

Pharmaceutical Development and Manufacturing: Trends in Processing of Oral Solid Dose Forms

**R. Christian Moreton, Ph.D
FinnBrit Consulting Waltham MA, USA**

PharmSciFair, Nice, France; June 8-12, 2009

Presentation Outline

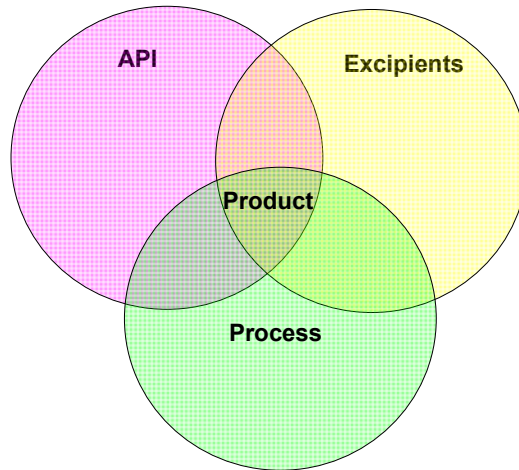
- 1. Introduction**
- 2. Product variability**
 - API variability
 - Excipient variability
 - Process variability
- 3. Quality by Design**
- 4. Continuous processing of
pharmaceutical finished
products**

Introduction

The Objective

- **To develop a robust medicinal product that will deliver the drug to the patient:**
 - In the required amount (content and assay).
 - At the optimum rate necessary to achieve the desired therapeutic benefit (*in vivo* dissolution).
 - **Consistently:**
 - Within lots (blend uniformity for all components).
 - Between lots (validated manufacturing process).
 - For the shelf life of the product (stability).
 - That can be manufactured at full production scale and production speeds.

Components of a medicinal product



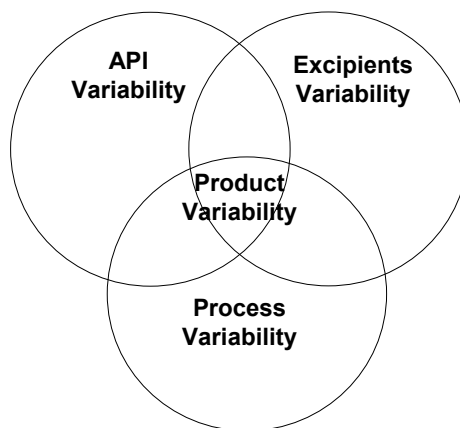
What is a Robust Formulation?

- **A formulation that is able to accommodate the typical variability seen in:**
 - API
 - Excipients
 - Processes

Without compromising the manufacture, stability, performance or any other attribute of the product critical to the patient's care or well being.

Product Variability

Product variability



$$\sigma_{\text{Product}}^2 = \sigma_{\text{API}}^2 + \sigma_{\text{Excipients}}^2 + \sigma_{\text{Process}}^2 + \sigma_{\text{Interactions}}^2$$

Interactions in Product Manufacture

$$\sigma_{\text{Product}}^2 = \sigma_{\text{API}}^2 + \sigma_{\text{Excipients}}^2 + \sigma_{\text{Process}}^2 + \sigma_{\text{Interactions}}^2$$

Where :

$$\sigma_{\text{Interactions}}^2 = \sigma_{\text{Interaction (1)}}^2 + \sigma_{\text{Interaction (2)}}^2 + \dots + \sigma_{\text{Interaction (n)}}^2$$

- Interactions include:
 - Powder – Powder
 - Powder – Liquid
 - Powder – Equipment
 - Liquid – Equipment
 - Powder – Operator
 - Liquid – Operator
 - Equipment – Operator
 - etc.
- For each unit process
- For each component

Why is variability so important

- All processes and products have an inherent variability:
 - Normal (Gaussian) distribution
 - Log-normal distribution
- The patient requires that their medicine performs as needed/intended for as long as necessary.
- In order to meet the patients needs, we need to understand product variability and maintain it within an acceptable range
- We cannot eliminate variability.
- We need to:
 - Understand it,
 - Come to terms with it
 - Learn to live with it.
- Both QbD and continuous processing require that we recognize, understand and adapt to the inherent variability of our materials and processes.

Active Pharmaceutical Ingredients

- **Chemical specifications:**
 - This is really a patient safety issue and ICH has helped.
 - We have a good understanding of e.g. the impurity profile of most APIs.
- **Physical specifications:**
 - Have we really done as good a job?
 - Have we really optimized the API physical properties?
 - Typically, we mill everything, do we need to?
 - We need to do a much better job in this area.

Excipients

- **A diverse group of materials:**
 - Synthetic, animal, vegetable or mineral
- **Many chemical types:**
 - Esters, carbohydrates, hydrocarbons, inorganics, etc.
- **Not typically made only for the pharmaceutical industry.**
- **Some manufactured by batch processing; many manufactured by continuous processing:**
 - Inherent variability in the unit processes as well as raw materials.
- **We do not know why many excipients work:**
 - Most work because they are not 'pure', but
 - We typically do not know enough about excipient composition to be certain of what is critical to functionality

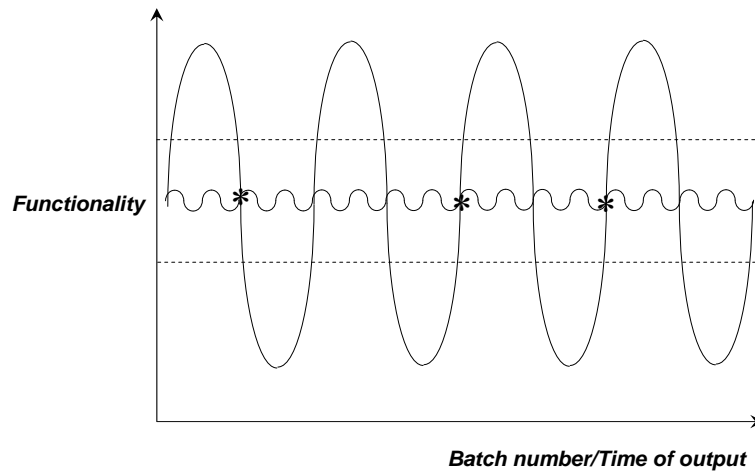
Sources of Excipient Variability

- **Scale – capacity of the equipment train**
- **Variability of raw materials (often of natural origin)**
 - Conditions during growing season
 - Conditions at harvest
 - Variation in growing season year upon year
- **Changes in raw material source due to**
 - Drought
 - Flood
 - War
 - Accident
- **Weather at the time of manufacture**
 - Hot or cold
 - Dry or humid

So what is the answer?

- **Robust formulations?**
- **Robust processes?**
- **Tighter specifications?**
 - Custom grades?
 - Batch selection?
 - Sounds attractive – BUT!

What is the functional variability A BIG Difference!



Excipient Samples at the Extremes of Specification

- Most excipient processes are designed to deliver material at the mid-point of a particular set of in-process parameters
- Most Users want material from the extremes of the specified range.
- Options include:
 - Holding batches that are found to be a the extremes of specification – **NOT RECOMMENDED!**
 - Difficult and expensive
 - No guarantees
 - Use closely related grades, e.g. based on viscosity, particle size, etc.
 - Use blended grades (e.g. viscosity), dilution (e.g. viscosity) or sieve cuts (e.g. particle size)

Process variability

- **Scale-up factors**
 - What is the smallest scale of equipment that can be reliably scaled up?
 - How confident are we that investigations carried out at a particular scale are predictive of what will happen at production scale?
- **What needs to be changed as we move up in scale?**
 - Is the processing easier at larger or smaller scales?
 - What changes in formulation and/or process will be required at the larger scale?
- **Fixed time processing vs. end-point control**
 - PAT instrumentation

Interaction variability

- **One of the biggest problems can be the operator interaction:**
 - **Same operator different campaigns:**
 - The 'break'!
 - **Different operators:**
 - Loading the blender
 - Overfeeding or underfeeding the mill
- **Granulation solvent (usually water)**
 - Temperature
 - Rate of addition
 - Time of massing

Quality by Design

International Conference on Harmonisation*

- **ICH Q8 (R1) – Pharmaceutical Development**
 - Quality by Design
 - Design space
- **ICH Q9 – Risk Management**
- **ICH Q10 – Quality Management Systems**

**International Conference on Harmonisation of Technical Requirements for
Registration of Pharmaceuticals for Human Use: <http://www.ich.org>*

See also:

- **FDA: Quality in the 21st Century**
 - Process Analytical Technologies (PAT)
 - Quality by Design

Why the changes?

- **A recognition that the old paradigm of ‘three-batch’ validation was inadequate:**
 - **Inefficient and wasteful of resources:**
 - Too many supplements/variations for marketing authorizations
 - Manufacturing was not able to respond properly to change
 - Processes were not properly optimized
 - **Did not allow Companies to adopt modern production strategies**
 - **Did not prevent failures and recalls**
 - **Did not guarantee availability of medicines to the patient.**

The new paradigm

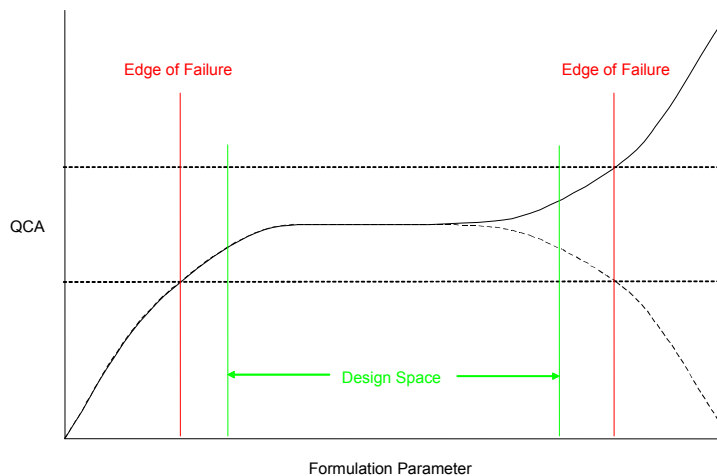
- **In the new paradigm (Quality by Design (QbD) in the US):**
 - **Invest in development by using Design of Experiments (DoE) to define the Design Space**
 - Understand your product and process limitations
 - Find the limits within which a product compliant with specifications can be assured
 - **Get regulatory flexibility post-launch to make changes within the agreed Design Space**
 - **Notification through Annual Report – no Prior Approval Supplements or Variation applications**
 - **In the US, QbD applications will have to be notified ahead of time and the data package agreed with the regulatory agency**

Design Space

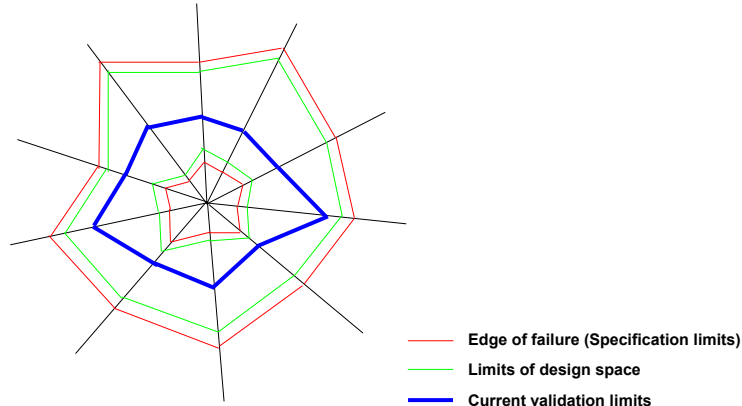
- The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

(Guidance for Industry; ICH Q8 (R) – Pharmaceutical Development, Nov. 2008)

Design Space Concepts



Visualization of a Multi-dimensional Design Space for a Pharmaceutical Formulation



Stages in a formulation project

1. **Preformulation**
 - Including excipient compatibilities
2. **Formulation and process design**
3. **Formulation and process development**
 - Initial scale up 1x
4. **Scale up**
 - Pilot/intermediate scale 10x
 - ICH – 100 000 units or not less than 1/10th full scale, whichever is the greater
 - Full scale 100x
5. **Technical transfer and validation**

Where do we start?

- **We start with preformulation!**
 - Preformulation underpins every formulation project.
 - If the preformulation is inadequate, there is an increased likelihood that the formulation project will not succeed.
- **We do not need a sophisticated Design of Experiments (DoE) at every stage in the development process, particularly in the early stages.**
 - But we do need *GOOD QUALITY DATA!*
- **We need to ensure we can make:**
GOOD DECISIONS BASED ON GOOD SCIENCE!

When does QbD finish?

- **When the product is withdrawn or discontinued!**
- **Quality by Design is not a one-time activity (cf. validation).**
- **QbD is a continuing activity:**
 - Need to continue to monitor batch data to make sure the batches all stay within the design space:
 - Validation becomes a continuous verification program.
 - If a batch falls outside the Design Space, we have an opportunity to extend the Design Space:
 - We need to determine what further work is required to extend the design space, agree the protocol with the regulators, and execute the plan.

Prospects for continuous processing in pharmaceutical product manufacture

Traditional Pharmaceutical Manufacturing

- **Batch processing:**
 - Defined quantities of materials are processed together and pass through the process as a defined lot.
 - Validation using three lots made at full production scale
- **Traditionally for tablets and capsules:**
 - Wet granulation
 - Dry granulation (roller compaction/slugging)
 - Direct compression/encapsulation
- **More recently:**
 - Hot melt granulation
 - Moisture-activated dry granulation
- **But still batch processing!**

Continuous processing in pharmaceutical product manufacture

- **Why?**
 - High containment manufacturing
 - Most pharmaceutical product manufacturing equipment stands idle for 12 hours per day
 - Maximize return on investment/amortization of equipment investment
 - ‘Lights out’ operations
 - Increase production without increasing staffing levels
 - Reduce shift payments (unsociable hours)
 - Reduce the uncertainties and cost of scale-up
 - In continuous processing, an increase in batch size simply means a longer run-time
 - Labour costs
 - Production staff
 - Analytical staff
 - Reduce the operator interaction

Continuous processing in pharmaceutical product manufacture

- **How will we have to change our thinking to make this happen?**
- **How will we have to change our:**
 - Formulations?
 - Equipment?
 - Processes?
 - Sampling plans?
 - Analytical approach (including Process Analytical Technologies)?
- **Better understanding of raw materials, and the implications of variability:**
 - But not necessarily tighter control of specifications.

Continuous Processing for Pharmaceutical Finished Products

- **Can we do it?**
 - Yes!
 - Equipment is available
 - Concepts worked out in/for other industries
- **Ultimate application of Process Analytical Technologies (PAT)**
- **What is missing?**
 - Sufficiently robust formulations (in some cases)
 - Integration of:
 - Size and throughput for the different unit processes
 - Metering systems
 - Process monitoring
 - Process control/feedback control
 - In-process testing (increased?)
 - Finished product testing (reduced?)
 - Batch record review vs. in-process data review
 - **Software validated to pharmaceutical industry standards.**

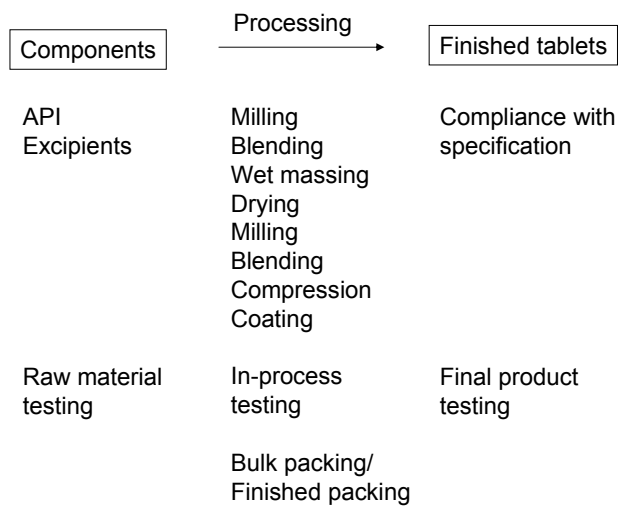
Installation requirements for Continuous Processing

- **A robust formulation**
- **Well established Design Space**
 - Scientifically justifiable correlation between critical material and process attributes and product performance
- **Appropriately instrumented equipment, adapted to continuous processing**
 - Dispensing and metering systems
 - Wet granulator
 - [Roller compactor]
 - Dryer
 - Milling
 - Blender
 - [Tablet machine]
 - Coating equipment
 - [Bulk Packing/Finished packing]

Installation requirements for Continuous Processing (contd.)

- **Installation and qualification (DQ, IQ, OQ and PQ)**
- **Integration plan**
- **Cleaning and inspection**
 - Clean-in-place
 - Inspection ports
- **In-process analytical methods**
 - PAT
 - On-line, in-line or at-line methods
- **Validatable software to integrate all the information and controls**

Film-coated tablet prepared by wet granulation



How do we adapt wet granulation to continuous processing?

- **Plug flow:**
 - Three or four small mixers used in parallel
- **Move from vertical main drive axis to horizontal main drive axis (Diosna and Gral types compared to Lödige type)**
- **Extrusion (without spheronization)**
- **Vertical continuous mixer**
- **Key points:**
 - How do we prevent excessive build up of product on sides of mixer and impellers?
 - How do we deal with start-up and shut-down?

How do we adapt fluid-bed drying to continuous processing?

- **Change from a round drying chamber to a rectangular drying chamber**
 - For example, several short chambers connected in series to improve air-flow control
- **Automated filter-bag shaking**
- **Instrumentation using e.g. ΔT method**

Lubrication in Continuous Processing

- **Magnesium stearate is the most common lubricant**
- **It is typically used at 0.5 – 1.0% w/w**
- **Disadvantages of magnesium stearate**
 - Hydrophobic
 - Can be over-mixed easily, particularly with larger batches
 - Can reduce tablet hardness
 - Can interfere with dissolution
- **Typically mixed for short period at the end of the final blending**

Lubrication in Continuous Processing

- **What are we trying to achieve during tablet blend lubrication?**
 - Sufficient distribution of the lubricant to achieve lubrication but not to over mix.
 - An incomplete coating of the lubricant on the surface of the dry granules.
- **Can we achieve this by mixing a smaller concentration for longer? (i.e. over-mixing a much smaller quantity such that a complete coating of the granules cannot occur.)**
 - Will such an approach be reliable enough for filling/compaction?
- **Will the smaller scale blending in continuous processing reduce the risk of over-mixing?**

Continuous Film-coating

- **Already in development**
 - The key issues include start-up and shut down
- **Industrial scale model in testing from at least one manufacturer (on display at Interphex New York, March 2009).**
- **Consistency/Robustness/Variability**
 - Immediate release coatings vs. functional coatings (modified release)

Disadvantages of Continuous processing

- **Risk:**
 - **Failing process/product:**
 - Start-up and shutdown
 - How to determine how much material to reject
 - How to isolate out of specification material
 - Adequate testing and protocols
 - **Cross-contamination if not dedicated plant**
 - **Batch/lot size and recall**
- **Size/throughput of plant:**
 - **May not be appropriate for every product**
 - Orphan drugs?
 - **Requires a minimum manufacturing requirement:**
 - Solid sales projections.
- **Regulatory Agency acceptance.**

Conclusions

- **The way we carry out formulation development projects is changing due to the advent of QbD.**
- **The formulation scientists will need to understand their APIs and excipients, particularly their limitations and variability.**
- **Design space will be very important.**
- **Better understanding of all our materials is needed.**
- **Continuous processing for the manufacture of pharmaceutical finished products is closer, but perhaps for many companies, still in the future.**
- **We need to understand what we need to achieve rather than assume that old processes will translate directly to the new processing.**

Thank you!
Any questions?

www.finnbrit.com