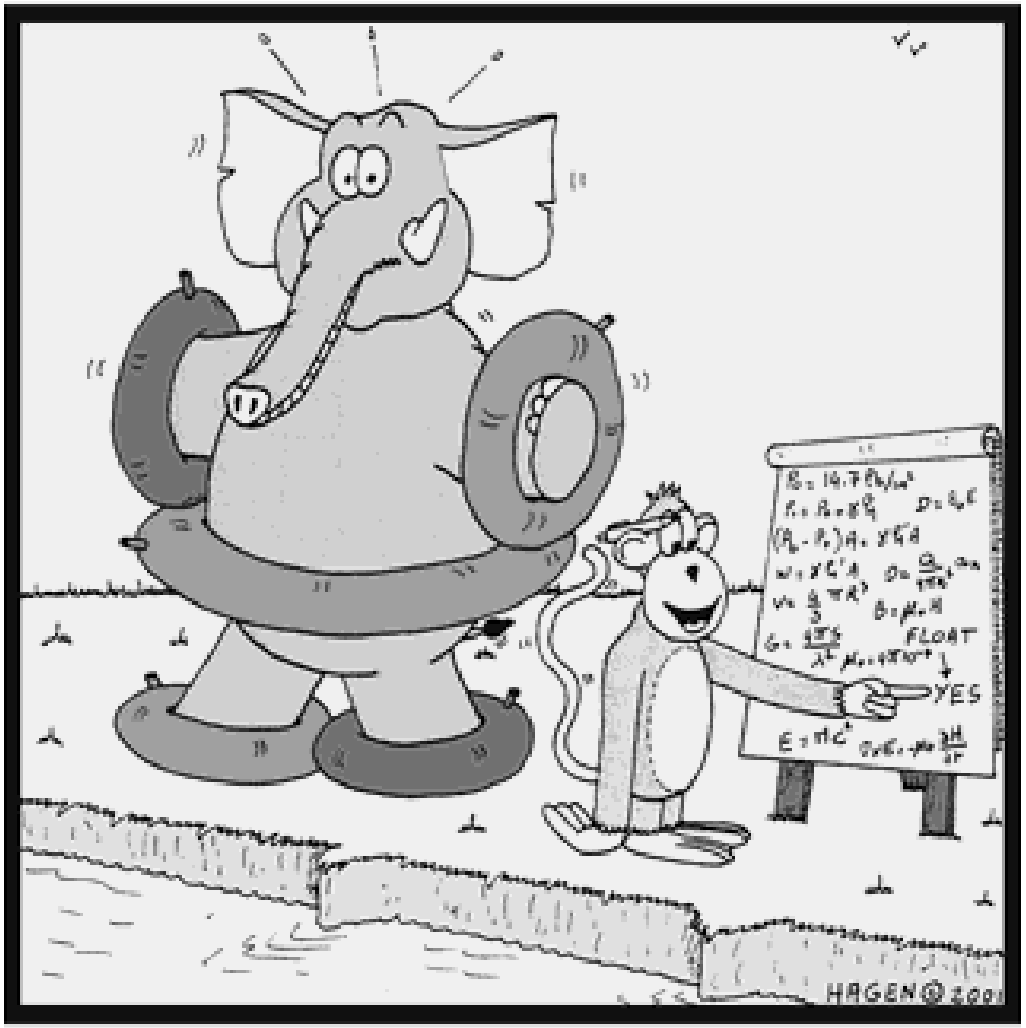
- Executable control strategy under site PQS
- Utilize PQSs to help drive/control any changes, document learning's during and post transfer

Lifecycle View of Control Strategy

(Adapted from ISPE PQLI Control Strategy team)



Scale-Up Can Be Complex



According to my calculations,
you should float now... I think...

Insufficient Process Knowledge Results in a Poorly Scaled-up Process

- Sub Robust Processes (Decreased CpK)
- Reduced Production Rates
- Increased number of atypicals (i.e. product defects, elegance issues etc.)
- Decreased process reliability
- Not being capable of handling variations of raw materials, API, Process controls, operators, etc.
- Inefficient Validation
- Etc.

ICH Q10
"Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy."

Process/Scale-Up Understanding Through Models

Empirical:

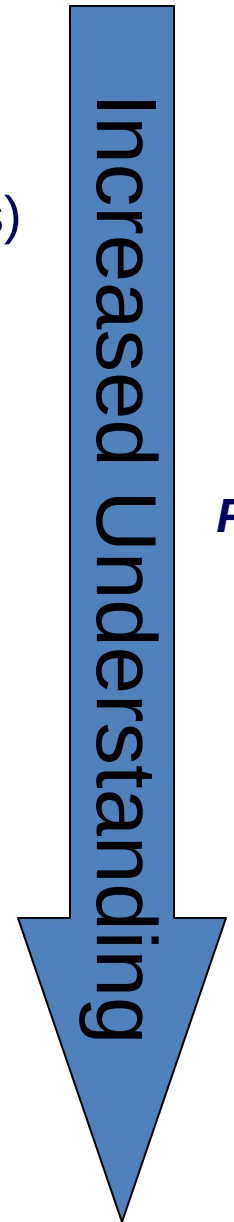
- Based on experimental relationships/correlations.
- Used frequently
- Examples: IVIVC correlations, DOE's (Regression Models)

Semi-Empirical/Hybrid:

- Combination of Empirical/Mechanistic
- Based on Mechanistic understanding and requires some experimentation to fit parameters to verify.
- Example: Population model for granule growth. Uses probability of granules colliding and adhering.

Mechanistic:

- Are predictive models based on underlying physics and chemistry principals.
- Predicts property response without experimentation.
- Can do empirical experiment to confirm
- Still evolving in powder processing but progressing
- Examples: Lyophilization, liquid flow based on computational fluid dynamics



Process Validation

- Regulatory agencies are emphasizing the need for a more thorough understanding of product and process prior to validating.

- Traditional:
  - Based largely univariant and empirical approach to development
  - Three validation lots
  - Not a lot of emphasis on material variability

- The 21st Century (Process Validation Lifecycle Approach):
  - A Holistic QBD life cycle approach to development supports (i.e. Fundamental first principals understanding, increased mechanistic understanding etc.) a robust validation.
  - Uni/Multi variant
  - Use of modeling tools
  - Use of prior knowledge
  - Leverages control strategy implementation
  - Utilizes proactive process monitoring/PAT for trending/continuous verification
  - Continuous proactive improvement (We are Always Learning)

Process Validation Lifecycle Approach

Scale-up is a Critical Link in this Lifecycle

Stage I Process Design

- Lifecycle development experiences/conclusions
- Forms basis for validation protocol design
- ICH Q8, 9, 10 concepts applied
- More comprehensive product design → more robust product

Stage II Process Qualification

- Assures consistency of manufacturing
- Design/qualification of equipment, facilities, and utilities
- Reproducibility of process design evaluated commercially
- Provides assurance of commercial readiness

Stage III Continuous Verification

- Continuous process verification
- Control strategy
- Ongoing assurance process is in control
- Trending/Statistical Analysis/Proactive Improvement

Case Study #1 In-line Blend Uniformity Monitoring

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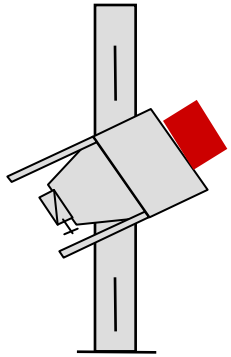
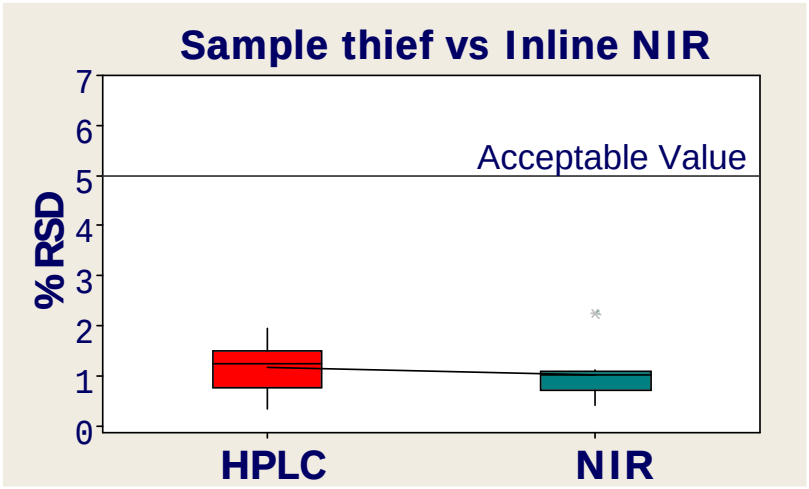
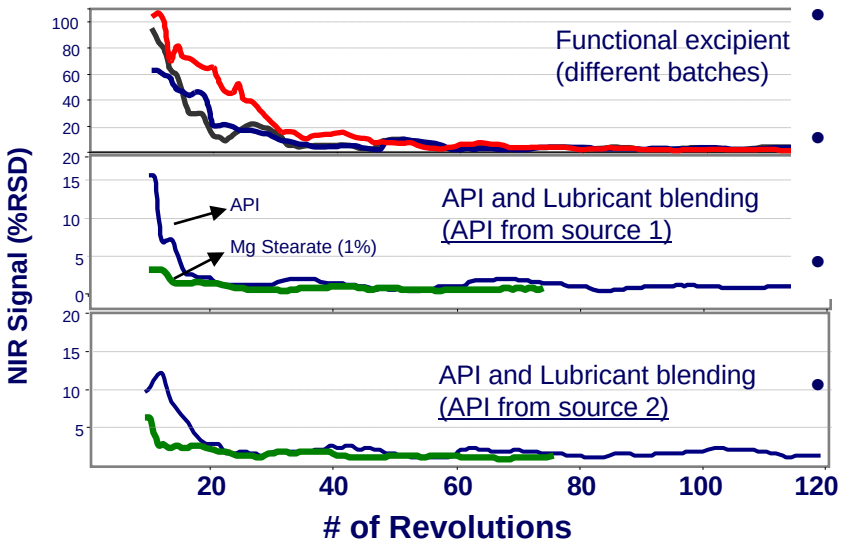
Technology:

- NIR instrument mounted on bin blender
- Data acquisition when NIR on bottom
- Analysis of variance of spectral data





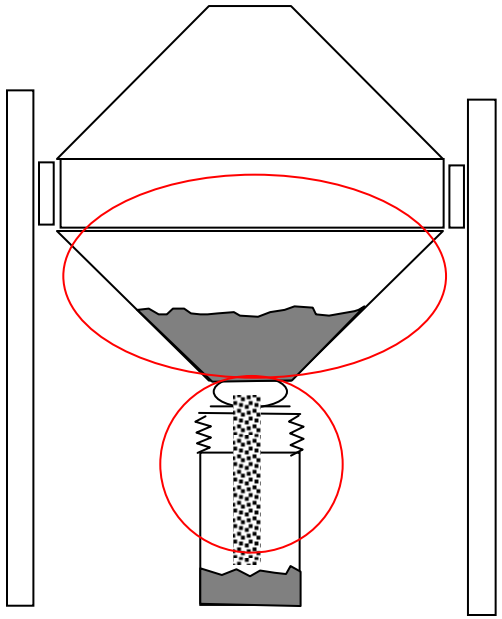
Blending uniformity monitoring in real time



- Real time monitoring of , Active Pharmaceutical ingredient (API) functional excipients, lubricant (1%).
- API and functional excipient sources do not impact blending
- Process parameters established in development, then confirmed in supply
- Allows future design space expansion, flexibility in Raw Material as experienced
- PAT system gives process insight and potentially gives blending end point control with data feed back/control.

Case Study #2 Blend Uniformity Issue During Process Validation

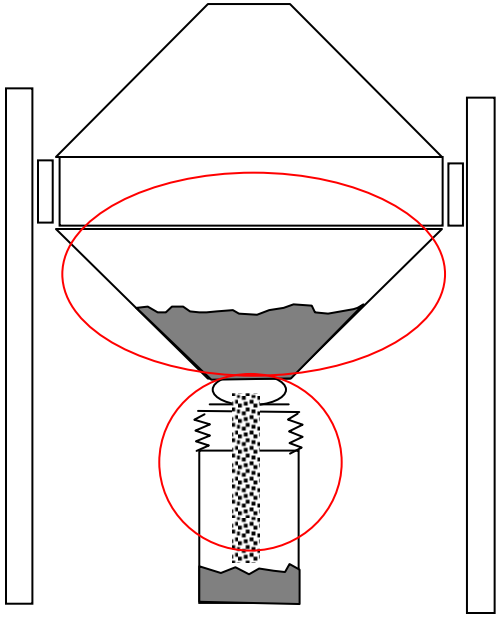
- Situation:
  - Thought this was a well understood unit operation
  - Did not find it as an issue of concern during risk assessment (Simple well characterized unit operation)
  - Drug load was not that low.
  - Went to validation and saw a blend uniformity issue upon material transfer.
  - Resulted in delay and revalidation following identification of root cause



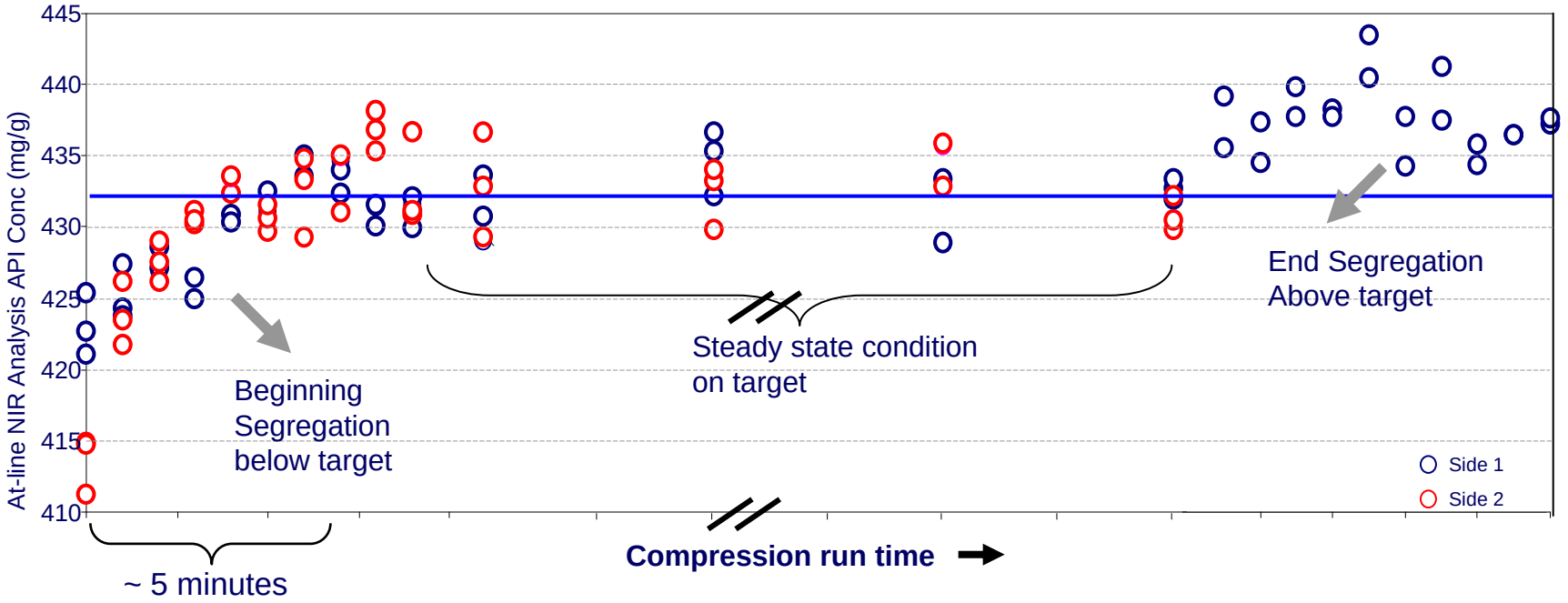
- Solution:
  - Risk assessment evaluating all possible sources of material segregation was performed, during blending, during material transfer and during further down stream storage and transfer.
  - Optimizations identified and implemented
  - Revalidation completed successfully

Case Study #2 Blend Uniformity Issue During Process Validation

- Lessons Learned:
  - During scale-up/technology transfer there is a need to understand all potential issues that could occur.
  - Need to consider material handling and equipment in your risk assessment as well as formulation/process factors (Equipment /material handling at facilities can vary)
  - Need to be operating at optimal blend capacity
  - Need to understand drop heights of material from Blender to drum/tote.
  - Need to understand impact of drums vs. IBC
  - Need to understand down stream impact on material segregation
  - A NIR blend control strategy could have been helpful in hind site



Case Study #3 PAT in Compression: NIR assay/CU on tablets



- At-line NIR assay of tablets as part of real time release testing
- Large number of samples per batch
- HPLC is resource intensive, slow, not possible for near real time use
- NIR provided time-resolved data (during short press run time)

Dual use of data:
- Intra-batch: Release data for CU and CA
  => control/release
- Inter-batch: Detailed data for trending
  => process monitoring

"The Payoff"

Robustness:

- A well developed process based on scientific principals
- Positive identification of CPP's and CQA's and other important parameters and assurance that they are watched and controlled
- Robust validations

Compliance/Regulatory:

- A superior quality product
- Knowledge build that is well documented via CAPA and Change management process
- Quicker resolution of atypicals (i.e. Deviation events)
- Scientific support for identifying true root cause for atypicals
- Working within established design space results in global regulatory flexibility
- Fewer deviations
- Proactive improvement
- More Efficient PAI's

Commercial Capability:

- Better manufacturing efficiencies
- Higher yields
- Enhanced process control

Conclusions

- Using a sound scientific/principals based approach (QBD) to development supports the development of a robust/safe product.
- Approaches to development require a certain degree of rigor to enable a robust technology transfer commercialization.
- Developing a robust and continually improved process in conjunction with Pharmaceutical Quality Systems assures meeting or exceeding GMP requirements
- Do not underestimate the complexities during Scale-up and utilize all tools available to you.
- It is a collaborative effort with Research and Development, Manufacturing Technical Operations, Quality, Manufacturing etc. that is needed to assure a successful technology transfer and a Robust final manufactured product.

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Questions?